Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of transcatheter aortic valve implantation (TAVI) in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications

November 2019

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Office of the Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Aortic stenosis is a chronic, slowly progressive disease resulting from thickening, fibrosis, and calcification of the aortic valve. The prevalence of severe aortic stenosis is 3.4% in high income countries, of which 76% are symptomatic. Without intervention to replace the damaged valve, the prognosis for patients with severe symptomatic aortic stenosis is extremely poor. Mortality associated with untreated severe symptomatic aortic stenosis is approximately 40% after 5 years.

Surgical aortic valve replacement (SAVR) is the standard treatment for patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications. It is an open cardiovascular surgical procedure that involves surgically removing the diseased aortic valve and replacing it with an artificial valve.

Transcatheter aortic valve implantation (TAVI) is an alternative to SAVR treatment. It is a minimally invasive procedure whereby the aortic valve is functionally replaced by implanting a new valve within the existing diseased aortic valve. TAVI is routinely used in patients who are inoperable or at high risk of surgical complications. It is now also considered as a treatment option in patients with a lower surgical risk profile.

The aim of this assessment was to ascertain the clinical effectiveness, cost-effectiveness and budget impact of providing TAVI to patients at low and or intermediate risk of surgical complications. The social, organisational and ethical impact of extending TAVI to these patient populations was also considered.

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise HIQA during the course of the assessment. HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Advice to the Minister for Health and the HSE

The purpose of this health technology assessment (HTA) is to provide advice to the Minister for Health, the Department of Health and the Health Service Executive (HSE) on the implementation of a transcatheter aortic valve implantation (TAVI) pathway in the public health care system for patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications. The Health Information and Quality Authority (HIQA) agreed to undertake the HTA following a formal request from the HSE.

The key findings of this HTA, which informed HIQA's advice, are:

- Aortic stenosis is a chronic, slowly progressive disease resulting from thickening, fibrosis, and calcification of the aortic valve. Internationally there is substantial variation across studies in reported prevalence of severe aortic stenosis and the applicability of the estimates to Ireland is unclear. The average prevalence of severe aortic stenosis in high income countries is estimated to be 3.4%, of which 76% are symptomatic. Mortality associated with untreated severe symptomatic aortic stenosis is approximately 40% after five years.
- The standard treatment for patients is surgical aortic valve replacement (SAVR), an open cardiovascular surgical procedure requiring general anaesthesia and use of cardiopulmonary bypass. The diseased aortic valve is surgically removed and replaced with an artificial valve prosthesis. TAVI is a minimally invasive procedure whereby the aortic valve is functionally replaced by implanting a new valve within the existing diseased valve.
- Between 2015 and 2018, a total of 2,291 aortic valve replacement (AVR) procedures were carried out in Irish public acute hospitals. There was a linear increase in the proportion of procedures completed as TAVI, from 17% of all procedures in 2015 to 36% in 2018. Approximately 100 patients aged 70 years and older undergo SAVR (with a bioprosthetic valve) as an isolated procedure each year. This is the cohort most likely to be eligible for TAVI if this option is extended to all patients irrespective of their level of surgical risk.
- A systematic review of the literature was undertaken to assess the effectiveness and safety of TAVI compared with SAVR in patients at intermediate and low risk of surgical complications:
    - For patients at intermediate surgical risk, TAVI is no less effective than SAVR in terms of cardiac and all-cause mortality. TAVI may be associated with an increased risk of aortic valve re-intervention compared with SAVR, although the certainty of evidence is low and may be influenced by the fact that much of the evidence is based on first-generation TAVI devices, which have worse complication profiles than newer/second-generation

devices. TAVI is also associated with an increased risk of vascular complications (such as aortic rupture). However, TAVI is associated with a shorter length of hospital stay of three to four days and a reduced intensive care unit (ICU) stay. While patients experience substantial symptom improvement with both procedures, in the short-term (one to three months from baseline), TAVI is associated with greater improvements in health-related quality of life outcomes, as might be expected with a less invasive procedure. It is uncertain whether differences persist over the longer term.

  - In patients at low surgical risk, TAVI is no less effective than SAVR in terms of all-cause and cardiac mortality. TAVI is associated with a shorter length of hospital stay of four days and reduced ICU stay, and reduced incidence of atrial fibrillation and life threatening or disabling bleeds. It is not associated with an increased risk of aortic re-intervention. The available evidence on low risk patients is almost entirely based on second generation TAVI devices.
  - Published data from randomised controlled trials (RCTs) are limited to one year follow up for those at low surgical risk and two years for those at intermediate risk. There are limited data to support the use of TAVI in those aged less than 70 years. The long term durability of TAVI valves is therefore unknown.

- A cost-utility analysis (CUA) that compared the costs and consequences of TAVI compared with SAVR in patients aged 70 years and older at low and intermediate risk of surgical complications was undertaken from the perspective of the publicly funded health and social care system in Ireland. The model assumed a 15 year time horizon, which is the expected lifespan of a TAVI valve. In both the intermediate and low surgical risk populations, TAVI was less costly and delivered more quality-adjusted life years than SAVR (due to the short-term improvement in patients' health-related quality of life). The probability that TAVI was cost-effective at the €20,000 per QALY gained threshold was 61.8% in intermediate risk patients and 57.1% in low risk patients. The cost-utility findings were robust to a wide range of sensitivity and scenario analyses.
- Over a five year period, TAVI is estimated to save €0.1 million (95% CI: €-3.1 to €2.9 million) compared with SAVR, which therefore may be considered budget neutral. The estimated budget impact is based on treating 100 patients each year, comprising 67 low and 33 intermediate surgical risk patients. In the base case analysis, it was assumed that additional catheterisation laboratory infrastructure would be required to facilitate the increased demand for TAVI. The potential increase in demand for aortic valve replacement (AVR) due to an ageing population will increase the budget impact of TAVI and SAVR in Ireland, but the

incremental cost of delivering a TAVI care pathway relative to SAVR will remain budget neutral.

- By switching patients from SAVR to TAVI there will be reduced demand for ICU beds, patients will have shorter lengths of hospital stay and there will be reduced demand for theatre time and associated staff. At a hospital level, expenditure on devices will increase due to the higher device cost for TAVI.
- An increase in TAVI procedures will require additional catheterisation laboratory capacity and may displace other activity unless there is investment in additional capacity. The increased demand for TAVI will vary across the four treatment centres. Planning at a hospital level will be required which should be aligned with regional plans. These plans should take consideration of other national strategies and policies including the ongoing national review of specialist cardiac service and in particular any requirements for common support services. Planning considerations should include requirements for pre-procedural diagnostics, adequate catheterisation laboratory capacity and associated staff, and post-procedural beds with telemetry monitoring.
- While patients aged 80 years and older would not form part of the cohort at low and intermediate surgical risk, they form the majority of TAVI patients at present and anticipated increases in that population of the order of 6 to 7% per annum will have important consequences for capacity of TAVI services. TAVI service planning should take into account anticipated demographic changes to ensure that the service is able to meet demand, particularly if the service is to be extended to patients at low and intermediate surgical risk.
- Consistent with international best practice and as documented in the HSE TAVI care pathway, an essential part of any implementation plan should include data collection through a national prospective TAVI registry to enable continuous monitoring of clinical outcomes and provider performance against agreed national standards.
- On-going refinement of regional referral pathways in the HSE TAVI Model of Care will be required to ensure equity of access for eligible patients.

Arising from the findings above, HIQA's advice to the Minister for Health, the Department of Health and the HSE is as follows:

- TAVI should be available for patients aged 70 years and over with severe symptomatic aortic stenosis at low and intermediate surgical risk in the Irish public healthcare system.
- The current clinical evidence suggests TAVI is no less effective than SAVR in terms of cardiac and all-cause mortality. TAVI is associated with a shorter length of stay in hospital following the procedure than SAVR and, as a less invasive procedure, delivers additional health gains in terms of patients' health-related quality of life in the short-term.
- Compared with SAVR, TAVI is considered a highly cost-effective treatment option for patients aged 70 years and over at low or intermediate surgical risk.
- The estimated five-year budget impact of extending the TAVI care pathway to include approximately 100 patients at low and intermediate surgical risk is likely to be budget neutral. This estimate incorporates the cost of additional catheterisation laboratory capacity.
- Greater use of TAVI as an alternative to SAVR will result in shorter length of hospital stay and a reduced demand for ICU beds and theatre time, which may release resources to address demands elsewhere in the system.
- The uptake of TAVI will vary across each of the four designated centres in the TAVI model of care. Planning at a hospital level will be required, which should be aligned with regional plans. These plans should take consideration of other national strategies and policies including the ongoing national review of specialist cardiac services and in particular any requirements for common support services.
- TAVI service planning should take into account projected growth in the population aged over 80 years (a high surgical risk group) in addition to any requirements arising from an extension of the service to those at lower levels of surgical risk.

Executive summary

Subsequent to a request from the HSE, the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis at low and intermediate surgical risk. In 2017, the HSE established a national pathway of care for patients with severe symptomatic aortic stenosis in which TAVI is primarily offered as an alternative to surgical aortic valve replacement (SAVR) in patients that are inoperable or at high risk of surgical complications. The purpose of this HTA was to examine the clinical and cost-effectiveness of extending TAVI to those at low and intermediate risk of surgical complications.

The Terms of Reference agreed between HIQA and the National Clinical Advisor and Group Lead of the Acute Hospital Operations Division (HSE) were to:

- describe the treatment options and standard of care in Ireland for patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications
- describe the epidemiology of aortic stenosis in Ireland
- examine the current evidence of clinical effectiveness and safety of TAVI as a treatment for severe aortic stenosis in patients at intermediate and low risk of surgical complications
- review the international literature on cost-effectiveness of TAVI as a treatment for severe aortic stenosis in patients at intermediate and low risk of surgical complications
- assess the cost-effectiveness and budget impact of extending existing TAVI services to patients at lower levels of surgical risk in the context of the Irish healthcare setting
- review the potential resource and organisational implications for specialist cardiac services in Ireland of extending existing TAVI services
- consider any ethical and social implications that extending existing TAVI services may have for patients, the general public or the healthcare system.

Methods

This research was carried out in accordance with HIQA's guidelines for the conduct of HTAs. In summary, the following took place:

- The Terms of Reference of the HTA were agreed between HIQA and the National Clinical Advisor and Group Lead of the Acute Hospital Operations Division (HSE).

- An Expert Advisory Group was convened, with representation from the Department of Health, clinicians with specialist expertise in interventional cardiology and cardiothoracic surgery, HSE's clinical programmes for older persons, and a patient representative. An Evaluation Team was appointed comprising HIQA staff.
- The treatment options available to patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications were described. These included surgical aortic valve replacement (SAVR), which is the current standard of care in patients that require an aortic valve replacement (AVR), and transcatheter aortic valve implantation (TAVI), which is the technology under consideration in this HTA.
- The epidemiology of aortic valve disease and the diagnosis, risk factors, and burden of disease of aortic stenosis were assessed.
- A systematic review of the clinical effectiveness and safety of TAVI compared with SAVR in those at intermediate and low surgical risk was undertaken.
- A systematic review was undertaken to summarise the available international evidence on the cost-effectiveness of TAVI compared with SAVR, and assess its applicability to inform a decision on the cost-effectiveness of TAVI in Ireland.
- In the absence of applicable cost-effectiveness evidence to Ireland, an economic model was developed to estimate the cost-effectiveness of TAVI compared with SAVR in patients at low and intermediate risk of surgical complications, from the perspective of the public health and social care system.
- A budget impact analysis estimating the incremental cost of implementing a TAVI care pathway relative to SAVR in the Irish public health care system over five years for patients at low and intermediate risk of surgical complications was undertaken from the perspective of the public health and social care system.
- An analysis was undertaken of the social, organisational and ethical issues that may arise if a TAVI care pathway is expanded to patients at low and intermediate risk of surgical complications.
- The complete draft report was reviewed and endorsed by the Expert Advisory Group.
- A final draft of the report was reviewed and approved by the Board of HIQA.
- The completed assessment was submitted to the HSE, the Department of Health and the Minister for Health as advice, and published on the HIQA website.

Description of the technology

International clinical guidelines outline four options for the management of patients with severe symptomatic aortic stenosis: aortic valve replacement (AVR) using either TAVI or SAVR, aortic balloon valvuloplasty and medical management. AVR is

considered standard of care with successful intervention leading to reduced morbidity and mortality and improved quality of life. Treatment with aortic balloon valvuloplasty or medication alone has limited clinical effect and can only be palliative.

SAVR is the standard treatment for patients with severe symptomatic aortic stenosis. It is an open cardiovascular surgical procedure that requires general anaesthesia and use of cardiopulmonary bypass. The diseased aortic valve is surgically removed and an artificial valve is inserted in its place. The artificial valve may be mechanical or a bioprosthesis.

TAVI is minimally invasive procedure whereby the aortic valve is functionally replaced by implanting a new valve within the existing diseased aortic valve. TAVI devices were first CE marked in 2007 for treatment of patients with severe symptomatic aortic stenosis for patients that were inoperable or at high risk of surgical complications. CE marking for use of TAVI in patients at intermediate risk of surgical complications was first granted in 2016, with the first device granted a CE mark in November 2019 for use in patients at low risk of complications. In August 2019, the Food and Drug Administration (FDA) approved an expanded indication for a number of devices marketed by Medtronic (Evolut™ R, Evolut™ PRO) and Edward Lifesciences (SAPIEN 3, SAPIEN 3 Ultra) for use in patients at low risk of surgical complications.

As the devices are subject to iterative development, along with contemporary changes in the management of patients undergoing AVR, earlier trial data on TAVI may be of limited applicability.

Burden of disease

Aortic stenosis is a chronic, slowly progressive disease resulting from thickening, fibrosis, and calcification of the aortic valve. Without intervention to replace the damaged aortic valve, the prognosis for patients with severe symptomatic aortic stenosis is extremely poor. Mortality associated with untreated severe symptomatic aortic stenosis is approximately 40% after five years.

The prevalence of aortic stenosis in patients over 75 years old in studies in high income countries is estimated at 12.4%. The prevalence of severe aortic stenosis is 3.4%. Approximately 76% of those with severe aortic stenosis are symptomatic. There is substantial variation in reported prevalence across studies and the applicability of the estimates to Ireland is unclear. There were also no data for Ireland supporting estimates of the relative proportions of patients at high, intermediate and low risk of surgical complications.

Data for TAVI and SAVR procedures in Ireland were collated by accessing Hospital Inpatient Enquiry (HIPE) system data. Between 2015 and 2018, 591 TAVI procedures and 1,700 SAVR procedures were carried out in Irish public acute hospitals. There has been a linear increase in the proportion of AVR procedures completed as TAVI, from 18% of all procedures in 2015 to 38% in 2018. TAVI procedures are also undertaken in the private hospital system, although the numbers of procedures carried out is not known.

HIPE data indicate that, on average, hospital stay is five days shorter in those undergoing TAVI compared with SAVR as an isolated procedure, with one day less in an intensive care unit (ICU). In the event that TAVI is made available to all patients irrespective of level of surgical risk, it is likely that the majority of patients aged 70 years and over currently undergoing SAVR with a bioprosthesis as an isolated procedure will be eligible for TAVI. This cohort is approximately 100 patients per annum.

Prevalence of aortic stenosis rises with age. As the number of people aged 70 years and over living in Ireland is increasing at a rate of 4 to 5% per annum, there will be a corresponding increase in future demand for AVR.

Clinical effectiveness and safety

A systematic review was carried out to identify relevant studies of TAVI in the treatment of patients with severe symptomatic aortic stenosis at low and intermediate surgical risk. Ten studies of six unique RCTs were included in the review of clinical effectiveness. These studies were published between 2015 and 2019, and included 6,596 patients of low or intermediate surgical risk (or no pre-specified surgical risk in the NOTION trial). Three registry studies were found to provide additional data on safety outcomes.

For patients at intermediate surgical risk the available evidence is almost entirely based on first generation TAVI devices. TAVI was found to be no less effective than SAVR in terms of all-cause and cardiac mortality from 30 days to two year follow-up. TAVI may be associated with an increased risk of aortic valve reintervention (AVR) compared with SAVR although the certainty of evidence is low. TAVI is associated with increased incidence of vascular complications, such as aortic rupture. There was no observable difference in improvement in symptoms (NYHA classification) between the two interventions at one or two year follow-up. TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (one to three months from baseline) although it is uncertain whether differences persist over the longer term.

Regarding patients at low surgical risk, the available evidence is almost entirely based on second generation TAVI devices. TAVI was no less effective than SAVR in terms of all-cause and cardiac mortality based on follow-up data from 30 days to one year and was not associated with an increase in aortic valve reintervention. TAVI was found to be associated with reduced incidence of atrial fibrillation and life threatening or disabling bleeds.

For patients at either low or intermediate surgical risk the available evidence was based on first generation TAVI devices. There was no observable difference in effect between TAVI and SAVR for improvement in symptoms (NYHA classification) at one or two year follow-up. TAVI was associated with a higher rate of new permanent pacemaker insertion and a shorter length of hospital stay compared with SAVR.

While the risk of bias was generally rated as 'low' or 'unclear', the certainty of the evidence for the outcomes under review was rated as 'low' or 'moderate'. A number of the trials were subject to limitations in terms of first generation devices and the use of interim analyses. There was substantial variation across studies in terms of pacemaker insertion, potentially reflecting local clinical practice. Several of the studies were designed as non-inferiority trials and all were possibly underpowered to detect differences in safety outcomes. There are potentially different adverse event profiles between generations of valves and also between manufacturers. However, the limited trial and registry data available constrain the potential for any detailed analysis. Published RCT data are limited to one year follow up for those at low surgical risk and two years for those at intermediate risk. There are limited data to support the use of TAVI in those aged less than 70 years. The long term durability of TAVI valves is therefore unknown.

Review of cost-effectiveness

A systematic review was undertaken to assess the available evidence on the cost-effectiveness of TAVI versus SAVR among low or intermediate risk patients with severe symptomatic aortic stenosis, and its applicability to an Irish healthcare setting. Seven studies were identified that evaluated the cost-effectiveness of TAVI in intermediate risk patients, none of which were performed in Ireland.

Six studies were model-based cost-utility analyses and one was a cost-effectiveness analysis which investigated the additional reimbursement cost to a hospital per life saved by using TAVI over SAVR. The literature generally supported the finding that TAVI was cost-effective compared with SAVR. The finding was also more pronounced in those studies that evaluated newer generation devices.

The cost-utility analyses were broadly relevant, or applicable, to this HTA in that a decision-analytic framework was used to evaluate the cost-effectiveness of TAVI versus SAVR in patients with severe symptomatic aortic stenosis at intermediate risk of surgical complications.

A number of concerns regarding the quality and credibility of the economic evaluations were identified, largely relating to model structure and choice of input parameters. Overall, the evidence base proved insufficient in determining the cost-effectiveness of TAVI among low or intermediate risk patients in Ireland.

Economic evaluation

Given the lack of an applicable economic model for Ireland, a probabilistic Markov model was developed to evaluate the cost-effectiveness and budget impact of TAVI compared to SAVR in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications. The analysis was from the perspective of the publicly funded health and social care system. For the cost-utility analysis (CUA), costs and consequences were simulated over a 15 year time horizon which was the assumed lifespan of a TAVI valve. Future costs and consequences were discounted at 4% per annum and results were presented using a conservative willingness-to-pay threshold of €20,000 per quality-adjusted life year (QALY) gained.

In terms of clinical effectiveness, the economic model used the best available evidence on TAVI devices currently in clinical use to estimate the clinical benefits of the procedure relative to SAVR. In the base case analysis, evidence from the PARTNER 2 trial on the first-generation SAPIEN XT valve was used in intermediate risk patients, while evidence from the PARTNER 3 trial on the second-generation SAPIEN 3 valve was used in low risk patients.

In both the intermediate and low surgical risk populations, TAVI was less costly and delivered a greater number of QALYs than SAVR. Although some uncertainty was observed in both populations, the probability that TAVI was cost-effective at the €20,000 willingness-to-pay threshold was 61.8% and 57.1% in the intermediate and low risk populations, respectively.

Uncertainty in the cost-effectiveness of TAVI in intermediate and low surgical risk patients was mainly influenced by uncertainty in the cost of the TAVI and SAVR procedures. At the higher procedural cost estimate for TAVI (and lower procedural cost estimate for SAVR), TAVI was no longer cost-effective at the €20,000 per QALY gained threshold. However, the cost of the procedure was derived from Irish hospital discharge data and therefore the point estimates should be accurate. It should be noted that the data on TAVI procedures in Ireland are for a predominantly high

surgical risk cohort while the SAVR cost data pertain mostly to intermediate and low surgical risk patients. It is therefore plausible that the TAVI procedure cost for low and intermediate risk patients may be lower given the age and health status of those cohorts.

For the budget impact analysis it was assumed that TAVI would be extended to patients at intermediate and low surgical risk. In the base case analysis, over the first five years TAVI was estimated to save €0.1 million (95% CI: €-3.1 to €2.9) compared with SAVR, which may be considered budget neutral. The estimated budget impact was sensitive to changes in the cost of the SAVR and TAVI procedures. The base case analysis assumed that additional catheterisation laboratory capacity would be required to facilitate the increased demand for TAVI. However, if the additional procedures can be performed without requiring additional infrastructure, the estimated cost saving over five years is €0.8 million (95% CI: €-3.8 to €2.3). Increased demand for AVR due to an ageing population will increase the budget impact of TAVI and SAVR in Ireland, but the incremental cost of delivering a TAVI pathway relative to SAVR will remain budget neutral.

Social, organisational and ethical issues

In 2018 there were 98 isolated SAVR procedures with bioprosthesis in patients aged 70 years and over, and that represents the cohort likely to switch to TAVI if it is extended to patients with severe aortic stenosis at low or intermediate surgical risk. However, the estimated demand for TAVI does not factor in patients treated in the private hospitals.

By switching patients from SAVR to TAVI there will be reduced demand for ICU beds, patients will have shorter lengths of stay and there will be reduced demand for theatre time and associated staff. By extending TAVI to patients at low and intermediate surgical risk there will be an increased demand for access to catheterisation laboratories at the four TAVI centres. This increase in TAVI activity may displace other activity. The numbers of people in Ireland aged 80 years and older is expected to increase by 6 to 7% per annum in the coming decade. While patients aged 80 years and older would not form part of the cohort at low and intermediate surgical risk, they form the majority of TAVI patients at present and increases in that population will have important consequences for capacity for TAVI services. TAVI service planning should take into account anticipated demographic changes to ensure that the service is able to meet demand, particularly if the service is to be extended to patients at low and intermediate surgical risk.

The increased demand for TAVI will vary across the four treatment centres and local-level service planning will be required to ensure adequate diagnostic, staff and

catheterisation lab capacity is in place to meet demand. At a hospital level, expenditure on devices will increase due to the higher device cost for TAVI, so service planning may need to take consideration of budget silos to ensure potential efficiency gains that can be gained by switching to TAVI can be achieved.

From an ethical perspective, TAVI is unlikely to be associated with any significant concerns. Although some potential ethical considerations were identified in relation to the long term durability of TAVI valves, the materials used to manufacture bioprosthetic valves and equity of access associated with four centres providing care for the whole of Ireland, they were general in nature. Equity of access is complicated by the provision of TAVI procedures through the private hospital system. If the increased demand for TAVI is not matched by increased capacity, then patients in the public system may have poorer access than those in the private system. On-going refinement of regional referral pathways in the HSE TAVI Model of Care will be required to ensure equity of access for eligible patients.

To ensure appropriate clinical governance and consistent with international best practice, an essential part of any implementation plan should include data collection through a national prospective TAVI registry. This will facilitate continuous monitoring of clinical outcomes and provider performance against agreed national standards as documented in the HSE TAVI care pathway.

Conclusions

The extension of the TAVI care pathway to include patients with severe symptomatic aortic stenosis at low and intermediate surgical risk should be considered in the Irish public healthcare system. The current clinical evidence suggests TAVI is no less effective than SAVR in terms of cardiac and all-cause mortality. TAVI is associated with a shorter length of stay in hospital following the procedure than SAVR and, as a less invasive procedure, delivers additional health gains in terms of patients' health-related quality of life in the short-term.

Compared with SAVR, TAVI is considered a highly cost-effective treatment option for patients aged 70 years and over at low or intermediate surgical risk. The estimated five-year budget impact of extending the TAVI care pathway to include approximately 100 patients at low and intermediate surgical risk is likely to be budget neutral. This estimate incorporates the cost of additional catheterisation laboratory capacity. Greater use of TAVI as an alternative to SAVR will result in shorter length of hospital stay and a reduced demand for ICU beds and theatre time, which may release resources to address demands elsewhere in the system.

The uptake of TAVI will vary across each of the four designated centres in the TAVI model of care. Planning at a hospital level will be required which should be aligned with regional plans. These plans should also take consideration of other national strategies and policies including the ongoing national review of specialist cardiac services and in particular any requirements for common support services. Planning considerations should include requirements for pre-procedural diagnostics, adequate catheterisation laboratory capacity and associated staff, and post-procedural beds with telemetry monitoring. TAVI service planning should take into account projected growth in the population aged over 80 years (a high surgical risk group) in addition to any requirements arising from an extension of the service to those at lower levels of surgical risk.

Plain English summary

The Health Information and Quality Authority (HIQA) has carried out an assessment on whether transcatheter aortic valve implantation (TAVI) should be considered as a treatment option for certain patients with severe symptomatic aortic stenosis. In this condition, one of the heart valves, the aortic valve, is narrowed, making it difficult for the heart to work properly. Surgery to replace the narrowed valve is recommended. Standard care was open heart surgery (so called surgical aortic valve replacement (SAVR)); however this surgery is too risky for some patients, so they are now treated with TAVI which is a less invasive procedure. As TAVI does not involve open surgery it may offer health benefits to patients, such as faster recovery from the procedure. This assessment considered whether TAVI should also be provided to patients who are considered at low or intermediate risk of surgical complications from open heart surgery.

The aortic valve is one of four valves in the human heart. If one of these valves becomes narrowed, there is an increased risk of death as well as other complications such as stroke or heart attack. Left untreated, the obstruction gradually increases until eventually patients develop symptoms, such as breathlessness, chest pain (angina), fainting, or rapid heartbeat and the risk of death accelerates. Aortic stenosis typically affects older people, those aged 70 years or older; however, it can occur in younger patients. The only known cure is replacement of the damaged valve.

In Ireland, TAVI is currently performed instead of SAVR in patients at high risk of surgical complications as clinical trials have shown that the procedure is just as safe as open heart surgery in these patients. TAVI is also performed in some patients at intermediate and low risk of surgical complications. In this assessment we looked at all the available evidence on the effectiveness and safety of the procedure in patients at low and intermediate surgical risk. We found that based on follow-up clinical trial data up to a maximum of two years, patient outcomes for TAVI are comparable to those for SAVR.

HIQA also assessed the costs of TAVI and SAVR in patients at low and intermediate risk of surgical complications and compared these against the health benefits of the procedures. Since TAVI costs less and produces greater health benefits than SAVR in terms of patients' health-related quality of life, the procedure is considered cost-effective in Ireland. The cost of providing a TAVI service or pathway in these patients over five years was also estimated and shown to be approximately budget neutral compared with SAVR, and perhaps even cost-saving.

TAVI is undertaken in catheterisation laboratories (cath labs). The introduction of a TAVI care pathway for patients at low and intermediate surgical risk will lead to an increased demand for TAVI procedures. The ability of the hospital system to meet this demand may be impacted by existing capacity constraints in cath labs. Additional capacity within hospitals dedicated to cardiac care, may be required to provide a TAVI care pathway for these patients.

Based on this assessment, HIQA advises that the HSE should consider extending the TAVI care pathway to patients at low and intermediate risk of surgical complications. However, they will need to ensure that adequate resources are in place to meet the increased demand for this procedure in terms of pre-procedural diagnostics, adequate catheterisation laboratory capacity and associated staff, and post-procedural beds with telemetry monitoring.

Contents

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The membership of the EAG was as follows:

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Members of the Evaluation Team

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* Resigned from HIQA during the HTA

Conflicts of interest

There were no reported conflicts of interest for the Expert Advisory Group or Evaluation Team.

List of abbreviations

AS	Aortic stenosis
AVR	Aortic valve replacement
BIA	Budget impact analysis
CCU	Coronary care unit
CE	Conformité Européenne
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CT	Computed tomography
CUA	Cost-utility analysis
DRG	Diagnostic Related Group
EUnetHTA	European Network for Health Technology Assessment
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDA	Food And Drugs Authority
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HIPE	Hospital Inpatient Enquiry
HRQoL	Health-related quality of life
HSE	Health Service Executive
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INMB	Incremental net monetary benefit
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
LOS	Length of stay
MI	Myocardial infarction
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
RR	Relative risk
SAVR	Surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischemic attacks
WTP	Willingness-to-pay

1 Introduction

1.1 Background to the request

Subsequent to a request from the HSE, the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis at low and intermediate surgical risk. The topic was selected for inclusion on the 2019 HIQA Board-approved HTA work plan following a review by the HTA Prioritisation Advisory Group. The HSE has a national care pathway for patients with severe symptomatic aortic stenosis in which TAVI is primarily offered as an alternative to surgical aortic valve replacement (SAVR) in patients that are inoperable or at high risk of surgical complications. The purpose of this HTA was to examine the clinical and cost-effectiveness of extending TAVI to those at low and intermediate risk of surgical complications.

HIQA is one of the national representative bodies for the European Network for Health Technology Assessment (EUnetHTA), work by which is funded by a grant from the European Commission. It is intended that work undertaken by, and output from, EUnetHTA will be applicable at local (regional and national) level across Europe and will therefore limit unnecessary duplication and improve efficiency in the assessment of new medical technologies. Work on a relative effectiveness assessment (REA) of TAVI in patients at intermediate surgical risk was undertaken, co-authored by HTA colleagues from Italy and Norway, and was published by EUnetHTA in December 2018.[1] HIQA contributed to this EUnetHTA work in the role of dedicated reviewer.

The EUnetHTA REA report[1] concluded that TAVI for patients with severe aortic stenosis at intermediate surgical risk is probably non-inferior to SAVR in terms of all-cause mortality and cardiac mortality at 30-day follow-up. The REA was updated and adapted to include data on the epidemiology of aortic stenosis in Ireland. It was included as part of this comprehensive HTA which also includes a systematic review of the clinical effectiveness of TAVI in patients at low risk of surgical complications, a review of the cost-effectiveness literature, an economic model to estimate cost-effectiveness and budget impact, as well as a review of the organisational, social and ethical implications in the context of the Irish healthcare system.

1.2 Remit of the HTA

The terms of reference for this HTA report were to:

- describe the treatment options and standard of care in Ireland for patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications
- describe the epidemiology of aortic stenosis in Ireland
- examine the current evidence of clinical effectiveness and safety of TAVI as a treatment for severe aortic stenosis in patients at intermediate and low risk of surgical complications
- review the international literature on cost-effectiveness of TAVI as a treatment for severe aortic stenosis in patients at intermediate and low risk of surgical complications
- assess the cost-effectiveness and budget impact of extending existing TAVI services to patients at lower levels of surgical risk in the context of the Irish healthcare setting
- review the potential resource and organisational implications for specialist cardiac services in Ireland of extending existing TAVI services
- consider any ethical and social implications that extending existing TAVI services may have for patients, the general public or the healthcare system.

Based on the assessment, provide advice on the extension of TAVI services in Ireland to patients at lower levels of surgical risk.

1.3 Overall approach

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health, clinicians with specialist expertise in interventional cardiology and cardiothoracic surgery, the HSE's clinical programmes for older persons and a patient representative. The role of the Expert Advisory Group was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference for the Expert Advisory Group were to:

- Contribute to the provision of high-quality and considered advice by the Authority to the Health Service Executive.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.

- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprising staff from the HTA Directorate to carry out the HTA.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. Draft versions of the assessment were submitted to the Expert Advisory Group for review and discussion at formal meetings of the group, with amendments made, where appropriate. A final draft of the report was reviewed and approved by the Board of HIQA. The completed assessment was submitted to the HSE and Minister for Health as advice and published on the HIQA website.

2 Description of the technology

Aortic stenosis is defined as a congenital or acquired disorder of the aortic valve leading to abnormal narrowing of the orifice and increasing obstruction of the blood flow out of the heart into the aorta.[2] It can lead to left ventricular hypertrophy and heart failure. In the absence of intervention to replace the damaged valve, prognosis in symptomatic patients is poor with one-year mortality rates of nearly 50 percent.

The purpose of this chapter is to describe the management of patients with severe symptomatic aortic stenosis and specifically to describe transcatheter aortic valve implantation (TAVI) as a potential alternative to surgical aortic valve replacement (SAVR).

2.1 Management of severe aortic stenosis

The epidemiology of aortic stenosis is outlined in detail in Chapter 3. In summary, the aortic valve allows one-way unobstructed flow of blood from the left ventricle to the aorta. Disorders of the aortic valve include aortic valve insufficiency leading to aortic regurgitation and aortic stenosis. Aortic stenosis increases cardiac workload leading to left ventricular hypertrophy and heart failure. Causes of aortic stenosis include rheumatic fever (although this is now less common in the developed world) and degenerative calcification of the valve, with the latter the most common cause in the elderly. Those born with abnormalities in the aortic leaflets such as bicuspid aortic valve are at increased risk of aortic stenosis and become symptomatic at an earlier age. Degenerative aortic stenosis is a chronic progressive disease. The latent phase where patients remain asymptomatic varies in duration; however, in the absence of mechanical intervention to relieve obstruction to the aortic outflow, prognosis is poor in those with severe symptomatic disease.

International clinical guidelines outline four options for the management of patients with severe symptomatic aortic stenosis.[2, 3] Management depends on patient criteria including their cardiac and extracardiac characteristics, their risk of surgical complications, and treatment feasibility. Due to the high morbidity and mortality in this cohort, early intervention to replace the damaged aortic valve is standard of care. Valve replacement options include TAVI or SAVR – these are described in detail in sections 2.2 and 2.3, respectively.

Balloon aortic valvuloplasty is indicated as a bridging therapy to SAVR or TAVI in hemodynamically unstable patients or in patients with symptomatic aortic stenosis who require urgent major non-cardiac surgery.[3] It is a palliative procedure that can provide immediate symptom relief, however the clinical and haemodynamic benefits are temporary. Early restenosis and recurrent hospitalisations are common post

procedure and long term survival is poor. Balloon aortic valvuloplasty may also be considered as a diagnostic in some patients to identify those suitable for intervention.[3, 4] As it is not a long term treatment option, it is not considered as an alternative to TAVI in this HTA.

Medical treatment is indicated in patients with hypertension and or symptoms of heart failure who are unsuitable candidates for surgery or TAVI and in those awaiting intervention.[3] Medical therapy alone using statins, non-statin lipid lowering therapy, antihypertensive drugs, or therapies that target phosphate and calcium metabolism have not been shown to reduce the progression of aortic stenosis or to improve prognosis in those with subclinical disease.[5] Therefore, medical treatment is also not considered as an alternative to TAVI in this HTA.

2.2 Transcatheter aortic valve implantation (TAVI)

TAVI is a minimally invasive procedure whereby the aortic valve is functionally replaced by implanting a new valve within the existing diseased valve.[6] TAVI is also referred to as transcatheter aortic valve replacement (TAVR) and in some instances as percutaneous aortic valve replacement (PAVR). The fully collapsible valve is compressed inside a catheter with the access route influenced by patient vasculature and anatomy. The most common and preferred approach is via the transfemoral approach whereby the aortic valve is reached via the femoral vein in the groin. Alternative approaches may be required in patients with diseased or small femoral and pelvic arteries for whom this approach is precluded. Other percutaneous routes include access via the subclavian artery (beneath the collar bone) and transcaval access via the inferior vena cava and the adjoining abdominal aorta.[7] More invasive approaches include transapical access (in which a mini-thoracotomy is used to access the aortic valve through the apex of the left ventricle of the heart) or a direct transaortic access which requires a mini-thoracotomy or upper hemisternotomy to insert the delivery catheter directly into the aorta. Once the catheter is in place, the TAVI device is deployed, expanding in position to compress the native diseased valve against the walls of the aorta.

TAVI is typically undertaken by interventional cardiologists in a cardiac catheterisation laboratory (cath lab) or hybrid operating theatre. Access to onsite cardiac surgery is required in the event that emergency surgery is required.[3, 8] International societies have published guidelines with criteria for TAVI programmes including recommendations for minimum institution and procedure volumes, training, facilities, other institutional resources, and the requirement for a multidisciplinary team comprising interventional cardiology, cardiac surgery, anaesthesiology, radiology and intensive care expertise.[3, 8] These requirements will be discussed in further detail in Chapter 7.

TAVI can be undertaken under local anaesthesia with moderate or conscious sedation or under general anaesthetic. The choice is influenced by the access approach adopted: a general anaesthetic is required with the more invasive transapical approach, whereas the more commonly adopted transfemoral approach is now routinely undertaken under local anaesthesia only. Diagnostic work-up pre TAVI includes echocardiography to quantify the degree of stenosis, the mean trans-aortic valve gradient and peak trans-aortic blood flow velocity.[9] It is also used to identify the presence of other valve disease and to capture the overall function of the right and left ventricles. The positioning of the device is critical to prevent and minimise complications. Correct placement is assured by intraprocedural coronary angiography. Echocardiography can be used to complement angiographic imaging and is used for long-term post-procedural assessment.[10] Post-procedure patients require telemetry monitoring which could occur in a step down ward. Admission to an intensive care unit (ICU) is not routinely required, but may occur in the absence of monitoring being available in a lower resource setting, for patients experiencing peri-procedural complications, and in those that undergo alternative access TAVI (non-TF approach).[11]

The TAVI procedure exposes the patient and operating team to the deterministic and stochastic effects of ionising radiation. Adverse events of radiation are dose-related and are influenced by the equipment including the use of protective equipment and shielding, route of administration, procedure complexity, working techniques, experience and competence of the operators.[1, 12] Given the substantial morbidity and mortality associated with severe symptomatic aortic stenosis, the additional risk of radiation-induced cancer and injury is small relative to the potential for benefit. Attempts to minimise radiation exposure and consideration of the cumulative lifetime dose is necessary however in the context of the expanded use of TAVI in younger patients and those at lower surgical risk for whom SAVR is an option. Strict monitoring criteria and novel mechanisms to reduce exposure are also recommended for the operating team given their occupational exposure to high radiation doses.[1]

2.1.1 TAVI devices

TAVI procedures typically involve the following components: transcatheter heart valve, delivery system, introducer set, crimper and balloon valvuloplasty catheter. The devices come in a range of diameter sizes and have been optimised for different delivery routes. There has been iterative development of the devices to reduce the risk of clinical complications since the first TAVI system was awarded the European Conformity (CE) mark in 2007. Developments include reductions in the device height; changes to the structure and profile of the device; the advent of repositionable devices; novel mechanisms to anchor the device as well as

innovations in the delivery system to facilitate optimal positioning and deployment of the valve. These developments aim to reduce the risk of prosthesis-patient mismatch, vascular complications, coronary artery occlusion, paravalvular leak, and conduction abnormalities necessitating a new permanent pacemaker which were common complications post TAVI.[13-15] Improvements in the delivery system have improved the efficiency of offloading facilitating a reduction in TAVI procedure time. Differences between devices may reduce the generalisability of early trial data to later generation devices.

TAVI valves are bioprosthetic devices based on either bovine or porcine pericardium mounted on a cobalt or nitinol frame. Bioprosthetic (biological) valves are less thrombogenic than mechanical valves and do not require long term anticoagulation; however, the valves are less durable and may lead to more frequent valve replacement.[16] While long term anticoagulation may not be required, TAVI patients are at high risk of peri- and post-procedure thrombus formation (leading to stroke and bioprosthetic leaflet thrombosis causing potentially early valve failure). There is a lack of consensus on the optimal antithrombotic management post TAVI in patients without an indication for anticoagulation. Patients are also at high risk of bleeding (vascular access site and non-access site) events, making it difficult to achieve a balance.[17] Differences in antiplatelet and or anticoagulation practices between countries and over time may limit the generalisability of trial data.[16, 17]

TAVI devices may be broadly classified into balloon-expandable and self-expandable bioprostheses. Self-expanding valves have been associated with higher rates of conduction abnormality and permanent pacemaker implantation. Balloon-expandable valves may be associated with lower rates of paravalvular leak due to the higher radial force they extend which allows for better annular sealing.[14] There is also evidence to suggest that the incidence of stroke may be lower with balloon-expandable valves, but that they may be associated with a higher risk of major or life-threatening bleeding.[18] Due to innovations in the design of both valve types, the adverse event profile of new-generation valves may differ from that of earlier versions, limiting the generalisability of earlier clinical trial data. The clinical effectiveness and safety of TAVI relative to SAVR is reviewed in detail in Chapter 4.

A range of TAVI devices were identified that have been CE marked for use in patients with severe symptomatic aortic stenosis (Table 2.1). As noted, there has been iterative development of TAVI devices with launch of second or next generation devices. Earlier versions are not marketed and may no longer be available. While all devices identified are indicated for use in patients who are inoperable or at high risk of morbidity and mortality following surgery, only five devices were identified as being currently CE marked for use in patients at intermediate risk of surgical complications. Trials to support a CE application for use

in patients at low risk of surgical complications were published in 2019,[19, 20] with Edward Lifesciences announcing receipt of a CE mark for this indication for their SAPIEN 3 device in November 2019.[19] In August 2019, the Food and Drug Administration (FDA) approved an expanded indication for a number of devices marketed by Medtronic Evolut™ R, Evolut™ PRO) and Edward Lifesciences (SAPIEN 3, SAPIEN 3 Ultra) for use in patients at low risk of surgical complications.[21] A condition of their approval by the FDA was a requirement for continued follow up by manufacturers of patients enrolled in their RCTs for ten years to further monitor the safety and effectiveness of the devices, including their long term durability. This includes participation in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry to provide the regulator with additional surveillance data.

TAVI systems are subject to EU Regulation 2017/745 on Medical Devices (MDR) which came into force at the end of May 2017.[22] These regulations have a staggered transitional period with full application after three years (May 2020). These Regulations replaced a number of existing directives and are intended to strengthen the current regulatory system by providing:

- clearer requirements for clinical data on medical devices, and their assessment
- more specific product requirements, such as a unique identifier for medical devices
- improved pre-market assessment and post-market surveillance of all high risk devices
- improved governance and coordination of device markets by improved coordination and cooperation between the notified bodies for medical devices.

TAVI devices are classified as Risk Class III (high risk) under the MDR and as such must meet extensive clinical safety and performance requirements.

Table 2.2 outlines details on current TAVI systems that have been CE marked for use in patients at low and or intermediate risk of surgical complications.

Table 2.1 Treatment indications for CE marked TAVI devices

Device	Manufacturer	CE Mark Indication		
		Inoperable patients / high surgical risk	Intermediate surgical risk	Low surgical risk
ACURATE TA™*	Boston Scientific	2011	No	
ACURATE TF™*	Boston Scientific	2011	No	
ACURATE neo™	Boston Scientific	2014	No	No
Allegra	New Valve Technology	2017	No	No
CENTERA™*	Edwards Lifesciences	2018	No	No
CoreValve™	Medtronic	2007	No	No
Direct Flow*	Direct Flow Medical	2013	No	No
Engager	Medtronic	2013	No	No
Evolut™ Pro	Medtronic	2017	2017	No
Evolut™ R	Medtronic	2014	2016	No
JenaValve*	Jena Technology	2011	No	No
Lotus Edge	Boston Scientific	2016	No	No
Myval™	Meril Life Sciences	2019	2019	No
Portico	Abbott	2012	No	No
SAPIEN 3	Edwards Lifesciences	2014	2016	2019
SAPIEN XT	Edwards Lifesciences	2010	No	No
SAPIEN 3 Ultra	Edwards Lifesciences	2018	2018	No

Key: * - No longer on the market / available in the EU.

Table 2.2 TAVI systems CE marked for patients at either low or intermediate risk of surgical complications

Device	Manufacturer	Indications	Expansion	Valve	Stent	Delivery approach
Evolut R	Medtronic	Extreme high risk, high risk, intermediate risk	Self-expanding	Porcine pericardium	Nitinol	TF, SC, DA
Evolut Pro	Medtronic	Inoperable, high risk, intermediate risk	Self-expanding	Porcine pericardium	Nitinol (with an outer wrap)	TF, SC, DA
Myval	Meril Life Sciences	Inoperable, high risk, intermediate risk	Balloon expanding	Bovine pericardium	Nickel-cobalt alloy	TF
SAPIEN 3	Edwards Lifesciences	Inoperable, high risk, intermediate risk, low risk	Balloon expanding	Bovine pericardium	Cobalt-chromium alloy	TF, TA, TAo
SAPIEN 3 Ultra	Edwards Lifesciences	Inoperable, high risk, intermediate risk	Balloon expanding	Bovine pericardium	Cobalt-chromium alloy	TF, TA, TAo

Key: DA: Direct aortic access, SC: subclavian, TA: transapical, TAo: transaortic, TF: transfemoral.

2.3 Surgical aortic valve replacement (SAVR)

Surgical aortic valve replacement (SAVR) is an open cardiovascular surgical procedure whereby a diseased aortic valve is surgically removed and an artificial valve prosthesis is inserted in its place.[2] It is the standard treatment for patients with severe symptomatic aortic stenosis, but may not be suitable for some patients at increased risk of surgical complications due to medical co-morbidities and other patient-related factors. Examples of absolute contraindications to SAVR include porcelain aorta or hostile chest (that is, chest conditions such as severe radiation damage or complications from prior surgery that make operation through a sternotomy or thoracotomy prohibitively hazardous).[2, 3] In addition to high levels of risk of surgical complications as estimated using algorithms such as STS-PROM or the EuroSCORE, relative contraindications to SAVR include frailty, severe liver disease or cirrhosis, prior coronary artery bypass graft (CABG) surgery with vulnerable graft location as assessed by computed tomography, and severe pulmonary hypertension or severe right ventricular dysfunction.[2, 3] The presence of

other cardiac comorbid conditions may also influence the optimal intervention. For example, a combined SAVR and CABG procedure may be preferred for patients with concomitant severe multi-vessel coronary artery disease.

SAVR is performed under general anaesthesia necessitating cross-clamping of the aorta, induction of ischemic cardiac arrest and use of cardiopulmonary bypass.[1] Access to the heart is by full sternotomy, although less invasive approaches have also been developed (such as partial sternotomy and use of a right anterior thoracotomy approach) to minimise complications and speed post-operative recovery.[23] The damaged aortic valve is removed and replaced with a prosthetic valve. Post-procedure, patients are routinely admitted overnight to ICU for monitoring. Immediate post-surgery prognosis sees a dramatic improvement in heart function with patients experiencing significant improvement in symptoms and quality of life in the early stages of recovery.

A wide range of prostheses are available, and as with TAVI, there has been iterative development to reduce the risk of surgical and post-operative complications. These include the development of rapid deployment valves and sutureless valves which facilitate a reduction in procedure time compared with traditional valves. Both mechanical and bioprosthetic valves are available.[1] The former require ongoing lifelong anticoagulation leading to potential bleeding complications, while the latter are less durable potentially leading to valve failure and the need for reintervention. Valve choice is influenced by patient life expectancy and the relative risks of chronic anticoagulation or accelerated valve deterioration.[24]

Changes in the surgical approach, type and generation of device used, as well as changes in antiplatelet and or anticoagulation practices between countries and over time may limit the generalisability of earlier trial and registry data.

2.4 Endocarditis

Prosthetic valve endocarditis occurs in one to six percent of patients with valve prostheses and is associated with an in-hospital mortality rate of 20 to 40%.[25] Management of complicated infective endocarditis includes prolonged antibiotic therapy and or surgery involving radical debridement of all infected foreign material including the original prosthesis.[25] Development of prosthetic valve endocarditis is therefore particularly problematic in AVR patients that were initially classified as being inoperable or at high risk of surgical complications, due to their limited treatment options. Clinical guidelines recommend that perioperative antibiotic prophylaxis should be considered in patients undergoing SAVR or TAVI and that, with the exception of urgent procedures, potential sources of sepsis should be eliminated at least two weeks prior to implantation of the prosthetic valve. Both of

these recommendations are Class IIa, Level C recommendations, reflecting some uncertainty regarding their effectiveness. Post procedure, and consistent with SAVR, clinical guidelines recommend antibiotic prophylaxis in tandem with strict aseptic measures during any invasive procedures in patients who have undergone TAVI to prevent infective endocarditis. Antibiotic prophylaxis is also recommended in patients undergoing selected dental procedures.[3]

2.5 Trends in use of TAVI

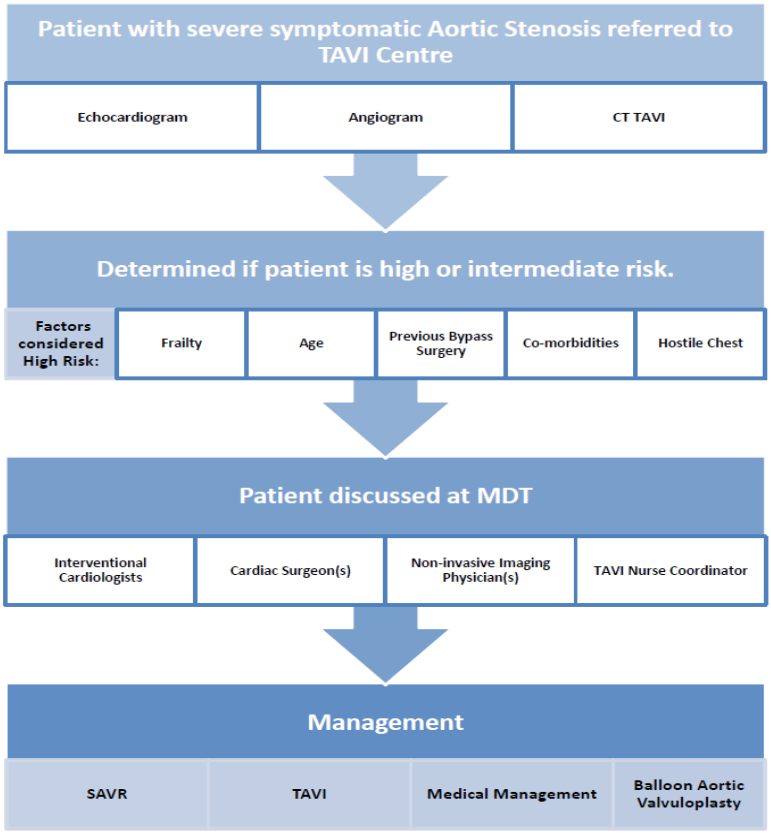
There has been an exponential increase in the use of TAVI since its commercialisation in 2007. Studies have suggested substantial variation in adoption across countries influenced most likely by differences in procedural reimbursement and healthcare funding. Germany was an earlier adopter, and based on 2011 data a study of TAVI use in 11 European countries suggested it had the highest adoption rate accounting for 46% of all implants performed with a TAVI implantation rate of 88.7 per one million population. Using estimates from an earlier study, the authors estimated a TAVI penetration rate of 17.9% (that is in patients with symptomatic severe aortic stenosis who were ineligible for SAVR or at high surgical risk and suitable for TAVI) suggesting however considerable unmet need.[26] Use in Germany has continued to increase with a 20-fold increase in procedures between 2008 and 2014. A concomitant decline in SAVR numbers has been documented with the number of TAVI procedures exceeding those of isolated SAVR procedures since 2013. While the age profile of TAVI patients remained unchanged (mean 80.9 years), there was a trend towards increased use of TAVI in patients at lower levels of surgical risk.[27] Similar trends have been observed in other European countries.[28]

Clinical trials are ongoing to support use of TAVI in patients at lower levels of surgical risk, in those that are asymptomatic, and based on newer device iterations that aim to improve procedure efficiency and lower complication rates. Current (2017) guidelines from the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) recommend SAVR in patients at low surgical risk. TAVI is recommended in those not suitable for SAVR as assessed by the Heart Team. For patients at increased surgical risk (intermediate risk and higher), the choice of TAVI or SAVR is based on the recommendation of the Heart Team, with TAVI favoured in elderly patients suitable for transfemoral access. All are Class I, Level B recommendations, indicating that there is evidence or general agreement that TAVI is effective based on a single RCT or on large non-randomised studies.[3]

In 2017, the HSE developed a national pathway for patients with severe symptomatic aortic stenosis at high or intermediate risk of surgical complications in which TAVI is considered as an alternative to SAVR in patients that are inoperable or

at high risk of surgical complications.[29] The pathway provides a clinical framework within which TAVI is provided that aims to minimise clinical variation and ensure equitable access to the procedure in the most appropriate setting. The pathway outlines the evaluation, diagnostic work up and referral pathway for patients as well as management options for those with severe symptomatic aortic stenosis (Figure 2.1).

Figure 2.1: Pathway for patients with severe symptomatic aortic stenosis referred to TAVI centre



According to the 2017 HSE TAVI care pathway, a core component of the clinical governance of the pathway should include participation in a National TAVI registry. Specifically that all sites will be obliged to prospectively enter a pre-specified dataset into a National TAVI registry for all patients undergoing TAVI at that site. This data entry should be performed by the TAVI coordinator at each site and is required to ensure that patient selection is appropriate, clinical goals are achieved and sufficient number of TAVI procedures are carried out at each TAVI site for quality purposes. The current recommendation is that sites should perform at minimum of 20 TAVI procedures per year (or a minimum of 40 over the preceding two years). The clinical goals outlined in the HSE TAVI pathway are:

- 30-day all-cause mortality < 5%
- 30-day all-cause neurology events (including TIA) <5%
- major vascular complications <10%
- >90% follow-up for all patients undergoing TAVI procedures
- 60% survival at one year among inoperable patients
- > 70% survival at one year among high-risk patients (note this is based on mortality at one year in PARTNER 1B trial of ~25%)
- > 80% survival at one year among intermediate risk patients (note this is based on mortality at one year in PARTNER 2 trial of 15%).

2.6 Discussion

SAVR is the gold standard for the management of patients with severe symptomatic aortic stenosis. TAVI provides a minimally invasive treatment option in those for whom surgery is contra-indicated and is a possible alternative to SAVR in patients at low, intermediate and high risk of surgical morbidity and mortality. Current guidelines recommend that where TAVI is possible, it should be used as first line therapy in those at high risk of surgical complications.[29] The effectiveness and safety of TAVI as an alternative to SAVR in patients at low and intermediate risk of surgical complications is assessed in detail in Chapters 4 and 5. Potential advantages of TAVI include a reduction in hospital length of stay, recovery time and post-discharge rehabilitation leading to improved quality of life in the short-term.

A wide range of TAVI delivery systems are CE marked for the treatment of patients with severe symptomatic aortic stenosis; however, only a limited number of the devices are indicated for use in patients who are not at high risk of surgical complications. While acknowledged, it is suggested that clinically this is of limited concern: in medicine, technologies typically may be investigated for use in patients at lower risk of complications, before use is expanded to subgroups of patients at greater risk. In contrast, the use of TAVI was first investigated and approved in patients that were inoperable and at high levels of surgical risk before being expanded to those at lower levels of surgical risk, that is, typically younger patients with fewer comorbidities. While no increase in short-term complications is anticipated in lower-risk patients, consideration must be given to the durability of the TAVI prostheses and the risk of long term complications given the longer life-expectancy of this cohort. There has been iterative development of the TAVI systems since the first devices were CE marked in 2007, so that published outcome data may not apply to newer generation devices. Innovations in SAVR valves have also occurred, as well as changes in the recommendations for post-procedure antithrombotic therapy. These changes may again limit the generalisability of older data.

2.6 Key messages

- International clinical guidelines outline four options for the management of patients with severe symptomatic aortic stenosis: aortic valve replacement using TAVI or SAVR, aortic balloon valvuloplasty and medical management.
- Aortic valve replacement is considered standard of care, with successful intervention leading to reduced morbidity and mortality and improved quality of life.
- Treatment with aortic balloon valvuloplasty or medication alone can only be palliative and have limited clinical effect.
- SAVR is the standard treatment for patients with symptomatic severe aortic stenosis. It is an open cardiovascular surgical procedure requiring general anaesthesia and use of cardiopulmonary bypass. The diseased aortic valve is surgically removed and an artificial valve prosthesis is inserted in its place.
- TAVI is minimally invasive procedure whereby the aortic valve is functionally replaced by implanting a new valve within the existing diseased aortic valve.
- TAVI devices were first CE marked in 2007 for treatment of patients with severe symptomatic aortic stenosis for patients that were inoperable or at high risk of surgical complications with CE marking subsequently first granted for use in patients at intermediate risk of complications in 2016 and at low risk in 2019.
- Iterative development of the replacement valves and systems used in TAVI and SAVR along with contemporary changes in the management of patients undergoing aortic valve replacement may limit the generalisability of earlier trial data.

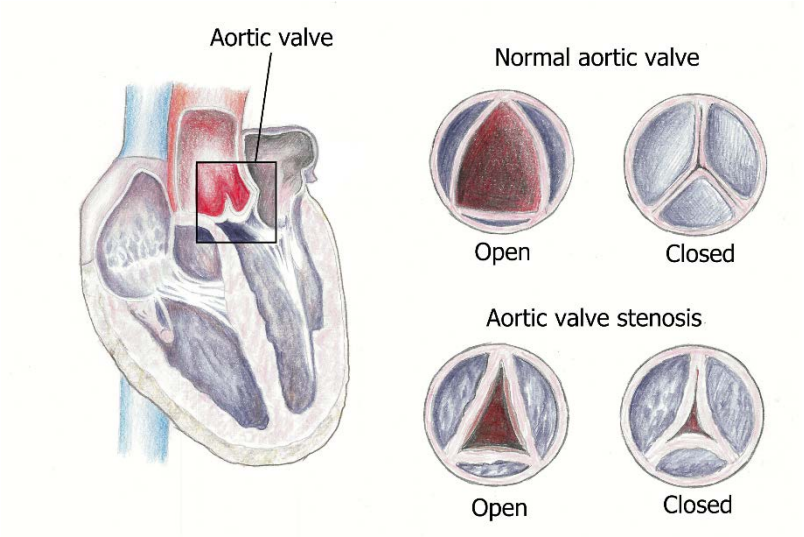
3 Burden of disease

This chapter describes the epidemiology of aortic valve disease. The chapter is stratified to outline the diagnosis, risk factors and burden of disease of aortic stenosis. The relevant surgical risk groups are described providing context for the different patient populations.

3.1 Pathophysiology of aortic stenosis

The aortic valve is one of four valves in the human heart. It is located between the left ventricle and the aorta. The valve regulates blood flow from the heart to the aorta (Figure 3.1). Aortic stenosis is the thickening, fibrosis, and calcification of aortic leaflets, impairing the outflow of blood from the heart. The valve normally has three cusps or leaflets, although approximately 0.9% to 1.4% of the population congenitally have only two (bicuspid aortic valve) leaflets.[30] Individuals with bicuspid aortic valves are prone to accelerated valve calcification.[31] Aortic stenosis is typically described as the presence of severe leaflet calcification, severely reduced leaflet opening (≤1.0 cm^2), significantly increased mean pressure gradient (≥40 mmHg), and a peak transvalvular velocity ≥4 m/s.

Figure 3.1 Aortic valve location and impact of stenosis on valve function



Patients with aortic stenosis may be asymptomatic and unaware of their condition for many years, with mortality increasing dramatically soon after onset of symptoms. A normally functioning aortic valve has an area of 3 to 4 cm^2, while symptoms of aortic stenosis tend to develop when the aortic valve area is 1 cm^2 or less.[32] The narrowing of the aortic valve increases workload to the heart as it attempts to maintain normal circulation. The impaired heart function is usually progressive and eventually leads to left ventricular hypertrophy and heart failure.[33, 34]

Eighty two percent of cases of aortic stenosis are degenerative in nature[35], and share many characteristics with atherosclerotic disease.[36] Cell disruption leads to inflammation followed by calcification. Other aetiologies of aortic stenosis include rheumatic (11%), congenital (5%), endocarditis (1%), and other (1%).[35]

Aortic stenosis is a chronic, slowly progressive disease. Patients with aortic stenosis are initially asymptomatic with an incidental finding of crescendo-decrescendo heart murmur. Patients can remain asymptomatic for a long period until the disease is advanced and considered severe. Duration of the latent, asymptomatic period varies widely among patients. Once symptoms develop, there is a rapid increase in mortality rate for untreated patients. [37] A small decrease in exercise tolerance may be the first noticeable symptom. Progressing stenosis causes an increase in pressure in the left ventricle, leading to compensatory left ventricular hypertrophy, impaired heart function, and eventually heart failure. Depending on the degree of left ventricular hypertrophy and heart function insufficiency, patients can develop dyspnoea and angina pectoris if the heart becomes ischaemic. Some patients can experience syncope, or presyncope on exertion. Without treatment, pressure overload on the left ventricle leads to systolic dysfunction and left ventricular failure, and patients can report symptoms of pulmonary oedema, including shortness of breath, fatigue, and palpitations. [38]

The only curative treatment is timely valve replacement therapy. Treatment with medication alone for symptomatic aortic stenosis has limited clinical effect and can only be palliative, easing some symptoms.

3.1.1 Diagnosis of aortic stenosis

The diagnosis of aortic stenosis begins with a physical examination, followed by transthoracic echocardiography or auscultation.[31] Further testing may include a complete blood count, basic metabolic profile, coagulation studies, troponin, brain natriuretic peptide (BNP) and a chest radiograph. In cases where non-invasive assessment of the aortic valve is inconclusive in a symptomatic patient or there is a discrepancy between symptoms and the severity of findings by non-invasive studies, the gold standard is left and right heart catheterisation.[32]

In 2017 the HSE produced the Pathway of Care for Transcatheter Aortic Valve Implantation & Transcatheter Pulmonary Valve Replacement (HSE TAVI Pathway).[29] This report outlined a national and clinical framework to minimise clinical variation and provide equitable access. The pathway notes that the clinical indications for treatment of aortic stenosis are based on clinical and echocardiographic criteria and with the presence of a systolic murmur (caused by turbulent blood flow across the stenosed aortic valve) indicative of the presence of aortic stenosis. A diagnostic echocardiogram then quantifies the degree of stenosis as mild, moderate or severe.

This is based on the aortic valve orifice area, the mean trans-aortic valve gradient and the peak trans-aortic blood flow velocity. In addition the presence or absence of other valve disease can be identified and the overall function of the left and right ventricles recorded.[29]

3.1.2 Classification of aortic stenosis

Assessment of the severity of aortic stenosis includes echocardiographic examinations and function tests together with consideration of patient age, symptoms, and comorbidities. Three-dimensional, tissue Doppler, 2D, and M-mode echocardiography are used to assess the main indicators of severity, such as valve area, transvalvular pressure gradients, flow rate, ventricular function, size and wall thickness, degree of valve calcification, and blood pressure.[3]

The New York Heart Association (NYHA) Functional Classification supports classifying the extent of heart failure. The NYHA places patients into one of four categories based on how much they are limited during physical activity. NYHA classification is widely used as a measure of patient functionality in study eligibility criteria and study outcomes. The following NYHA classes are recognised:

- I: no symptoms and no limitation in ordinary physical activity (e.g., no shortness of breath when walking or climbing stairs)
- II: mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
- III: marked limitation in activity because of symptoms, even during less-than-ordinary activity [e.g., walking short distances (20–100 m)]. Comfortable only at rest
- IV: severe limitations; experience symptoms even when at rest; mostly bedbound patients.

3.1.3 Risk factors for severe aortic stenosis

The most common cause of aortic stenosis in patients aged over 70 years is the calcific degeneration of aortic leaflets, leading to narrowing and, or leaking of the valve. The leading causes in younger patients are congenital heart defects, particularly the presence of a bicuspid aortic valve. Previous rheumatic fever and infections, such as infective endocarditis, increased age and cardiovascular risk factors can also be associated with the progression of aortic stenosis.[38]

Independent clinical factors associated with degenerative aortic valve disease (aortic sclerosis and stenosis) include age, male gender, present smoking and a history of hypertension. Other significant factors included height and high lipoprotein(a) and low density lipoprotein cholesterol levels.[39, 40]

3.1.4 Stratification of patients with aortic valve disease by surgical risk

Risk stratification is required to weigh the risk of intervention against the expected natural history of valvular heart disease. Surgical aortic valve replacement (SAVR) is an established and effective treatment for severe symptomatic aortic stenosis. The procedure requires thoracotomy, takes place under general anaesthesia and in some cases requires the use of cardiopulmonary bypass. SAVR is not suitable for those who are inoperable and may not be suitable for some patients who are at very high risk of surgical complications.[41]

The most commonly used risk algorithms include the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), and EuroSCORE II, which has been used since 2011. These systems aim to identify and quantify risk factors that help to predict mortality from cardiac surgery. STS-PROM is an online statistical tool (http://riskcalc.sts.org) that predicts the risk of mortality on the basis of the patient's demographic and clinical characteristics. EuroSCORE II is an online tool (http://euroscore.org/calc.html) that assigns scores to patient-related, cardiac-related, and surgery-related risk factors.

The most recent update of the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines for the management of valvular heart disease was in August 2017. The guidelines recommended that TAVI or SAVR should be considered in patients at increased surgical risk, defined as STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10% or with other risk factors not included in these scores. These scores include patients at intermediate risk, but not those at lower risk patients for whom SAVR is recommended. In the absence of an ideal risk model, the STS-PROM has mostly been applied for individual risk assessment and for comparison of trials results. In all cases, a heart team should make the decision between SAVR and TAVI based on assessment of the individual patient and associated risks.

The surgical risk scores are used along with an assessment of frailty as well as risk of major organ complications not covered by the scores to estimate overall risks in individual patients. This assessment which should be undertaken by a specialised multidisciplinary heart team is used to stratify patients to different treatment options, that is, palliative medical treatment (no valve replacement), medical treatment with reassessment on follow-up, SAVR, or TAVI.[3, 42]

A clear definition of what is understood by severe symptomatic aortic stenosis with intermediate surgical risk might not be possible because the criteria vary across classification systems. Stratification will always depend on the classification system used as well as on subjective input from the specialised team, and can vary across different studies and contexts.

The HSE 'Pathway of Care for Transcatheter Aortic Valve Implantation' (2017) incorporates a number of factors to consider when selecting a patient to undergo a TAVI procedure including clinical indications and surgical risk algorithms [(29)]:

- grade of heart failure according to the New York Heart Association Functional Classification, Class II, III or IV
- severe AS defined as either: aortic valve area< 0.8cm squared or mean aortic valve gradient of 40mm Hg or more peak aortic jet velocity of 4.0 per second or more. Also low-flow low-gradient aortic stenosis and paradoxical low-flow low-gradient aortic stenosis should be considered.
- life expectancy not less than a year
- certified as being at high surgical risk because of *any* of the following:
  - prior sternotomy with LIMA (left internal mammary artery) or complete arterial grafting
  - age > 80yrs (patients less than this age can be considered for TAVI and age alone should not be a factor restricting access to this treatment)
  - comorbid conditions that would significantly impair capacity of patient to physically recover from SAVR
  - generalised frailty – low body mass index (BMI), muscle mass, poor mobility.
  - AVR medically necessary in order to facilitate major urgent non-cardiac operative procedures or medical therapies (e.g. hip replacement, chemo)
  - prior radiation therapy to the chest that would adversely impact outcome from SAVR
  - severe chronic obstructive pulmonary disease
  - porcelain thoracic aorta.

A number of risk scoring tools (i.e., STS and EuroSCORE) can be used to assess the risk for surgical valve replacement, but these tools should be used in combination with the clinical evaluation of the patient by the Heart Team.

3.2 The epidemiology and burden of severe aortic stenosis

Aortic stenosis is the most common valvular heart disease, accounting for nearly half of cases in developed countries. As it is a slowly progressive disease, most new diagnoses of clinically significant aortic stenosis occur among older people.

Prevalence increases with age, reflecting an accelerated progression of the aortic mean gradient as the disease advances.

3.2.1 Prevalence of aortic stenosis

The Tromso study was a population-based prospective study that assessed the prevalence of aortic stenosis in Norway.[43] Over a 14 year period three echocardiographic examinations (1994, 2001 and 2008) were performed on a random sample of 2,373 participants. Overall 164 patients were diagnosed with aortic stenosis. Prevalence increased with age: 0.2% in people aged 50-59 years, 1.3% in the 60-69 year old cohort, 3.9% in the 70-79 year old cohort and 9.8% in the 80–89 year old cohort. The incidence of aortic stenosis was 4.9% per year.

The prevalence of aortic valve stenosis in people aged 75 years and older was estimated by a 2013 systematic review and meta-analysis of population-based studies.[44] The review included data from seven studies in six countries (the USA, Switzerland, Belgium, Finland, Taiwan, the Netherlands). Of the 9,723 participants in the studies, 86% (n=8399) were from two US based studies published in 1997 and 2006. The pooled prevalence of all aortic stenosis was 12.4% (95% confidence interval (CI): 6.6%–18.2%). Five studies reported prevalence of severe aortic valve stenosis; the pooled prevalence was 3.4% (95% CI: 1.1%–5.7%), equivalent to approximately 27% of aortic stenosis cases being classified as severe.

A 2018 review of international data investigated the prevalence of severe AS in the population aged 65 years and over.[45] The aim of this review was to identify the annual number of TAVI candidates and not just the prevalence of aortic stenosis. Results were presented as the prevalence of symptoms in patients with severe AS and percentage of patients not receiving SAVR despite suffering from severe AS. The incidence of severe aortic stenosis in the population aged 65 years and over pooled over five studies was 1.34% (95% CI: 0.70 to 1.98%). There was substantial heterogeneity in the study estimates, with individual trial estimates ranging from 0.27% to 3.80%, which may be partly explained by the different definitions of severity used across studies. Applying the pooled estimate of 1.34% to the Irish population aged 65 years and older produces a prevalence figure similar to applying the estimate of 3.4% to the population aged 75 years and older. The two reviews are therefore considered to be in broad agreement. However, given the heterogeneity across studies, there is substantial uncertainty around the pooled point estimate of prevalence.

The most recent study included in the review was the BELFRAIL study.[46] This population-based prospective cohort study of the very elderly (>80 years old) in

Belgium recruited 567 subjects between 2008 and 2009. There was a prevalence of 22.8% (95% CI: 19.4-26.6%) relating to 127 events of mild, moderate and severe aortic stenosis in patients. This study may be more applicable to Ireland as it is based on a European population and the data are more recent.

3.2.2 Prevalence of symptomatic aortic stenosis

From the systematic review of aortic stenosis in persons aged 75 years and over, 75.6% (95% CI: 65.8%–85.4%) of those with severe aortic stenosis were symptomatic.[44] Although the meta-analysis of seven studies was subject to heterogeneity (I^2 = 96.3%), this was largely due to a single study (with an estimate of 54%).

The subsequent review based on patients aged 65 years and over found that aortic stenosis-related symptoms were present in 68.3% (95% CI: 60.8–75.9%) of patients with severe aortic stenosis.[45] There was very substantial heterogeneity across studies (I^2 = 96.7%), with individual study estimates ranging from 46% to 86% of patients being symptomatic.

The higher estimate of symptomatic cases for older patients is consistent with the fact that it is a progressive disease. By applying the above estimates to 2018 population estimates for Ireland, it is likely that there are between 6,000 and 7,000 people in Ireland with symptomatic severe aortic stenosis.

3.2.3 Level of surgical risk in patients with symptomatic aortic stenosis

Surgical risk is defined by the original thresholds set by the Society for Thoracic Surgeons for risk of death from surgery. Based on US data from 1991 to 2007, 5.2% of all elderly patients who underwent SAVR were considered high-risk (≥ 10% risk of death), 15.8% were intermediate-risk (5% to 9.9% risk of death), and 79.1% were low-risk (< 5% risk of death).[47] In a further US study using data from 2002 to 2010, 6.2% of patients who underwent SAVR were considered high-risk, 13.8% were intermediate-risk, and 80% were low-risk.[48] It must be borne in mind that there may have been a level of self-selection in those who underwent SAVR, and therefore the data excludes those whose risk was excessive or who elected not to undergo SAVR having considered it to be too invasive.

Data from the German aortic valve registry classified patients according to operative risk in terms of the European System for Cardiac Operative Risk Evaluation (EuroSCORE).[49] Across all ages between 2011 and 2013, 5.3% of all patients who underwent surgery were considered high-risk (≥ 20% on EuroSCORE), 14.7% were intermediate-risk (10% to 20% on EuroSCORE), and 80.0% were low-risk (<10% on EuroSCORE).

3.2.4 Mortality associated with severe aortic stenosis

The overall prognosis of patients with symptomatic aortic stenosis who do not undergo surgical intervention is poor. [50, 51] The prognosis of patients with asymptomatic aortic stenosis is more favourable and a watchful waiting approach has been shown to be safe.[52]

Historical studies of aortic stenosis have reported extremely high mortality rates. A 1973 study noted a 90% mortality rate after 10 years.[50] This trend was apparent in a study published in 1980, mortality rates from onset of symptoms were 26% (one year), 48% (two years) and 57% (three years).[53] Survival of patients undergoing aortic valve replacement was shown to be effective as early as 1982. A retrospective study of 299 patients, of which 252 were operated on reported survival of 87% after three years compared to 21% in patients that did not undergo valve replacement.[54] Finally, a 1988 study noted a mean survival of 23 (+/- five months), with all patients dead after 12 years of follow up.[50, 51]

A prospective study of 5,888 patients in the USA on the impact of aortic sclerosis provided some data on mortality in patients with aortic stenosis. Of the 5,621 participants that underwent echocardiogram investigations in 1990-1991, 2% (n=92) had aortic stenosis. Over a mean follow-up period of five years, 38 (41.3%) patients had died, 18 (19.6%) from cardiovascular causes. Concerning morbidity, 17 patients had angina, 21 congestive heart failure and 10 had a stroke.[55] The proportion with symptomatic disease was not reported.

A US-based retrospective cohort study identified 740 patients between 1993 and 2003 that had been diagnosed with aortic stenosis. Of these patients 287 had their aortic valve replaced and 453 did not undergo valve replacement. The latter group formed the study cohort as the focus was on patients that were not surgically managed. The survival of patients with aortic stenosis who did not undergo surgery was 62%, 32% and 18% at one year, five years and 10 years was, respectively.[56] The authors compared this with survival rates of 87%, 78% and 68% with conventional SAVR intervention after one year, five years and 10 years, respectively.

3.2 Treatment of severe symptomatic aortic stenosis in Ireland

Data for TAVI and SAVR procedures in Ireland were collated by accessing Hospital Inpatient Enquiry (HIPE) system data. The HIPE system includes all inpatient discharges from the public acute hospital network in Ireland. Prior to 2015, TAVI did not have a dedicated procedure code and was distinguished from SAVR through the use of an additional code for percutaneous intervention. It is not possible to reliably differentiate between TAVI and SAVR prior to 2015, and therefore our analysis is

based on discharges from 2015 to 2018. The data are for discharges with TAVI or SAVR in any of the procedure codes, as in some cases it is not listed as the primary procedure.

The HSE has established that TAVI is reimbursed for patients with severe symptomatic aortic stenosis at intermediate or high risk of surgical mortality or complications. TAVI is also reimbursed by private insurers, so the HIPE data also comprise private procedures in public hospitals. The number of procedures for SAVR was also taken from the HIPE database. The reported number of SAVR procedures reflects the combined total of SAVR procedures using either a mechanical prosthesis or bioprosthesis.

Table 3.4 shows the number of TAVI procedures in public hospitals in Ireland has steadily increased from 2015 to 2018. Of the six centres that have carried out TAVI, two have completed only two procedures each in the time period and are not one of the four designated centres in the 2017 HSE National TAVI plan. Comparing the number of TAVI procedures performed in 2018 to 2015, the four treatment centres have all shown increases in the number of procedures carried out. It should be noted that nationally about 15% of discharges from the public hospital system are for private patients. The data do not capture activity that takes place in private hospitals. The proportion of patients treated as private may have been affected by the timing of when each site secured funding to provide TAVI.

Table 3.4 Discharges for TAVI procedures in public hospitals for patients of all ages, 2015-2018

Hospital	2015	2016	2017	2018	Total
Our Lady's Children's Hospital, Crumlin	0	1	1	0	2
Mater Misericordiae University Hospital	24	33	45	50	152
St. James's Hospital; Dublin	26	35	43	62	166
Cork University Hospital	0	7	15	33	55
University Hospital Limerick	0	0	1	1	2
Galway University Hospitals	34	49	66	65	214
Total	**84**	**125**	**171**	**211**	**591**

Note: figures include all hospital discharges where TAVI (procedure code 3848808) is included as one of the procedures undertaken.

Table 3.5 presents the annual number of SAVR procedures in public hospitals between 2015 and 2018. There was a decline in the number of procedures in this interval primarily due to decreases in the number of procedures at St James's hospital (from 124 (2016) to 88 (2018)) and Galway University Hospital (from 67 (2016) to 43 (2018)).

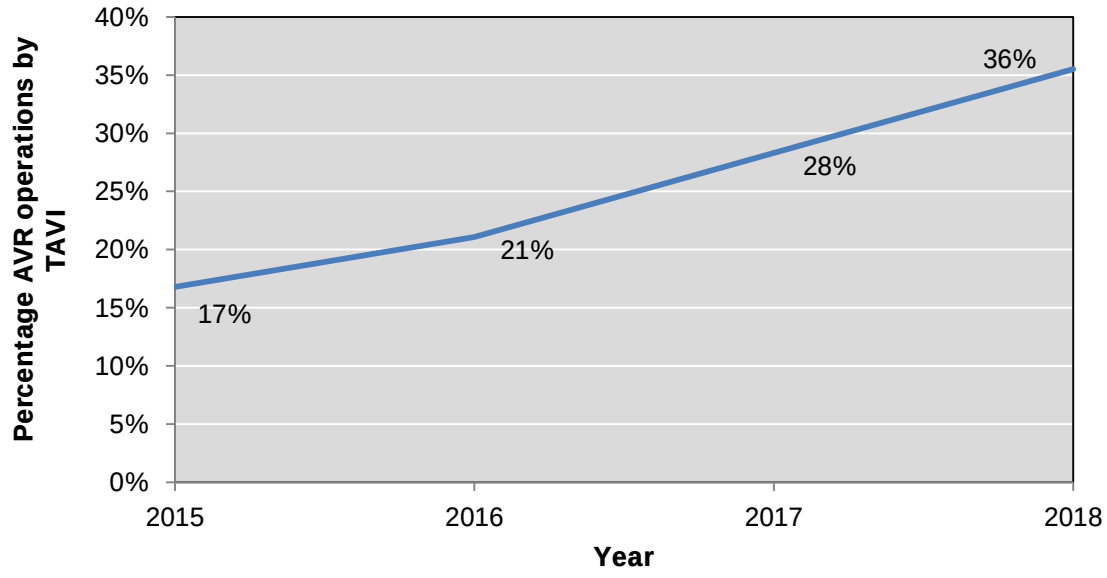
Table 3.5 Discharges for SAVR procedures in public hospitals for patients of all ages, 2015-2018

Hospital	2015	2016	2017	2018	Total
Our Lady's Children's Hospital, Crumlin	4	5	7	7	23
Mater Misericordiae University Hospital	98	103	118	99	418
St. James's Hospital; Dublin	124	118	116	88	446
Cork University Hospital	123	158	136	146	563
University Hospital Limerick	0	0	1	0	1
Galway University Hospitals	67	84	55	43	249
Total	**416**	**468**	**433**	**383**	**1,700**

Note: figures include all hospital discharges where SAVR (procedure codes 3848800 and 3848801) is included as one of the procedures undertaken.

Compared with 2015, there has been an approximate 20% increase in the annual number of AVR procedures completed in public hospitals. Notably there has been a linear increase in the proportion of AVR procedures that are undertaken as TAVI (from 16.8% (84 of 500) in 2015 to 35.5% (211 of 594) in 2018) (Figure 3.2).

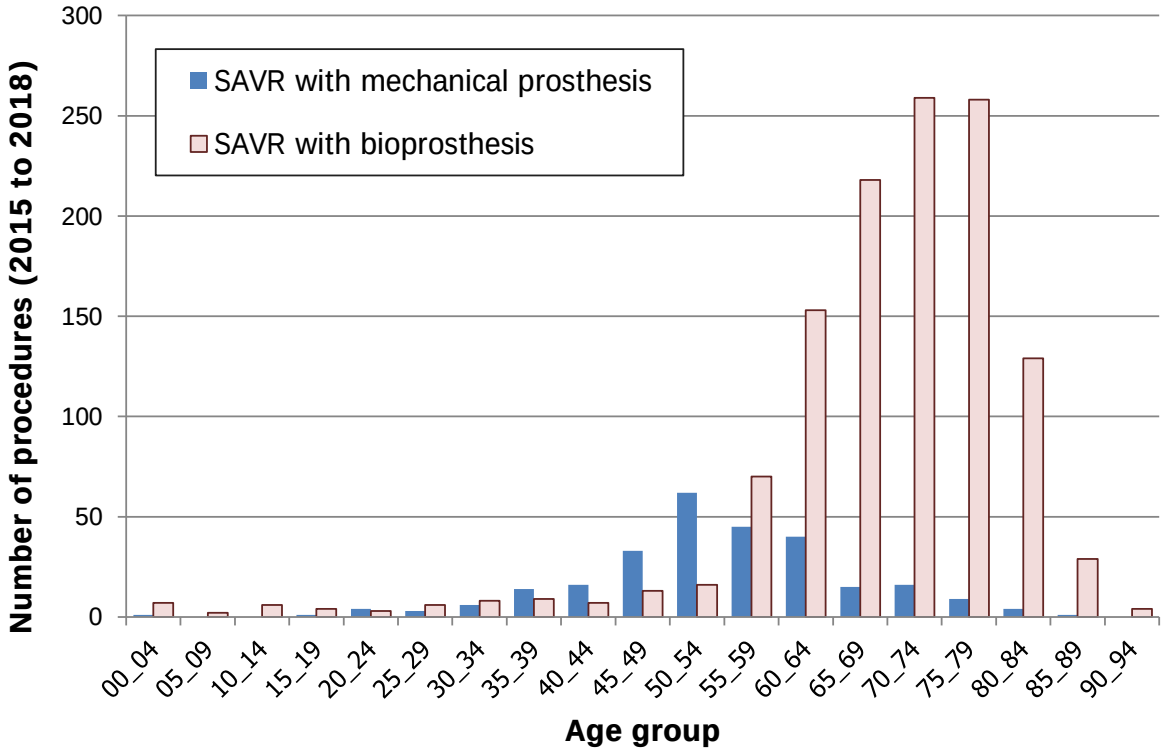
Figure 3.2 Proportion of aortic valve replacement procedures that were undertaken as TAVI in Ireland, 2015 to 2018



In the period 2015 to 2018, the proportion of patients undergoing SAVR each year who are male has been between 65% and 70%. For TAVI, the proportion each year that are male has been between 50% and 58%.

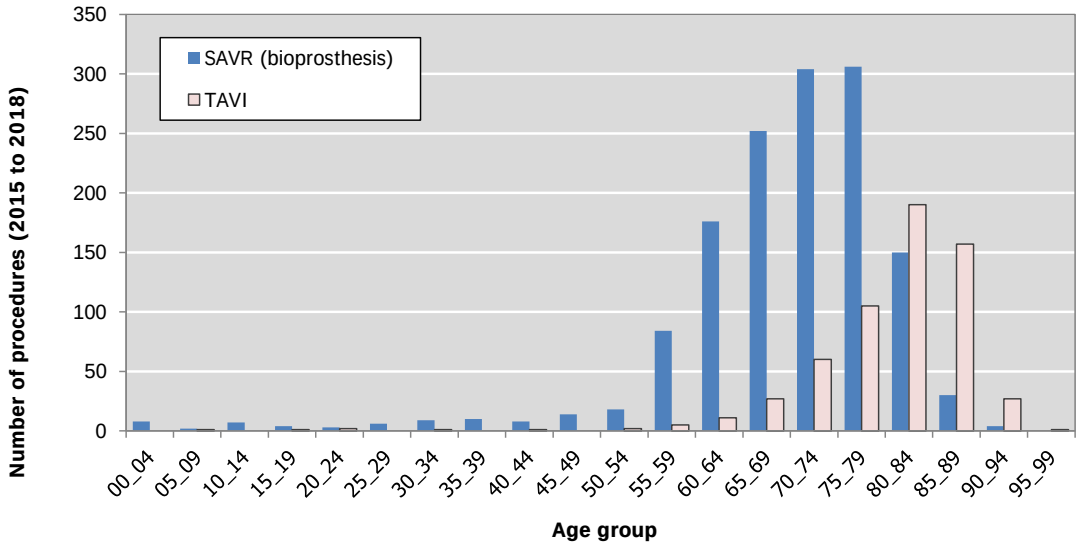
Patients undergoing SAVR with a mechanical prosthesis have a markedly different age profile to those receiving a bioprosthesis (Figure 3.3). Bioprostheses are predominantly used in older patients (aged 60 years and over) while mechanical prostheses are favoured in patients aged 30 to 54 years.

Figure 3.3 Numbers of SAVR procedures by type of prosthesis in Ireland, 2009 to 2018 stratified by patient age group



The age profile of patients undergoing aortic valve replacement using a bioprosthesis between 2015 and 2018 is presented in Figure 3.4. The age profile differs substantially between those undergoing TAVI versus SAVR (with bioprosthesis) with TAVI patients having an older profile.

Figure 3.4 Age of patients undergoing AVR procedures with a bioprosthesis in public hospitals in 2018



In the event that TAVI is made available to all patients with severe aortic stenosis irrespective of level of surgical risk, it is likely that the majority of patients aged 70 years and over undergoing SAVR with a bioprosthesis as an isolated procedure will be eligible for TAVI. By isolated procedure, we mean that the patient does not also undergo other surgical procedures in the same episode, such as coronary artery bypass grafting or mitral valve repair. Patients who undergo other surgical procedures in the same episode may not be considered candidates to switch to TAVI as surgery would still be necessary. Based on 2018 data, there were 98 patients aged 70 years and over who underwent SAVR with a bioprosthesis as an isolated procedure.

Data from HIPE indicate that patients undergoing TAVI have a shorter median length of hospital stay and length of ICU stay than those undergoing isolated SAVR. From 2016 to 2018, patients undergoing TAVI had a median length of hospital stay of seven days and a median length of ICU stay of two days (Table 3.6). Over the same period, patients aged 70 years and over undergoing isolated SAVR with a bioprosthesis had a median length of hospital stay of 12 days and a median length of ICU stay of two days. Seventy eight percent of TAVI patients were admitted to an ICU bed compared with 83% of SAVR patients. It is possible that the high proportion of TAVI patients being admitted to ICU reflects low availability of high dependency unit beds with telemetry monitoring.

It should be noted that patients undergoing TAVI are more likely to be high surgical risk than those undergoing SAVR, but equally those undergoing SAVR may also undergo other surgical procedures as part of the same episode. In both cases the distribution is heavily skewed by a small number of cases with extended lengths of

stay, as is evident from the difference in mean and median length of stay (Figure 3.6). As there are four treatment centres, it is possible the length of stay data may be affected by patients that are transferred from other hospitals.

Table 3.6 Hospital and ICU length of stay for patients undergoing TAVI and isolated SAVR

	SAVR		TAVI	
	Hospital	ICU	Hospital	ICU
Mean	18.5	4.1	13.9	3.2
Median	12	2	7	2
Mode	9	1	2	0

For isolated SAVR the most common length of stay was nine days, but only 3% of patients had a length of stay of less than seven days. In contrast, the most common length of stay for TAVI was two days, with 50% of patients having a length of stay less than seven days. For both SAVR and TAVI, length of stay was heavily skewed. From a service utilisation perspective, the mean is the most relevant measure of central tendency as it reflects average resource usage.

In terms of hospital costs, inpatient episodes are reimbursed through the mechanism of activity-based funding. Episodes are coded to one of a set of diagnosis-related groups (DRGs), each of which is associated with a specified cost. In the case of aortic valve replacement, the majority of TAVI and SAVR cases are coded into one of five DRGs (Table 3.7). For SAVR, episodes are mainly classified into one of the three F04 codes, while TAVI cases are mostly classified as F03B and F04C.

Figure 3.5 Length of hospital stay for patient undergoing TAVI and isolated SAVR procedures in public hospitals

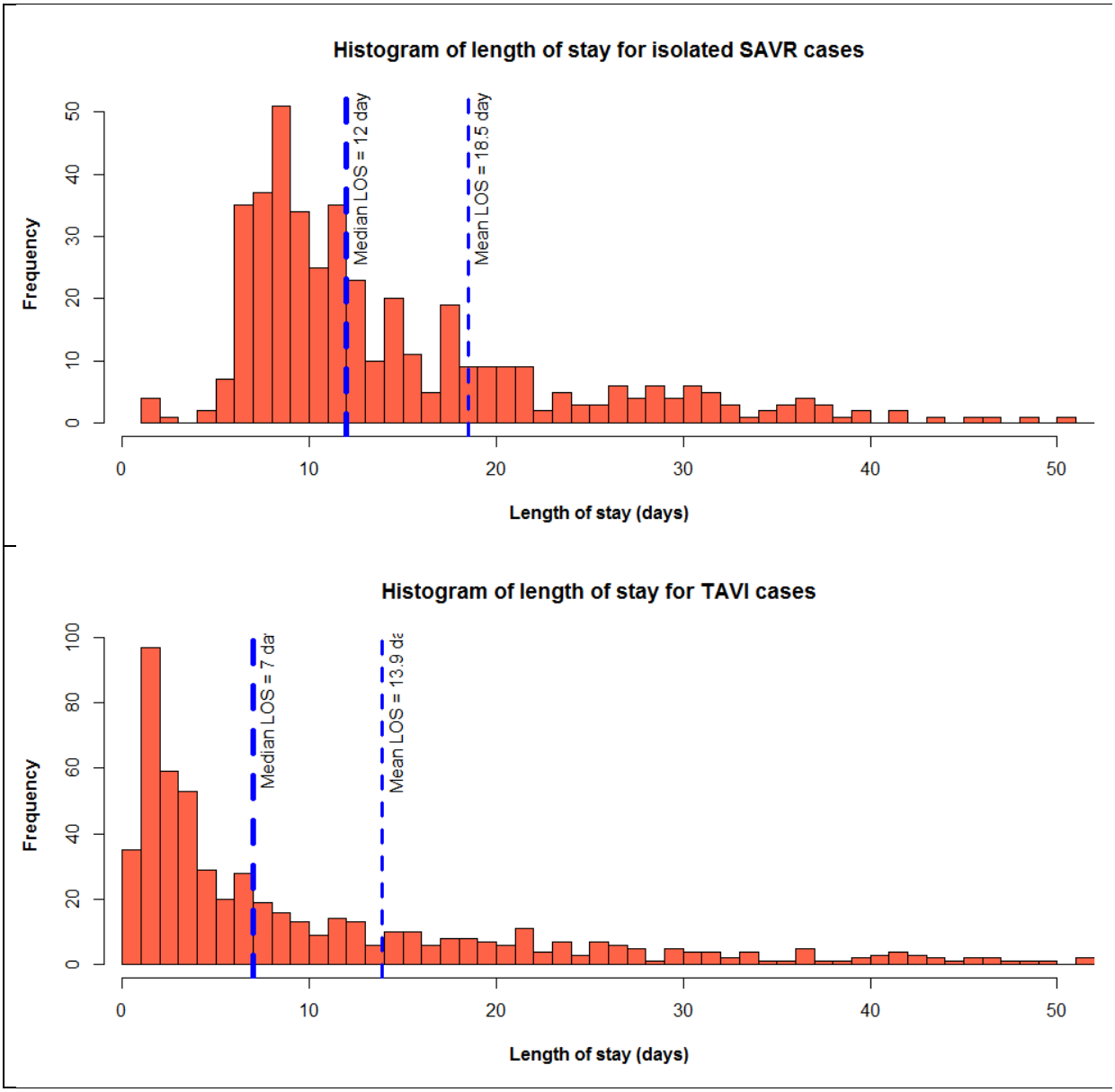


Table 3.7 Most common diagnosis-related groups used to classify episodes for patients undergoing TAVI and SAVR

DRG code	Description	Cost (€)
F03A	Cardiac Valve Procedures W CPB Pump W Invasive Cardiac Investigation; Major Comp	39,788
F03B	Cardiac Valve Procedures W CPB Pump W Invasive Cardiac Investigation; Minor Comp	32,620
F04A	Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest; Major Comp	45,101
F04B	Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest; Interm Comp	32,040
F04C	Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest; Minor Comp	24,000

Note: costs based on 2019 DRG prices for inpatients[57]

Population projections for Ireland indicate that even under the most conservative assumptions regarding migration, the number of people aged 70 years and over will increase by 45% between 2016 and 2026, and by a further 35% between 2026 and 2036.[58] That rate of population change equates to an increase of between 4% and 5% per annum. Beyond 2026 the rate of population increase in patients aged 80 years and over will be between 6% and 7% per annum. The consequences of such a large increase in the population aged 70 years and over will be a substantially increased demand for aortic valve replacement. Based on the number of AVR procedures carried out in the public hospital system in Ireland between 2009 and 2018, there is a rate of increase of approximately 5% per annum, 58% over ten years. This rate of increase exceeds the rate of increase in the population aged 70 years and over (34%) over the same time period. The difference could reflect historical capacity constraints or under-provision of services, an increasing prevalence of severe AS, or changing clinical practice or diagnosis of severe AS.

Based on activity recorded in HIPE, 11% of SAVR procedures are in patients aged 80 years and over, compared with 64% of TAVI procedures. Patients aged 80 years and older will generally be considered at high risk of surgical complications and are therefore not part of the cohort defined for this assessment. However, these patients are clearly a significant proportion of the population eligible for TAVI. Given the trend for population increases in those aged 80 years and over, demand for TAVI may increase substantially irrespective of whether it is formally extended to those at low and intermediate risk of surgical complications.

The 2018 international review of aortic stenosis and eligibility for surgery found that in the pre-TAVI era, 41.6% (95% CI 36.9–46.3%) of all patients with severe

symptomatic aortic stenosis did not receive SAVR.[45] There was substantial heterogeneity across the 20 included studies (I^2 = 88.4%), and the estimates from individual studies ranged from 26.9% to 62.7%. While it was considered that patients not receiving SAVR were possible candidates for TAVI, it is unclear how many would genuinely be eligible or interested in undergoing the procedure. The proportion of patients who were not considered for SAVR and also not treated with TAVI was reported across nine studies with a pooled estimate of 38%. Again, there was substantial heterogeneity across studies with individual estimates ranging from 12.6% to 84.9%.

There are limited data on the surgical risk of patients who have been treated with TAVI in Ireland. One study from the Mater Misericordiae University Hospital group based on 354 patients treated between 2008 and 2018 reported that 20% were high surgical risk, while the remaining 80% were split equally between intermediate and low surgical risk.[59] The ratio of high:intermediate:low was very similar to that reported in the German GARY registry (of 18:42:40).[60] It is worth emphasising that surgical risk is multifaceted, and categorisation on the basis of STS-PROM is a simplification that does not necessarily capture the context of individual cases. Scoring systems are used as a guide by clinicians alongside many other factors, and the level of surgical risk for an individual patient is ultimately judged by a multi-disciplinary team. However, it is clear that many patients treated with TAVI in Ireland to date would have been classified as low or intermediate surgical risk based on the trial criteria.

3.3 Discussion

Aortic stenosis is the most commonly diagnosed valvular heart disease in developed countries. Prevalence increases with age, with a marked increase ≥ 75 years and is primarily due to degenerative calcification of the valve. The condition is chronic and progressive. While there may be a long latent period when patients are asymptomatic, without intervention, severe symptomatic aortic stenosis has a poor prognosis with a mean survival of two years. Aortic valve replacement (AVR) is indicated in patients with severe symptomatic disease with successful surgery leading to reductions in morbidity and mortality.

No population-based studies of the prevalence of aortic stenosis in Ireland were identified. Estimates of the prevalence of aortic stenosis, the proportion with severe aortic stenosis, and the proportion of these that are symptomatic and subsequently classified as low, intermediate and high levels of surgical risk is derived from international prevalence studies. These data have been combined with Irish census data to estimate the population aged over 70 years for whom AVR and specifically TAVI may be indicated – approximately 100 patients. While under-diagnosis is

common, international variation in the proportion of patients treated with AVR may reflect variation in the proportion diagnosed, referred or accepted for surgery. Variation in the assessment of surgical risk as well as the consideration of other cardiac and extra-cardiac risk factors may impact the proportion of patients considered at high, intermediate or low risk of surgical complications.

A number of studies have reported data on prevalence of aortic stenosis, proportion classified as severe, proportion symptomatic, and proportions being offered SAVR and TAVI. There was substantial heterogeneity across studies which may reflect differences in patient demographics, definitions used, and health systems. There may also be a temporal aspect reflecting changing practice. As such, there is substantial uncertainty regarding what the equivalent figures may be for Ireland. However, given the increased prevalence with age and the increasing numbers of people in Ireland aged 70 years and over, it is clear that the absolute number of people with severe aortic stenosis will increase over time.

The HSE implemented a TAVI referral pathway in 2016. The document outlines referral pathways for adults requiring TAVI to one of four designated TAVI centres. Use of TAVI is suggested as the treatment of choice in patients that are inoperable or at high risk of mortality with conventional SAVR. It is considered as a possible alternative in those at intermediate risk of mortality. HIPE data suggest a 20% increase in the annual provision of AVR procedures since 2015. Notably, there has been a linear increase in the proportion of AVR procedures completed as TAVI, from 17% of all procedures in 2015 to 36% in 2018. HIPE data do not permit identification of the patient surgical risk classification, so it is not known what proportion of AVR, and of TAVI specifically, that were completed in those at low, intermediate or high risk of complications. The 2017 HSE care pathway suggests that patients may be certified at high surgical risk if aged over 80 years. Based on HIPE data, TAVI was the most common AVR procedure in those aged 80 years and older between 2015 and 2018. It is also important to note that HIPE does not capture all TAVI activity in Ireland, as it is also offered in the private hospital system. Using TAVI coupled with SAVR with bioprosthesis in older patients as a reflection of demand for TAVI may underestimate actual demand as it does not take into account waiting lists, for example.

In the event that TAVI is made available to all patients with severe aortic stenosis irrespective of level of surgical risk, the majority of additional cases undergoing TAVI will be patients aged 70 years and over undergoing SAVR with a bioprosthesis as an isolated procedure. Based on 2018 data, there were 98 patients aged 70 years and over who underwent SAVR with a bioprosthesis as an isolated procedure who would likely switch to TAVI if it was extended to patients at low and intermediate surgical risk.

3.4 Key messages

- Aortic stenosis is a chronic, slowly progressive disease as a result of thickening, fibrosis, and calcification of aortic valve.
- Without intervention to replace the damaged aortic valve, the prognosis for patients with severe symptomatic aortic stenosis is extremely poor. Mortality associated with untreated severe symptomatic aortic stenosis is approximately 40% after 5 years.
- The prevalence of aortic stenosis in patients over 75 years old is estimated at 12.4%. The prevalence of severe aortic stenosis is 3.4%. Approximately 76% of those with severe aortic stenosis are symptomatic.
- There is substantial variation in reported prevalence across studies and the applicability of the estimates to Ireland is unclear.
- Between 2015 and 2018, 591 TAVI procedures and 1,700 SAVR procedures were carried out in Irish public acute hospitals. There has been a linear increase in the proportion of AVR procedures completed as TAVI, from 17% of all procedures in 2015 to 36% in 2018.
- Patients undergoing TAVI have, on average, a five day shorter length of stay in hospital and one day less in an intensive care unit than those undergoing SAVR as an isolated procedure.
- In the event that TAVI is made available to all patients irrespective of level of surgical risk, it is likely that the majority of patients aged 70 years and over currently undergoing SAVR with a bioprosthesis as an isolated procedure will be eligible for TAVI. This cohort is approximately 100 patients per annum.
- As prevalence rises with age and the number of people aged 70 years and over living in Ireland is increasing at a rate of 4 to 5% per annum, there will be a corresponding increase in demand for aortic valve replacement in the future.

4 Clinical effectiveness and safety

This chapter examines the current evidence of efficacy and safety for TAVI in the treatment of patients with severe symptomatic aortic stenosis classified as being at low and intermediate risk of surgical complications.

4.1 Methods

4.1.1 Literature Search

The reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[61] A systematic literature search was performed to identify randomised controlled trials (RCTs) published between 1 January 2007 and May 2019 for efficacy and safety, and prospective national registry studies for safety between 1 January 2013 and July 2019. Studies were identified via electronic searches in databases (Cochrane Library, Embase and Medline [OVID], and Medline Pub status ahead of print). Studies of any language were considered.

All search strategies were adapted from the EUnetHTA REA report on TAVI for the treatment of patients at intermediate surgical risk.[1] To improve the efficiency of the search process, search strings were added to assist in identifying the studies relevant to low and/or intermediate surgical risk populations. Detailed search terms and methodology for efficacy and safety outcomes (including registry data) are further outlined in Appendix A.

In addition to the systematic search for RCTs, the citation lists of any relevant systematic reviews identified, as well as the reference lists of all included studies, were cross-referenced to ensure the capture of all relevant publications. Forward citation of the identified papers was also checked for any other potential studies for inclusion. A hand search of selected members of the International Network of Agencies for Health Technology Assessment (INAHTA) home pages was also performed.

Relevant ongoing RCTs were also searched on ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) to identify all upcoming evidence. Furthermore, the medical device companies with CE marked TAVI devices suitable for use in lower surgical risk populations (Boston Scientific, Edwards Lifesciences and Medtronic) were contacted to obtain any additional relevant RCT data for the populations of interest.

4.1.2 Selection criteria

The inclusion and exclusion of studies was based on the Population, Intervention, Control, Outcomes, and Study Design (PICOS) protocol presented in Table 4.1 (a detailed table is provided in Appendix A). Comparators and outcomes were chosen based on CE mark-specific indications and information from relevant published clinical guidelines for the treatment of severe aortic stenosis and assessment guidelines published by the European Network of Health Technology Assessment (EUnetHTA).[62-64] Research letters and conference abstracts were excluded.

Table 4.1 PICOS analysis for identification of relevant studies

Population	Patients with severe aortic stenosis (AS) at low or intermediate risk of death or complications associated with SAVR.
Intervention	TAVI as a therapeutic intervention for the defined target population. The assessment was restricted to systems with a CE mark.
Comparator	SAVR can be performed using different approaches (full sternotomy and more minimally invasive procedures), different kinds of valves, and different kinds of valve-anchoring techniques (i.e., sutured and sutureless).
Outcomes	Clinical efficacy outcomes taken as surrogate markers of clinical effectiveness including: mortality, symptom improvement, health-related quality of life, and health service utilisation. Safety outcomes taken as surrogate markers of adverse events or outcomes including any major or minor adverse event, and ,radiation causing harm to both patient and staff
Study design	Clinical efficacy ▪ Randomised controlled trials Safety ▪ Randomised controlled trials ▪ Real-world data derived from published studies from prospective national registries

Abbreviations: EuroSCORE – European System for Cardiac Operative Risk Evaluation; EQ-5D – EuroQOL-5D; KCCQ – Kansas City Cardiomyopathy Questionnaire; NYHA – New York Heart Association; SAVR – Surgical Aortic Valve Replacement; SF-36 – Medical Outcomes Study Short-Form 36; STS-PROM – Society of Thoracic Surgeons Predicted Risk Of Mortality; TAVI – Transcatheter Aortic Valve Implantation;

4.1.3 Data collection and analysis

All titles and abstracts retrieved by electronic searching were downloaded. Duplicates were removed and citations were screened by two reviewers to eliminate clearly irrelevant studies. Two reviewers independently screened the remaining citations. Full texts were obtained and reviewed as per the inclusion criteria.

Data extraction using a standardised data extraction form was performed independently by two reviewers, with any disagreements being resolved by discussion or inclusion of a third reviewer. Where necessary, the study author was contacted to obtain available data already published, but not sufficiently detailed, and outcome data that were not reported.

Outcomes assessed as part of the clinical effectiveness and safety evaluation are listed in Table 4.1. For context:

- The New York Heart Association (NYHA) Functional Classification system measures improvement of symptoms. The classification system assesses the extent of heart failure in patients based on their ability to perform physical activities. Patients may have no limitation of physical activity (NYHA I), slight limitation (NYHA II), marked limitation (NYHA III), or be unable to carry out any physical activity without discomfort (NYHA IV);

- The health-related quality-of-life instruments comprised the:

    - Kansas City Cardiomyopathy Questionnaire (KCCQ) assesses 23 items covering physical function, social function, symptoms, self-efficacy and knowledge, and quality of life on a 0- to 100-point scale; higher scores indicate better quality of life

    - Medical Outcomes Study Short Form-36 (SF-36) assesses 36 items covering 8 dimensions of health status as well as physical and mental summary scores; higher scores represent better health status

    - EuroQOL-5D (EQ-5D) assesses 5 dimensions of general health on a 3-level scale, with utility scores ranging from 0 [death] to 1 [ideal health].

4.1.4 Risk of bias and quality of evidence

Given that data on safety outcomes were available from RCTs, the real-world data studies were only presented narratively and the level of evidence was not graded. The risk of bias of the included RCT studies for the reviews was assessed by two reviewers independently using the Cochrane Collaboration's tool and the criteria

specified in the Cochrane Handbook for Systematic Reviews of Interventions[65] with any disagreement being resolved by discussion or inclusion of a third reviewer.

The overall quality of evidence for each outcome was assessed using the GRADE criteria. In this context, quality reflects the extent to which we are confident that an estimate of the effect is correct.[66-68] GRADE assessments were undertaken by a single reviewer and checked by a second reviewer. Results are presented in summary of findings (SOF) tables, grading the quality of evidence for each outcome as 'high', 'moderate', 'low' or 'very low'.

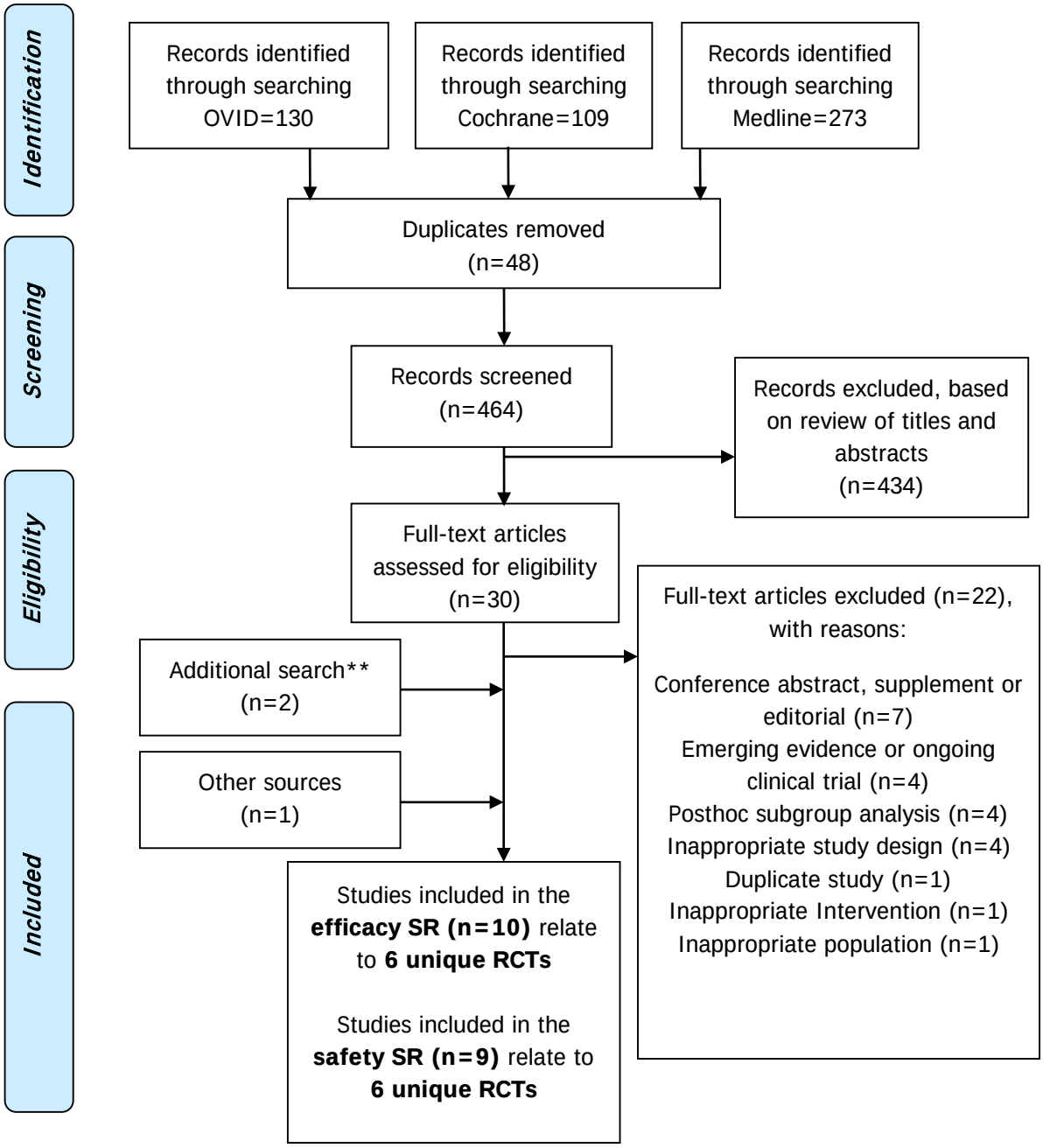
4.1.5 Statistical analysis

Meta-analysis of the available evidence was not performed due to a limited number of included studies (detailed in section 4.3). For many of the outcomes, only two studies provided evidence on clinical effectiveness. Instead of pooling results, the findings of the individual studies are reported separately. Results are presented by surgical risk population (that is, low, intermediate, and mixed (low and intermediate) surgical risk populations). Where there were zero events in either the intervention or control arm of a trial, the relative risk was calculated using a beta-binomial model.[69]

4.2 Included Studies

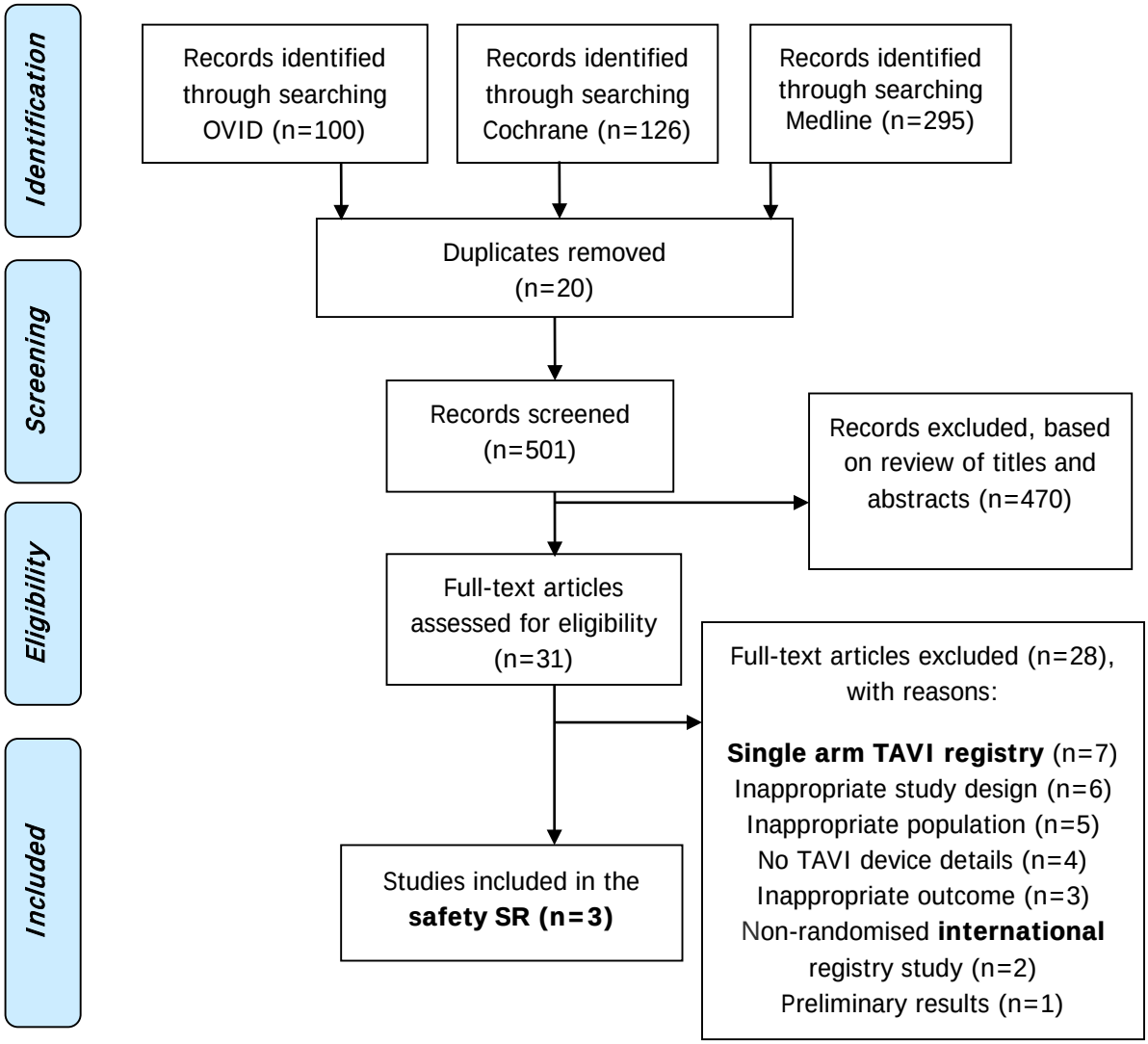
Figure 4.1 shows the PRISMA flow chart of study selection for RCTs. The literature search for RCTs on TAVI in severe aortic stenosis patients at low and intermediate surgical risk published between 1 January 2016 and May 2019. Of the 512 titles retrieved, 30 titles were identified to be potentially relevant, and full text copies were reviewed. Ten articles met the inclusion criteria for the efficacy review, with nine articles for the safety review; all reference six unique RCTs.[19, 70-75] The literature search was extended to include the years 2007 to 2015 which led to the identification of one additional relevant study to add to the effectiveness and safety review. The safety review of RCTs focused on these studies along with one additional study on the NOrdic AorTic Valve InterventiON (NOTION) trial which reported on TAVI device durability. Details of the studies excluded from the reviews and the reason for their exclusion are provided in Appendix B.

Figure 4.1 PRISMA flowchart of study selection for RCTs (2007-2019)



The literature search for the safety review included comparative prospective studies from national registries published between 1 January 2013 and May 2019. Of the 521 titles retrieved, 31 were considered potentially relevant, and full text copies were reviewed. Three articles met the pre-specified inclusion criteria (Figure 4.2).

Figure 4.2 PRISMA flowchart of study selection of prospective comparative national TAVI registry studies [2013-2019]



4.2.1 Description of included literature

RCTs (Clinical effectiveness and Safety)

The characteristics of the published papers included in the effectiveness (n=10) review are reported in Tables 4.2 and 4.3. All publications refer to multi-centre trials. The STACCATO trial was conducted in Denmark;[71] the Placement of AoRtic TraNscathetER valves (PARTNER) 2 trial was conducted in the USA and Canada; the NOTION trial was conducted in Denmark and Sweden. The remaining three trials, Evolut Low Risk, PARTNER 3 and SUrgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI), were larger multinational trials focused on USA and

Canada with additional centres in Japan, Australia and New Zealand[19, 20] and or Europe.[20, 72]

Six RCTs with a total of 6,596 patients were included for the intention-to-treat population assessment of clinical effectiveness split across intermediate surgical risk (n=3,778), low risk (n=2,468) and mixed low and or intermediate risk (n=350). Within the studies, 3,306 patients were randomised to the intervention and 3,290 to control, respectively. Study sizes ranged from 70 (STACCATO) to 2,032 (PARTNER 2) participants.

Four trials used the Society of Thoracic Surgeons Predicted Risk Of Mortality (STS-PROM) score to assign levels of surgical risk; however there was variability in the definition applied. The trials relating to those at intermediate risk applied STS-PROM scores of 4.0 to 8.0% (PARTNER 2) and ≥3 and <15% (SURTAVI). Trials relating to those at low risk applied scores of <4% (PARTNER 3) and ≤3% (Evolut Low Risk). The NOTION trial, which related to those at low and intermediate risk, was limited to those aged ≥70 years who were considered eligible regardless of their predicted risk of mortality provided they had been referred for SAVR for severe degenerative aortic stenosis and were also candidates for TAVI. The majority of those enrolled (81.8%) in the NOTION were considered to be at low risk based on an STS-PROM score <4%. The STACCATO trial did not specify levels of risk. However, based on the reported STS-PROM scores, it can be interpreted that the population was at low or mixed surgical risk. For this review we have assumed that the population was representative of a mixed surgical risk patient group.

Patients enrolled in the intermediate and mixed population trials were older (mean age 79-82 years) compared with the low risk population trials (mean age 73-74 years). Intermediate and mixed population trials also had a lower proportion of male participants (30%-58%) than the low risk population trials (63-71%). The trial enrolment periods ranged from 19 months (PARTNER 3) to 52 months (NOTION).

Table 4.2 Characteristics of included studies on RCTs for assessment of clinical effectiveness and safety

Trial Author (year)	Country (no of centres)	Study enrolment period	Risk profile and inclusion criteria	Age (years) and gender (% male)	Participant numbers	Outcome reporting intervals
PARTNER 2A **Baron (2017)[76]**	USA & Canada (57)	2 years Dec 2011 - Dec 2013	Intermediate (STS-PROM 4-8%)	Age: 81.4±6.8 Male: 54.9%	TAVI=950 SAVR=883	30d, 1y, 2y
PARTNER 2 **Leon (2016)[70]**	USA & Canada (57)	2 years Dec 2011 - Dec 2013	Intermediate (STS-PROM 4-8%)	Age: 81.6±6.7y Male: 54.5%	TAVI=1011 SAVR=1021	30d, 1y, 2y
SURTAVI **Reardon (2017)[72]**	USA, Canada & Europe (87)	4 years June 2012 - June 2016	Intermediate (STS-PROM ≥3% to <15% and other factors)	Age: 79.6±6.2y Male: 56.4%	TAVI=864 SAVR=796	30d, 1y, 2y
PARTNER 3 **Mack (2019)[19]**	USA, Canada, Japan, Australia & New Zealand (71)	19 months Mar 2016 - Oct 2017	Low risk (STS-PROM <4%)	Age: 73.8±6.0y Male: 69.3%	TAVI=503 SAVR=497	30d, 1y
Evolut Low Risk **Popma (2019)[20]**	USA, Canada, France, Netherlands Japan, Australia & New Zealand (86)	2 years 8 months Mar 2016 - Nov 2018	Low risk (no more than a 3% risk of death by 30 days)	Age: 73.6±5.9y Male: 65.2%	TAVI=734 SAVR=734	30d, 1y, 2y
STACCATO **Nielsen (2012)[71]**	Denmark (2)	2 years 7 months Nov 2008 – May 2011	Low and intermediate	Age: 81.0±4.2 Male: 30.0%	TAVI=34 SAVR=36	30d, 3m
NOTION **Sondergaard (2016)[73]**	Denmark & Sweden (3)	4 years 4 months Dec 2009 - Apr 2013	Low and intermediate	Age: 79.1±4.8y Male: 53.2%	TAVI=145 SAVR=135	3m, 1y, 2y
NOTION **Thyregod (2015)[75]**					TAVI=145 SAVR=135	30d, 1y
NOTION **Thyregod (2019)[74]**					TAVI=145 SAVR=135	5y
NOTION **Sondergaard (2019)[77]**					TAVI=139 SAVR=135	6y

Abbreviations: STS-PROM – Society of Thoracic Surgeons Predicted Risk Of Mortality.

Five different TAVI devices from two companies were used. The most common route of implantation was transfemoral (TF). However, other routes used included transthoracic (TT), transaortic (TAo) and subclavian/transaxillary (S/T). The STACCATO trial exclusively used a transapical approach. In four trials the same TAVI devices were used for all participants. Table 4.3 provides a summary of the TAVI device types used in the trials. The STACCATO, PARTNER 2, SURTAVI and NOTION trials were based predominantly or entirely on first generation TAVI devices.

Table 4.3 Summary of the TAVI devices used in the RCTs

Trial	Surgical risk	Valve	Company	Valve type
STACCATO	Low and intermediate	SAPIEN*	Edwards Lifesciences	Balloon-expandable
PARTNER 2	Intermediate	SAPIEN XT*	Edwards Lifesciences	Balloon-expandable
PARTNER 3	Low	SAPIEN 3	Edwards Lifesciences	Balloon-expandable
SURTAVI	Intermediate	CoreValve (84%)* Evolut R (16%)	Medtronic	Self-expandable
Evolut Low Risk	Low	CoreValve (3.6%)* Evolut R (74.1%) Evolut PRO (22.3%)	Medtronic	Self-expandable
NOTION	Low and intermediate	CoreValve*	Medtronic	Self-expandable

* First generation TAVI devices.

The comparator in all trials was SAVR. Three trials were non-inferiority RCTs along with two superiority trials (NOTION and STACCATO) and one powered as a superiority and non-inferiority trial (PARTNER 3). The primary populations of interest were the intention-to-treat (ITT) and as-treated populations unless otherwise stated. A modified ITT (based on patients for whom a procedure was attempted) and per protocol (PP) analyses were also reported for some outcomes. In the context of non-inferiority trials, ITT and PP results were compared as the use of the ITT population may not be the conservative position in a non-inferiority trial.

All six trials specified composite endpoints as the primary outcome. For the PARTNER 2, SURTAVI) and Evolut Low Risk trials, the primary endpoint was a composite of death from any cause and disabling stroke at two year follow-up. For PARTNER 3 the primary outcome was a composite of death from any cause, stroke, or rehospitalisation at one year follow-up. For the mixed risk NOTION trial, the primary outcome was a composite of all-cause death, stroke, or MI at one year. For

the STACCATO trial, the primary endpoint was the composite of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis.

Outcomes for the NOTION trial were reported for one, two, five and six year follow-up. Both studies for the intermediate risk group (PARTNER 2 and SURTAVI) and the Evolut Low Risk trial studies reported most outcomes at follow-ups of 30 days, one year and two years. The PARTNER 3 trial reported to one year only. The STACCATO trial was ended early due to safety concerns and only reported outcomes at 30 days and at 3 months.

The SURTAVI and Evolut Low Risk trials reported outcomes based on Bayesian analyses. For the SURTAVI trial, the reported data represented the results of a Bayesian statistical method interim analysis after one year follow-up.[72] Most patients reached this follow-up point; however, at the two year follow-up, there were considerably fewer patients. Thus, data for patients without a known outcome were not used at the two year follow-up. The Evolut Low Risk trial used similar methods reporting outcomes as estimated incidence percentages, which were medians of the posterior probability distribution as calculated by Bayesian analysis for the pre-specified interim analyses at 12 and 24 months.[20] At 12 months, data were available for 58.9% and 48.0% of the TAVI and SAVR groups, respectively while at 24-months follow-up data were limited to 9.9% and 8.9% of the TAVI and SAVR groups, respectively. In comparison, one year follow-up data were available for 98.4% of the patients for the PARTNER 3 trial.

For the PARTNER and NOTION trial studies, outcomes were reported using Kaplan Meier time-to-event analyses on the available evidence at each time point. Hazard ratios were reported for certain outcomes in the PARTNER trial studies.

Prospective national registry studies (Safety)

Three studies based on prospective national registry were identified for inclusion in the safety review (Table 4.4). Two were based on the German Aortic Valve Registry (GARY) which included data from 92 sites in Germany [78, 79]; one study was based on the Italian national registry (the Italian OBSERVANT study) from 93 participating hospitals in Italy [80]. The surgical risk categories of participants in the studies were intermediate risk [78, 80]and mixed low and intermediate risk.[79]

Table 4.4 Characteristics of included studies using prospective national registry data for assessment of safety

Registry Author (year)	Country (no of centres)	Study duration	Risk profile and inclusion criteria	Age and gender	Participant numbers	TAVI device	Safety outcomes (reporting intervals)
OBSERVANT Fraccaro (2016)[80]	Italy (93)	18 months Dec 2010 – Jun 2012	Intermediate risk patients with mean logistic EuroSCORE of 8.0± 5.7% (SAVR) vs 14.9± 11.8% (TAVI) group	Age (years): 83.7± 2.9 TAVI 83.7± 2.6 SAVR Male (%): 158 (37%) TAVI 166 (40%) SAVR [matched pairs]	Enrolled population ≥80 yrs (N=2,820) to pre-matching population n=2,161 (1178 TAVI; 983 SAVR patients) Post-propensity score matched population n=830 patients (415 patients for each group)	Sapien XT 47%; CoreValve 53%	MI; stroke; tamponade; shock; major vascular complications; NPMI; AKI, acute renal failure; infections; AVR (30 d)
GARY Fujita (2019) [78]	Germany (NR)	5 years Jan 2011 – Dec 2015	All comers registry – low-intermediate risk	Age (years): 81 (78–85) TAVI 72 (64–76) SAVR Male (%): TAVI (45%) SAVR (58%)	TAVI n=20,872* SAVR n=17,750 SAVR with conventional prosthesis n= 16,870* [*comparison cohorts]	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0%	Disabling stroke, AVR, NPMI, new AF (in-hospital)
GARY Werner (2018) [79]	Germany (92)	36 months Jan 2012 – Dec 2014	Intermediate surgical risk (Society of Thoracic Surgeons score 4%–8%)	Age (years): 82.5±5.0 TAVI 76.6±6.7 SAVR Male (%): TAVI (37.2%) SAVR (35.4%)	N=7,613 patients TAVI n=6,469 SAVR n=1,144	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	in-hospital mortality, myocardial infarction, stroke, acute kidney injury, permanent pacemaker implantation, bleeding or vascular complications, and aortic valve regurgitation ≥ grade II (in-hospital; 1 y)

The studies comprised registry data for patients (n=28,519 TAVI; n=18,997 SAVR) who underwent aortic valve replacement during an 18 month (Dec 2010 – June 2012)[80], five year (Jan 2011 – Dec 2015)[78] and 36 month (Jan 2012 – Dec 2014) period,[79] respectively. Safety outcome data were collected for patients at hospital discharge, 30 days or one year. The safety outcomes and duration of follow-up are detailed in Table 4.4.

The Italian registry study was limited to those aged 80 years and older; propensity scores were used to match the TAVI and SAVR cohorts. In both GARY studies, the median age of TAVI patients was substantially older that for the SAVR patients (81 vs. 72 years and 82.5 vs. 76.6 years, respectively). The gender balance was predominantly female in the Fraccaro and Werner studies (≥60%) yet balanced between the arms; while the study by Fujita had more males in the SAVR arm (57.5%) than the TAVI arm (45.2%).

4.2.2 Risk of bias in included RCT studies

The risk of bias in the included RCT studies was assessed using the Cochrane Risk of Bias tool with studies assessed as being at either low, high, or unclear risk of bias in each of seven domains.[65]

- All of the RCTs had adequate randomisation procedures, with patients uniformly assigned to TAVI or SAVR in a 1:1 ratio, and were considered to be at low risk of bias.

- Five studies[19, 20, 70-72, 76] based on the STACCATO, PARTNER 2 and 3, SURTAVI, and Evolut LR trials had an unclear risk of bias in terms of allocation concealment; the studies did not report whether the sequence of patient allocation to TAVI or SAVR was known by investigators. The studies based on the NOTION trial were considered to be at low risk of bias as the allocation sequence was based on permuted blocks, the size of which were unknown to investigators.

- All of the studies had a high risk of performance bias due to the non-blinded design of the RCTs; neither participants nor personnel could be blinded to the allocated treatment as both procedures differed in terms of performance and patients had to consent to enrollment due to the invasiveness of surgery.

- All of the studies had a high risk of detection bias as outcome assessors were often not blinded to patients' allocated treatment. Some outcomes were objective such as cardiac mortality and stroke, but others were subjective, such as improvement in quality of life, and were at high risk of bias if assessors were not blinded.

- The majority of studies were at low risk of attrition bias with modest attrition that was comparable in both groups. One study had a high risk of bias as attrition was substantially higher in the SAVR arm.[70]

- The majority of studies had a low risk of reporting bias as outcomes were generally reported in full and according to different principles (that is, per-protocol and/or intention-to-treat), consistent with pre-specified analyses, or protocols. There was an unclear risk of reporting bias in two studies[73, 75] which only reported outcomes for an as-treated population (that is, those for whom a procedure had been attempted).

- The STACCATO and NOTION trials received funding from the Danish Heart Foundation, while the remaining trials were industry sponsored. However, in each study, statistical analyses were conducted by industry researchers, so there was an unclear risk of bias in terms of the influence of industry on the included studies.

4.3 Trial findings

For consistent comparison, the intention-to-treat (ITT) population analysis of results is reported for the PARTNER 2 and SURTAVI trials; while the as-treated population analysis of results is reported for the PARTNER 3, Evolut Low Risk and NOTION trials; Appendix E details the summary of findings tables for the comparison of effectiveness and safety outcomes of TAVI versus SAVR in all the relevant surgical risk populations. Given that data on safety outcomes were available from RCTs, the real-world data studies were only presented narratively and the level of evidence was not graded.

4.3.1 Intermediate surgical risk

RCTs – clinical effectiveness and safety outcomes

The clinical effectiveness and safety outcomes for patients at intermediate surgical risk were reported in two trials (PARTNER 2; SURTAVI).[70, 72] The event rates for SURTAVI reported in tables 4.5 and 4.6 are taken from the EUnetHTA REA report evaluating TAVI in intermediate surgical risk patients.[1]

For all-cause and cardiac mortality, TAVI is non-inferior to SAVR at 30 days, 1 year and 2 years (Table 4.5). The certainty of the evidence is moderate (Appendix E).

The all-cause and cardiac mortality rates in both the intervention and control arms were higher in the PARTNER 2 trial compared with the SURTAVI trial at all time-points (Table 4.5). For example, the 30 day all-cause mortality rates in the TAVI and SAVR arms are 3.9% and 4.0% (PARTNER 2) versus 2.0% and 1.5% (SURTAVI),

respectively. The 30 day cardiac mortality rates in the TAVI and SAVR arms are 3.3% and 3.1% (PARTNER 2) versus 1.9% and 1.5% (SURTAVI), respectively. The difference in intervention arm mortality is statistically significant at all time-points for all-cause mortality and at one and two year follow-up for cardiac mortality.

Table 4.5 Clinical effectiveness outcomes – intermediate risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
All-cause mortality						
30 days	PARTNER 2	1011	39	1021	41	0.96 [0.63-1.48]
	SURTAVI	879	18	867	13	1.37 [0.67-2.77]
1 year	PARTNER 2	1011	123	1021	124	1.00 [0.79-1.27]
	SURTAVI	879	55	867	51	1.06 [0.74-1.54]
2 years	PARTNER 2	1011	166	1021	170	0.99 [0.81-1.20]
	SURTAVI	879	77	867	70	1.08 [0.80-1.48]
Cardiac mortality						
30 days	PARTNER 2	1011	33	1021	32	1.04 [0.65-1.68]
	SURTAVI	879	17	867	13	1.29 [0.63-2.64]
1 year	PARTNER 2	1011	70	1021	77	0.92 [0.67-1.25]
	SURTAVI	879	39	867	41	0.94 [0.61-1.44]
2 years	PARTNER 2	1011	97	1021	104	0.94 [0.72-1.22]
	SURTAVI	879	52	867	51	1.01 [0.69-1.46]
Aortic valve reintervention						
30 days	PARTNER 2	1011	4	1021	0	17.36 [1.28-8772]
	SURTAVI	879	7	867	1	6.90 [0.85-56.00]
1 year	PARTNER 2	1011	11	1021	4	2.78 [0.89-8.69]
	SURTAVI	879	17	867	3	5.59 [1.64-19.00]
2 years	PARTNER 2	1011	13	1021	5	2.63 [0.94-7.34]
	SURTAVI	879	20	867	3	6.58 [1.96-22.05]

Rates of aortic valve reintervention were higher with TAVI than SAVR at all time-points in both trials, and the relative risk was statistically significant at one and two-year follow-up in the SURTAVI trial and at 30 days in PARTNER 2 (Table 4.5). Arguably the trials were underpowered to detect a difference in what is a relatively uncommon outcome. The certainty of the evidence is low, downgraded due to the low event rate (Appendix E).

In addition, the SURTAVI trial assessed the estimated incidence of re-hospitalisations because of aortic valve dysfunction with no reported difference between the TAVI and SAVR groups at 30 days and one year;[72] however, based on the Bayesian analysis there was a credible difference between TAVI and SAVR with incidences of 13.2 versus 9.7 at two year follow-up. The PARTNER 2 trial assessed any rehospitalisation at 30 day, one year, and two year follow-up, with no reported differences between the TAVI and SAVR groups.[70]

Both the PARTNER 2 and SURTAVI trials reported on improvement of symptoms (that is, reduction in NYHA class). The percentage of patients that were NYHA class III or higher at baseline was 80% in PARTNER 2 and 59% in SURTAVI. At two years, the percentage of surviving patients that were NYHA class III or higher was 7% in PARTNER 2 and 5% in SURTAVI. No differences in effect were observed between the intervention and control groups. Overall, the certainty of the evidence is low (Appendix E).

For the haemodynamic function of the valve, in the SURTAVI trial,[72] from baseline to discharge, the mean aortic gradient improved in both the TAVI group (8.9±4.1 mmHg) and the SAVR group (12.4±5.7 mmHg); the difference between the two groups was statistically significant ($p < 0.001$). This difference persisted throughout the two year follow-up. In addition, from baseline to discharge, the TAVI group had larger aortic valve areas than the SAVR group (2.1±0.6 cm2 versus 1.8±0.6 cm2, respectively) with a statistically significant difference. These improvements persisted throughout the two year follow-up. In the PARTNER 2 trial,[70] in both the TAVI and SAVR groups, there was an improvement in the aortic valve area (1.7±0.5 cm2 versus 1.5 cm2 ± 0.4, respectively; $p < 0.001$) and LVEF (56.9±10.2% versus 55.0±11.0%, respectively; $p < 0.004$) as well as a decrease in the mean aortic valve gradients (9.7±3.5 mmHg versus 10.9±4.3 mmHg, respectively; $p < 0.001$). These improvements persisted throughout the two year follow-up.

In terms of length of stay (LOS), the duration of the index hospitalisation was significantly shorter for TAVI compared with SAVR in both the Partner 2 (median, 6 versus 9 days; $p < 0.001$) and SURTAVI (5.75±4.85 days versus 9.75±8.03 days) trials. The certainty of the evidence is moderate (Appendix E).

For health-related quality of life (HRQoL) reported from the PARTNER 2 trial, Baron et al (2017) compared the health status of patients in the TAVI and SAVR groups at baseline, one month, one year, and two years using the KCCQ, SF-36 and EQ-5D.[76] The within-group changes in health status after TAVI or SAVR are categorised by TAVI access route – transfermoral or transthoracic cohort. For the transthoracic TAVI cohort versus SAVR, the results demonstrated no substantial difference in HRQoL at all timepoints. The health status results for the transfemoral TAVI cohort

versus SAVR in the PARTNER 2 trial are shown in Table 4.6. Transfemoral access accounted for 76% of TAVI procedures in PARTNER 2.

Table 4.6 Health status outcomes for intermediate risk trials

Interval	Trial	TAVI		SAVR		Treatment Effect
		Total	Paired difference (95% CI)	Total	Paired difference (95% CI)	Difference in paired differences
KCCQ-OS						
1 month	PARTNER 2 (TF)	678	17.5 (15.8-19.3)	551	3.2 (1.3-5.5)	+14.3
	SURTAVI	819	18.4 (-4.4-41.2)	700	5.9 (-21.1-32.9)	+12.5
1 year	PARTNER 2 (TF)	596	22.1 (20.4-23.9)	479	22.1 (20.1-24.1)	0
2 years	PARTNER 2 (TF)	530	20.2 (18.2-22.2)	438	18.4 (16.3-20.6)	+1.8
SF-36 (PS)						
1 month	PARTNER 2 (TF)	669	4.6 (3.9-5.3)	532	1.0 (-0.8-0.8)	+3.6
3 months	SURTAVI	753	7.4 (-3.1-17.9)	659	5.6 (-4.9-16.1)	+1.8
1 year	PARTNER 2 (TF)	585	4.4 (3.7-5.2)	470	5.1 (4.2-6.0)	-0.7
2 years	PARTNER 2 (TF)	521	3.3 (2.5-4.2)	426	3.0 (2.0-4.0)	+0.3
EQ-5D						
1 month	PARTNER 2 (TF)	675	0.058 (0.04-0.07)	543	-0.002 (-1.02-0.01)	+0.056
3 months	SURTAVI	776	0.06 (-0.12-0.24)	680	0.050 (-0.13-0.23)	+0.01
1 year	PARTNER 2 (TF)	591	0.044 (0.03-0.06)	471	0.066 (0.05-0.08)	-0.022
2 years	PARTNER 2 (TF)	527	0.027 (0.01-0.04)	437	0.037 (0.02-0.06)	-0.010

The SURTAVI trial compared the health status of patients in the TAVI and SAVR groups at baseline and 30 days or three months using the KCCQ (30d), SF-36 (3m) and EQ-5D (3m).[72] The health status results for the TAVI versus SAVR groups are shown in Table 4.6. Results were not disaggregated by access route, although 94% of cases were transfemoral in the SURTAVI trial. Although, TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (one to three months from baseline) for intermediate surgical risk patients, it is uncertain whether TAVI has any effect on improving HRQoL symptoms compared with SAVR at one or two year follow-up. The certainty of the evidence is low (Appendix E). No other generic or disease-specific quality-of-life instrument data were reported in either of the two trials.

Table 4.7 presents the post-operative complications reported from the intermediate surgical risk populations in the PARTNER 2 and SURTAVI trials.

Table 4.7 Safety outcomes – intermediate risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
Stroke						
30 days	PARTNER 2	1011	55	1021	61	0.91 [0.64-1.30]
	SURTAVI	864	28	796	43	0.60 [0.38-0.96]
1 year	PARTNER 2	1011	78	1021	79	1.00 [0.74-1.35]
	SURTAVI	864	44	796	52	0.78 [0.53-1.15]
2 years	PARTNER 2	1011	91	1021	85	1.08 [0.82-1.43]
	SURTAVI	864	48	796	58	0.76 [0.53-1.10]
Disabling Stroke						
30 days	PARTNER 2	1011	32	1021	43	0.75 [0.48-1.18]
	SURTAVI	864	10	796	19	0.48 [0.23-1.04]
1 year	PARTNER 2	1011	49	1021	56	0.88 [0.61-1.28]
	SURTAVI	864	18	796	26	0.64 [0.35-1.15]
2 years	PARTNER 2	1011	59	1021	61	0.98 [0.69-1.38]
	SURTAVI	864	19	796	29	0.60 [0.34-1.07]
Major vascular complications						
30 days	PARTNER 2	1011	80	1021	51	1.58 [1.13-2.23]
	SURTAVI	864	51	796	8	5.87 [2.80-12.30]
1 year	PARTNER 2	1011	84	1021	54	1.57 [1.13-2.19]
	SURTAVI	864	54	796	8	6.22 [2.98-12.99]
2 years	PARTNER 2	1011	86	1021	55	1.58 [1.14-2.19]
	SURTAVI	864	54	796	8	6.22 [2.98-12.99]
Atrial Fibrillation						
30 days	PARTNER 2	1011	91	1021	265	0.35 [0.28-0.43]
	SURTAVI	879	113	867	376	0.30 [0.25-0.36]
1 year	PARTNER 2	1011	100	1021	272	0.37 [0.30-0.46]
	SURTAVI	**NR**	**NR**	**NR**	**NR**	**NR**
2 years	PARTNER 2	1011	110	1021	273	0.41 [0.33-0.50]
	SURTAVI	**NR**	**NR**	**NR**	**NR**	**NR**
New Permanent Pacemaker Implantation (NPMI)						
30 days	PARTNER 2	1011	85	1021	68	1.26 [0.93-1.72]
	SURTAVI	864	217	796	48	4.17 [3.09-5.61]
1 year	PARTNER 2	1011	98	1021	85	1.16 [0.88-1.54]
	SURTAVI	864	239	796	62	3.55 [2.73-4.62]
2 years	PARTNER 2	1011	114	1021	96	1.20 [0.93-1.55]
	SURTAVI	864	253	796	67	3.48 [2.71-4.47]

Table 4.7 continued

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
Life threatening or disabling bleed						
30 days	PARTNER 2	1011	105	1021	442	0.24 [0.20-0.29]
	SURTAVI	864	49	796	47	0.96 [0.65-1.42]
1 year	PARTNER 2	1011	151	1021	460	0.33 [0.28-0.39]
	SURTAVI	864	60	796	60	0.92 [0.65-1.30]
2 years	PARTNER 2	1011	169	1021	471	0.36 [0.31-0.42]
	SURTAVI	864	64	796	63	0.94 [0.67-1.31]
Trans Ischaemic Attack (TIA)*						
30 days	PARTNER 2	1011	9	1021	4	2.27 [0.70-7.35]
	SURTAVI	864	1.5%	796	1.1%	
1 year	PARTNER 2	1011	23	1021	16	1.45 [0.77-2.73]
	SURTAVI	864	3.2%	796	2.0%	
2 years	PARTNER 2	1011	34	1021	20	1.72 [1.00-2.96]
	SURTAVI	864	4.3%	796	3.1%	
Myocardial Infarction (MI)						
30 days	PARTNER 2	1011	12	1021	19	0.64 [0.31-1.31]
	SURTAVI	864	7	796	7	0.92 [0.32-2.61]
1 year	PARTNER 2	1011	24	1021	29	0.84 [0.49-1.43]
	SURTAVI	864	15	796	11	1.26 [0.58-2.72]
2 years	PARTNER 2	1011	33	1021	37	0.90 [0.57-1.43]
	SURTAVI	864	18	796	13	1.28 [0.62-2.59]

* Results of these outcomes in the SURTAVI trial were only reported as rates.

At all time-points there were no differences in event rates for stroke and disabling stroke except for stroke in the SURTAVI trial at 30 days, where there was a lower rate in the TAVI arm (RR 0.60; 95% CI: 0.38-0.96).

In both the PARTNER 2 and SURTAVI trials there was a higher risk of major vascular complications associated with TAVI at all time-points. The relative difference was higher in the SURTAVI trial (RR 5.87 at 30 days) than in the PARTNER 2 trial (RR 1.58 at 30 days). Almost all events occurred in the first 30 days after surgery. There were no additional vascular complications in either group during the second year of follow-up. It is worth noting that the rates of major vascular complications at 30 days differed substantially between the two trials, both in the intervention arm (7.9% in PARTNER 2 vs. 4.4% in SURTAVI) and the control arms (5.0% in PARTNER 2 vs. 1.0% in SURTAVI) possibly reflecting differences in the classification of what comprised a major vascular complication. Rates of atrial fibrillation were significantly lower with TAVI than SAVR at all time points (30 days, one year and two years) in

the PARTNER 2 trial. Data for the SURTAVI trial were limited to 30 day follow-up with a significant higher relative risk in the SAVR arm.

Rates of new permanent pacemaker implantation (NPMI) were higher with TAVI than SAVR at all time-points in both trials. The increased relative risk (ranging from 4.17 at 30 days to 3.48 at two years) was statistically significant in the SURTAVI trial at all time points. Of note, the rate of NPMI was substantially higher in the TAVI arm of the SURTAVI trial compared with the PARTNER 2 trial at all time points with up to a three-fold difference in NPMI rates (30 day: 25.1% vs. 8.4%, respectively) despite consistently relatively similar NPMI rates in the SAVR arm (30 day: 6.0% vs 6.7%, respectively). Over 70% of all NPMI in both the TAVI and SAVR arms occurred within the first 30 days, with the highest proportion (86%) noted in the TAVI arm of the SURTAVI trial.

Rates of life threatening and disabling bleed were lower with TAVI than SAVR at all time points in both trials; however, the relative risk was not statistically significantly in the SURTAVI trial. The relative risk (ranging from 0.24 at 30 days to 0.36 at two years) was significantly lower with TAVI in the PARTNER 2 trial at all three time-points. Of note, the rates of life threatening or disabling bleed in both the TAVI and SAVR arms differed substantially between the two trials at all time points, with higher rates reported in the PARTNER 2 trial (e.g., at 30 days: 43.3% vs 5.9% in the SAVR arm of the PARTNER 2 and SURTAVI trials, respectively). This suggests a difference in the management of patients between trials or how the outcome was defined or assessed.

In the PARTNER 2 trial, there was no statistically significant difference in the risk of transient ischemic attacks (TIA) or myocardial infarction (MI) between TAVI and SAVR at any time-point. For the SURTAVI trial, TIA and MI were reported as rates. At all three time-points the credible interval for the difference between TAVI and SAVR included the possibility of no effect. The rates of TIA and MI were similar in the PARTNER 2 and SURTAVI trials.

Registry studies – safety outcomes

The safety outcomes for patients at intermediate surgical risk were reported in two prospective national registry studies.[79, 80] The results of the comparative safety review of registry studies are reported in Appendix D. In-hospital results from Werner et al. indicated a reduced risk of AF, MI and cardiac tamponade in the TAVI group compared with the SAVR group; however, the in-hospital results from this study indicated a greater risk of stroke, vascular complications, NPMI and aortic valve regurgitation for the TAVI group.[79] At one year, the results indicated a similar risk of stroke between the groups, with higher risk of both MI and NPMI and a lower risk of TIA, in the TAVI group compared with the SAVR group. It should be noted

the study did not include similar patient numbers and the authors did not conduct a propensity score matching analysis of the cohorts for safety outcomes.

The study by Fraccaro et al. presented results from a propensity score matched analysis of the TAVI and SAVR populations aged over 80 years old.[80] Results at 30 days indicated an increased risk of cardiac tamponade, major vascular complications and NPMI, along with reduced risk of stroke and acute renal failure with TAVI compared with SAVR.

The results from these registry studies appear to highlight an increased risk of vascular complications and NPMI in TAVI versus SAVR in the intermediate surgical risk population that is consistent with the results observed in the RCTs. However, it needs to be noted that the RCTs represent an idealised population with patients excluded for bicuspid anatomy or pre-existing co-morbidities and prior cardiovascular surgical interventions. Although the registry studies are for a real-world population, they are nation-specific which may limit the generalisability of the findings. While propensity score matching may assist in eliminating confounding factors, it reduces the numbers of patients for analysis, which may limit the detection of rarer adverse events.

4.3.2 Low surgical risk

RCTs – clinical effectiveness and safety outcomes

The clinical effectiveness and safety outcomes for patients at low surgical risk were reported in two trials (PARTNER 3; EVOLUT Low Risk (LR)). [19, 20] The characteristics of these trials are outlined in Table 4.3.The PARTNER 3 trial evaluated the SAPIEN 3 device and the EVOLUT Low Risk trial included patients treated with the CoreValve (3.6%), Evolut R (74.1%) and the Evolut PRO (22.3%) devices. PARTNER 3 presented event rates for an ITT population, whereas the EVOLUT low risk results are presented as Bayesian posterior median incidence percentages in an ITT population. No clear methodology was outlined and therefore absolutes numbers of events could not be determined. Medtronic were unable to provide completed trial data with numbers of events. The results for both trials were reported at 30 days and at one year. However, the Evolut Low Risk trial only reported interim-analysis at one year;[20] it should be noted that the follow-up patient numbers were substantially lower than those originally randomised to TAVI and surgery in this trial.

Table 4.8 Clinical effectiveness outcomes – low surgical risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
All-cause mortality						
30 days	PARTNER 3	496	2	454	5	0.37 [0.07-1.88]
	EVOLUT LR	734	0.5%	734	0.8%	
1 year	PARTNER 3	496	5	454	11	0.42 [0.15-1.19]
	EVOLUT LR	734	2.4%	734	2.9%	
2 years	NOTION*	118	7	108	8	0.80 [0.30-2.13]
5 years	NOTION*	121	27	108	30	0.80 [0.51-1.26]
Cardiac mortality						
30 days	PARTNER 3	496	2	454	4	0.46 [0.08-2.49]
	EVOLUT LR	734	0.5%	734	0.6%	
1 year	PARTNER 3	496	4	454	9	0.41 [0.13-1.31]
	EVOLUT LR	725	1.7%	678	2.6%	
Aortic valve reintervention						
30 days	PARTNER 3	496	0	454	0	N/A
	EVOLUT LR	734	0.2%	734	0.4%	
1 year	PARTNER 3	496	3	454	2	1.37 [0.23-8.18]
	EVOLUT LR	725	0.7%	678	0.6%	

Legend: The NOTION low risk (STS-PROM <4%) sub-group referenced as NOTION*

For outcomes of all-cause mortality, cardiac mortality and aortic valve reintervention, there was no evidence of a difference in effect between TAVI and SAVR in the PARTNER 3, EVOLUT LR and NOTION trials. Absolute event rates were broadly similar across the trials.

The PARTNER 3 trial assessed rehospitalisation rates at 30 day and one year follow-up, with reported differences between the TAVI and SAVR groups.[19] TAVI was associated with reduced rehospitalisation, with reported rates of 3.4% (30 day) and 7.3% (one year) in the TAVI group and 6.5% (30 day) and 11.0% (one year) in the SAVR group.

Both the PARTNER 3 and Evolut Low Risk trial reported on improvement of symptoms (that is reduction in NYHA class).In the PARTNER 3 trial,[19] 28% of all patients were NYHA class III or higher at baseline with differences between the trial arms at baseline(31% vs 24% in the TAVI and SAVR arms, respectively). At 30-day follow-up, 20% of TAVI patients and 33% of SAVR patients were NYHA class II or higher decreasing to 17% and 18% at one year follow-up, respectively, In the Evolut Low Risk trial,[20] 25% of the TAVI group and 28% of the SAVR group were NYHA

class III or higher at baseline. A significant improvement in symptoms was noted in both the TAVI and SAVR arms at 30 day follow up. Only 2% of TAVI patients and 5% of SAVR patients were classed as NYHA class III or higher, with the majority of patients now classified as NYHA class I (TAVI 77% and SAVR 67%) at 30 days. No differences in effect were observed between the two groups at one year follow-up. Overall, the certainty of the evidence is low (Appendix E).

For the haemodynamic function of the valve in the Evolut Low Risk trial,[20] from baseline to discharge, the mean aortic gradient improved in both the TAVI group (8.4±3.5 mmHg) and the SAVR group (10.5±4.0 mmHg). These improvements persisted throughout the two year follow-up. In the PARTNER 3 trial,[19] in both the TAVI and SAVR groups, there was an improvement from baseline in the aortic valve area (1.7±0.02 cm^2 versus 1.8 cm^2±0.02, respectively) and in the LVEF (84.2±0.71% versus 76.6±0.81%, respectively), as well as a decrease in the mean aortic valve gradients (12.8±0.2 mmHg versus 11.2±0.21 mmHg, respectively). These improvements persisted through to one year follow-up.

Examining length of stay (LOS) in the PARTNER 3 trial,[19] patients in the TAVI group had a significantly shorter index hospitalisation than the SAVR group (median, 3±1 versus 7±1 days; $p < 0.001$) as well as a shorter duration of stay in the intensive care unit than those in the surgery group (median, 2±1 versus 3±1 days). The certainty of the evidence is high (Appendix E). No data regarding hospital and intensive care unit length of stays were provided for the Evolut Low Risk trial.[20]

For health-related quality of life (HRQoL) reported from the PARTNER 3 trial,[19] the KCCQ-OS score change from baseline was 18.5±0.83 (TAVI) and 2.5±1.05 (SAVR) at 30 days, and 19.4±0.87 (TAVI) and 17.4±0.99 (SAVR) at one year. In the Evolut Low Risk trial,[20] the mean KCCQ change from baseline was 20.0±21.1 (TAVI) and 9.1±22.3 (SAVR) at 30 days. Again, TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (30 days from baseline) for low surgical risk patients, while it is uncertain whether TAVI has any effect on improving HRQoL symptoms compared with SAVR at one year follow-up. The certainty of the evidence is moderate (Appendix E).

Table 4.9 presents the post-operative complications reported from the low surgical risk populations in the PARTNER 3 and EVOLUT Low Risk trials.

Table 4.9 Safety outcomes – low surgical risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
Stroke						
30 days	PARTNER 3	496	3	454	11	0.25 [0.07-0.89]
	EVOLUT LR	734	2.1%	734	1.9%	
1 year	PARTNER 3	496	6	454	14	0.39 [0.15-1.01]
	EVOLUT LR	734	4.0%	734	4.2%	
Disabling Stroke						
30 days	PARTNER 3	496	0	454	2	0.18 [0.01-3.80]
	EVOLUT LR	734	0.4%	734	0.9%	
1 year	PARTNER 3	496	1	454	4	0.27 [0.03-2.45]
	EVOLUT LR	734	0.8%	734	2.1%	
Major vascular complications						
30 days	PARTNER 3	496	11	454	7	1.44 [0.56-3.68]
	EVOLUT LR	725	3.8%	678	3.2%	
1 year	PARTNER 3	496	14	454	7	1.83 [0.75-4.50]
	EVOLUT LR	725	3.8%	678	3.5%	
Atrial Fibrillation						
30 days	PARTNER 3	496	21	454	145	0.13 [0.09-0.21]
	EVOLUT LR	725	7.7%	678	35.4%	
1 year	PARTNER 3	496	29	454	150	0.18 [0.12-0.26]
	EVOLUT LR	725	9.8%	678	38.3%	
New Permanent Pacemaker Implantation (NPMI)						
30 days	PARTNER 3	496	32	454	18	1.56 [0.89-2.75]
	EVOLUT LR	725	17.4%	678	6.1%	
1 year	PARTNER 3	496	36	454	24	1.32 [0.80-2.18]
	EVOLUT LR	725	19.4%	678	6.7%	
Life threatening or disabling bleed						
30 days	PARTNER 3	496	18	454	111	0.15 [0.09-0.24]
	EVOLUT LR	725	2.4%	678	7.5%	
1 year	PARTNER 3	496	38	454	117	0.30 [0.21-0.42]
	EVOLUT LR	725	3.2%	678	8.9%	
Trans Ischaemic Attack (TIA)						
30 days	PARTNER 3	496	0	454	3	0.13 [0.00-2.53]
	EVOLUT LR	734	0.5%	734	0.2%	
1 year	PARTNER 3	496	5	454	5	0.92 [0.27-3.14]
	EVOLUT LR	734	1.6%	734	1.9%	

Table 4.9 continued

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
Myocardial Infarction (MI)						
30 days	PARTNER 3	496	5	454	6	0.76 [0.23-2.48]
	EVOLUT LR	734	0.9%	734	0.6%	
1 year	PARTNER 3	496	6	454	10	0.54 [0.20-1.50]
	EVOLUT LR	734	1.7%	734	1.6%	

* Results of outcomes in the EVOLUT LR trial were only reported as rates.

The risk of stroke was lower at 30 days for TAVI than SAVR in the PARTNER 3 trial (RR 0.25; 95% CI: 0.07 to 0.89), with the difference no longer statistically significant at one year follow-up. No difference was observed in the EVOLUT LR trial. The PARTNER 3 trial also reported rates of disabling stroke at 30 days and one year follow. The trials may have been underpowered to detect a difference due to the low event rate.

There was no statistically significant difference between TAVI and SAVR in terms of rates of major vascular complications in either the PARTNER 3 or EVOLUT LR trials at 30 day or one year follow-up.

TAVI was associated with a statistically significantly lower incidence of atrial fibrillation than SAVR in both the PARTNER 3 and EVOLUT LR trials. The effect was observed at both 30 days and one year follow-up, although the majority of events occurred within the first 30 days.

New permanent pacemaker implantation (NPMI) procedures predominantly occurred within the first 30 days. There was no statistically significant difference between TAVI and SAVR in NPMI rates in the PARTNER 3 trial. However, a credible difference was observed in the EVOLUT LR trial, finding that NPMI rates were higher in the TAVI arm. The rates of pacemaker implantation in the TAVI arm were much higher in the EVOLUT LR trial than in the PARTNER 3 trial (17.4% vs. 7.3%).

The incidence of major or life threatening bleed was substantially higher in patients undergoing SAVR compared to TAVI after 30 days in both the PARTNER 3 and EVOLUT LR trials. The difference was less pronounced after one year as only 47% (n=18) of all cases of bleed occurred in the TAVI group in the first 30 days compared to 95% of cases in the SAVR group. This indicates that the TAVI group suffered from serious cases of bleeding at a similar incidence both during the index procedure and in the following 11 months. The rate of life threatening or disabling bleeds at 30 days in the SAVR arm of PARTNER 3 (24.4%) was much higher than the equivalent figure in EVOLUT LR (7.5%).

There was no difference between TAVI and SAVR in terms of incidence of trans ischaemic attacks (TIA) and myocardial infarction. Incidence of TIA and MI were both less than 2% in both included trials.

Data on device durability from the NOTION trial were published based on six year follow-up.[77] At five years the rate of bioprosthetic valve deterioration was 56% in the TAVI arm and 67% in the SAVR arm, and the difference was not statistically significant (p=0.07). There was no difference in non-structural valve deterioration (54% versus 58%). At six years there was a significant difference in structural valve deterioration, which was 5% in the TAVI arm and 24% in the SAVR arm (p<0.0001). An important consideration is the clinical significance of the different types of valve deterioration and whether they necessitate further intervention. On the basis of the limited data available, over a short to medium term time horizon the TAVI and SAVR valves appear to have similar durability.

Registry studies – safety outcomes

No registry study for a low surgical risk population was identified in the review.

4.3.3 Mixed (low to intermediate) surgical risk

RCTs – clinical effectiveness and safety outcomes

The clinical effectiveness and safety outcomes for patients at mixed surgical risk were reported in two trials: STACCATO and NOTION. The STACCATO trial was terminated prematurely because of safety concerns. At the time of termination only 70 patients had been enrolled and outcomes were reported for 30 days and three months. The NOTION trial was reported across four studies including outcomes at 30 days, and one, two, five and six years. The NOTION trial included patients treated with the CoreValve TAVI device. Results are presented as event rates for an as-treated population across all time intervals. The ITT population results are reported only in the five year study by Thyregod et al. (2019).

Table 4.10 Clinical effectiveness outcomes – mixed surgical risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
All-cause mortality						
30 days	NOTION	142	3	134	5	0.57 [0.14-2.32]
	STACCATO	34	2	36	0	10.13 [0.53-5657]
3 months	STACCATO	34	3	36	0	15.04 [0.92-6622]
1 year	NOTION	142	7	134	10	0.66 [0.26-1.69]
2 years	NOTION	142	11	134	13	0.80 [0.37-1.72]
5 years	NOTION	142	39	134	37	0.99 [0.68-1.46]
6 years	NOTION	139	59	135	51	1.12 [0.84-1.50]
Cardiac mortality						
30 days	NOTION	142	3	134	5	0.57 [0.14-2.32]
1 year	NOTION	142	6	134	10	0.57 [0.21-1.52]
2 years	NOTION	142	9	134	12	0.71 [0.31-1.63]
5 years	NOTION	142	29	134	29	0.94 [0.60-1.49]

There were no statistically significant differences in all-cause mortality or cardiac mortality at any time-point in either trial. The certainty of the evidence is moderate (Appendix E).

There are no reported data for aortic valve reintervention in the NOTION trial studies. In the STACCATO trial, there was one reintervention among the 34 TAVI patients.

For assessment of improvement of symptoms (that is reduction in NYHA class), in the mixed-risk NOTION trial,[73] 48% of the TAVI group and 45% of the SAVR group were NYHA class III or higher at baseline. After 30 day follow-up, there was a significant reduction in these classifications, with 5% NYHA class III or higher in the TAVI and 4% in the SAVR group. No differences in effect for this functional status classification were observed between the two groups at one and two year follow-up. In the STACCATO trial, the percentage patients NYHA class III or higher at baseline was 53% in the TAVI arm and 33% in the SAVR arm. At three months the percentage of patients NYHA class III or higher was 24% in the TAVI arm and 11% in the SAVR arm. The certainty of the evidence is low (Appendix E).

For the haemodynamic function of the valve in the NOTION trial,[73, 74] from baseline to discharge, the mean aortic gradient improved in both the TAVI group (8.3 mmHg) and the SAVR group (12.2 mmHg). In addition, from baseline to discharge, the TAVI group had larger effective orifice areas than the SAVR group (1.7 cm^2 versus 1.4 cm^2, $p<0.001$ respectively).These improvements persisted through to five year follow-up.[74] However, there was evidence of a slight deterioration in effective

orifice area to 1.2 cm^2 in the SAVR group. In the STACCATO trial, the mean aortic valve area increased for both the TAVI (from 0.65±0.16 to 1.39±0.28 cm^2) and SAVR (0.71±0.17 to 1.29±0.27 cm^2) arms. Peak aortic gradient decreased significantly in both groups (TAVI from 81±26 to 20±6 mmHg, SAVR 66±23 to 24±11 mmHg).

Examining length of stay (LOS) in the NOTION trial,[75] the mean in-hospital time after the index procedure was shorter for TAVI (8.9±6.2 days versus 12.9±11.6 days; p <0.001). In the STACCATO trial the mean hospital stay was 8.8±6.7 and 7.6±2.4 days in the TAVI and SAVR groups, respectively. The difference was not statistically significant. The certainty of the evidence is moderate (Appendix E).

Aside from the reduction in NYHA class, no other generic or disease-specific quality-of-life instrument data was reported from the NOTION trial studies.[73-75] The STACCATO trial reported SF-36 outcomes before and at three months. Physical and mental health functional scores improved from baseline to three months in both the TAVI and SAVR arms. There was no difference in scores between the intervention and control arms at baseline or at three months.

Table 4.11 presents the post-operative complications reported from the mixed surgical risk population in the STACCATO and NOTION trials.

There was no statistically significant difference between TAVI and SAVR in the incidence of stroke, major vascular complications, life threatening or disabling bleeds, TIA or myocardial infarction. In the NOTION trial, TAVI was associated with a lower incidence of atrial fibrillation and increased pacemaker implantation at all time-points. At 30 days, 32% of patients in the TAVI arm had had a pacemaker implanted, compared with 1.5% in the SAVR arm.

In terms of safety, the STACCATO trial was terminated prematurely specifically because of safety concerns. There were 13 adverse events among the 34 TAVI patients, and three events among the 36 SAVR patients. Due to the small number of patients enrolled, there is limited scope for analysing the relative risk of adverse events in the TAVI arm.

Table 4.11 Safety outcomes – mixed surgical risk RCTs

Interval	Trial	TAVI		SAVR		Relative Risk Ratio (95% CI)
		Total	Events	Total	Events	
Stroke						
30 days	NOTION	142	2	134	4	0.47 [0.09-2.53]
	STACCATO	34	3	36	1	3.18 [0.35-29.07]
1 year	NOTION	142	4	134	6	0.63 [0.18-2.18]
2 years	NOTION	142	5	134	7	0.67 [0.22-2.07]
5 years	NOTION	142	13	134	10	1.23 [0.56-2.70]
Major vascular complications						
30 days	NOTION	142	8	134	2	3.72 [0.80-17.22]
Atrial Fibrillation						
30 days	NOTION	142	24	134	77	0.29 [0.20-0.44]
1 year	NOTION	142	30	134	79	0.36 [0.25-0.51]
2 years	NOTION	142	32	134	80	0.38 [0.27-0.53]
5 years	NOTION	142	35	134	82	0.40 [0.29-0.55]
New Permanent Pacemaker Implantation (NPMI)						
30 days	NOTION	142	46	134	2	21.7 [5.37-87.66]
1 year	NOTION	142	51	134	3	16.04 [5.13-50.17]
2 years	NOTION	142	55	134	5	10.38 [4.29-25.14]
5 years	NOTION	142	58	134	10	5.47 [2.92-10.26]
Life threatening or disabling bleed						
30 days	NOTION	142	16	134	28	0.54 [0.31-0.95]
	STACCATO	34	1	36	1	1.06 [0.07-16.27]
Trans Ischaemic Attack (TIA)						
30 days	NOTION	142	2	134	0	4.71 [0.23-97.40]
	STACCATO	34	1	36	0	5.17 [0.20-2166]
1 year	NOTION	142	3	134	2	1.42 [0.24-8.34]
2 years	NOTION	142	8	134	4	1.86 [0.57-6.04]
5 years	NOTION	142	9	134	5	1.70 [0.58-4.94]
Myocardial Infarction (MI)						
30 days	NOTION	142	4	134	8	0.47 [0.15-1.53]
1 year	NOTION	142	5	134	8	0.59 [0.20-1.76]
2 years	NOTION	142	7	134	8	0.83 [0.31-2.21]
5 years	NOTION	142	11	134	11	0.94 [0.42-2.10]

Registry studies – safety outcomes

The safety outcomes for patients at mixed (low and intermediate) surgical risk were reported in one prospective national registry study.[78] The results of the

comparative safety review of registry studies are reported in Appendix D. In-hospital results from Fujita et al (2019) suggested an increased risk of stroke, AF, NPMI and aortic valve regurgitation for the TAVI group compared with the SAVR group. However, it should be noted that the characteristics of the patient groups (in terms of age, gender, STS-PROM, and multimorbidity) were markedly different between the TAVI and SAVR groups. As the authors did not conduct a propensity score matching analysis of the cohorts, it was not possible to assess differences in safety outcomes.

4.4 Discussion

The assessment of effectiveness is based on ten studies that report on six unique RCTs, with a total of 6,596 patients. All participants were patients with symptomatic severe aortic valve stenosis. Trials were classified according to the risk profile of the patient population: low, intermediate, or mixed low and intermediate risk. The baseline characteristics of age and gender were similar for the intermediate and mixed-risk cohorts, while the low risk trials contained younger patients. Publications based on registry data were also included to identify additional safety data. However, it was apparent that patients who had undergone TAVI tended to be systematically different in terms of age, gender and multimorbidity such that comparisons were only valid on the basis of propensity score matched groups.

Five different TAVI devices were used in the trials. In the SURTAVI and Evolut Low Risk trials,[20, 72] there were multiple devices used in differing proportions with the choice of valve type and size at the discretion of the participating surgeon or interventional cardiologist. The evolution of the TAVI systems over time has led to the newer generation valves being included in the most recent RCTs; this is also true for the PARTNER trials with SAPIEN XT used in the intermediate risk patients,[70, 76] and the newer SAPIEN 3 used in low risk patients.[19] Incremental innovation to the TAVI system overtime has impacted on the TAVI procedure, and trials involving early versions of the device are likely to have less applicability than trials using the current generation devices. Of the TAVI patients across the six RCTs, 59% received TAVI with a first generation device. Hence there may be concerns that the trial results are more representative of TAVI based on devices that are no longer marketed.

In the intermediate risk group, based on moderate certainty of evidence, there was no difference in effect between TAVI and SAVR in terms of all-cause and cardiac mortality from 30 days to two year follow-up.[70, 72] Based on NYHA classification, both TAVI and SAVR are associated with a substantial improvement in symptoms from baseline with no observable difference in effect between the two groups at one or two year follow-up. There was a higher proportion of aortic valve reintervention in the TAVI group than in the SAVR group at 30 day and two year follow-up.[70, 72] The

difference was statistically significant in the SURTAVI trial but not the PARTNER 2 trial. It is important to note that the SURTAVI trial predominantly used the CoreValve device (84%), which is a first generation device that is no longer marketed. Based on moderate certainty of evidence, TAVI is associated with a reduced length of hospital stay compared with SAVR.[70, 72] TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (one to three months from baseline) for intermediate risk patients, but it is of low certainty whether TAVI has any effect on improving HRQoL symptoms compared with SAVR at one or two year follow-up.[72, 76] TAVI was associated with a higher rate of major vascular complications in both trials and a lower incidence of atrial fibrillation at 30 days. The rate of new pacemaker implantation was significantly higher for TAVI patients in the SURTAVI trial.

In the low risk group, based on low and moderate certainty of evidence, no difference in effect was found between TAVI and SAVR in terms of all-cause mortality at 30 days, one, two and five year follow-up. TAVI was also found to be non-inferior to SAVR in terms and cardiac mortality and aortic valve reintervention at 30 days and one year follow-up. Consistent with the intermediate risk group, based on NYHA classification, both TAVI and SAVR are associated with a substantial improvement in symptoms, with no observable difference in effect between the two groups at one year follow-up. Based on high certainty of evidence, TAVI probably reduces the duration of hospital stay compared with SAVR.[19] Also consistent with the intermediate surgical risk group, and based on evidence of moderate certainty, TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (30 days from baseline), while it is uncertain whether the effect is sustained at one year follow-up. TAVI was associated with a reduced incidence of atrial fibrillation ate 30 days and one year.

In the mixed-risk (low to intermediate surgical risk) group, based on moderate certainty of evidence, there is no difference between TAVI and SAVR in terms of all-cause and cardiac mortality from 30 days to six year follow-up. There was also no difference in cardiac mortality. Both TAVI and SAVR are associated with a substantial improvement in symptoms according to the NYHA classification, with no observable difference in effect between the two groups at one and two years follow-up.[73] Based on moderate certainty of evidence, TAVI probably reduces the duration of hospital stay compared with SAVR.[75] In relation to safety, in a mixed low and intermediate risk population TAVI was associated with reduced incidence of atrial fibrillation and life threatening or disabling bleeds. TAVI was associated with increased new pacemaker implantation.

Of interest, the haemodynamic function of the aortic valves in both the TAVI and SAVR arms demonstrated consistent and durable improvements in aortic pressure

gradient, aortic orifice area and LVEF in all the included studies across all observed risk groups.[19, 20, 70, 72-75] All the results favoured TAVI, with the exception of the PARTNER 3 trial in low risk patients which reported fractionally better results in the SAVR group to one year.[19]

Overall, the studies appear to report consistent findings of no difference across the efficacy outcomes for TAVI versus SAVR in the included trials. These findings are consistent with the results of earlier trials that found TAVI to be non-inferior to SAVR in those at high surgical risk or inoperable.[37, 81-83]

Differences between TAVI and SAVR were observed for selected safety outcomes. In low and mixed low and intermediate risk populations, TAVI was associated with a lower incidence of atrial fibrillation. For the intermediate risk population there was a finding of decreased incidence at 30 days, and at one and two year follow-up. TAVI may be associated with a higher rate of new pacemaker insertion, although the findings are inconsistent across risk groups. It is important to note the very substantial variation in absolute rates of pacemaker insertion across trials. Rates in the SAVR arms range from 1.5% to 6.7%, while rates in the TAVI arm range from 6.5% to 32.4% with no apparent correlation between the two. While it is likely that the rate of pacemaker insertion is higher in TAVI patients, the magnitude of the increase may be dependent on a variety of factors including characteristics of the patient population and local clinical practice, although there was little variation in pacemaker insertion rates across the SAVR trial arms. The highest rates of pacemaker insertion were highest in trials that were entirely or predominantly based on first generation devices. The rates of pacemaker insertion were low in the TAVI arms of the PARTNER 2 and PARTNER 3 trials, both of which used SAPIEN devices. Data on device durability was limited to the low surgical risk population in the NOTION trial. The evidence suggests that durability may be similar for TAVI and SAVR valves.

There was inconsistent use of imaging for patient selection and valve sizing, within and between the trials, which may have had an impact on patient outcomes. For example, echocardiography was used exclusively to assess aortic valve sizing for the NOTION trial; while computed tomography imaging was more commonly available in the more recent trials of the low and intermediate risk patients. The different valve types may also influence outcomes. While this review focused on TAVI versus SAVR, studies have compared balloon- and self-expandable valves.[84, 85] While early findings suggested greater device success for balloon-expandable valves, there was no difference in outcomes at one year follow-up. Changes to device design also mean that comparisons of early generation devices may have limited applicability to current generation devices. Future larger studies on TAVI in the lower risk populations will assist in definitively determining non-inferiority of the treatment

effect of TAVI versus SAVR in selected outcomes (e.g. aortic valve reintervention).The RCTs in the intermediate risk populations were non-inferiority trials,[70, 72, 76] while those in the low risk populations were powered for both superiority and non-inferiority. However, the NOTION 'superiority' trial may have been under-powered to detect differences between the two interventions or for sub-group analyses.[73] The SURTAVI and Evolut Low Risk trials were conducted as Bayesian interim analyses when a percentage of participants had reached 12 month follow-up, but complete 12 or 24 month follow-up of the cohort was not attained by the study authors.[20, 72] Therefore, it was necessary to exclude the one year data reported from the Evolut Low Risk trial.[20] The manufacturer provided completed follow-up data to validate the interim two year results from the SURTAVI trial (Reardon et al, 2017).[72] For consistency in comparison of the efficacy outcome results, the intention-to-treat population is used for the intermediate risk trials, and the as-treated population is used in the low and mixed-risk trials.

Transfemoral delivery of the valve was preferred in the included trials (76-100%) with the exception of the STACCATO trial, which specifically used transapical TAVI. Based on the data reported by the registry studies, transapical access is used in approximately 20% of cases ordinarily. Overall, the heterogeneity of studies by population risk type, and the differences in TAVI device type, size, mechanism of implantation and access route, limited the merits of quantitatively pooling the retrieved data in a meta-analysis. For the evidence synthesis and interpretation of the RCTs, the trials results were left unpooled and categorised by risk group for the systematic review. All trial studies reported on primary outcomes of composite efficacy and safety endpoints, with the exception of the study on the health status benefits of the interventions in PARTNER 2.

There are limitations to the interpretation of the evidence presented for the efficacy of TAVI in low and intermediate risk patients. The exclusion of patients with co-morbidities, such as coronary artery disease, recent cardio-vascular accident or transient ischaemic attack (TIA), or congenital bicuspid valve anatomy from the trials limits the transferability of the findings to typical TAVI patients in a real-world setting, who are likely to be aged 70 years and older and have multimorbidity. The categorisation of surgical risk was presented on the basis of risk scores, which may not adequately capture surgical risk and does not directly correspond to the process used to categorise patients in clinical practice. The included trials were focused on experienced treatment centres and operators of the TAVI system. The technological advancement of TAVI, with newer versions of the original device being used in later trials, limits the ability to interpret the comparison of trial results. Future studies are needed to confirm whether the observed heterogeneity across the trials was related

to the TAVI device and system, the treatment centre and/or the operator of the TAVI system.

The included studies were generally powered for non-inferiority or superiority based on a composite outcome. For less common outcomes or for outcomes where the effect size may be small, the prospect of observing an effect is limited. The number of outcomes considered and number of time-points for which they were measured raises the issue of multiple testing and possibility of observing effects by chance. There were a select number of outcomes for which a consistent effect or lack of effect was observed in some or all risk groups. For example, an increased incidence of major vascular complications was observed in intermediate surgical risk patients receiving TAVI. In some cases no statistically significant effect was observed but there was a consistency in the magnitude and direction of effect (e.g., reduced incidence of disabling stroke in intermediate surgical risk patients receiving TAVI) that suggest an appropriately powered trial may detect a difference. Ordinarily the lack of power in an individual trial can be partly overcome by combining trials in a meta-analysis. However, the differences across trials in terms of patients, devices used, local practice and limited number of available trials meant that pooling of data was considered inappropriate in this case.

Strengths of the review include the high level of agreement between both independent reviewers in producing a transparent assessment of the quality and certainty of the evidence. It is necessary to acknowledge that some of the certainty around the evidence reported was categorised as 'low' or 'moderate', and the use of GRADEpro can be criticised as subjective. The majority of the trials identified in the review are sponsored or funded by TAVI device manufacturers. This was flagged as an unclear risk of bias under 'other biases'. However, these trials tended to be international, multi-centre trials with sizeable population numbers. The majority of studies can be classified as having 'low' or 'unclear' risk of bias for the seven risk of bias domains. The unblinded nature of the studies may have contributed to a high risk of performance bias, and also detection bias for subjective outcomes.

4.5 Key messages

- A systematic review was carried out to identify relevant studies of TAVI in the treatment of patients with severe symptomatic aortic stenosis at low and intermediate surgical risk.
- Ten studies of six unique RCTs were included in the review of clinical effectiveness. These studies were published between 2015 and 2019, and included 6,596 patients of low or intermediate surgical risk (or no pre-specified surgical risk in the NOTION trial). Three registry studies were found to provide

additional data on safety outcomes.

- In terms of patients at intermediate surgical risk:
  - The available evidence is almost entirely based on first generation TAVI devices.
  - TAVI is non-inferior to SAVR in terms of all-cause and cardiac mortality from 30 days to two year follow-up.
  - TAVI is associated with a reduced average length of stay of between 3 and 4 days.
  - TAVI may be associated with an increased risk of aortic valve reintervention (AVR) compared with SAVR although the certainty of evidence is low.
  - TAVI is associated with increased incidence of major vascular complications.
  - For improvement in symptoms (NYHA classification), there was no observable difference in effect between the two interventions at one or two year follow-up.
  - TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (one to three months from baseline) although it is uncertain whether differences persist over the longer term.
- In terms of patients at low surgical risk, compared to SAVR:
  - The available evidence is almost entirely based on second generation TAVI devices.
  - TAVI is non-inferior to SAVR in terms of all-cause and cardiac mortality and aortic valve reintervention from 30 days to one year follow-up.
  - TAVI is associated with a reduced average length of stay of four days.
  - TAVI is associated with reduced incidence of atrial fibrillation and life threatening or disabling bleeds.
- For patients at either low or intermediate surgical risk:
  - The available evidence is based on first generation TAVI devices.
  - There was no observable difference in effect between TAVI and SAVR for improvement in symptoms (NYHA classification) at one or two year follow-up.
  - TAVI is associated with a higher rate of new permanent pacemaker insertion compared with SAVR.
  - TAVI is associated with shorter length of hospital stay compared with SAVR.
- While the risk of bias was generally rated as ‘low’ or ‘unclear’, the certainty of the evidence for the outcomes under review was rated as ‘low’ or ‘moderate’.

5 Systematic review of economic evaluations

The aim of this chapter is to summarise the available international evidence on the cost-effectiveness of TAVI compared to SAVR in patients at low or intermediate risk of surgical complications, and to assess the applicability of the evidence to inform an assessment of cost-effectiveness in Ireland.

5.1 Methods

5.1.1 Search strategy

A systematic review was undertaken to investigate the evidence on the cost-effectiveness of TAVI versus SAVR in patients at low or intermediate risk. A search string was developed to identify relevant studies. This comprised key words pertaining to the epidemiology of aortic stenosis, TAVI, SAVR, and economic evaluation. The search of electronic databases was conducted from 01/01/2013 (before the first clinical trial of TAVI among intermediate risk patients was published) until 28/06/2019. The following databases were searched: PubMed, Embase, the Cochrane Library, and the University of York Centre for Reviews and Dissemination (CRD) database, which included the Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS EED), and HTA database (see Appendix F for further details of the electronic searches). A grey literature search was also conducted and Scopus was searched to identify any relevant papers that were not captured by either the electronic or grey literature search.

5.1.2 Criteria for the inclusion and exclusion of studies

Table 5.1 outlines the population, intervention, comparator, outcome, and study design (PICOS) criteria for the selection of studies.

Table 5.1 Inclusion criteria for the review of cost-effectiveness studies

Population	Patients with aortic stenosis at low or intermediate risk of surgical complications
Intervention	Transcatheter aortic valve implantation / replacement (TAVI / TAVR)
Comparator	Surgical aortic valve replacement (SAVR)
Outcomes	Any measure of costs and benefits (for example, utilities or relevant health outcome)
Study Designs	Economic evaluations (for example, cost-utility analysis or cost-effectiveness analysis)

The following exclusion criteria were applied:

- studies based on patients at high surgical risk
- studies in which TAVI was not the intervention
- studies that compared TAVI against procedures other than SAVR (for example, medical management)
- cost-consequence analysis, cost-benefit analysis, or other types of cost analyses and comparative resource use studies.

5.1.3 Data extraction and management

Titles and abstracts retrieved from the electronic searches were downloaded and stored in Covidence. References obtained from the grey literature search were added to the database and duplicates were removed. Citations were independently screened by one reviewer, per the inclusion and exclusion criteria. Full-texts were then reviewed by two reviewers.

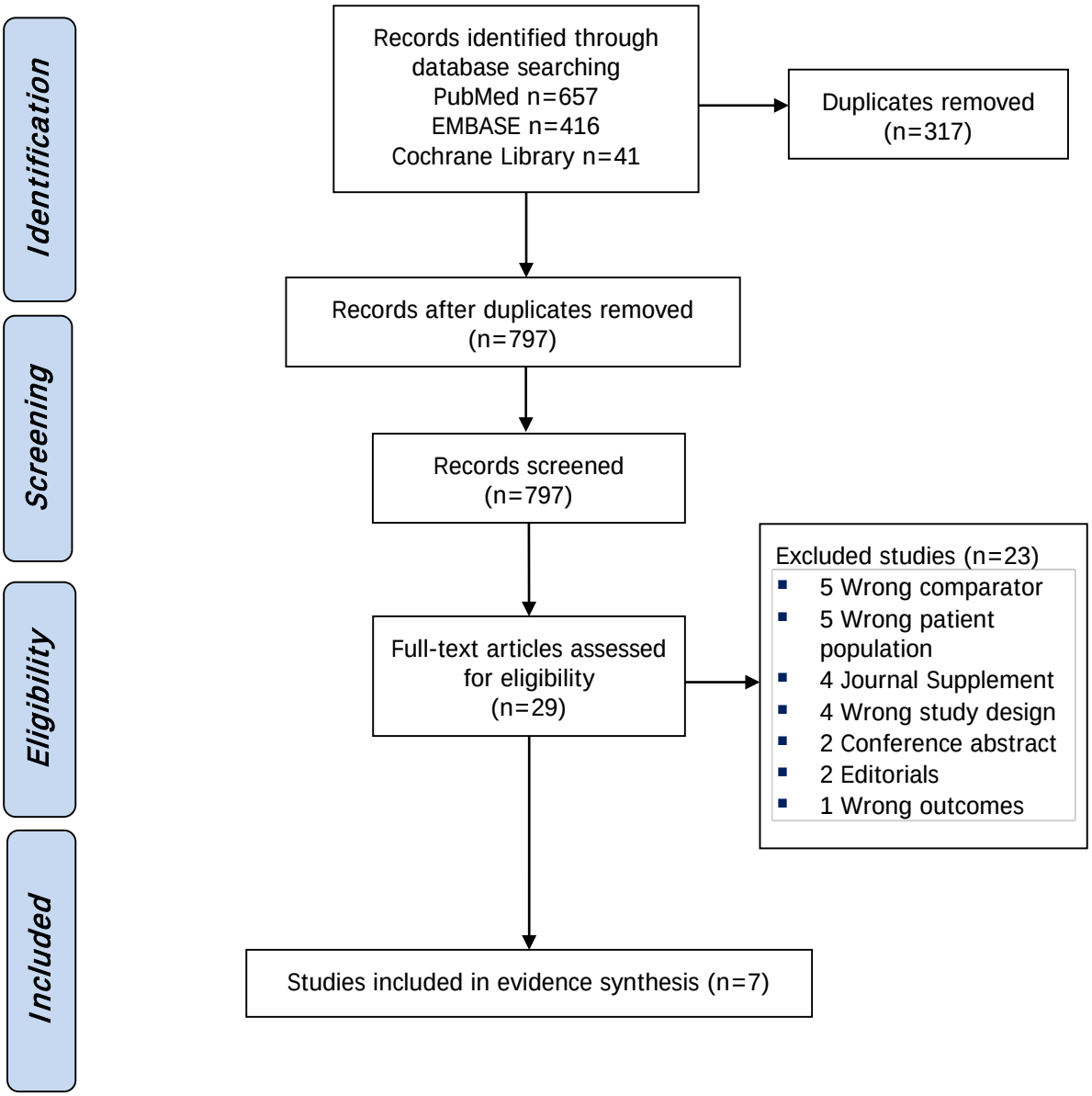
Data were extracted using standardised data extraction templates by two reviewers independently. The quality of the studies was assessed by two reviewers using the Consensus on Health Economic Criteria (CHEC) list[86] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire.[87] The CHEC list assesses the methodological quality of economic evaluations in a systematic review, and the ISPOR questionnaire assesses the relevance, or applicability, and credibility of modelling studies. Disagreements were resolved by discussion, or a third reviewer if necessary

5.2 Results

The PRISMA flow chart of the systematic search is presented in Figure 5.1. The electronic search returned 797 records for title and abstract screening, after duplicates were removed. An additional study was obtained from the grey literature search that had not yet been indexed in any electronic database due to being “in press” (that is, not yet published or indexed in any relevant online library or database). Thirty full-text articles were assessed for eligibility, of which seven[88-94] met the inclusion criteria for this systematic review.

An overview of the included studies is provided in section 5.2.1. A critique on the quality of the evidence is presented in section 5.2.2, and the applicability of the

Figure 5.1 Flow chart: studies identified and included in the systematic review of cost-effectiveness



findings to Ireland is discussed in section 5.2.3. Throughout this chapter, original cost data from the included studies are presented, with Irish-equivalent 2018 prices, adjusted for inflation and purchasing power parity, reported in parentheses.[95]

5.2.1 Overview of studies

Study characteristics

The key characteristics of the seven studies are presented in Table 5.2. Two of the

Table 5.2 Characteristics of economic evaluations included in the systematic review

Study	Setting	Surgical risk category	TAVI device	Access route	Study design	Outcome measure	Analysis type
Baron et al. (2019)	US	Intermediate (STS-PROM)	SAPIEN XT (Edwards), SAPIEN 3 (Edwards)	Transfemoral & transthoracic	CUA	Cost / QALY	Within-trial economic analysis & Markov model
Goodall et al. (2019)	France	Intermediate (STS-PROM)	SAPIEN 3 (Edwards)	Transfemoral & transthoracic	CUA	Cost / QALY	Markov model
Kaier et al. (2019)	Germany	Intermediate (EuroSCORE I)	All devices	Transfemoral	CEA	Cost / life saved	Secondary data analysis
Kodera et al. (2018)	Japan	Intermediate (STS-PROM)	SAPIEN XT (Edwards)	Transfemoral	CUA	Cost / QALY	Markov model
Tam et al. (2018a)	Canada	Intermediate (STS-PROM)	SAPIEN XT (Edwards)	Transfemoral & transthoracic	CUA	Cost / QALY	Markov model
Tam et al. (2018b)	Canada	Intermediate (STS-PROM)	CoreValve / Evolut R (Medtronic)	Transfemoral & transthoracic	CUA	Cost / QALY	Markov model
Zhou et al. (2019)	Australia	Intermediate (STS-PROM)	SAPIEN 3 (Edwards)	Transfemoral & transthoracic	CUA	Cost / QALY	Markov model

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; QALY — quality-adjusted life year; SAVR – surgical aortic valve replacement; STS-PROM – The Society of Thoracic Surgeons Predicted Risk Of Mortality; TAVI – transcatheter aortic valve implantation

studies were conducted in Canada[92, 93] and one each was undertaken in Australia,[94] France,[89] Germany,[90] Japan,[91] and the US,[88] respectively. The studies evaluated outcomes for patients at intermediate risk of surgical complications only (that is, no study looked at the cost-effectiveness of TAVI versus SAVR in low risk patients). With the exception of one study by Kaier et al. (2019),[90] surgical risk status was defined using The Society of Thoracic Surgeons Predicted Risk Of Mortality (STS-PROM) score. As per STS-PROM, a patient is categorised as being at intermediate risk of complications if their score (or risk of complications) is ≥4 and <8%; a score of <4% is indicative of low risk.[96] Kaier et al. (2019)[90] defined surgical risk using the EuroSCORE classification system, which uses a scoring system with similar cut-offs to define intermediate (≥4 and ≤9) and low (<4) surgical risk.[97] Across all studies, the intervention was TAVI and the comparator was SAVR. In six of the seven studies, the TAVI device was specified:

- SAPIEN XT: a first-generation balloon-expandable device, manufactured by Edwards Lifesciences, was compared in three studies[88, 91, 92]
- SAPIEN 3: a second-generation balloon-expandable device, also manufactured by Edwards Lifesciences, was evaluated in three studies [88, 89, 94]
- CoreValve (first-generation) and Evolut R (second-generation): self-expanding devices manufactured by Medtronic were compared in one study.[93]

One study, by Kaier et al. (2019),[90] did not distinguish between TAVI devices; instead, it evaluated the overall cost-effectiveness of TAVI via transfemoral access. Transfemoral access was the predominant access route evaluated in the other six studies; five of these studies[88, 89, 92-94] also considered access via the transthoracic route (using either subclavian, transapical, or direct aortic access), as determined by the trial data informing the analyses.

All studies performed a cost-utility analysis (CUA) with cost-effectiveness expressed using cost per quality-adjusted life year (QALY) gained, with the exception of one study,[90] which undertook a cost-effectiveness analysis (CEA) with outcomes expressed using cost per life saved. All of the CUAs adopted a decision-analytic framework using a Markov model to model costs and consequences; one study adopted the approach alongside a within-trial economic evaluation to project future costs and consequences beyond the trial. The CEA used secondary data from electronic health records in Germany to evaluate costs and mortality associated with TAVI and SAVR. In this study, the outcome, or incremental cost-effectiveness ratio (ICER), was calculated as the difference in risk-adjusted reimbursement and mortality between TAVI and SAVR, or cost per life saved by using TAVI over SAVR.

Cost-utility (model-based) study characteristics

The characteristics of the CUAs, or model-based studies, are presented in Table 5.3. All six studies used a probabilistic Markov model to evaluate costs and consequences and assumed a health system perspective. The models used monthly cycles, with costs and consequences modelled over varying time horizons: four adopted a lifetime time horizon,[88, 92-94] while one each adopted a 15 year[89] and a ten year[91] time horizon, respectively. The discount rate used to adjust future costs and consequences was influenced by the jurisdiction in which each study was set and ranged from 1.5% in Canada[92, 93] to 5% in Australia for both costs and effects.[94]

Studies comparing SAPIEN XT or CoreValve and Evolut R against SAVR derived clinical evidence on the effectiveness of the procedures from clinical trials. The PARTNER 2 randomised controlled trial (RCT), conducted in the US and Canada, provided information on SAPIEN XT, while clinical evidence on CoreValve and Evolut R was derived from the SURTAVI trial, which was conducted in the US, Canada, and Europe. Both trials are described in detail in Chapter 4. Briefly, the trials were unblinded non-inferiority trials on intermediate risk patients with severe symptomatic aortic stenosis. Two thousand and thirty two patients were enrolled in PARTNER 2 and randomised to SAPIEN XT (N=1,011) or SAVR (N=1,021) and followed up for two years.[70] SURTAVI randomised 1,746 patients to TAVI (N=879; 84% (n=724) and 16% (n=139) received CoreValve and Evolut R, respectively) or SAVR (N=867) and, to date, has followed them for two years.[72] Studies comparing SAPIEN 3 used observational data from PARTNER S3i on the clinical effectiveness of the device and compared it against trial data on SAVR from PARTNER 2. PARTNER S3i is a registry, or observational study, of TAVI procedures performed on 1,077 patients across multiple centres in the US.[98] Patients received SAPIEN 3 and have been followed up for one year, to date.

Broadly similar Markov model structures were adopted by each study to model patient outcomes following TAVI or SAVR. The procedure could go well, in which case patients entered an ‘alive / well’ health state, or patients could suffer a major complication, namely stroke, and enter and remain in this health state, or die. Patients in the ‘alive / well’ health state were at risk of stroke or death at any time in the model. However, some variations in this structure were observed. Tam et al. (2018a)[92] allowed patients to enter a ‘dialysis’ health state if patients previously experienced an acute kidney injury. Kodera et al. (2018)[91] grouped three major complications (stroke, myocardial infarction, and vascular complications) into one health state (‘hospitalised’), where patients recovering from any one of these events were seemingly at further risk of being hospitalised. Tam et al. (2018a and 2018b)[92, 93] included ‘rehospitalisation’ as a health state into which patients could

Table 5.3 Characteristics of model-based economic evaluations

Study	Cycle length	Time horizon	Discount rate	Source of clinical evidence	Health states	Complications modelled	
						At 30 days	Beyond 30 days
Baron et al. (2019)	Not reported	Lifetime	3%	PARTNER 2 & PARTNER S3i	Not reported	Not reported	Not reported
Goodall et al. (2019)	Monthly	15 years	4%	PARTNER S3i	• Alive / well • History of stroke • Death*	• Acute kidney injury • Atrial fibrillation • Endocarditis • Hospitalisation • Stroke • Major bleeding • Major vascular injury • Myocardial infarction • Pacemaker • Transient ischaemic attack	Same as at 30 days
Kodera et al. (2018)	Monthly	10 years	2%	PARTNER 2	• Stable • Hospitalised • Death	• Myocardial infarction • Stroke • Vascular complications	Same as at 30 days
Tam et al. (2018a)	Monthly	Lifetime	1.5%	PARTNER 2	• Alive / well • History of stroke • Dialysis • Death	• Acute kidney injury • Atrial fibrillation • Major bleeding • Stroke† • Rehospitalisation • Vascular injury	• Dialysis • Disabling stroke • Rehospitalisation
Tam et al. (2018b)	Monthly	Lifetime	1.5%	SURTAVI	• Alive / well • History of stroke • Hospitalisation • Death	• Acute kidney injury • Atrial fibrillation • Cardiogenic shock • Major bleeding • Stroke† • Pacemaker • Rehospitalisation • Vascular injury	• Disabling stroke • Rehospitalisation

Table 5.3 Characteristics of model-based economic evaluations

Study	Cycle length	Time horizon	Discount rate	Source of clinical evidence	Health states	Complications modelled	
						At 30 days	Beyond 30 days
Zhou et al. (2019)	Monthly	Lifetime	5%	PARTNER S3i	• Alive / well • History of stroke • Death	• Acute kidney injury • Atrial fibrillation • Major bleeding • Moderate/severe paravalvular leak • Myocardial infarction • Pacemaker • Stroke • Vascular injury	• Stroke

Note: All studies assumed a health system perspective in their analysis
* Although Goodall et al. (2019) reported modelling outcomes by NYHA class, the authors seemingly used this structure due to limited data by NYHA class
† Includes disabling and non-disabling stroke

transition in and out of for a period of one cycle at any time during the model. Goodall et al. (2019)[89] reported modelling transitions to death by patients' New York Heart Association (NYHA) classification,[99] but seemingly adopted a simpler structure due to limited data for NYHA class III and IV.

Although the structure of the Markov models was broadly comparable in each study, vast differences in the range of postoperative complications modelled at 30 days were observed. Stroke and vascular complications were modelled in all five studies[89, 91-94] reporting clinical events; acute kidney injury, atrial fibrillation, and major bleeding were modelled in four studies[89, 92-94]; and myocardial infarction, new pacemaker insertion, and rehospitalisation were modelled in three studies.[89, 92, 93] Separately, cardiogenic shock,[93] endocarditis,[89] paravalvular leak,[94] and transient ischaemic attack[89] were modelled in four studies. Yet, all of these complications were captured in PARTNER 2, PARTNER 3Si, and SURTAVI (with the exception of endocarditis, which was not captured in SURTAVI, and transient ischaemic attack, which was aggregated with stroke). Excluding stroke, some variation in the modelling of longer-term complications was observed; Kodera et al. (2018)[91] modelled myocardial infarction and vascular complications beyond thirty days; Tam et al. (2018a)[92] modelled dialysis; and Tam et al. (2018a and 2018b)[92, 93] modelled rehospitalisation. Goodall et al. (2019)[89] additionally modelled the same complications at one year as at 30 days, although it is unclear from the paper whether the authors adjusted the rate of complications at one year to avoid double-counting events that occurred at 30 days.

Beyond the observed trial/registry data (two years in PARTNER 2 and SURTAVI and one year in PARTNER S3i), each study appropriately assumed the rate of complications was the same in patients that received TAVI as SAVR as there was no evidence to suggest that these further differed by treatment strategy. All-cause mortality specific to each jurisdiction also replaced observed all-cause mortality from the trials/registry in each study, with the exception of Goodall et al. (2019),[89] who extrapolated these data until all patients died in their model.

Baron et al. (2019)[88] provided no information on model structure; the different health states included in their Markov model; or, the range of complications modelled.

Estimating costs and consequences

Somewhat similar approaches to costing TAVI and SAVR were undertaken in the model-based economic evaluations. Tam et al. (2018a and 2018b)[92, 93] micro-costed the TAVI/SAVR procedure by valuing the cost of the device, length of stay following the procedure, resource use in terms of physician fees, and other cost

inputs, for example angiogram and percutaneous angioplasty. The cost of the TAVI and SAVR valves were derived from device manufacturers, estimated at $24,000 (€15,003) for SAPIEN XT, $22,000 (€13,753) for CoreValve or Evolut R, and $6,000 (€3,750) for SAVR. The cost of postoperative complications was estimated using Case Mix Groupings, or hospital cost data. Zhou et al. (2019)[94] followed a similar approach to costing TAVI and SAVR. The authors used list prices in Australia to assign a unit cost to the TAVI ($22,932 [€12,479]) and SAVR valve ($6,858 [€3,732]), and separately estimated the cost associated with length of stay following the procedure, derived from PARTNER 3Si,[98] but excluded the cost of other resource use items, such as physician fees and angiogram or angioplasty. Complication costs were derived from Australian Diagnostic-Related Group (DRG) codes. Procedural costs estimated by Kodera et al. (2018)[91] similarly included the cost of the device, along with hospital and material costs; however, the authors provided little information on the cost or source of these data. The authors estimated that the SAPIEN XT valve cost ¥4,530,000 (€35,217) in Japan, while the overall cost of the procedure was estimated at ¥6,000,000 (€46,646). The cost of the SAVR valve was not reported, but the overall cost of the procedure was estimated at ¥4,500,000 (€34,985). Kodera et al. (2018)[91] derived complication costs from a previous economic evaluation in Japan.

In contrast, Goodall et al. (2019)[89] used hospital cost data on index hospitalisation and cardiac rehabilitation to estimate a weighted mean cost of a typical TAVI (€27,154 [€28,130]) and SAVR (€25,564 [€26,482]) admission. As the cost of the TAVI valve is excluded from hospital tariffs in France, the cost of the device, valued at its 2016 published price, was added to the overall cost of admission; however, the authors did not report the price of the valve in their paper. Additionally, the authors applied the cost of postoperative complications using hospital cost data in the event that these occurred. It is unclear, however, whether these costs were already captured in the cost of the index hospitalisation, suggesting some costs may have been double-counted.

Baron et al. (2019)[88] used within-trial patient data on resource use associated with the procedure (in terms of the cost of the valve, length of stay, and other consumables), and subsequent complications (during the trial period), but provided no information on the value assigned to these inputs. The overall procedural costs associated with SAPIEN XT, SAPIEN 3, and SAVR were reported and estimated at $61,433 (€49,960), $54,256 (€44,124), and $58,545 (€47,612), respectively.

Unlike the model-based studies, Kaier et al. (2019)[90] evaluated the additional reimbursement cost per life saved by using TAVI over SAVR. As the authors were simply interested in the cost per hospital activity (that is, the cost paid to hospitals

per procedure), they used German DRGs to assign costs to TAVI (€33,614 [€36,509]) and SAVR (€19,175 [€20,826]).

Utility estimates used in the model-based economic evaluations largely derived from related RCTs/registry data on TAVI and SAVR. In the case of SAPIEN 3, Goodall et al. (2019)[89] and Zhou et al. (2019)[89] derived appropriate utility estimates from PARTNER S3i on intermediate risk patients, reported in Baron et al. (2018).[100] Baron et al. (2019)[88] similarly used these data in their within-trial economic evaluation of the device, along with data from PARTNER 2 in their evaluation of SAPIEN XT.[76] However, the other studies on SAPIEN XT by Kodera et al. (2018)[91] and Tam et al. (2018a),[92] and CoreValve and Evolut R by Tam et al. (2018b),[93] used utility estimates for high risk patients, derived from the PARTNER 1a trial, reported in Reynolds et al. (2012),[101] and the CoreValve US High Risk Pivotal trial, reported in Arnold et al. (2015),[102] respectively, which had inherently low utility estimates given the population's advanced age, for example. Curiously, appropriate utility estimates for intermediate risk patients were available for SAPIEN XT from PARTNER 2, as reported in Baron et al. (2017).[76] These values were higher than the utility values observed in high risk patients, suggesting different findings may have been obtained had appropriate utility estimates been used in these studies.

Utilities and utility decrements associated with health states (for example, stroke) and postoperative complications were derived from published sources in each study.

In the CEA, Kaier et al. (2019)[90] used in-hospital mortality following TAVI/SAVR in 2015 as their outcome, and obtained these data from electronic health records in Germany.

Summary of findings

The cost-effectiveness findings from all seven studies included in this systematic review are presented in Table 5.4. In most cases, the cost-effectiveness of TAVI was supported.

All studies found TAVI was more favourable than SAVR in terms of the effectiveness of the device: the CUAs found TAVI generated higher QALY gains than SAVR, while the CEA found TAVI was associated with significantly lower in-hospital mortality than SAVR. The SAPIEN 3 valve performed the best in terms of relative QALY gains versus SAVR. The device was also associated with lower overall costs versus SAVR, despite having higher procedural costs in one study, by Goodall et al. (2019).[89] SAPIEN 3 was subsequently determined to dominate SAVR in these studies; an intervention is said to dominate another if it is less costly and more effective. The

Table 5.4 Cost-effectiveness findings of included studies

Study	TAVI / SAVR	Procedural costs*	Total costs*	QALYs	ICER†
Baron et al. (2019)	SAPIEN XT	$61,433 (€49,960)	$227,363 (€184,902)	5.16	Dominant
	SAVR	$58,545 (€47,612)	$235,312 (€191,367)	5.01	
	SAPIEN 3	$54,256 (€44,124)	$231,179 (€188,006)	5.29	Dominant
	SAVR	$58,410 (€47,502)	$240,871 (€195,888)	5.01	
Goodall et al. (2019)	SAPIEN 3	€27,154 (€28,130)‡	€34,157 (€35,384)	4.06	Dominant
	SAVR	€25,564 (€26,482)	€34,596 (€35,839)	3.65	
Kaier et al. (2019)	TAVI	€33,614 (€36,509)	€33,614 (€36,509)	2.07%◇	€1,486,118 (€1,614,088) / life saved
	SAVR	€19,175 (€20,826)	€19,175 (€20,826)	2.65%◇	
Kodera et al. (2018)	SAPIEN XT	¥6,000,000 (€46,646)	¥8,039,694 (€62,504)	4.81	¥7,523,821 (€58,493) / QALY
	SAVR	¥4,500,000 (€34,985)	¥6,316,178 (€49,104)	4.59	
Tam et al. (2018a)	SAPIEN XT	$40,274 (€26,248)	$46,904 (€30,569)	5.63	$46,083 (€30,034) / QALY
	SAVR	$29,856 (€19,458)	$36,356 (€23,695)	5.40	
Tam et al. (2018b)	CoreValve/ Evolut	$39,753 (€25,909)	$44,299 (€28,872)	6.42	$76,736 (€50,012) / QALY
	SAVR	$27,918 (€18,195)	$32,994 (€21,504)	6.28	
Zhou et al. (2019)	SAPIEN 3	$41,615 (€22,645)	€50,515 (€27,488)	4.13	Dominant
	SAVR	$47,384 (€25,784)	€60,144 (€32,728)	3.82	

* Irish-equivalent 2018 prices are presented in parentheses, adjusted for inflation and purchasing power parity, where applicable
† Versus SAVR
‡ Plus the cost of the device, which was not made available by the authors
◇ Risk-adjusted in-hospital mortality
Key: ICER – incremental cost-effectiveness ratio; QALY — quality-adjusted life year; SAVR – surgical aortic valve replacement; TAVI – transcatheter aortic valve implantation

SAPIEN XT valve dominated SAVR in one study by Baron et al. (2019),[88] who found the device was less costly overall versus SAVR, despite having higher procedural costs. In Tam et al. (2018a)[92] and Kodera et al. (2018),[91] SAPIEN XT was shown to have both higher procedural and overall costs, leading to ICERs of $46,083 (€30,034) and ¥7,523,821 (€58,493), respectively. Kodera et al. (2018)[91] concluded that the device was not likely to be cost-effective in Japan as the associated ICER exceeded the commonly used willingness-to-pay threshold of ¥5,000,000 (€38,872) per QALY gained. Tam et al. (2018a), on the other hand, concluded that SAPIEN XT was likely to be cost-effective in Canada as it fell below the commonly used WTP threshold of $50,000 per QALY gained. The CoreValve and Evolut R device performed the least well in terms of relative QALY gains, leading to a considerably high ICER. Tam et al. (2018b)[93] found the device was associated with an ICER of $76,736 (€50,012), which reflects only intermediate economic value in Canada. The authors subsequently concluded the device was likely cost-effective.

With respect to the CEA, Kaier et al. (2019)[90] found that although TAVI was associated with significantly lower in-hospital mortality, the additional reimbursement due to TAVI was considerable, leading to an ICER of €1,486,118 (€1,614,088) per life saved. The authors concluded TAVI was less cost-effective in this population of intermediate risk patients than what was observed in high risk patients, for example, or adults aged over 85.

In the model-based studies, the findings were often sensitive to changes in key parameter inputs.

Kodera et al. (2018)[91] found that an increase in mortality following TAVI at one year from 7.6% in the base case analysis to 8.2% in a scenario analysis adversely affected the ICER. At the higher rate, TAVI had an ICER of ¥56,528,188 (€439,471). The ICER improved, however, in certain scenarios; for instance, an extension in the time horizon from 10 to 15 or 20 years improved the cost-effectiveness of the device, while a reduction in procedural costs from ¥6,000,000 (€46,646) to ¥5,427,439 (€42,194) brought the ICER below the commonly used WTP threshold of ¥5,000,000 (€38,872).

Tam et al. (2018a)[92] found the results were sensitive to variations in similar input parameters. For example, the authors found that a moderate increase in the rate of mortality or stroke following TAVI increased the ICER to above a $50,000 (€32,587) per QALY WTP threshold. A modest increase (<5%) in the cost of the SAPIEN XT valve from $24,000 (€15,642) to $25,000 (€16,294) also pushed the ICER above $50,000 per QALY. The ICER improved, however, when the population was

restricted to those that received the device via transfemoral access only, due to a modest improvement in QALY gains.

Tam et al. (2018b)[93] found that the ICER of TAVI versus SAVR increased (that is, became less cost-effective) when the cost of the surgical valve was reduced; however, TAVI was considered cost-effective at a WTP threshold of $50,000 (€32,587) per QALY if the cost of the CoreValve and Evolut R system was reduced by 21% from $22,000 (€14,338) to $17,397 (€11,338). The authors also found that under no circumstances did the ICER fall below $50,000 per QALY when mortality and complications were varied within tested ranges.

Goodall et al. (2019)[89] found their results were robust to changes in the discount rate, time horizon, and rehospitalisation rate, among other input parameters. However, the authors found that SAPIEN 3 was no longer dominant when TAVI admission costs were held at their extreme value, but had an ICER of €27,263 (€28,242). Similarly, when SAVR admission costs were held at their lowest value, SAPIEN 3 was not dominant and had an ICER of €18,737 (€19,410). Whether TAVI may be considered cost-effective in these scenarios is unclear as there is no stated WTP threshold against which the cost-effectiveness of interventions can be compared in France.

Zhou et al. (2019)[94] performed a range of scenario analyses that involved lowering the discount rate, shortening the time horizon, and limiting the population to patients that received the TAVI device via transfemoral access only. Under all scenarios, SAPIEN 3 remained dominant. The authors repeated the same scenario analyses but with a 50% inflated cost of the valve. In each scenario, SAPIEN 3 was no longer dominant, but remained cost-effective at a WTP threshold of $50,000 (€27,208) per QALY.

Baron et al. (2019)[88] found their results were relatively insensitive to variations in the discount rate (0-5%), cost of the SAPIEN 3 valve ($25,000-$35,000 [~€20,000-€28,000]), late mortality associated with TAVI (at an increased hazard ratio of 1.20), and inclusion of excess mortality associated with moderate/severe paravalvular regurgitation following TAVI (hazard ratio of 1.585). When annual follow-up costs for TAVI were increased by 10% (to approximately $2,000 (€1,626) per year), neither TAVI device was dominant but both remained cost-effective at a WTP threshold of $50,000 per QALY. When follow-up costs were increased by 20% (to approximately $4,000 (€3,253) per year), the devices yielded intermediate economic value, as per current US recommendations; SAPIEN XT had an ICER of $107,267 (€87,235) while SAPIEN 3 had an ICER of $57,748 (€46,963).

5.2.2 A critique on the quality of the evidence

A quality assessment of each study included in the systematic review was undertaken using the CHEC list.[86] The list contains a set of items against which the methodological quality of each economic evaluation can be assessed. In particular, the items assess the research question, study design, patient population, perspective and time horizon, measurement and valuation of costs and outcomes, analysis and sensitivity analyses, reporting, and transparency.

Overall, the studies were considered to be of moderate to high quality, with the exception of one study by Baron et al. (2019),[88] which was judged to be of low quality due to poor reporting and lack of transparency on model structure, data inputs, and valuation of costs and outcomes (for reference, the CHEC list for each study is provided in Appendix G). The authors stated that their "data, analytic methods, and study materials for [their] analysis will not be made available to other researchers", perhaps due to the commercial sensitivity of their within-trial data. However, the economic evaluation could not be fully assessed, despite likely meeting criteria to be considered high quality. The other studies broadly had a well-defined research question (that is, to evaluate the costs and consequences of TAVI versus SAVR), used an appropriate study design (for example, CUA or CEA), and evaluated outcomes for a well-defined study population (that is, patients with severe symptomatic aortic stenosis at intermediate risk of surgical complications). The CUAs commonly and appropriately assumed a health system perspective to model costs and consequences, and applied sufficiently long time horizons to project future outcomes. Discounting was applied in each case; costs were generally valued appropriately, and usefully in the case of three studies[92-94] which essentially micro-costed the TAVI/SAVR procedure; and appropriate utility weights were often applied. In some studies, however, utilities for a different population (namely, high risk patients who are an inherently older, sicker population) were inappropriately applied as relevant data on intermediate risk patients were available. A probabilistic Markov model was uniformly adopted, although some variation in model structure and data inputs (namely, health states and complications modelled at 30 days) was observed, despite often using the same source of clinical evidence, raising concerns about the quality of the findings. An incremental analysis was undertaken in each study and sufficient sensitivity/scenario analyses were performed.

Several studies had clear conflicts of interest due to either being industry supported or contributing authors having close financial ties to device manufacturers. Two studies were industry funded (by Edwards Lifesciences) with seven authors in Baron et al. (2019)[88] and two authors in Goodall et al. (2019)[89] disclosing a financial relationship with Edwards Lifesciences. Two authors in Zhou. et al. (2019)[94] served as proctors for Medtronic, while the senior author was supported by an Edwards

Fellowship. Tam et al. (2018a and 2018b) separately analysed devices by Edwards Lifesciences[92] and Medtronic,[93] and, in both cases, a contributing author disclosed a financial relationship with both manufacturers. Finally, Kaier et al. (2019)[90] did not report their source of funding but declared they had no conflicts of interest, while Kodera et al. (2018)[91] received no industry funding and reported no conflicts of interest.

In addition to the CHEC list, the ISPOR questionnaire was used to assess the relevance and credibility of the model-based economic evaluations included in the systematic review. Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted, and whether the authors had any conflicts of interest.

The results of the ISPOR questionnaire are provided in Appendix H. Overall, the CUAs were partially relevant, or applicable, to this HTA in that a decision-analytic framework was used to evaluate the cost-effectiveness of TAVI versus SAVR in patients with severe symptomatic aortic stenosis at intermediate risk of surgical complications. However, some concerns regarding the credibility of the results were identified due to issues associated with model structure and choice of input parameters, as detailed below.

With respect to model structure, none of the models were validated, raising concerns about the reliability of the economic analyses. The economic model constructed by Goodall et al. (2019)[89] did not have sufficient face validity due to poor reporting on the structure of the model (that is, whether the authors modelled outcomes by NYHA class and whether they accounted for previous events (at 30 days) when modelling subsequent complications). Similar concerns were raised about the way in which Kodera et al. (2018)[91] modelled complications in their model structure. The authors replicated the same set of complications throughout the model, seemingly allowing some patients to experience the same major clinical events, such as stroke, multiple times, without any adjustment to the probability of the event occurring. Tam et al. (2018a)[92] problematically included a 'dialysis' health state in their model, which allowed patients that previously experienced an acute kidney injury to transition to this state. However, the risk of dialysis was not reported in PARTNER 2; it was only reported in PARTNER 1a for high risk patients, which may not reflect the risk in an intermediate risk population.

In terms of input parameters, the range of complications modelled at 30 days was largely incomplete in each study, and there was no justification provided for the

inclusion/exclusion of clinical outcomes. For example, SURTAVI reported significantly higher rates of paravalvular leak, or regurgitation, in TAVI patients, yet this complication was not modelled by Tam et al. (2018b) in their evaluation of CoreValve and Evolut R;[93] the complication was considered by Zhou et al. (2019)[94] who evaluated SAPIEN 3 using PARTNER S3i, which reported no difference in the rate of regurgitation in TAVI and SAVR patients. Tam et al. (2018b)[93] instead modelled cardiogenic shock, which was significantly lower in TAVI patients. Further to this, aortic reintervention was not considered in any study. This was particularly pertinent to those that evaluated SAPIEN XT using PARTNER 2 data, as the trial showed that aortic reintervention was significantly higher in TAVI patients at 30 days, although it may be less relevant to those that evaluated newer generation devices, such as SAPIEN 3. Stroke was appropriately modelled as a long-term clinical event in each study, but only three studies [91, 92, 94] reported applying a higher rate of mortality in this patient group, despite the increased risk of death relative to the general population, or all-cause mortality. Although Kodera et al. (2018) appropriately applied a higher rate of mortality to patients that suffered a stroke in their analysis, the authors used expert opinion to inform this parameter and applied the same rate to patients experiencing myocardial infarction, and vascular complications, which may over/underestimate the risk of death in some patients.

One further concern regarding the credibility of the input parameters relates to utilities. Three studies [91-93] used utility weights for an older, sicker population (namely, high risk patients), who reported considerably lower quality of life scores than what has been observed in intermediate risk patients.[76, 100] The studies reported using these data in the absence of quality of life data for an intermediate risk population. However, data were available from Baron et al. (2017)[76] on intermediate risk patients from PARTNER 2 and could have been used in those studies evaluating SAPIEN XT.[91, 92] Had appropriate utility estimates been used, different findings may have been obtained.

5.2.3 Applicability of the evidence

This systematic review was undertaken to assess the available international evidence on cost-effectiveness and its applicability to an Irish setting. Although some studies were partially applicable to this HTA in that they evaluated the cost-effectiveness of TAVI/SAVR in a patient group of interest (that is, intermediate risk patients with severe symptomatic aortic stenosis), none were directly applicable to an Irish setting, meaning the evidence base could not be used to guide cost-effectiveness recommendations in Ireland. The main issues with respect to applicability related to:

- TAVI devices: the CUAs were performed for a given device, for example SAPIEN XT or SAPIEN 3. However, this HTA was undertaken to evaluate the average cost-effectiveness of TAVI, which takes into consideration the variability in costs,

effectiveness, and utility across a mix of devices currently used in Ireland, where applicable.

- outdated (legacy) devices: CoreValve and Evolut R have been replaced by a newer generation self-expanding device (Evolut Pro) and are no longer used in clinical practice in Ireland, rendering the results from Tam et al. (2018a)[92] outdated for (or inapplicable to) Ireland.
- the surgical risk population: none of the studies considered the cost-effectiveness of TAVI in low risk patients, which was a primary objective of this HTA (alongside intermediate risk patients). As a consequence, the cost-effectiveness of TAVI in this surgical risk population remains unclear.
- implausible model structures / health state transitions: concerns regarding model structure and health state transitions put into question the reliability of some of the cost-effectiveness findings, as detailed in section 5.2.2.
- incomplete evaluation of complications: studies may have ignored important information on the different complications that can arise following TAVI/SAVR, which has unknown implications for cost-effectiveness.
- the discount rate: in Ireland, the recommended discount rate applied to future costs and consequences in cost-effectiveness analyses is 4%. Only one study by Goodall et al. (2019)[89] applied a discount rate of 4%, however, a number of concerns regarding the model structure and parameter inputs were associated with this study, as detailed in Appendix H. Use of lower, or higher, discount rates can have a profound effect on cost-effectiveness findings.
- conflicts of interest: only one study by Kodera et al. (2019)[90] had no clear conflicts of interest; however, the credibility of the model structure used in this study was questionable. The influence of industry on the other studies was largely unclear.

In addition to the above applicability issues, none of the studies considered the cost-effectiveness and budget impact of implementing a population-based programme, or care pathway, which is the primary objective of this economic analysis. Instead, the studies evaluated the cost-effectiveness of TAVI versus SAVR on an individual or cohort basis, which would have inherently different cost inputs. As a consequence, the cost-effectiveness and budget impact of implementing a TAVI care pathway for intermediate or low risk patients remains unclear.

5.3 Discussion

This systematic review identified seven studies to date that evaluated the cost-effectiveness of TAVI versus SAVR in intermediate risk patients. The cost-effectiveness of the device was generally supported in these studies; however, a number of concerns regarding the quality and credibility of the economic evaluations were identified. These largely related to model structure (for example, many studies

modelled implausible health state transitions) and choice of input parameters (for example, few studies comprehensively evaluated postoperative complications). The systematic review found no studies that considered the cost-effectiveness of the device in patients at low surgical risk. However, since completing the review, a cost-effectiveness analysis of TAVI in patients at predominantly low surgical risk was published by Geisler et al. (2019).[103] The paper used data from the Nordic Aortic Valve Intervention (NOTION) Trial, which was conducted in Denmark – further information on the trial can be found in Chapter 4. Although the authors found TAVI was cost-effective in patients at low surgical risk, the findings are not applicable to Ireland as the study relied on clinical data from an outdated device, namely CoreValve, which is no longer used in clinical practice. The available evidence, to date, is therefore insufficient in determining the cost-effectiveness of TAVI among low or intermediate risk patients in Ireland.

5.4 Key messages

- A systematic review was undertaken to assess the available evidence on the cost-effectiveness of TAVI versus SAVR among low or intermediate risk patients with severe symptomatic aortic stenosis, and its applicability to an Irish healthcare setting.
- Seven studies were identified that evaluated the cost-effectiveness of TAVI in intermediate risk patients, none of which were performed in Ireland.
- Six studies were model-based cost-utility analyses and one was a cost-effectiveness analysis which investigated the additional reimbursement cost to a hospital per life saved by using TAVI over SAVR.
- The cost-effectiveness of TAVI was generally supported in the literature; new-generation devices were more cost-effective than older generations.
- The cost-utility analyses were broadly relevant, or applicable, to this HTA in that a decision-analytic framework was used to evaluate the cost-effectiveness of TAVI versus SAVR in patients with severe symptomatic aortic stenosis at intermediate risk of surgical complications.
- A number of concerns regarding the quality and credibility of the economic evaluations were identified, largely relating to model structure and choice of input parameters.
- Overall, the evidence base proved insufficient in determining the cost-effectiveness of TAVI among low or intermediate risk patients in Ireland.

6 Economic evaluation

This chapter reports the costs and consequences of TAVI compared with SAVR in patients at low or intermediate risk of surgical complications in Ireland. Details of the model structure and parameter inputs used to evaluate TAVI are presented along with the results of a cost-utility analysis. A detailed budget impact analysis (BIA) estimating the total cost of implementing a TAVI care pathway in the public health care system in Ireland was also undertaken and is reported in this chapter.

6.1 Health-economic analysis: an overview

In the absence of applicable published cost-effectiveness evidence from another setting, an economic analysis specific to Ireland was undertaken. This section presents an overview of the economic evaluation in terms of its objectives, methodology, setting, and viewpoint. Details of the health technology (that is, TAVI) and standard of care (SAVR) are also provided.

6.1.1 Study objective

A primary objective of the HTA was to evaluate the cost-effectiveness of TAVI compared with SAVR in patients with severe symptomatic aortic stenosis at low or intermediate risk of complications during surgery, and estimate the budget impact of delivering a TAVI care pathway for this cohort in the Irish public health care system over five years.

6.1.2 Type of economic evaluation

A cost-utility analysis (CUA) was undertaken to compare the costs and consequences of TAVI compared with SAVR. A CUA compares the incremental cost and health benefit of an intervention (in this case, TAVI) relative to a comparator (in this case, SAVR). Specific to CUA, costs are compared against a single type of health benefit, or outcome, namely quality-adjusted life years (QALYs).[104] QALYs reflect the impact of an intervention on patients' quality and quantity of life, and are estimated using self-reported utilities, or health-related quality of life.[105]

The CUA was undertaken within a decision-analytic framework,[106] which simulated patient outcomes and associated costs and consequences following TAVI or SAVR.

6.1.3 Target population and setting

The model considered outcomes for patients with severe symptomatic aortic stenosis at low or intermediate risk of complications, treated in the public health care system in Ireland. Chapter 3 describes the epidemiology of aortic stenosis and outlines the different classification systems that are used to define patients' risk status. Typically,

patients' surgical risk status is determined using the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) algorithm. STS-PROM is an online statistical tool that predicts the risk of mortality on the basis of patients' demographic and clinical characteristics. A patient is categorised as being at intermediate risk of complications if their score (or risk of complications) is ≥4 and <8%; patients that have a score of less than 4% are classified as low risk.[96] Other commonly used classification systems include the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), and EuroSCORE II. EuroSCORE II is another online tool (http://euroscore.org/calc.html) that assigns scores to patient-related, cardiac-related, and surgery-related risk factors using similar cut-offs, or thresholds.

An assumption of the model was that all patients aged 70 years or older requiring isolated aortic valve replacement would be treated with TAVI. The lower age limit was based on expert clinical opinion to represent the conservative approach given the current absence of long term follow up data for TAVI and specifically in relation to the durability of the valves. The limited data for TAVI in patients aged less than 70 years is also acknowledged in clinical guidelines.[3] Hospital In-Patient Enquiry (HIPE) data were used to estimate the number of patients currently receiving SAVR that would instead be candidates for TAVI. The HIPE data were based on isolated cases of SAVR (that is, SAVR without any other procedure, such as coronary artery bypass graft) that involved a bioprosthetic valve, performed between 2015 and 2018 on patients aged between 70 and 100 years. Given that TAVI is now routinely performed in patients at high surgical risk, these data likely reflect the current profile of patients at low or intermediate risk of surgical complications in Ireland. Based on these HIPE data, at model entry, patients at low or intermediate surgical risk were assumed to be aged 76 years and 55% were male.

6.1.4 Study perspective, time horizon, and discount rate

In line with national guidelines,[95] the economic evaluation was undertaken from the perspective of the publicly funded health and social care system. Hence, only direct medical costs were considered in the analysis. Indirect costs, such as out-of-pocket expenses borne by the patient, were not considered as these costs are consistent with a broader perspective. The model assumed a 15-year time horizon in the base case analysis to reflect the likely survival of a bioprosthetic valve. The long-term durability of the valve is unknown, so any projection of future costs and consequences beyond 15 years would be speculative. Nonetheless, a lifetime time horizon, along with a shortened five-year time horizon, was assessed in a scenario analysis. A discount rate of 4% was applied to future costs and consequences in the base case analysis, as per the revised 2019 Irish guidelines.[107] Lower and higher discount rates were applied in sensitivity analyses. The BIA projected costs over a five-year time horizon, consistent with national guidelines.

6.1.5 The health technology (TAVI)

Chapter 2 provides a detailed description of the health technology. Briefly, TAVI is a minimally invasive procedure that involves functionally replacing the diseased aortic valve with a bioprosthetic valve, which is deployed using a catheter.[6] The aortic valve is predominantly accessed via the femoral vein in the groin, known as the transfemoral approach, although it may be accessed via the subclavian artery (beneath the collar bone); the inferior vena cava and the adjoining abdominal aorta (transcaval access); the apex of the left ventricle of the heart (transapical access); or directly (transaortic access), which requires a mini-thoracotomy or upper hemisternotomy to insert the catheter into the aorta.[7] Once the catheter is in place, the fully-collapsible TAVI device is deployed, functionally replacing the diseased valve by compressing it against the walls of the aorta.

TAVI systems typically comprise a transcatheter heart valve, delivery system, introducer set, crimper and balloon valvuloplasty catheter. The devices come in a range of diameter sizes and have been optimised for different delivery routes. There has been iterative development of the devices to reduce the risk of clinical complications since the first TAVI system was awarded the European Conformity (CE) mark in 2007. Developments include reductions in the device height; changes to the structure and profile of the device; the advent of repositionable devices; novel mechanisms to anchor the device as well as innovations in the delivery system to facilitate optimal positioning and deployment of the valve. These developments aim to reduce the risk of prosthesis-patient mismatch, vascular complications, coronary artery occlusion, paravalvular leak, and conduction abnormalities necessitating a new permanent pacemaker which were common complications post TAVI.[13-15]

6.1.6 Standard of care (SAVR)

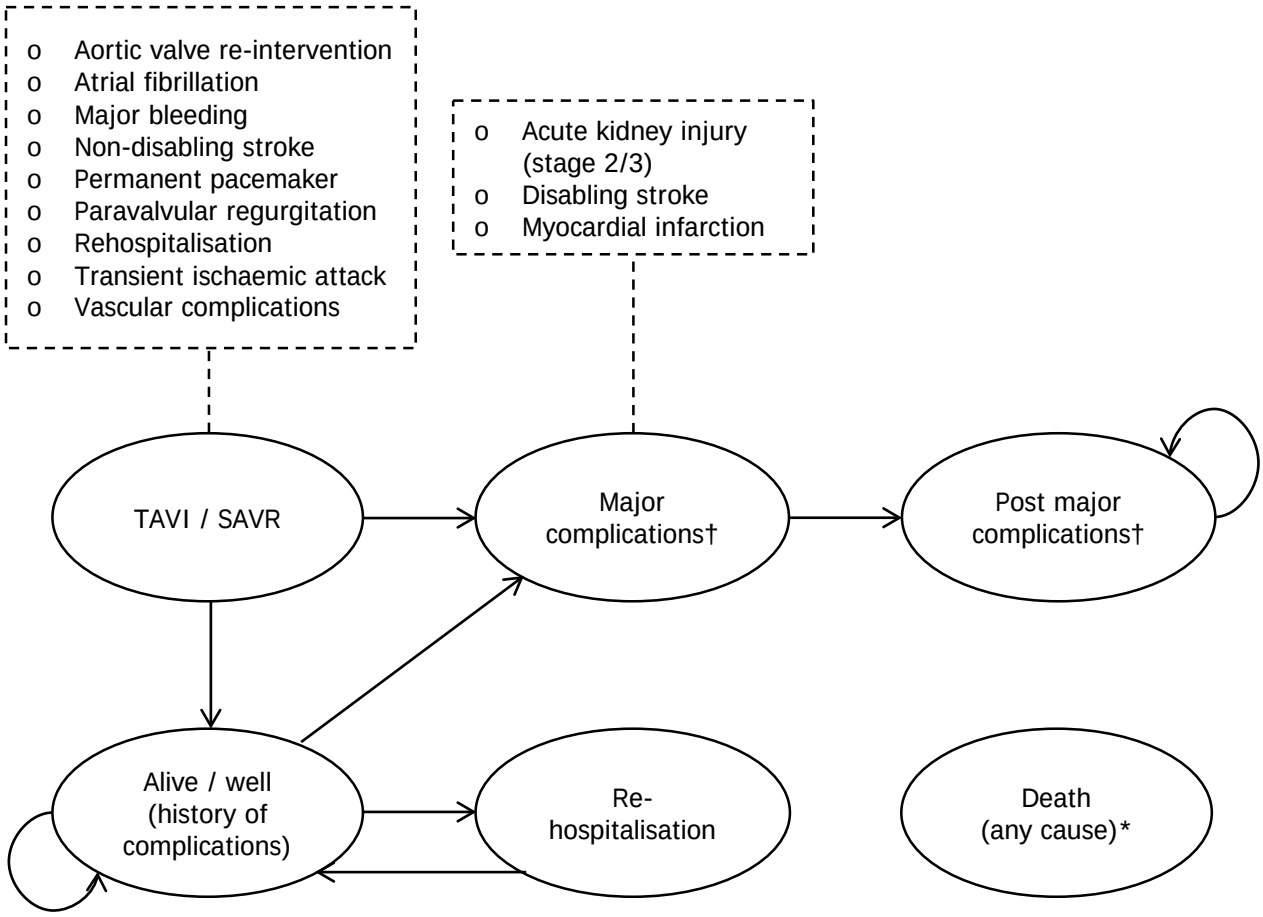
The standard treatment for patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications is surgical aortic valve replacement (SAVR). SAVR is an open cardiovascular surgical procedure that involves removing a diseased aortic valve and replacing it with an artificial valve prosthesis.[2] A wide range of prostheses are available as either mechanical or bioprosthetic valves.[1] Mechanical valves are routinely used in adults aged less than 60 years due to the durability of the valve in the long-term; however, they require ongoing anticoagulation, which may lead to potential bleeding complications. Bioprosthetic valves are generally used in older adults, but they are less durable and may potentially lead to valve failure and the need for reintervention. Choice of prosthesis is influenced by patient life expectancy and the relative risks of chronic anticoagulation or accelerated valve deterioration. Due to the advanced age of

patients at low or intermediate surgical risk, SAVR is typically performed using a bioprosthetic valve.

6.1.7 Model structure

A decision-analytic model was developed to investigate cost-effectiveness. The model comprised a Markov model that simulated patient outcomes following TAVI or SAVR. A schematic of the Markov model is presented in Figure 6.1.

Figure 6.1 Markov model schematic



† Contains three health states, one for each complication
* Patients can die at any stage in the model

Following the procedure (TAVI or SAVR), patients could transition to one of two health states, depending on the success of the procedure. If the procedure went well, or patients experienced a postoperative complication at 30 days, such as aortic valve reintervention, atrial fibrillation, major bleeding, non-disabling stroke, permanent pacemaker insertion, paravalvular regurgitation, rehospitalisation, transient ischaemic attack, or vascular complications, patients transitioned to the 'alive/well (history of minor complications)' health state. However, if patients experienced a 'major complication' at 30 days, such as acute kidney injury (stage

2/3), disabling stroke, or myocardial infarction, they transitioned to this health state for a period of one cycle, before moving to the 'post-major complications' health state, which carried an increased risk of mortality. Although not graphically represented, the 'major complications' and 'post-major complications' health states each contained three health states; one for each complication (that is, acute kidney injury, disabling stroke, and myocardial infarction) to reflect the different risk of mortality associated with each complication. Patients in the 'alive/well' health state were at risk of experiencing a major complication at any time during the model, as well as being rehospitalised due to vascular complications. Patients that were rehospitalised returned to the 'alive/well' health state after transitioning to this health state for a period of one cycle. Finally, patients could die at any time during the model due to all-cause mortality.

The model was replicated over fifteen years using monthly cycles.

6.2 Model parameters

The economic model required a range of input parameters that describe epidemiological factors and costs. Parameters are typically defined by statistical distributions that reflect the uncertainty in their true values.

6.2.1 Study population (cohort)

The economic model required data on the total number of SAVR procedures performed in a year to estimate the potential number of TAVI cases that could be undertaken if a TAVI pathway was implemented in public hospitals in Ireland. As SAVR is routinely performed on patients at low or intermediate risk of surgical complications, hospital activity data for the open-cardiovascular procedure provides the best information on the number of TAVI procedures that could be performed. Similarly, it provides the best indication of the total number of SAVR procedures that will be performed in a given year, in the absence of a TAVI pathway for this cohort. As per the HIPE Reporting Database, there were 98 SAVR procedures using a bioprosthetic valve performed on patients aged between 70 and 100 years in public hospitals in Ireland in 2018 (Table 6.1). Although some of these procedures may have been performed on patients at high surgical risk, the proportion is likely to be low as TAVI is now routinely performed on this population.

It is unclear what proportion of patients was low versus intermediate risk from the HIPE database. Evidence from a large German Registry (GARY) on isolated TAVI suggests that the ratio of low to intermediate risk patients with severe symptomatic aortic stenosis is 49 to 51%.[60] A study of isolated TAVI at a single site in Ireland (Mater Misericordiae University Hospital) reported a similar ratio of low to intermediate risk patients (50:50).[59] However, given the implementation of a TAVI

pathway by the HSE in 2017, which included TAVI for patients at intermediate or greater risk of complications, the risk profile of patients currently undergoing SAVR is likely different from the reported risk profile of patients with TAVI. In the GARY registry, TAVI accounts for 49% of AVR activity, whereas in HIPE, it accounts for 35%. It is likely that substantially more patients are at low than intermediate risk of surgical complications. For the purposes of this analysis, a ratio of 67 to 33% was assumed to reflect the proportion of low to intermediate risk patients currently undergoing SAVR. Uncertainty in this parameter was investigated using a lower and upper threshold of 20% and 48%, respectively, for intermediate risk patients, and a beta distribution in the probabilistic analysis.

Table 6.1 Isolated SAVR procedures performed on patients aged between 70 and 100 in public hospitals: 2015-2018

Hospital	2015	2016	2017	2018	Total
Mater Misericordiae University Hospital	23	11	18	15	67
St. James's Hospital; Dublin	25	27	29	19	100
Cork University Hospital	45	59	40	53	197
University Hospital Limerick	0	0	1	0	1
Galway University Hospitals	36	17	20	11	84
Total	**129**	**114**	**108**	**98**	**449**

For the purposes of the CUA, a starting cohort of 100 patients (the estimated number of procedures currently performed as SAVR) was assumed for each group of patients (that is, low and intermediate risk patients). The CUA was designed as a closed-cohort model, whereby the same 100 patients were followed for 15 years, with cost-effectiveness estimated for the population. In the BIA, a starting cohort of 100 patients, comprising 76 low risk patients and 33 intermediate risk patients, was assumed using information on the ratio of low to intermediate risk patients to accurately reflect the expected budget impact of implementing a TAVI care pathway in Ireland. The BIA was designed as an open-cohort model so that the cost of treating 100 patients in year one, plus an additional 100 patients in year two, and so on, could be estimated over five years.

6.2.2 Clinical events (effectiveness and safety)

A review of the clinical effectiveness and safety of TAVI compared with SAVR in patients at low and intermediate risk of surgical complications was undertaken as part of this HTA. The findings are detailed in Chapter 4. Briefly, the review found six unique clinical trials[19, 20, 70-72, 74, 76, 77] that evaluated the effectiveness and safety of TAVI relative to SAVR in patients at low (n=2)[19, 20] or intermediate (n=4)[70-72, 77] surgical risk. The studies were published between 2015 and 2019, and included data on 6,596 patients of low or intermediate surgical risk. The findings indicated that

TAVI was non-inferior to SAVR in terms of all-cause mortality and cardiac mortality from 30 days to one year in low risk patients and 30 days to two years in intermediate risk patients. TAVI performed better than SAVR in some circumstances, for example, health-related quality of life, and worse in others, for instance, vascular complications. However, the available evidence was often based on first generation devices that no longer commercially available, such as CoreValve™ and SAPIEN in intermediate risk patients and Evolut™ R in low risk patients. These have largely been replaced in clinical practice by newer devices, such as SAPIEN XT, SAPIEN 3, and Evolut R. For the purposes of the economic model, only evidence on devices currently used in clinical practice in Ireland was used, as detailed below for each patient group.

Intermediate risk patients

To date, four clinical trials have evaluated the effectiveness and safety of TAVI compared with SAVR in patients at intermediate surgical risk: PARTNER 2, SURTAVI, NOTION, and STACCATO.[70-72, 77] The evidence from these trials is almost entirely based on first-generation devices, which have worse complication profiles than newer generation devices, for example, on aortic valve reintervention and vascular complications. The SURTAVI, NOTION, and STACCATO trials were largely or entirely based on the CoreValve™ device, which is no longer marketed and has been replaced by the Evolut PRO and Evolut™ R devices, for which there is currently no RCT data for intermediate risk patients. The PARTNER 2 trial[70] was based on the first-generation SAPIEN XT valve, which is still marketed and used in clinical practice. For the purposes of this analysis, evidence from the PARTNER 2 trial was used in the base case analysis.

The PARTNER 2 trial[70] provided data on the number of postoperative clinical events at 30 days, along with the number of major complications and all-cause mortality at 30 days, one year, and two years. Since the trial data were reported cumulatively, the total number of events at one- and two-years was adjusted (to avoid double-counting) by subtracting the number of events that occurred at 30 days and one year, respectively. For the SAVR arm, the event rates were applied as probabilities, adjusted to reflect the monthly cycle length of the model (Table 6.2). The absolute numbers of clinical events were used to inform beta distributions in the probabilistic analysis.

A treatment effect for TAVI relative to SAVR was estimated and applied using relative risks (RRs), with uncertainty investigated using lognormal distributions in the probabilistic analysis (Table 6.3). The treatment effect was only applied to those

Table 6.2 Probabilities of postoperative and major complications in intermediate risk patients following SAVR

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention	0.000	0.000	0.000	None	PARTNER 2
Atrial fibrillation	0.260	0.233	0.287	Beta	PARTNER 2
Major bleeding	0.433	0.403	0.463	Beta	PARTNER 2
Non-disabling stroke	0.018	0.010	0.027	Beta	PARTNER 2
Pacemaker implantation	0.067	0.052	0.083	Beta	PARTNER 2
Paravalvular regurgitation	0.005	0.001	0.012	Beta	PARTNER 2
Rehospitalisation	0.061	0.047	0.076	Beta	PARTNER 2
Transient ischaemic attack	0.004	0.001	0.009	Beta	PARTNER 2
Vascular complications	0.050	0.037	0.064	Beta	PARTNER 2
Major complications					
Disabling stroke, 30 days	0.042	0.031	0.055	Beta	PARTNER 2
Disabling stroke, year 1	0.001	0.001	0.002	Beta	PARTNER 2
Disabling stroke, year 2+	0.000	0.000	0.001	Beta	PARTNER 2
Myocardial infarction, 30 days	0.019	0.011	0.028	Beta	PARTNER 2
Myocardial infarction, year 1	0.001	0.000	0.002	Beta	PARTNER 2
Myocardial infarction, year 2	0.001	0.000	0.001	Beta	PARTNER 2
Acute kidney injury, 30 days	0.032	0.022	0.043	Beta	PARTNER 2
Acute kidney injury, year 1	0.002	0.001	0.002	Beta	PARTNER 2
Acute kidney injury, year 2	0.001	0.000	0.001	Beta	PARTNER 2
Rehospitalised, year 1	0.007	0.006	0.009	Beta	PARTNER 2
Rehospitalised, year 2	0.002	0.001	0.003	Beta	PARTNER 2
All-cause mortality, 30 days	0.040	0.029	0.053	Beta	PARTNER 2
All-cause mortality, year 1	0.008	0.006	0.010	Beta	PARTNER 2
All-cause mortality, year 2	0.005	0.004	0.006	Beta	PARTNER 2

Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

events for which there was an observable difference in outcomes between TAVI and SAVR; these included acute kidney injury, atrial fibrillation, major bleeding, paravalvular regurgitation, and vascular complications at 30 days, and rehospitalisation at two years. There was an observable difference in the rate of aortic reintervention at 30 days between TAVI and SAVR in PARTNER 2; however, the event was modelled as a probability in the TAVI arm (rather than a RR) as there were no events observed in the SAVR arm upon which a meaningful RR could be estimated. For all other events, the same probabilities were applied to TAVI as SAVR given the lack of evidence of a difference in treatment outcomes. The model also assumed the same rate of clinical events in both arms beyond the observed trial data (that is, two years) as there was no evidence to suggest that outcomes differed between TAVI and SAVR beyond two years.

Table 6.3 Relative risks of postoperative and major complications in intermediate risk patients following TAVI (PARTNER 2)

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention (probability)	0.004	0.001	0.009	Beta	PARTNER 2
Atrial fibrillation*	0.347	0.278	0.433	Lognormal	PARTNER 2
Major bleeding*	0.240	0.198	0.291	Lognormal	PARTNER 2
Non-disabling stroke	1.290	0.701	2.376	Lognormal	PARTNER 2
Pacemaker implantation	1.262	0.929	1.716	Lognormal	PARTNER 2
Paravalvular regurgitation*	7.162	2.549	20.123	Lognormal	PARTNER 2
Rehospitalisation	1.042	0.743	1.462	Lognormal	PARTNER 2
Transient ischaemic attack	2.272	0.702	7.355	Lognormal	PARTNER 2
Vascular complications*	1.584	1.127	2.226	Lognormal	PARTNER 2
Major complications					
Disabling stroke, 30 days	0.752	0.480	1.178	Lognormal	PARTNER 2
Disabling stroke, year 1	1.291	0.631	2.643	Lognormal	PARTNER 2
Disabling stroke, year 2	1.991	0.683	5.803	Lognormal	PARTNER 2
Myocardial infarction, 30 days	0.638	0.311	1.307	Lognormal	PARTNER 2
Myocardial infarction, year 1	1.195	0.519	2.753	Lognormal	PARTNER 2
Myocardial infarction, year 2	1.125	0.436	2.904	Lognormal	PARTNER 2
Acute kidney injury, 30 days*	0.406	0.214	0.769	Lognormal	PARTNER 2
Acute kidney injury, year 1	1.154	0.597	2.230	Lognormal	PARTNER 2
Acute kidney injury, year 2	0.434	0.134	1.405	Lognormal	PARTNER 2
Rehospitalised, year 1	1.085	0.800	1.473	Lognormal	PARTNER 2
Rehospitalised, year 2*	2.017	1.204	3.379	Lognormal	PARTNER 2
All-cause mortality, 30 days	0.961	0.625	1.476	Lognormal	PARTNER 2
All-cause mortality, year 1	1.019	0.763	1.361	Lognormal	PARTNER 2
All-cause mortality, year 2	0.945	0.631	1.414	Lognormal	PARTNER 2

* Treatment effect applied in the base case analysis
Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

Since the base case analysis was based on a first-generation TAVI device (namely, SAPIEN XT), the complications associated with the device were likely more pronounced than what would be expected from a second-generation device, such as SAPIEN 3. SAPIEN 3 has yet to be evaluated in a clinical trial, however, Thourani et al. (2016)[98] reported the effectiveness of the second-generation device using evidence from PARTNER S3i (Table 6.4), which is a registry-based observational study. The authors compared the effectiveness of the TAVI device relative to SAVR using evidence from PARTNER 2. These data were applied in a scenario analysis to assess the impact of the second-generation device on cost-utility findings. As in the base case analysis, a treatment effect was applied to those events for which there was an observable difference in outcomes between TAVI and SAVR. Since PARTNER S3i only reported outcomes to one-year, the analysis assumed the same rate of complications in both arms beyond this point.

Table 6.4 Relative risks of postoperative and major complications in intermediate risk patients following TAVI (PARTNER S3i)

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention (probability)	0.001	0.000	0.003	Beta	PARTNER S3i
Atrial fibrillation*	0.193	0.146	0.256	Lognormal	PARTNER S3i
Major bleeding*	0.107	0.081	0.142	Lognormal	PARTNER S3i
Non-disabling stroke	0.948	0.496	1.812	Lognormal	PARTNER S3i
Pacemaker implantation*	1.520	1.136	2.032	Lognormal	PARTNER S3i
Paravalvular regurgitation*	7.249	2.599	20.224	Lognormal	PARTNER S3i
Rehospitalisation	0.749	0.520	1.079	Lognormal	PARTNER S3i
Transient ischaemic attack	0.948	0.238	3.781	Lognormal	PARTNER S3i
Vascular complications	1.227	0.860	1.750	Lognormal	PARTNER S3i
Major complications					
Disabling stroke, 30 days*	0.243	0.126	0.468	Lognormal	PARTNER S3i
Disabling stroke, year 1	0.886	0.413	1.902	Lognormal	PARTNER S3i
Myocardial infarction, 30 days*	0.150	0.044	0.504	Lognormal	PARTNER S3i
Myocardial infarction, year 1*	0.044	0.003	0.745	Lognormal	PARTNER S3i
Acute kidney injury, 30 days*	0.147	0.057	0.375	Lognormal	PARTNER S3i
Acute kidney injury, year 1	0.147	0.057	0.375	Lognormal	PARTNER S3i
Rehospitalised, year 1	0.879	0.641	1.204	Lognormal	PARTNER S3i
All-cause mortality, 30 days*	0.277	0.147	0.525	Lognormal	PARTNER S3i
All-cause mortality, year 1*	0.720	0.528	0.981	Lognormal	PARTNER S3i

* Treatment effect applied
Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

A meta-analysis of PARTNER 2 and PARTNER S3i was also undertaken to evaluate the effectiveness of TAVI relative to SAVR for a mix of the two devices (Table 6.5). Since outcomes were only reported to one-year in PARTNER S3i, the model assumed evidence from PARTNER 2 in year-two, and assumed the same rate of complications in both arms beyond this point. The same assumptions as the base case analysis were applied.

Table 6.5 Relative risks of postoperative and major complications in intermediate risk patients following TAVI (PARTNER 2 & S3i)

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention (probability)	0.002	0.001	0.005	Beta	PARTNER 2 & S3i
Atrial fibrillation*	0.261	0.147	0.462	Lognormal	PARTNER 2 & S3i
Major bleeding*	0.161	0.073	0.355	Lognormal	PARTNER 2 & S3i
Non-disabling stroke	1.116	0.716	1.740	Lognormal	PARTNER 2 & S3i
Pacemaker implantation*	1.392	1.127	1.719	Lognormal	PARTNER 2 & S3i
Paravalvular regurgitation*	7.207	3.480	14.924	Lognormal	PARTNER 2 & S3i
Rehospitalisation	0.895	0.698	1.147	Lognormal	PARTNER 2 & S3i
Transient ischaemic attack	1.576	0.643	3.857	Lognormal	PARTNER 2 & S3i
Vascular complications*	1.402	1.096	1.791	Lognormal	PARTNER 2 & S3i
Major complications					
Disabling stroke, 30 days	0.438	0.145	1.326	Lognormal	PARTNER 2 & S3i
Disabling stroke, year 1	1.082	0.642	1.826	Lognormal	PARTNER 2 & S3i
Disabling stroke, year 2	1.991	0.683	5.803	Lognormal	PARTNER 2
Myocardial infarction, 30 days	0.337	0.082	1.380	Lognormal	PARTNER 2 & S3i
Myocardial infarction, year 1	0.305	0.013	7.426	Lognormal	PARTNER 2 & S3i
Myocardial infarction, year 2	1.125	0.436	2.904	Lognormal	PARTNER 2
Acute kidney injury, 30 days*	0.259	0.096	0.699	Lognormal	PARTNER 2 & S3i
Acute kidney injury, year 1	1.154	0.597	2.230	Lognormal	PARTNER 2
Acute kidney injury, year 2	0.434	0.134	1.405	Lognormal	PARTNER 2
Rehospitalised, year 1	0.980	0.787	1.220	Lognormal	PARTNER 2 & S3i
Rehospitalised, year 2*	2.017	1.204	3.379	Lognormal	PARTNER 2
All-cause mortality, 30 days	0.528	0.157	1.782	Lognormal	PARTNER 2 & S3i
All-cause mortality, year 1	0.860	0.612	1.208	Lognormal	PARTNER 2 & S3i
All-cause mortality, year 2	0.945	0.631	1.414	Lognormal	PARTNER 2

* Treatment effect applied
Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

Low risk patients

Two clinical trials, to date, have evaluated the clinical effectiveness and safety of TAVI compared with SAVR in patients at low surgical risk: EVOLUT Low risk and PARTNER 3.[19, 20] The EVOLUT Low Risk trial[20] reported outcomes using Bayesian posterior median incidence percentages, which could not be converted to absolute numbers of clinical events for analysis in the economic model. More problematically, follow-up at one year was based on an interim analysis, which means the total number of patients at follow-up was considerably less than the number of patients randomised to TAVI and SAVR. As a consequence, follow-up data could not be meaningfully adjusted to reflect the number of clinical events that occurred at the previous time-point (that is, 30 days). The PARTNER 3 trial[19] reported clinical outcomes at 30 days and one year, based on the second-generation SAPIEN 3

device, which is currently used in clinical practice. Evidence from the PARTNER 3 trial was used in the base case analysis of low risk patients.

The same approach was taken in modelling clinical events in low risk patients as intermediate risk patients in the economic model. That is, a treatment effect was applied to those events for which there was a difference in outcomes between TAVI and SAVR. Where zero events were observed for any complication in the SAVR arm, a probability was applied in the TAVI arm, rather than a RR. Since PARTNER 3 reported outcomes to one year, the same rate of complications beyond this point was assumed in both arms. Table 6.6 and Table 6.7 present the estimated probabilities and RRs for postoperative complications (at 30 days) and major complications (at 30 days and one year) for SAVR and TAVI, respectively. Beta distributions were assumed for all probabilities in the probabilistic analysis, along with lognormal distributions for all RRs.

In a sensitivity analysis, the full complement of RRs was applied to both patient groups (that is, low and intermediate risk patients) to assess the impact of assuming differences in complications between TAVI and SAVR on cost-utility findings.

Table 6.6 Probabilities of postoperative and major complications in low risk patients following SAVR

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention	0.001	0.000	0.006	Beta	PARTNER 3
Atrial fibrillation	0.393	0.344	0.443	Beta	PARTNER 3
Major bleeding	0.244	0.206	0.285	Beta	PARTNER 3
Non-disabling stroke	0.020	0.009	0.034	Beta	PARTNER 3
Pacemaker implantation	0.040	0.024	0.059	Beta	PARTNER 3
Paravalvular regurgitation	0.000	0.000	0.006	Beta	PARTNER 3
Rehospitalisation	0.064	0.043	0.088	Beta	PARTNER 3
Transient ischaemic attack	0.007	0.001	0.016	Beta	PARTNER 3
Vascular complications	0.015	0.006	0.029	Beta	PARTNER 3
Major complications					
Disabling stroke, 30 days	0.004	0.001	0.012	Beta	PARTNER 3
Disabling stroke, year 1	0.000	0.000	0.001	Beta	PARTNER 3
Myocardial infarction, 30 days	0.013	0.005	0.026	Beta	PARTNER 3
Myocardial infarction, year 1	0.001	0.000	0.002	Beta	PARTNER 3
Acute kidney injury, 30 days	0.018	0.008	0.032	Beta	PARTNER 3
Acute kidney injury, year 1	-	-	-	-	Not reported
Rehospitalised, year 1	0.005	0.003	0.007	Beta	PARTNER 3
All-cause mortality, 30 days	0.033	0.019	0.051	Beta	PARTNER 3
All-cause mortality, year 1	0.011	0.009	0.014	Beta	PARTNER 3

Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

Table 6.7 Relative risks of postoperative and major complications in low risk patients following TAVI (PARTNER 3)

Complication	Estimate	LCI	UCI	Distribution	Source
Postoperative complications, 30 days					
Aortic reintervention (probability)	0.000	0.000	0.000	None	PARTNER 3
Atrial fibrillation*	0.128	0.083	0.198	Lognormal	PARTNER 3
Major bleeding*	0.148	0.092	0.240	Lognormal	PARTNER 3
Non-disabling stroke	0.305	0.083	1.120	Lognormal	PARTNER 3
Pacemaker implantation	1.627	0.926	2.858	Lognormal	PARTNER 3
Paravalvular regurgitation (probability)	0.008	0.002	0.018	Beta	PARTNER 3
Rehospitalisation*	0.537	0.299	0.963	Lognormal	PARTNER 3
Transient ischaemic attack	0.131	0.007	2.525	Lognormal	PARTNER 3
Vascular complications	1.438	0.562	3.679	Lognormal	PARTNER 3
Major complications					
Disabling stroke, 30 days	0.183	0.009	3.803	Lognormal	PARTNER 3
Disabling stroke, year 1	0.454	0.041	4.986	Lognormal	PARTNER 3
Myocardial infarction, 30 days	0.763	0.234	2.482	Lognormal	PARTNER 3
Myocardial infarction, year 1	0.227	0.026	2.027	Lognormal	PARTNER 3
Acute kidney injury, 30 days	0.229	0.049	1.072	Lognormal	PARTNER 3
Acute kidney injury, year 1	-	-	-	-	Not reported
Rehospitalised, year 1	0.814	0.441	1.504	Lognormal	PARTNER 3
All-cause mortality, 30 days	0.366	0.071	1.878	Lognormal	PARTNER 3
All-cause mortality, year 1	0.451	0.113	1.793	Lognormal	PARTNER 3

* Treatment effect applied
Note: At all time intervals beyond 30 days, the number of clinical events were adjusted to avoid double-counting events that occurred at the previous interval
Key: LCI – lower confidence interval; UCI – upper confidence interval

6.3.2 Mortality

All-cause mortality

The trials provided evidence of all-cause mortality up to one year in low risk patients and two years in intermediate risk patients. Beyond this point, all-cause mortality was based on National Life Tables for Ireland from 2015, stratified by age and sex.[108] As patients with severe symptomatic aortic stenosis are likely at an increased risk of mortality relative to the general population, a higher relative risk was applied to the all-cause mortality rates using data from Chakos et al. (2017).[109] It was estimated that patients at low surgical risk had a relative risk of mortality of 1.20 (95%CI: 1.11 to 1.30), while patients at intermediate surgical risk had a relative risk of 1.41 (95% CI: 1.31 to 1.53) (Table 6.8). In a sensitivity analysis, the relative risk of mortality due to aortic stenosis was dropped on the assumption that it was already captured in the all-cause mortality rates of the general population.

Table 6.8 Relative risk of mortality due to aortic stenosis in patients at low and intermediate surgical risk

Complication	Estimate	LCI	UCI	Distribution	Source
Low risk	1.197	1.107	1.295	Lognormal	Chakos et al. (2017)[109]
Intermediate risk	1.412	1.306	1.527	Lognormal	Chakos et al. (2017)[109]

Key: LCI – lower confidence interval; UCI – upper confidence interval

Mortality due to major complications

In the economic model, patients that experienced a major complication, such as acute kidney injury, myocardial infarction, or disabling stroke, were at an increased risk of mortality relative to other patients. Although the risk may have been captured in the trials (up to two years in intermediate risk patients and one year in low risk patients), it was assumed that the risk was understated in these patients. Beyond the observed trial data, general population mortality rates likely understated the risk of mortality also. The model, therefore, applied a RR of mortality for each major complication, as detailed in Table 6.9. In addition to an increased risk of mortality following myocardial infarction, the model also applied an instantaneous risk of death due to the complication, which is reportedly high in patients that experience a myocardial infarction.[110]

Table 6.9 Relative risk of mortality due to major complications

Complication	Estimate	LCI	UCI	Distribution	Source
Acute kidney injury	2.500	1.106	6.000	Lognormal	Ramos et al. (2018)[111]
Myocardial infarction (instant)	7.033	6.876	7.193	Lognormal	Norgaard et al. (2010)[110]
Myocardial infarction	1.660	1.594	1.728	Lognormal	Norgaard et al. (2010)[110]
Stroke	2.899	2.010	3.420	Lognormal	Ontario HTA (2016)[112]

Key: LCI – lower confidence interval; UCI – upper confidence interval

6.3.4 Cost estimates

Table 6.10 presents the cost inputs used in the analysis. All cost estimates were valued at 2019 prices and expressed in Euro (€) currency.

The model considered both procedure-related and health state costs, with estimates mainly deriving from relevant Diagnostic Related Group (DRG) codes in Ireland. Procedure-related costs included the cost of the procedure and follow-up outpatient costs. To estimate the cost of TAVI and SAVR, all DRG codes associated with the procedures between 2015 and 2018 were collated using the HIPE Reporting Database and a weighted cost was estimated.

The DRG codes captured the different adverse events, or complications, associated with the index hospital admission. As such, costs for postoperative complications were not considered in the model as it was assumed that these were already captured in the weighted cost of the procedures. Although some events may occur after the index hospital admission, the majority of postoperative complications reported in trials at 30 days reportedly occur during the index admission, including new pacemaker implantation. The estimated weighted cost of TAVI and SAVR was €27,777 (95% CI: €22,833 to €33,792) and €29,342 (95% CI: €24,120 to €35,696), respectively. Procedure-related outpatient costs for follow-up care were also included and applied to those patients still alive at 30 days following TAVI or SAVR. The cost for outpatient care was €737 (95% CI: €606 to €897).

Health state costs associated with each major complication and rehospitalisation were included in the economic model, and derived from related DRGs. A monthly cost of follow-up care in patients that experienced a disabling stroke was included and taken from a previous HIQA HTA on mechanical thrombectomy.[113] The HTA estimated that the monthly cost of follow-up care was €2,229 (95% CI: €1,832 to €2,712).

In the base case analysis, the cost of purchasing and developing a new catheterisation laboratory (hereafter, cath lab) for a single hospital was considered to address potential capacity constraints in the current system to meet the increased demand for TAVI procedures. The cost of a cath lab is uncertain and likely specific to the hospital in which it is being installed as it may be influenced by site access issues, existing infrastructure etc. The cost used in the model is based on publicly cited costs for cath labs (and their ancillary infrastructure) recently installed or commissioned in the public system. It was assumed that it would cost €4.9 million to purchase and develop the cath lab.[114, 115] For an expected throughput of 17.5 TAVI patients per week (midpoint of the approximate number of TAVI procedures (15-20) that could be performed in a given week), with equipment depreciated at 10% per annum and running costs of €2,700 per week,[116] it was estimated that the capital cost per (TAVI) patient was €1,193. The cath lab capital cost was applied to all patients in the CUA. In the BIA, the upfront cost of purchasing and developing the cath lab was included in year one, with running and maintenance costs included in subsequent years. These costs were spread over 100 patients; the proportion of cath lab activity attributable to TAVI in low and intermediate risk patients. The estimated upfront cost in year one was €624,124, while the running cost in each subsequent year was €25,366.

All cost inputs assumed lognormal distributions in the probabilistic analysis.

Table 6.10 Cost estimates

Complication	Estimate	LCI	UCI	Distribution	Source
TAVI procedure	€27,777	€22,833	€33,792	Lognormal	HIPE (2015-18)
SAVR procedure	€29,342	€24,120	€35,696	Lognormal	HIPE (2015-18)
Outpatient costs	€737	€606	€897	Lognormal	HIPE (2017)
Acute kidney injury	€8,875	€7,295	€10,796	Lognormal	DRG L60
Disabling stroke	€27,598	€22,686	€33,574	Lognormal	DRG B70A
Disabling stroke, follow-up care (monthly)	€2,229	€1,832	€2,712	Lognormal	HIQA (2017)[113]
Myocardial infarction	€7,467	€6,138	€9,084	Lognormal	DRG F10
Rehospitalisation	€5,325	€4,377	€6,478	Lognormal	DRG F62
Cath lab capital costs (per patient)	€1,193	€981	€1,451	Lognormal	Assumption

Key: LCI – lower confidence interval; UCI – upper confidence interval

In a scenario analysis, the cost of purchasing and developing a cath lab to facilitate the increased demand for TAVI was dropped from the CUA and BIA on the assumption that the additional procedures could be performed within existing capacity constraints.

6.3.5 Quality of life estimates

Table 6.11 presents the published utility estimates used to calculate QALYs in the CUA. Utility estimates for TAVI in a low risk population were unavailable at the time of analysis, so the same utility estimates were used in the base case analysis of intermediate and low risk patients. Procedure-related and health state utilities were considered in the economic model, along with disutilities for postoperative complications.

Utility estimates for TAVI and SAVR were taken from Baron et al. (2017),[76] who reported patients' health-related quality of life using the 3-level EuroQol 5-dimensional questionnaire (EQ-5D)[117] at baseline, 30 days, six months and one year. The utilities were based on intermediate risk patients from PARTNER 2,[70] and were applied to patients in the 'alive/well' health state in the economic model. In the first cycle of the model, a utility penalty, or disutility, was applied to those patients that experienced a postoperative complication to reflect the impact of these events on patients' health-related quality of life. Since utilities were only reported to one year, the model replicated the last observed utility estimate (at one year) for TAVI and SAVR throughout the model. Health state utilities for acute kidney injury,[118] myocardial infarction,[119] and stroke,[120] were also applied in the model, along with a health state utility for rehospitalisation.[121] To reflect the impact of advancing age on patients' health-related quality of life beyond observed trial data (which inherently captured advancing age), a utility decrement was applied annually using information from Ara and Brazier (2011).[122] Uncertainty in utility parameters was investigated using beta or normal distributions, as detailed in Table 6.11.

In a scenario analysis, the disutilities applied to postoperative complications were dropped from the model on the assumption that these were captured in the trial data and, therefore, may be double-counted in the base case analysis. Finally, utility estimates derived from the PARTNER S3i study[100] were assumed in the scenario analysis that compared the second-generation device (SAPIEN 3) with SAVR in intermediate risk patients.

Table 6.11 Quality of life estimates

Complication	Estimate	LCI	UCI	Distribution	Source
TAVI					
Baseline	0.750	0.738	0.762	Beta	Baron et al. (2017)[76]
30 days	0.808	0.794	0.822	Beta	Baron et al. (2017)[76]
6 months	0.794	0.778	0.809	Beta	Baron et al. (2017)[76]
12 months	0.794	0.778	0.809	Beta	Baron et al. (2017)[76]
SAVR					
Baseline	0.730	0.716	0.744	Beta	Baron et al. (2017)[76]
30 days	0.728	0.712	0.744	Beta	Baron et al. (2017)[76]
6 months	0.796	0.778	0.813	Beta	Baron et al. (2017)[76]
12 months	0.796	0.778	0.813	Beta	Baron et al. (2017)[76]
Acute kidney injury*	0.690	0.650	0.729	Beta	Villeneuve et al. (2016)[118]
Disabling stroke	0.390	0.172	0.635	Beta	Tengs and Lin (2003)[120]
Myocardial infarction*	0.704	0.664	0.742	Beta	Sullivan et al. (2006)[119]
Rehospitalisation	0.560	0.117	0.944	Beta	Ambrosy et al. (2016)[121]
Disutilities (complications)					
Aortic reintervention†	-0.003	-0.044	0.038	Normal	Lange et al. (2016)[123]
Atrial fibrillation	-0.038	-0.063	-0.013	Normal	Kaier et al. (2016)[124]
Major bleeding	-0.447	-0.739	-0.155	Normal	Kaier et al. (2016)[124]
Non-disabling stroke	-0.161	-0.267	-0.055	Normal	Kaier et al. (2016)[124]
Pacemaker implantation	-0.003	-0.044	0.038	Normal	Lange et al (2016)[123]
Paravalvular regurgitation†	-0.003	-0.044	0.038	Normal	Lange et al (2016)[123]
Rehospitalisation	-0.128	-0.178	-0.077	Normal	Lanitis et al (2014)[125]
Transient ischaemic attack‡	-0.161	-0.267	-0.055	Normal	Kaier et al. (2016)[124]
Vascular complications	-0.046	-0.076	-0.016	Normal	Kaier et al. (2016)[124]

* Standard deviation of 0.02 assumed due to lack of data
† Assumed same rate as pacemaker implantation, reported by Lange et al. (2016)
‡ Assumed same rate as non-disabling stroke, reported by Kaier et al. (2016)
Key: LCI – lower confidence interval; UCI – upper confidence interval

6.3 Analyses

6.3.1 Cost-utility analysis

Base case analysis

In the base case analysis, the cost-utility of TAVI compared with SAVR in patients at low or intermediate risk of surgical complications was estimated over a 15-year time horizon, with all future costs and consequences discounted at 4% per annum. The expected costs and QALYs per 100 patients (the current number of patients undergoing SAVR/eligible for TAVI in a given year) were estimated using probabilistic sensitivity analysis.[106] Ten thousand Monte Carlo iterations of the model were performed, with all parameter estimates randomly and simultaneously sampled from predefined probability distributions in each simulation using Microsoft Excel software.[126] Choice of probability distribution was informed by the nature and availability of the respective parameter. Where possible, published evidence was used and, where evidence was limited or unavailable, plausible distributions or ranges were derived with the support of the Expert Advisory Group.

The overall costs and QALYs associated with TAVI and SAVR were calculated by averaging the results of the Monte Carlo simulations. Summarising across simulations provides an estimate of overall average costs and consequences, as well as the uncertainty associated with those values. Summary cost-effectiveness measures included an incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (INMB). The ICER presents the additional costs divided by the additional benefits of TAVI relative to SAVR. The intervention was considered to be cost-effective if the ICER fell below €20,000 per QALY gained, which is the most conservative willingness to pay (WTP) threshold assumed in Ireland.[95] The INMB is an alternative summary measure that reflects the value of an intervention in monetary terms if a WTP threshold is known. It scales both costs and QALYs to the same metric (that is, costs) and summarises the cost-effectiveness of an intervention in the context of the assumed WTP threshold: an intervention is considered to be cost-effective at that threshold if the INMB is positive; conversely, it is not considered to be cost-effective if the summary statistic is negative. In this analysis, the INMB was estimated using the same €20,000 WTP threshold.

In addition to the above summary statistics, the probability that either TAVI or SAVR was the cost-effective procedure across a range of different WTP thresholds was estimated using cost-effectiveness acceptability curves (CEACs). The CEACs summarise the uncertainty in the optimal procedure by reporting the probability that it was the cost-effective option at a given WTP threshold.

Sensitivity and scenario analyses

Both univariate sensitivity analysis and scenario analyses were undertaken to assess the impact of variations in key parameters and model assumptions on cost-effectiveness findings. A univariate sensitivity analysis shows how influential uncertainty in each parameter is by itself and how sensitive the results are to fluctuations in each parameter value. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Deterministic univariate sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower bounds, while all other parameters were held at their base case value.

Scenario analyses involving changes in key sources of clinical evidence and model assumptions were undertaken to assess the robustness of the results. A list of the different scenario analyses performed is provided below.

- Evidence from an observational study (PARTNER S3i)[98] of TAVI was applied to assess the impact of a second-generation TAVI device (SAPIEN 3) on cost-effectiveness findings in intermediate risk patients, along with a mix of first- and second-generation devices.
- The full complement of treatment effects of TAVI relative to SAVR from the trials was applied to assess the impact of assuming differences in all outcomes between TAVI and SAVR on cost-effectiveness.
- The increased RR of mortality due to aortic stenosis was dropped on the basis that it may be captured in the all-cause mortality rates.
- The capital cost of purchasing and developing a new cath lab was dropped from the model on the assumption that additional capacity may not be required in the Irish healthcare system to facilitate the increased demand for TAVI procedures.
- The disutilities applied to postoperative complications were dropped from the model on the assumption that these were captured in the trial data.
- A five-year and lifetime time horizon was separately evaluated to assess the impact of a shortened and extended time horizon on cost-effectiveness findings.

6.3.2 Budget impact analysis

Base case analysis

The BIA was conducted from the perspective of the publicly funded health and social care system. The analysis estimated the incremental annual cost of delivering a TAVI care pathway relative to continued SAVR in patients at low or intermediate risk of complications in the public health care system in Ireland over five years. As with the CUA, indirect costs were not included in the analysis. Costs used in the BIA were the same as those used in the CUA analysis.

Sensitivity analysis

As in the CUA, a deterministic univariate sensitivity analysis was undertaken to assess the impact of variations in key parameters on the budget impact findings.

A scenario analysis that removed the capital cost of purchasing and developing a new cath lab was considered in the event that additional capacity would not be required in the Irish healthcare system to facilitate the increase in demand for TAVI procedures.

A scenario analysis that considered the budget impact of an ageing population on the demand for AVR was also undertaken. For the purposes of this analysis, it was assumed that demand for AVR (both SAVR and TAVI) would increase by 5% per annum, which is slightly higher than annual rate of increase (4%) in the population aged over 65 years (or over 70, over 75, over 80, or over 85) in Ireland.[58] A conservatively higher rate was assumed to account for other potential increases in demand that are not due to changing demographics alone, but increased prevalence of severe symptomatic aortic stenosis, for example.

6.4 Results

The results of the CUA and BIA are presented separately in this section.

6.4.1 Cost-utility findings

Base case analysis

Table 6.12 summarises the expected costs and QALYs of TAVI and SAVR in patients at low and intermediate risk of surgical complications, along with the cost-utility findings in both populations. Over 15 years, TAVI had lower expected costs and higher QALY gains compared with SAVR in low and intermediate risk patients. The cost saving in the patient cohorts was estimated to be €198 (95% CI: €-8,193 to €7,643) per patient in the intermediate risk population and €387 (95% CI: €-8,355 to €7,702) in the low risk population. QALYs were higher among TAVI patients than SAVR patients most likely due to the relative benefits of this minimally invasive procedure on patients' health-related quality of life in the short-term (up to six months). In intermediate risk patients, the incremental QALY gain over 15 years was 0.058 (95% CI: -0.060 to 0.181); in low risk patients, the QALY gain was 0.021 (95% CI: -0.129 to 0.172). The QALY gain associated with TAVI in intermediate risk patients was slightly more pronounced than low risk patients, likely due to the decreased risk of acute kidney injury at 30 days following TAVI in intermediate risk patients. The risk of major complications in the low risk population was comparable between TAVI and SAVR throughout the model.

Although considerable uncertainty in costs and QALYs were observed, since TAVI was less costly and more effective than SAVR in both patient populations, the intervention was considered the dominant procedure (an intervention dominates another if it is both less costly and more effective). At a WTP threshold of €20,000 per QALY gained, the INMB was positive in both patient populations, although with substantial uncertainty observed: the mean INMB was €1,359 (95% CI: €-6,755 to €9,685) in intermediate risk patients and €808 (95% CI: €-7,837 to €9,417) in low risk patients. In light of the uncertainty, the probability that TAVI was cost-effective at a WTP threshold of €20,000 per QALY gained was higher than SAVR in both groups: 61.8% and 57.1% in intermediate and low risk patients, respectively.

The results of the probabilistic analysis are summarised on an incremental cost-effectiveness plane in Figure 6.2 and Figure 6.3 for patients at intermediate and low risk of surgical complications, respectively. The planes plot the incremental costs and QALYs of TAVI relative to SAVR. The point-estimates largely fall below the €20,000 WTP threshold, with many in the south-east quadrant of the incremental cost-effectiveness planes (where the intervention is less costly and more effective), suggesting TAVI is cost-effective. However, substantial uncertainty in costs and QALYs can be observed in both populations, with many point-estimates falling above the €20,000 per QALY gained threshold, for example. Figures 6.4 and 6.5 present the cost-effectiveness acceptability curves in patients at intermediate and low risk of surgical complications, respectively. In both populations, TAVI had the highest probability of being cost-effective at all WTP thresholds up to €100,000.

Univariate sensitivity analysis

Deterministic univariate sensitivity analysis was undertaken to investigate the sensitivity of the base case findings to changes in input parameters. Changes to the INMB statistic are reported rather than the ICER, which had a negative base case value. The INMB statistic provides a more intuitive way to assess the impact of changes in input parameters on the cost-effectiveness of TAVI relative to SAVR, assuming a WTP threshold of €20,000. Although all parameter inputs were varied in the sensitivity analysis, the parameters that had the greatest impact on the INMB are reported here. As in the base case analysis, a positive INMB suggests TAVI is cost-effective, whereas a negative value suggests it is not.

Results of the univariate sensitivity analysis are presented in Figure 6.6 and 6.7 for intermediate and low risk patients, respectively. The cost-effectiveness of TAVI in intermediate risk patients was mainly affected by the cost of the TAVI and SAVR procedures. TAVI had a negative INMB (€-3,627) and was no longer cost-effective when the lower parameter estimate of €24,120 was assumed for the cost of the

Table 6.12 Cost-effectiveness findings – base case analysis

Procedure	Costs (95% CI)	QALYs (95% CI)	Incremental costs (95% CI)	Incremental QALYs (95% CI)	ICER	INMB (95% CI)*	p(CE)*
Intermediate risk patients							
SAVR	€42,879 (€36,493 to €49,946)	4.942 (4.668 to 5.227)	-	-	-	-	0.382
TAVI	€42,681 (€36,584 to €49,475)	5.000 (4.746 to 5.262)	€-198 (€-8,193 to €7,643)	0.058 (-0.060 to 0.181)	Dominant	€1,359 (€-6,755 to €9,685)	0.618
Low risk patients							
SAVR	€38,643 (€31,071 to €48,328)	6.181 (5.903 to 6.433)	-	-	-	-	0.429
TAVI	€38,256 (€31,064 to €47,690)	6.203 (5.929 to 6.448)	€-387 (€-8,355 to €7,702)	0.021 (-0.129 to 0.172)	Dominant	€808 (€-7,837 to €9,417)	0.571

* At €20,000 willingness-to-pay
Key: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; p(CE) – probability of being the cost-effective option at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

Figure 6.2 Incremental cost-effectiveness plane of TAVI versus SAVR in patients at intermediate risk

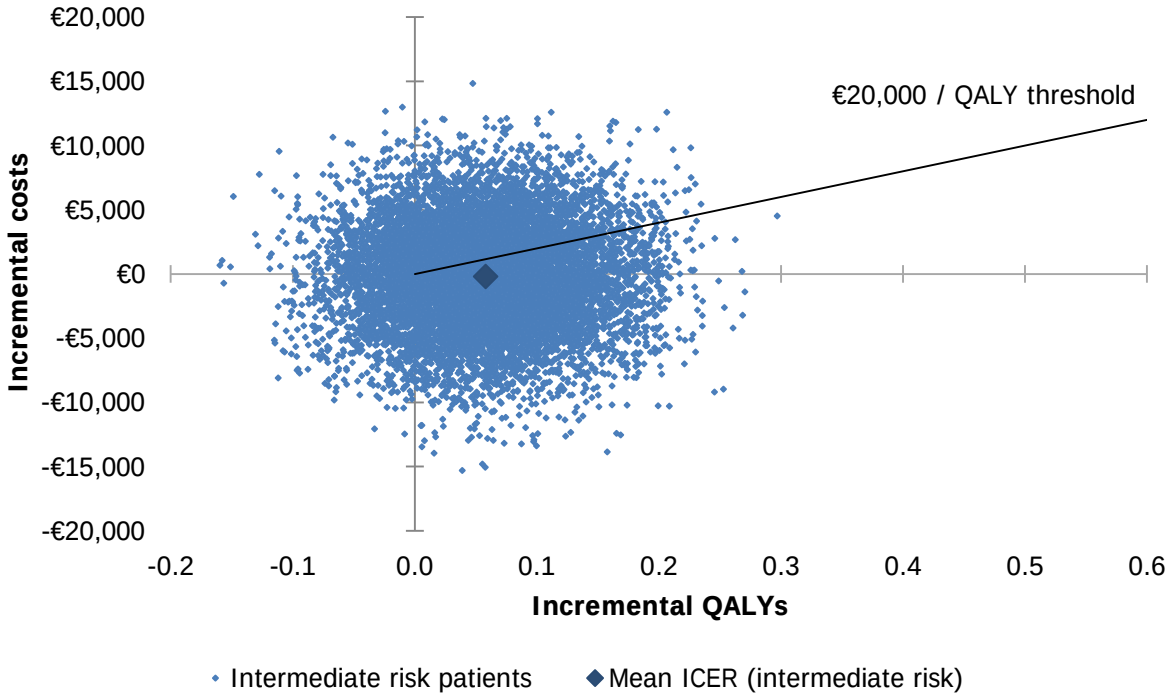


Figure 6.3 Incremental cost-effectiveness plane of TAVI versus SAVR in patients at low risk

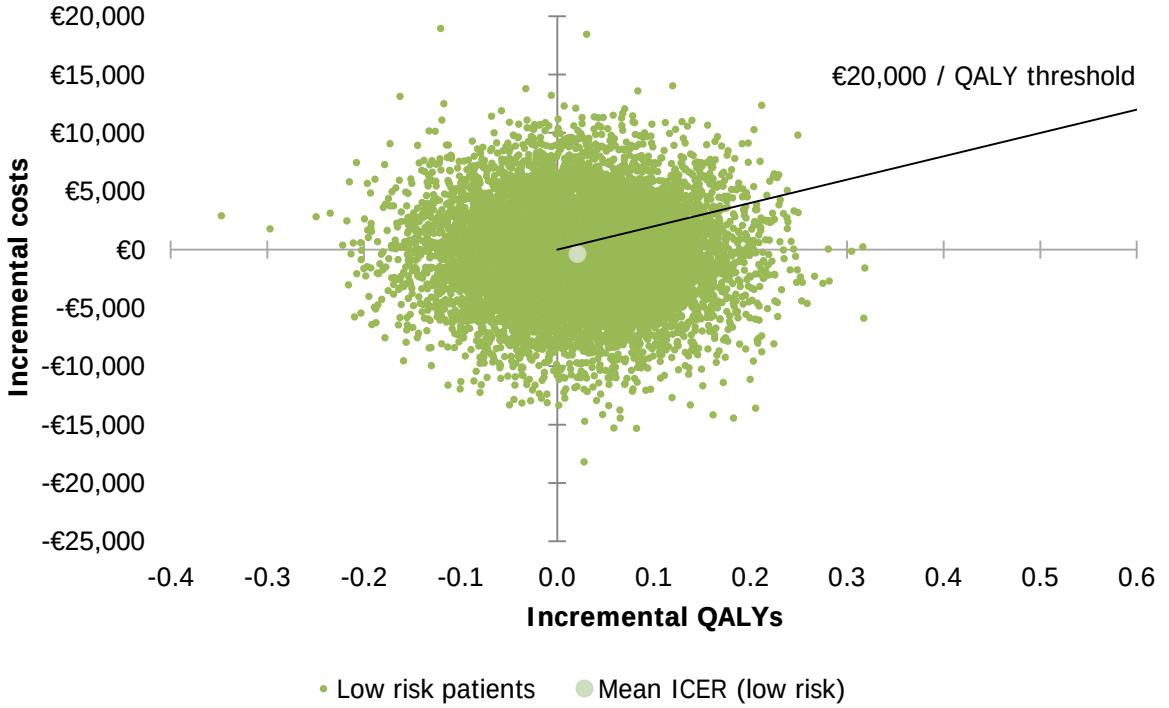


Figure 6.4 Cost-effectiveness acceptability curves: intermediate risk

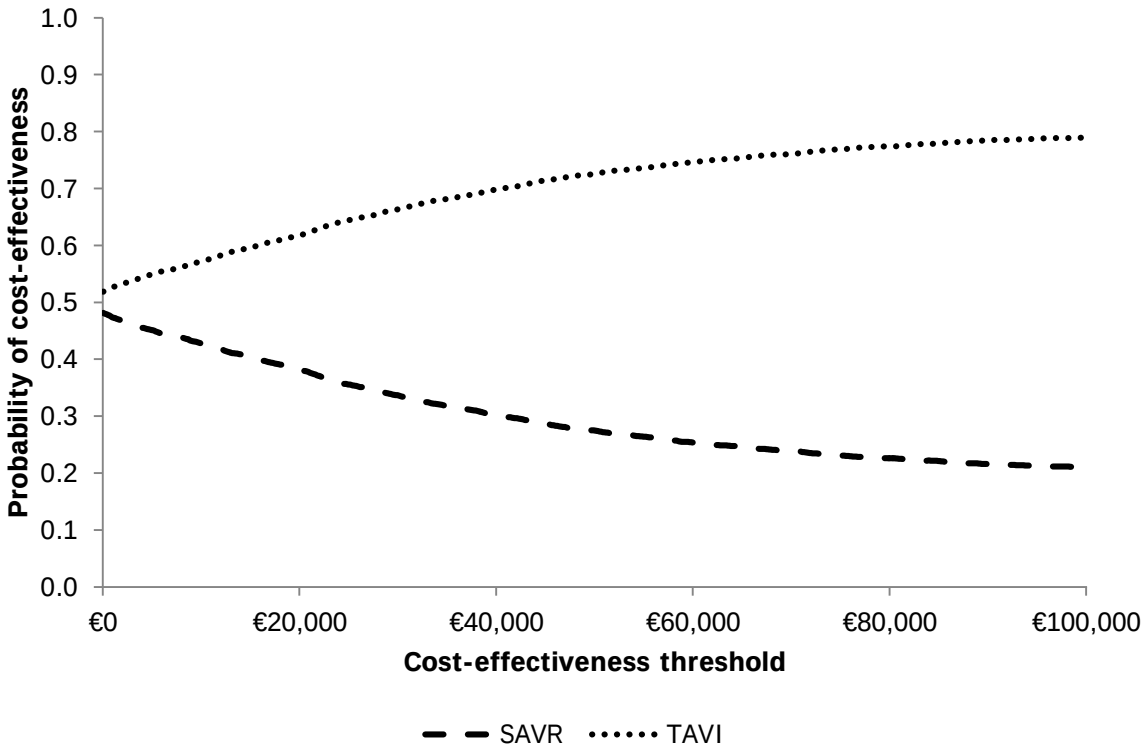
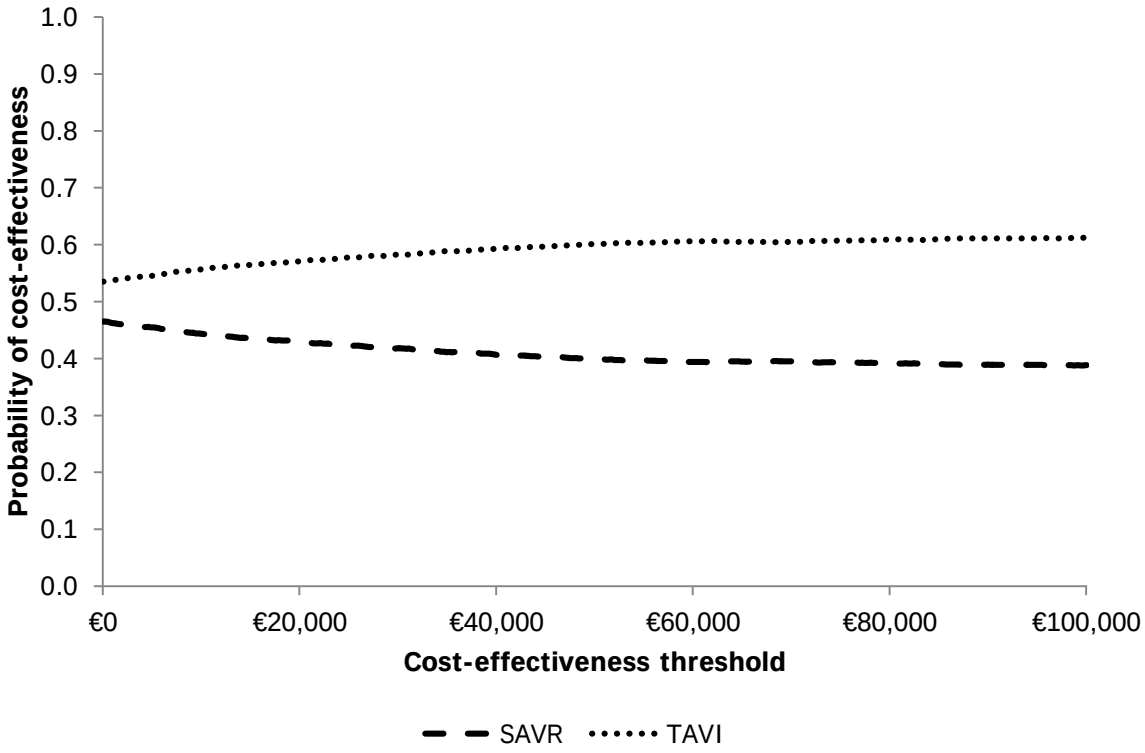


Figure 6.5 Cost-effectiveness acceptability curves: low risk



SAVR procedure (base case cost was €29,342). Similarly, at the higher cost of €33,792 for TAVI (base case cost was €27,777), the procedure had an INMB of €-4,419 and was no longer cost-effective. Conversely, the cost-effectiveness of TAVI improved when the higher cost estimate (€35,696) for the SAVR procedure was assumed; in this scenario, the INMB increased to €7,948. At the lower cost estimate (€22,833) for the TAVI procedure, the INMB increased to €6,539. Although the INMB was somewhat sensitive to changes in other parameters, such as utility at one year following TAVI or SAVR, the procedure remained cost-effective under all scenarios. In low risk patients, changes in the cost of TAVI and SAVR procedures had a similarly pronounced effect on the INMB of TAVI. The cost-effectiveness of the procedure was also sensitive to changes in utility at one year following TAVI or SAVR (Figure 6.7). For instance, at the higher utility value of 0.813 at one year following SAVR, the INMB of TAVI compared with SAVR was €-1,362. Few other parameters had an effect on the INMB of TAVI in low risk patients.

Figure 6.6 Univariate sensitivity analysis: intermediate risk patients

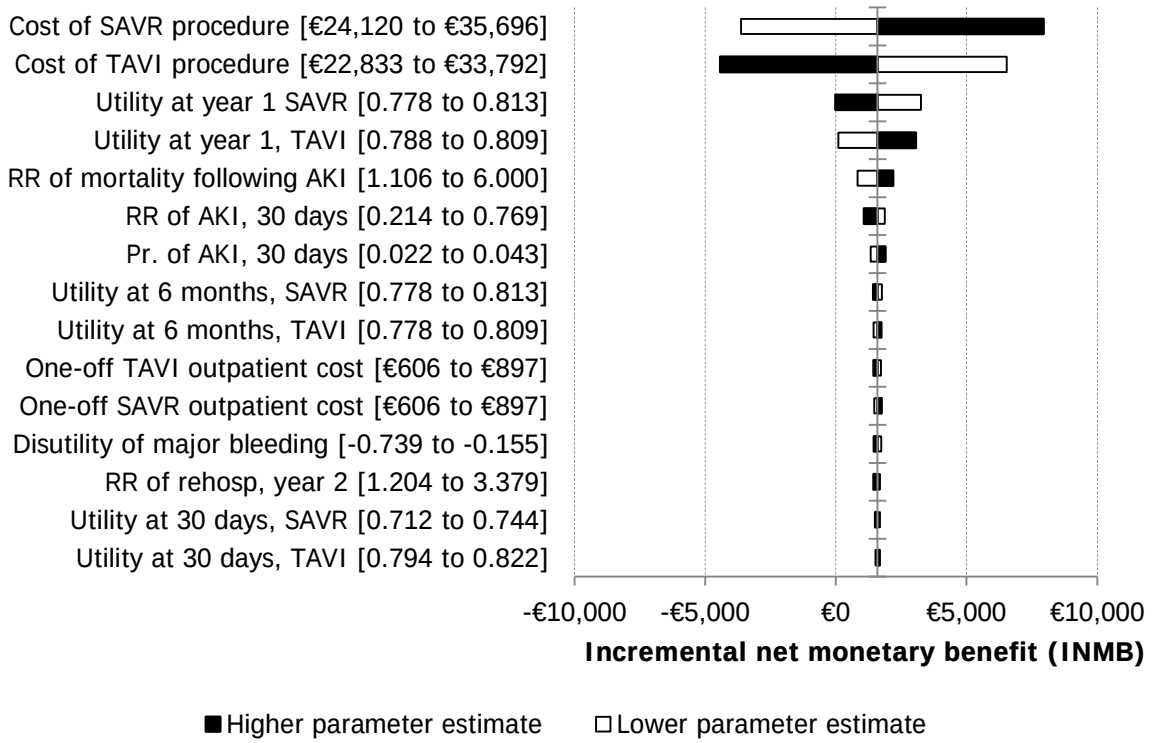
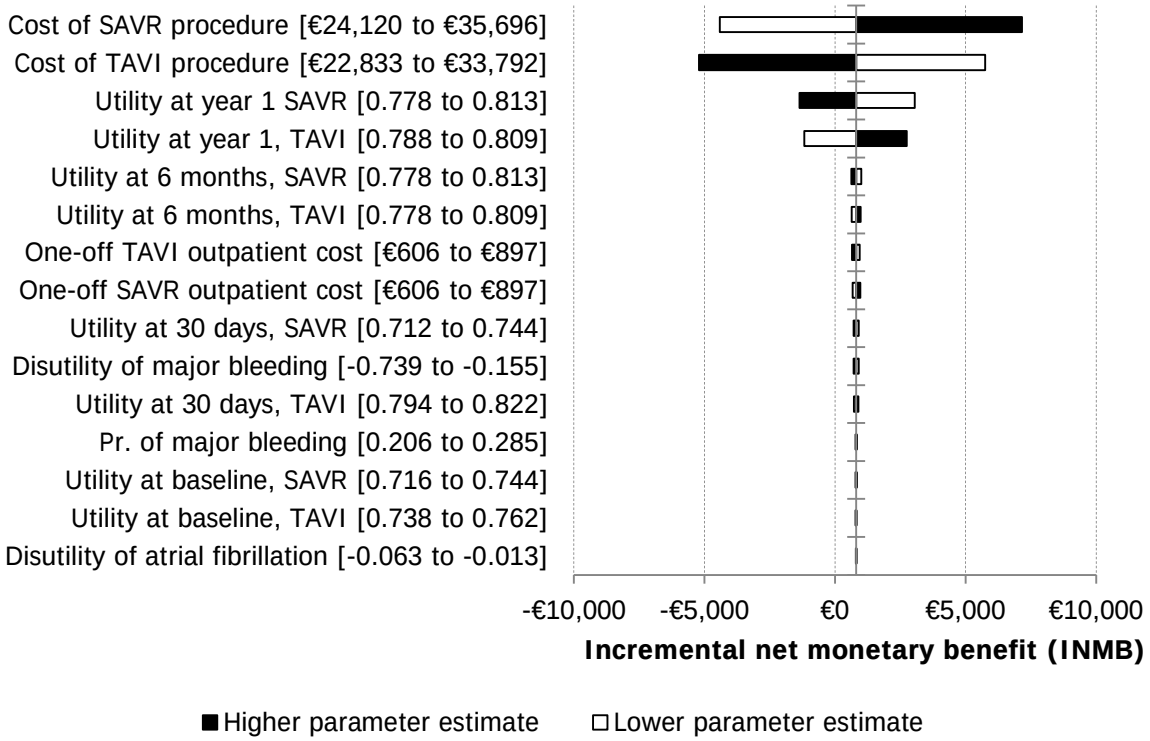


Figure 6.7 Univariate sensitivity analysis: low risk patients



Scenario analyses

A scenario analysis using evidence from the PARTNER S3i registry was undertaken to assess the impact on cost-utility findings of the second-generation device, SAPIEN 3, in intermediate risk patients (Table 6.13). With fewer postoperative and major complications, the device had considerably lower costs and greater QALY gains relative to SAVR than the first-generation device (SAPIEN XT). At a €20,000 WTP per QALY gained threshold, the device had an INMB of €14,826 (95% CI: €5,777 to €23,965). The probability that TAVI was cost-effective at the same threshold was 100%. A meta-analysis of the first- and second-generation devices was also undertaken to investigate the impact of assuming a mix of evidence from PARTNER 2 and PARTNER S3i on cost-utility findings in a separate scenario analysis. As detailed in Table 6.13, TAVI was still less costly and more effective than SAVR, although some uncertainty in the INMB of TAVI compared with SAVR was observed (mean INMB: €1,710 [95% CI: €-6,654 to €9,935]). The probability that the procedure was cost-effective remained high, estimated at 65.6%.

Table 6.13 Cost-effectiveness findings – scenario analysis using PARTNER S3i in intermediate risk patients

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
PARTNER S3i				
SAVR	€43,047 (€36,456 to €50,529)	4.974 (4.694 to 5.26)	-	0.000
TAVI	€39,015 (€32,916 to €45,986)	5.514 (5.253 to 5.768)	€14,826 (€5,777 to €23,965)	1.000
PARTNER 2 and S3i (meta-analysis)				
SAVR	€42,951 (€36,443 to €50,039)	4.947 (4.665 to 5.235)	-	0.344
TAVI	€42,612 (€36,619 to €49,708)	5.016 (4.756 to 5.278)	€1,710 (€-6,654 to €9,935)	0.656

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

Applying the full complement of treatment effects of TAVI relative to SAVR had no effect on the cost-effectiveness of TAVI in intermediate risk patients, but considerably improved the cost-effectiveness of TAVI in low risk patients (Table 6.14). With all effects applied, the probability that TAVI was cost-effective in this population was 75.7% (up from 57.2% in the base case analysis).

Table 6.14 Cost-effectiveness findings – scenario analysis with all treatment effects of TAVI relative to SAVR applied

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
Intermediate risk patients				
SAVR	€43,029 (€36,595 to €50,242)	4.939 (4.657 to 5.228)	-	0.374
TAVI	€42,737 (€35,678 to €51,196)	5.005 (4.642 to 5.337)	€1,596 (€-8,730 to €11,536)	0.626
Low risk patients				
SAVR	€38,707 (€31,167 to €48,701)	6.180 (5.913 to 6.43)	-	0.243
TAVI	€38,047 (€30,830 to €48,512)	6.310 (5.999 to 6.572)	€3,267 (€-7,068 to €12,997)	0.757

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

In the base case analysis, an increased risk of mortality due to aortic stenosis was applied to intermediate (RR 1.412) and low risk patients (RR 1.197) beyond the observed trial data. Both RRs were dropped in a scenario analysis on the assumption that mortality in these populations may be comparable to the general population. The findings from this scenario analysis are presented in Table 6.15. Dropping the RR of mortality due to aortic stenosis in both populations had the effect of increasing

costs and the number of QALY gains in the economic model as more patients lived for longer, but had no effect on the base case findings in that TAVI remained cost-effective. The same uncertainty was observed in both patient populations.

Table 6.15 Cost-effectiveness findings – scenario analysis with no increased risk of mortality due to aortic stenosis

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
Intermediate risk patients				
SAVR	€45,043 (€38,313 to €53,026)	5.47 (5.183 to 5.752)	-	0.364
TAVI	€44,807 (€38,170 to €52,856)	5.53 (5.265 to 5.785)	€1,433 (€-7,053 to €9,715)	0.637
Low risk patients				
SAVR	€39,564 (€31,718 to €50,131)	6.541 (6.295 to 6.749)	-	0.432
TAVI	€39,174 (€31,474 to €49,574)	6.561 (6.314 to 6.751)	€792 (€-7,577 to €9,495)	0.568

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

The capital cost of purchasing and developing a new cath lab was included in the base case analysis to reflect the additional capacity that will likely be required in the Irish healthcare system to facilitate an increased demand for TAVI procedures. In this scenario, the capital cost was excluded on the assumption that the additional procedures could be performed within existing capacity constraints. As detailed in Table 6.16, excluding the capital cost per patient of purchasing and developing a new cath lab had no major effect on the cost-effectiveness findings. TAVI was slightly less costly in both patient populations and more cost-effective: the procedure had a mean INMB of €2,695 (95% CI: €-5,487 to €10,989) and 72.9% probability of being cost-effective in intermediate risk patients, and a mean INMB of €2,032 (95% CI: €6,413 to €10,412) and 67.9% probability of being cost-effective in low risk patients.

In the base case analysis, a utility penalty, or disutility, was applied to the baseline utility of patients in TAVI and SAVR that experienced a postoperative complication at 30 days. However, the disutility of postoperative complications may have been captured in the reported trial data at 30 days, suggesting the base case analysis may have double-counted the effect of postoperative complications on patients health related quality of life. In a scenario analysis, the disutilities applied to postoperative complications were dropped from the model to investigate the impact on cost-utility findings. The results from the scenario analysis are presented in Table 6.17 for low

Table 6.16 Cost-effectiveness findings – scenario analysis with no cath lab capital costs included

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
Intermediate risk patients				
SAVR	€42,964 (€36,572 to €50,451)	4.942 (4.672 to 5.23)	-	0.272
TAVI	€41,479 (€35,401 to €48,813)	5.003 (4.751 to 5.258)	€2,695 (€-5,487 to €10,989)	0.729
Low risk patients				
SAVR	€38,545 (€30,999 to €48,726)	6.180 (5.899 to 6.433)	-	0.321
TAVI	€36,933 (€29,833 to €46,295)	6.201 (5.923 to 6.456)	€2,032 (€-6,413 to €10,412)	0.679

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

and intermediate risk patients. Excluding disutilities from the model had no effect on the results, suggesting any double-counting that may have occurred in the base case analysis is unimportant.

Table 6.17 Cost-effectiveness findings – scenario analysis with no disutilities (for postoperative complications) applied

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
Intermediate risk patients				
SAVR	€42,991 (€36,610 to €50,130)	4.957 (4.678 to 5.24)	-	0.375
TAVI	€42,633 (€36,382 to €49,836)	5.006 (4.742 to 5.268)	€1,341 (€-6,865 to €9,544)	0.625
Low risk patients				
SAVR	€38,644 (€31,143 to €48,266)	6.192 (5.907 to 6.439)	-	0.434
TAVI	€38,223 (€31,062 to €47,852)	6.206 (5.931 to 6.456)	€708 (€-7,657 to €9,259)	0.566

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

In a final scenario analysis, differential time horizons were assumed to investigate potential structural uncertainty. Both a shortened (five-year) and extended (lifetime) time horizon was modelled (Table 6.18). Over the shortened five-year time horizon, costs and QALYs were lower than in the base case analysis, but the INMB remained relatively unchanged in intermediate and low risk patients. In the extended time horizon, QALYs were somewhat higher since patients lived for longer, while costs remained broadly unchanged. Although TAVI was cost-effective in the lifetime time horizon, considerable uncertainty remains over the durability of the valve in the

Table 6.18 Cost-effectiveness findings – scenario analysis with differential time horizons

Procedure	Costs (95% CI)	QALYs (95% CI)	INMB (95% CI)*	p(CE)*
Intermediate risk				
5 years				
SAVR	€38,441 (€32,781 to €44,717)	2.835 (2.731 to 2.939)	-	0.388
TAVI	€38,146 (€32,833 to €44,397)	2.878 (2.777 to 2.980)	€1,153 (€-6,850 to €9,162)	0.612
30 years				
SAVR	€43,187 (€36,701 to €50,486)	5.077 (4.770 to 5.403)	-	0.359
TAVI	€42,888 (€36,580 to €50,037)	5.137 (4.844 to 5.434)	€1,491 (€-6,995 to €9,644)	0.642
Low risk				
5 years				
SAVR	€34,078 (€28,142 to €41,085)	3.325 (3.238 to 3.405)	-	0.404
TAVI	€33,595 (€28,084 to €40,080)	3.353 (3.268 to 3.431)	€1,047 (€-7,338 to €9,405)	0.596
30 years				
SAVR	€39,029 (€31,509 to €49,133)	6.450 (6.122 to 6.765)	-	0.444
TAVI	€38,788 (€31,524 to €48,669)	6.473 (6.145 to 6.777)	€687 (€-7,818 to €9,463)	0.556

* At €20,000 willingness-to-pay
Key: INMB – incremental net monetary benefit; p(CE) – probability of being cost-effective at a willingness-to-pay of €20,000; QALYs – quality-adjusted life years

longer-term. Valve failure requiring reintervention due to structural deterioration,[127] for example, would likely affect the costs and benefits of the intervention over the extended time horizon. However, due to a lack of long-term follow up on TAVI, the durability of the valve is unknown and cannot be modelled at this time.

6.4.2 Budget impact findings

Base case analysis

The BIA was estimated over five years for a cohort of 100 patients in year one, plus an additional 100 patients in year two, and so on. A proportional split of low (67%) versus intermediate (33%) risk patients was assumed to more accurately reflect the budget impact of implementing a TAVI care pathway in the public system in Ireland using a synthesis of evidence from the GARY registry in Germany[60] and Tanner et al.[59] on TAVI in Ireland. Table 6.19 presents the results of the base case analysis. Over five years, if patients at low and intermediate risk of surgical complications underwent TAVI, the procedure was estimated to cost approximately the same as SAVR. The results of probabilistic analysis suggest TAVI could save €0.1 million (95% CI: €-3.1 to €2.9) over five years, which is approximately budget neutral. The

Table 6.19 Budget impact findings – base case analysis in low and intermediate risk patients (millions)

Year	SAVR (95% CI)	TAVI (95% CI)	Cost difference (95% CI)
Year 1	€3.2 (€2.8 to €3.6)	€3.6 (€3.3 to €4.1)	€0.5 (€-0.1 to €1.1)
Year 2	€3.3 (€2.9 to €3.7)	€3.1 (€2.8 to €3.6)	€-0.1 (€-0.7 to €0.5)
Year 3	€3.4 (€3.0 to €3.8)	€3.2 (€2.8 to €3.7)	€-0.1 (€-0.7 to €0.5)
Year 4	€3.5 (€3.0 to €3.9)	€3.3 (€2.9 to €3.8)	€-0.1 (€-0.7 to €0.5)
Year 5	€3.6 (€3.1 to €4.0)	€3.4 (€3.0 to €3.9)	€-0.1 (€-0.7 to €0.5)
Total	**€16.8 (€14.8 to €19.2)**	**€16.8 (€14.8 to €18.9)**	**€-0.1 (€-3.1 to €2.9)**

up-front capital cost of building and purchasing additional cath lab capacity was estimated to add €0.5 million (95% CI: €-1.1 to €1.1) to the budget in year one, but the procedure would subsequently save €0.1 million (95% CI: €-0.7 to €0.5) in each subsequent year, proving approximately budget neutral over the five-year time horizon.

Sensitivity and scenario analyses

As in the CUA, a univariate sensitivity analysis was undertaken to assess the impact on the budget of variations in input parameters. The results are presented separately for low and intermediate risk populations, and based on the same proportional split of low (33%) versus intermediate (67%) risk patients assumed in the base case analysis. Although all parameter inputs were varied in the univariate sensitivity analysis, the parameters that had the greatest impact on the budget are summarised here.

Figure 6.8 and 6.9 present the results of the univariate sensitivity analysis in intermediate and low risk patients, respectively. In the base case analysis, potential savings of €0.1 million could be achieved over five years if patients at intermediate and low risk of surgical complications undergo TAVI rather than SAVR. Of the potential €0.1 million savings, €0.03 million arise from treating intermediate risk patients (Figure 6.8), and €0.05 million from treating low risk patients (Figure 6.9). In both populations, the budget impact was mainly affected by the cost of the TAVI and SAVR procedures. Savings of €1.1 million and €2.2 million could be achieved in intermediate and low risk populations, respectively, if the cost of SAVR was as high as €35,696, generating a potential total cost saving of almost €3.3 million. Further, savings of €0.8 million (intermediate risk patients) and €1.7 million (low risk patients) could be achieved if the cost of a TAVI procedure was as low as €22,833, generating a total cost saving of €2.5 million.

However, replacing SAVR with TAVI in intermediate and low risk patients could respectively add €0.8 million and €1.7 million to the budget (€2.5 million overall) if

Figure 6.8 BIA: univariate sensitivity analysis in intermediate risk patients

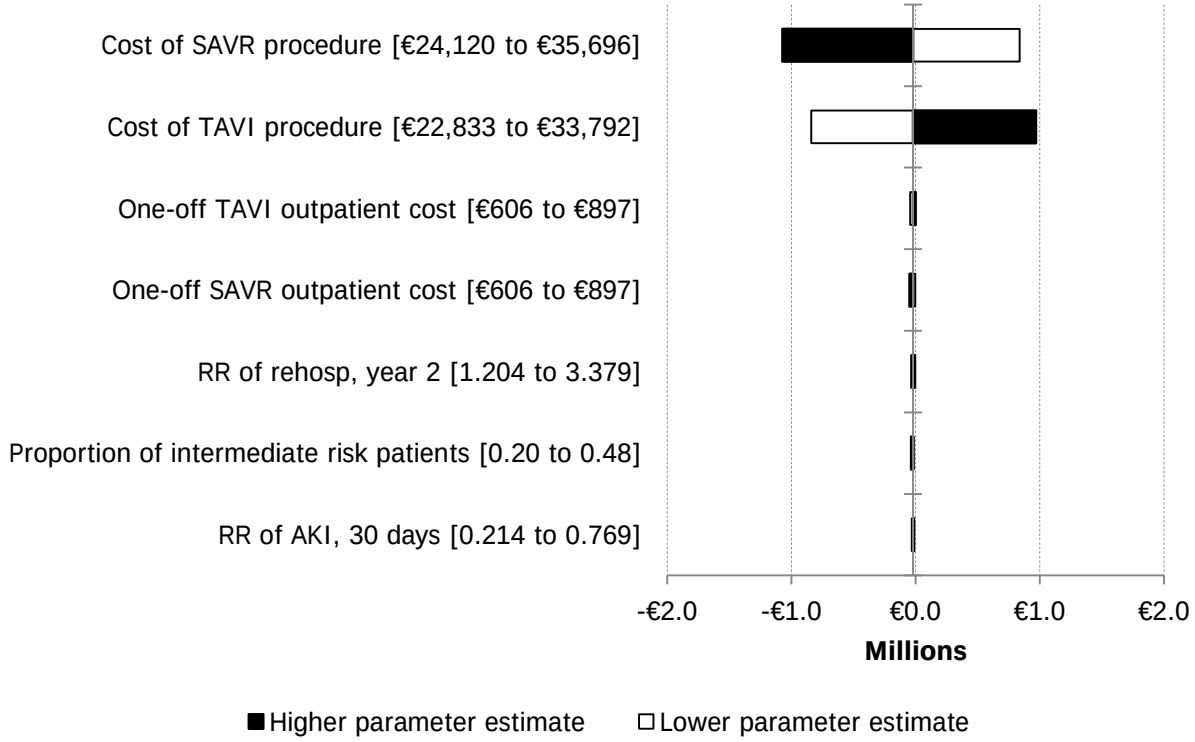
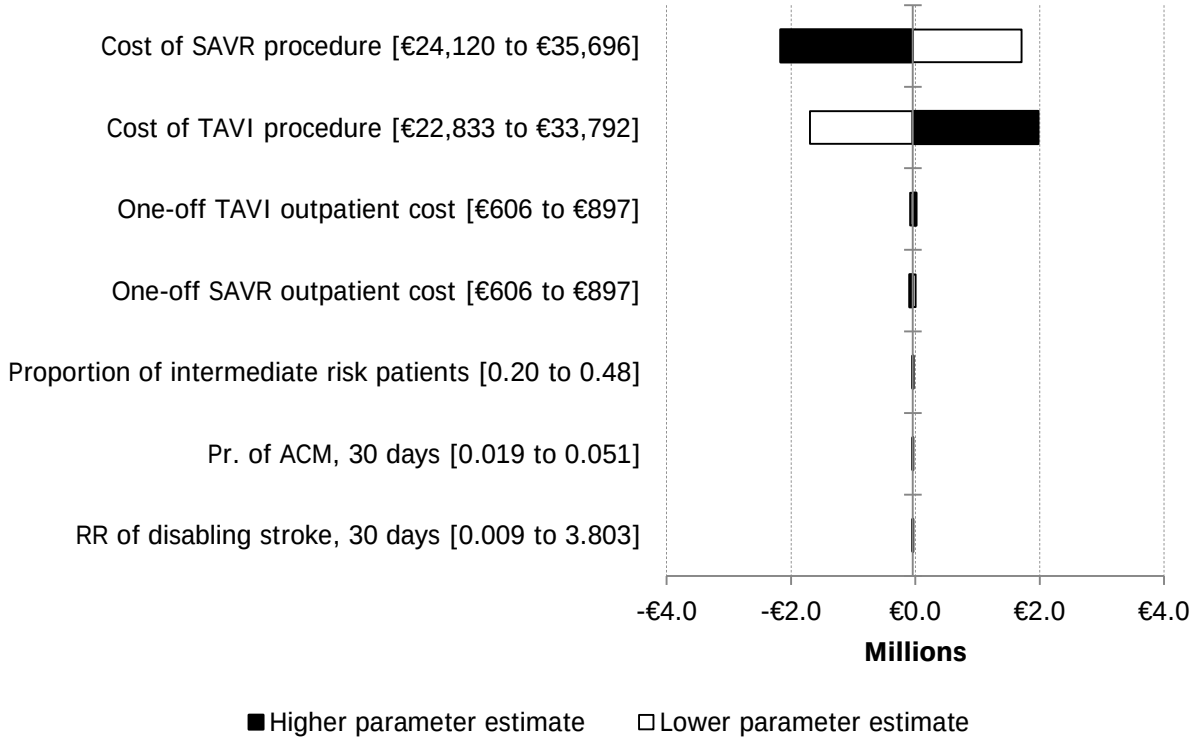


Figure 6.9 BIA: univariate sensitivity analysis in low risk patients



the cost of a SAVR procedure was as low as €24,120. If the cost of TAVI was as high as €33,792, the procedure could add €1.0 million and €2.0 million more to the budget than SAVR (€3.0 million overall) in intermediate and low risk patients, respectively.

The budget impact was robust to variations in the proportion of intermediate to low risk patients, along with all other parameters.

A scenario analysis that excluded the capital cost of purchasing and developing a new cath lab was undertaken on the assumption that the increased demand for TAVI could be facilitated within current capacity constraints. The results of the scenario analysis are presented in Table 6.20. If TAVI could be delivered within existing infrastructure, the estimated budget impact was cost-saving, or approximately budget neutral, as in the base case analysis. Over five years, TAVI was estimated to save €0.8 million (95% CI: €-3.8 to €2.3), with annual savings of approximately €0.2 million available each year.

Table 6.20 Budget impact findings – scenario analysis with no cath lab capital costs included (millions)

Year	SAVR (95% CI)	TAVI (95% CI)	Cost difference (95% CI)
Year 1	€3.2 (€2.8 to €3.7)	€3.0 (€2.6 to €3.5)	€-0.2 (€-0.8 to €0.4)
Year 2	€3.3 (€2.9 to €3.8)	€3.1 (€2.7 to €3.6)	€-0.2 (€-0.8 to €0.5)
Year 3	€3.4 (€2.9 to €3.9)	€3.2 (€2.8 to €3.7)	€-0.2 (€-0.8 to €0.5)
Year 4	€3.5 (€3.0 to €3.9)	€3.3 (€2.9 to €3.8)	€-0.2 (€-0.8 to €0.5)
Year 5	€3.6 (€3.1 to €4.1)	€3.4 (€3.0 to €3.9)	€-0.2 (€-0.8 to €0.5)
Total	**€16.9 (€14.7 to €19.2)**	**€16.1 (€14.1 to €18.3)**	**€-0.8 (€-3.8 to €2.3)**

A scenario analysis that considered the impact of an ageing population on the demand for AVR was undertaken. An increase in demand of 5% per annum was assumed to reflect the expected increase in patients aged over 70 that may require AVR. The effect of increased demand due to changing demographics simply increased the cost of SAVR and TAVI, but the incremental cost of providing a TAVI care pathway for patients at low and intermediate risk of surgical complications remained budget neutral (Table 6.21), as in the base case analysis (Table 6.19).

Table 6.21 Budget impact findings – scenario analysis reflecting 5% per annum increase in demand for AVR (millions)

Year	SAVR (95% CI)	TAVI (95% CI)	Cost difference (95% CI)
Year 1	€3.2 (€2.8 to €3.6)	€3.7 (€3.3 to €4.1)	€0.5 (€-0.1 to €1.0)
Year 2	€3.4 (€3.0 to €3.9)	€3.3 (€2.9 to €3.8)	€-0.1 (€-0.8 to €0.5)
Year 3	€3.5 (€3.1 to €4.0)	€3.4 (€3.0 to €3.9)	€-0.1 (€-0.8 to €0.5)
Year 4	€3.6 (€3.2 to €4.1)	€3.5 (€3.1 to €4.0)	€-0.1 (€-0.8 to €0.5)
Year 5	€3.7 (€3.3 to €4.2)	€3.6 (€3.2 to €4.1)	€-0.1 (€-0.8 to €0.5)
Total	**€17.6 (€15.4 to €20.0)**	**€17.5 (€15.5 to €19.8)**	**€-0.1 (€-3.2 to €2.9)**

6.5 Discussion

This chapter presented a health-economic analysis of TAVI compared with SAVR in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications in Ireland. A CUA was undertaken to evaluate the cost-effectiveness of TAVI, and a BIA was undertaken to estimate the costs to the State of implementing a TAVI care pathway in the Irish public health care system. A probabilistic model was used to evaluate the costs and consequences of TAVI and SAVR, and the associated uncertainty in the parameters informing these outcomes. The cost-utility and budget impact findings are summarised and discussed in this section. A discussion of the strengths and limitations of the analysis is also provided.

6.5.1 Summary of the cost-utility findings

The CUA evaluated the costs and consequences of TAVI compared with SAVR in patients at low and intermediate risk of surgical complications in Ireland. Consistent with CUAs, QALYs were used to measure the health benefits associated with TAVI and SAVR. The model considered outcomes for patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications, with cost-effectiveness estimated for a cohort of patients currently undergoing SAVR who could be eligible for TAVI (N=100). Outcomes were modelled over 15 years, which is the expected lifespan, or durability, of the TAVI valve. Beyond this any estimation of costs and QALYs would be speculative as repeat-TAVI is associated with unknown clinical outcomes. The model assumed the perspective of the publicly funded health and social care system in Ireland, and discounted future costs and QALYs at 4% per annum, in line with revised Irish guidelines.[107]

The cost-effectiveness of TAVI was supported in both intermediate and low risk patients in the base case analysis. The device was less costly and more effective than SAVR, meaning TAVI dominated SAVR. The incremental net monetary benefit (INMB) at the conservative willingness-to-pay (WTP) threshold of €20,000 per QALY gained was €1,359 (95% CI: €-6,755 to €9,685) and €808 (95% CI: €-7,837 to €9,417) in intermediate and low risk populations, respectively. Although some

uncertainty in the INMB of TAVI was observed in both populations, the probability that it was cost-effective at €20,000 per QALY gained was relatively high, estimated at 61.8% in intermediate risk patients and 57.1% in low risk patients.

A range of sensitivity and scenario analyses were undertaken to assess the robustness of the results to changes in input parameters and model assumptions. In the univariate sensitivity analysis, the cost-effectiveness of TAVI was mainly affected by the cost of the TAVI and SAVR procedures. At the lower and higher cost estimate for the SAVR (€24,120) and TAVI (€33,792) procedure, respectively, TAVI was no longer cost-effective in intermediate and low risk patients, assuming a WTP threshold of €20,000 per QALY gained. The cost of TAVI and SAVR were based on Irish HIPE data and should reflect the cost of treating cases in Ireland. SAVR costs are based primarily on intermediate and low risk patients, while TAVI costs are probably based primarily on high risk patients. It is possible that TAVI costs may be lower in intermediate and low risk patients on the grounds that they are younger and might be expected to experience fewer complications and may have a shorter length of stay, suggesting TAVI is likely less costly than the upper threshold assumed in this analysis. Few other parameters had an effect on the cost-effectiveness of TAVI in either population.

The cost-utility findings remained broadly unchanged across a variety of scenario analyses that applied the full complement of treatment effects of TAVI relative to SAVR; removed an increased relative risk of mortality due to aortic stenosis; excluded the capital cost of building a new cath lab; excluded disutilities applied to complications; and assumed differential time horizons (a shortened (five-year) time horizon and an extended (lifetime) time horizon). The most notable change in cost-effectiveness findings emerged in the scenario analysis that considered evidence from PARTNER S3i on the second-generation TAVI device, SAPIEN 3, in intermediate risk patients.[98] Although TAVI was cost-effective in the base case analysis, some uncertainty in relation to the INMB was observed, arising from the increased risk of vascular complications, for example. With the second iteration of the device, the complications associated with TAVI were substantially improved. In the scenario analysis, the expected cost per patient over 15 years was lower than in the base case analysis, while the expected QALY gain was higher. With no uncertainty observed in the INMB of TAVI compared to SAVR at the €20,000 per QALY gained threshold, the probability that TAVI was cost-effective was 100%. Although the performance of second-generation devices is superior to first-generation devices, the evidence on SAPIEN 3 in intermediate risk patients derives from an observational study, or registry, and should be interpreted with some caution.

6.5.2 Summary of the budget impact findings

A BIA was undertaken to estimate the expected five-year costs of implementing a TAVI care pathway in the public health care system in Ireland for patients at low and intermediate risk of surgical complications. A probabilistic analysis was used to investigate uncertainty in input parameters and an open-cohort model was assumed to estimate the cost of treating 100 patients each year, which is the number of patients aged 70 years and older currently undergoing isolated SAVR with a bioprosthetic valve and, hence, most likely to be eligible for TAVI. Using a synthesis of evidence from the GARY registry in Germany of isolated TAVI (N=45,567) and data from an Irish hospital on TAVI on the split of low versus intermediate risk patients with severe symptomatic aortic stenosis, the model assumed 67% of the cohort were low risk (n=67) and 33% were intermediate risk (n=33).[60]

The base case analysis found that TAVI was approximately budget neutral over five years relative to SAVR: the estimated budget impact, or cost-saving, was €0.1 million (95% CI: €-3.1 to €2.9). The majority of the savings arise from treating low risk patients (€0.05 million). As in the CUA, a univariate sensitivity analysis was undertaken to assess the impact of varying input parameters on the expected budget impact of TAVI. The estimates were sensitive to changes in the cost of the TAVI and SAVR procedures. Savings of €3.3 million or €2.5 million could be achieved overall if the cost of a SAVR procedure was as high as €35,696 or the cost of a TAVI procedure was as low as €22,833, respectively. Although there may be the potential to save money by moving patients from SAVR to TAVI, it is unlikely that these savings would be fully realised as surgical resources, such as theatre time and staff, would likely be utilised elsewhere. Nevertheless, by switching patients from SAVR to TAVI, there creates an opportunity to release important resources such as hospital and ICU beds and surgical staff to address other demands in the healthcare system. Conversely, TAVI could add €2.5 million or €2.0 million to the budget if the cost of a SAVR procedure was as low as €33,792 or TAVI was as high as €38,447, respectively. The budget impact of TAVI compared to SAVR remained robust to changes in other parameters, including the proportion of patients that were intermediate versus low risk of surgical complications.

To be conservative, the base case analysis assumed additional cath lab capacity would be required to facilitate the increased demand for TAVI in Ireland. However, there may be scope within the current system to facilitate the additional procedures. A scenario analysis in which it was assumed that existing cath lab capacity could meet demand suggested that TAVI could save €0.8 million (95% CI: €-3.8 to €2.3) over five years.

A scenario analysis that investigated the potential increase in demand for AVR due to an ageing population was also undertaken. A 5% per annum increase in demand for AVR increased the budget impact of providing TAVI and SAVR, but the incremental cost of providing a TAVI care pathway relative to SAVR remained budget neutral. The impact of providing a higher proportion of AVR as TAVI in the Irish public health care system is discussed in detail in Chapter 7.

6.5.3 Strengths and limitations

In the absence of applicable published cost-effectiveness evidence from another setting, an economic analysis specific to Ireland was undertaken to assess the costs and consequences of TAVI compared to SAVR in patients at low and intermediate risk of surgical complications. A de novo probabilistic model was developed to investigate the cost-effectiveness and budget impact of the technology. For quality assurance purposes, the model was validated internally at HIQA using a separate software programme. The model had sufficient face validity in that it considered the complete set of clinical endpoints reported in trials, and appropriately modelled those endpoints that showed a meaningful difference in outcomes between TAVI and SAVR. Previous economic analyses were often limited in their application of clinical endpoints. For example, Tam et al. (2018b)[93] in their evaluation of CoreValve™ excluded the risk of paravalvular regurgitation from their model, despite the evidence showing a significant association between the complication and the first-generation device. In two studies[91, 92] that evaluated SAPIEN XT using evidence from PARTNER 2, the risk of aortic reintervention was excluded without any justification. Yet, these studies, among others, included complications in their models for which trials showed no difference in outcomes between TAVI and SAVR.

The structure of the economic model also had sufficient face validity in terms of its structure, which reflected plausible health state transitions using available evidence from clinical trials. For example, the model simulated the long-term risk of important clinical endpoints such as acute kidney injury, disabling stroke and myocardial infarction using evidence from clinical trials. Using a post-clinical endpoint health state, such as post-disabling stroke, the model also simulated an increased risk of mortality in these patients relative to those that were alive and well. Previous economic analyses often included health states for major complications, such as disabling stroke, but few reported applying a higher rate of mortality in these patients. Previous analyses often also modelled implausible health state transitions. For example, Kodera et al.[91] (2018) replicated the same set of transitions throughout their model, seemingly allowing some patients to experience the same major clinical events, such as stroke, multiple times, without any adjustment to the probability of the event occurring. In another study, Tam et al. (2018a)[92] included a transition from an ‘acute kidney injury’ health state to a ‘dialysis’ health state using

evidence from high risk patients. The risk of dialysis in patients at lower surgical risk has not been reported in any trial, and may not reflect the risk observed in higher risk patients.

The economic model simulated outcomes for patients at low and intermediate risk of surgical complications using the best available clinical evidence. However, a number of limitations are acknowledged about these sources. In intermediate risk patients, evidence from a first-generation device (SAPIEN XT)[70] was used in the base case analysis given a lack of clinical evidence on second-generation devices in this population. Although the first-generation device was cost-effective, some uncertainty was observed in this population due to the poor performance of the valve on key complications, such as atrial fibrillation, paravalvular regurgitation, and vascular complications. Newer generation devices likely produce superior clinical outcomes and increased efficiencies from a health system perspective. Although clinical evidence on second-generation devices is lacking in intermediate risk patients, the model applied observational evidence from the PARTNER S3i registry[98] to assess the impact of a second-generation device on cost-effectiveness. The performance of the SAPIEN 3 valve was superior in terms of patient outcomes, which translated into greater cost-savings and QALY gains than the first-generation device.

As highlighted in Chapter 4, the underlying studies of efficacy were designed as either non-inferiority or superiority trials on a composite outcome. The trials had limited power to detect differences in effect on most of the secondary efficacy outcomes as well as the safety endpoints. For the base case analysis, endpoints were only included for which a statistically significant difference in effect was observed in the trials. Extensive sensitivity and scenario analyses were used to explore alternative interpretations of the data to test whether the cost-effectiveness would be different if effects on secondary outcomes had been observed.

Although the estimated cost of the TAVI procedure used in this analysis likely reflects the national average cost of the procedure and all associated postoperative complications, the true cost of the procedure may vary. A large proportion of the estimated cost is influenced by the cost of the TAVI valve, which varies by manufacturer. TAVI valves can range substantially in price from approximately €12,000 to just over €20,000. Depending on the choice of valve, the cost-effectiveness and budget impact of TAVI compared with SAVR may be positively or adversely impacted. Historically, individual hospitals secured privately negotiated contracts with manufacturers in an attempt to increase internal (budget) efficiencies. The same efficiencies could be achieved nationally with similarly negotiated contracts with manufacturers that could positively impact the cost-effectiveness and budget impact of TAVI in Ireland. However, it is recognised that there will be an

ongoing need for a range of valve types as no single device is appropriate in all circumstances.

The economic model did not simulate the risk of prosthetic valve endocarditis, which has been somewhat poorly reported in clinical trials. PARTNER 2 reported outcomes at one and two years in intermediate risk patients and found no significant difference in outcomes between TAVI and SAVR.[70] The complication was not reported in PARTNER 3 in low risk patients.[19] Although the risk of endocarditis is reportedly the same in TAVI and SAVR patients,[128] incidence of the complication, which is extremely rare, can adversely affect patients. Experience from a UK centre of 1,337 patients found that approximately one per cent of TAVI patients (n=13) developed endocarditis over a ten year follow-up, of which 53.8% died (n=7).[129] However, the evidence was likely based on patients that were inoperable or at high surgical risk. As noted in Chapter 3, management of complicated infective endocarditis includes prolonged antibiotic therapy and or surgery involving radical debridement of all infected foreign material including the original prosthesis. Development of prosthetic valve endocarditis is therefore particularly problematic in AVR patients that are initially classified as being inoperable or at high risk of surgical complications, due to their limited treatment options. Although there is no evidence to suggest the risk of endocarditis differs across TAVI and SAVR, it is important that consideration is given to the potential likelihood that patients will experience this event and that patient care pathways take consideration of guideline recommended pre-, peri- and post-operative care of all AVR patients.[3]

Another limitation associated with this analysis relates to utilities in the low risk population. To date, quality of life scores have only been reported for intermediate risk patients.[76] In the absence of relevant quality of life estimates for low risk patients, the model assumed the same utility scores in low risk patients as intermediate risk patients. The implications of this assumption are somewhat unclear as the utility change over time may be more pronounced in the younger, healthier population, suggesting the device may not be as cost-effective as what was reported here. Or, conversely, the utility change may be more pronounced because the low risk population is younger and healthier, meaning that TAVI may be more cost-effective than what was observed here. It is reasonable, however, to assume that the difference in quality of life scores between TAVI and SAVR would be the same in low and intermediate risk patients because of the impact of surgery on patients' health-related quality of life versus a non-surgical procedure.

A key limitation associated with the BIA relates to the ratio of low to intermediate risk patients in the studied cohort. It is unclear what proportion of patients with severe symptomatic aortic stenosis in Ireland is at low versus intermediate risk of surgical complications. A synthesis of evidence from the GARY registry in

Germany[60] on isolated cases of TAVI and a study on isolated TAVI at single site in Ireland[59] was used to estimate the expected proportion of patients that are low versus intermediate risk in Ireland. The evidence suggested that 67% of patients were low risk, and 33% were intermediate risk. These proportions may not accurately reflect the breakdown of low and intermediate risk patients in Ireland; however, sensitivity analyses showed that variations in the proportion of patients at low versus intermediate risk had a very modest effect on the budget impact of TAVI since the procedure was less costly in both populations.

6.6 Summary

The findings presented in this chapter suggest TAVI is less costly and more effective than SAVR in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications. The results were subject to extensive sensitivity and scenario analyses and the interpretation was unaffected by use of different assumptions and parameter values. The budget impact of implementing a TAVI care pathway in the public health care system in Ireland over five years was approximately budget neutral relative to SAVR

6.7 Key messages

- A probabilistic Markov model was developed to evaluate the cost-effectiveness and budget impact of TAVI compared with SAVR in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications in Ireland.
- The model assumed the perspective of the publicly funded health and social care system in the cost-utility analysis (CUA), and modelled costs and consequences over a 15 year time horizon; the expected lifespan of a TAVI valve. Future costs and consequences were discounted at 4% per annum. A conservative willingness-to-pay threshold of €20,000 per quality-adjusted life year (QALY) gained was used in the CUA to summarise cost-effectiveness.
- The economic model used the best available evidence on TAVI devices currently in clinical use to estimate the clinical benefits of the procedure relative to SAVR. In the base case analysis, evidence from the PARTNER 2 trial on the first-generation SAPIEN XT valve was used in intermediate risk patients, while evidence from the PARTNER 3 trial on the second-generation SAPIEN 3 valve was used in low risk patients.
- In both the intermediate and low surgical risk populations, TAVI was less costly and provided a greater number of QALYs than SAVR. Although some uncertainty was observed, the probability that TAVI was cost-effective at the €20,000 willingness-to-pay threshold was 61.8% in intermediate risk patients and 57.1%

in low risk patients.

- The cost-effectiveness of TAVI in intermediate and low risk patients was mainly affected by the cost of the TAVI and SAVR procedures. Sensitivity analyses showed that TAVI was no longer cost-effective at the €20,000 per QALY gained threshold when the higher procedural cost estimate for TAVI (and lower procedural cost estimate for SAVR) was applied in the economic model.
- In the base case budget impact analysis, TAVI was estimated to save €0.1 million (95% CI: €-3.1 to €2.9) compared with SAVR over five years, which is approximately budget neutral. The estimated budget impact was based on treating 100 patients each year, comprising low (n=67) and intermediate (n=33) risk patients, respectively. The cost of extending the TAVI care pathway to patients at all levels of surgical risk was sensitive to changes in the cost of the SAVR and TAVI procedures.
- If the additional TAVI procedures can be performed without requiring additional catheterisation laboratory capacity, the estimated budget impact over five years may be neutral, estimated at €-0.8 million (95% CI: €-3.8 to €2.3).

7 Social, organisational and ethical considerations

This chapter considers the potential social, organisational and ethical issues that may occur if a decision is taken to expand access to TAVI to patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications. This chapter was developed broadly in line with the structure described in the EUnetHTA Core Model®.

7.1 Organisational considerations

The review of clinical effectiveness and safety (Chapter 4) concluded that TAVI is comparable to SAVR in terms of several key clinical effectiveness and safety endpoints for patients at low and intermediate risk of surgical complications. Although some patients at low and intermediate surgical risk are already being treated with TAVI, formally extending TAVI to this patient population is likely to lead to a substantial increase in demand for TAVI. There are a number of organisational implications that would need to be considered in planning to deliver such a change.

As noted in Chapter 2, international clinical guidelines recommend that TAVI should be confined to specialist treatment centres to ensure volume outcomes advantages, with a minimum of 20 procedures per annum suggested.[29] There are currently TAVI centres at four public hospital sites in Ireland. Limiting TAVI to these four centres has addressed the issue of volume outcomes as all four centres meet the minimum volume requirement.

7.1.1 Current service provision of TAVI in Ireland

As stated in Chapter 3, there has been a substantial increase in the number of TAVI procedures since 2015 increasing from 84 in 2015 to 211 in 2018 (Table 7.1). The total number of aortic valve replacements (AVR) provided nationally increased by 18% from 2015 to 2016, but has remained stable since then. The proportion of AVR completed as TAVI increased from 20% to 41% over the same time period. Considering the most recent data, there was an increase of 23% in the number of TAVI procedures from 2017 (n=171) to 2018 (n=211). If TAVI is offered to patients at low and intermediate risk of surgical complications, this trend is likely to continue and potentially accelerate, which could have a significant impact on the organisation and provision of TAVI services in Ireland.

For the purposes of considering additional demand for TAVI, it is assumed that the eligible low and intermediate surgical risk cohort are aged 70 years and older and are currently treated with SAVR using a bioprosthesis. There has been a decline in the number of SAVR procedures in this cohort, since 2015 (Table 7.1).

Table 7.1 Aortic valve replacement procedures in public hospitals 2015-2018

Hospital		Year			
		2015	2016	2017	2018
Mater Misericordiae University Hospital	SAVR*	23	11	18	15
	TAVI	24	33	45	50
St. James's Hospital, Dublin	SAVR*	25	27	29	19
	TAVI	26	35	43	62
Cork University Hospital	SAVR*	45	59	40	53
	TAVI	0	7	15	33
University Hospital Limerick	SAVR*	0	0	1	0
	TAVI	0	0	1	1
Galway University Hospitals	SAVR*	36	17	20	11
	TAVI	34	49	66	65
Total	**SAVR***	**129**	**114**	**108**	**98**
	TAVI	**84**	**125**	**171**	**211**
	Combined	**213**	**239**	**279**	**309**

* SAVR here is restricted with replacement of aortic valve with bioprosthesis as an isolated procedure and in patients aged 70 years and over as that most closely represents the likely eligible cohort for TAVI if TAVI is extended to patients at low and intermediate surgical risk.

TAVI is current standard of care in Ireland for those patients that are inoperable and those at high risk of complications. The cohort most likely to be considered for TAVI as an alternative to SAVR are those patients aged 70 years and older currently undergoing SAVR with a bioprosthesis and not undergoing other surgical procedures such as coronary artery bypass graft or mitral valve repair within the same episode. It is possible that the majority of these patients will become eligible for and may be offered TAVI in preference to SAVR.

Another consideration is that some patients currently access aortic valve replacement (AVR) through private hospitals. The data are not publicly available, so it is not possible to state with any certainty how many patients access surgery through the private hospital system. The HIPE database does record patients treated privately in the public hospital system, and there is substantial regional variation in the proportion treated privately, perhaps suggesting variation in the availability of TAVI services in private hospitals. Between 2015 and 2018, only 8.5% of patients at the Dublin centres (Mater Misericordiae and St. James' Hospital) were private, while at the Cork and Galway University Hospitals the figures were 32.7% and 19.2%, respectively. While the lower percentage in Dublin may reflect greater provision of care locally in private hospitals, it may also reflect patient demographics, so we cannot clearly state what capacity exists in the private hospital system. The capacity at public hospitals is also a reflection of how and when funding for TAVI procedures was introduced at each hospital. From the perspective of demand for services, it is

unclear whether patients currently accessing services privately would switch to the public hospital system if there was a change in policy regarding eligibility for TAVI based on surgical risk. Numerous factors would have to be considered, such as capacity in the private system and whether private hospitals would also extend to provision of TAVI to low and intermediate surgical risk patients. The proportion patients treated as private in the public system has been stable in the period 2015 to 2018 despite changes in the volume of patients treated and the balance of SAVR and TAVI. Hence it may be plausible to assume that the cohort accessing private hospital services is distinct and is unlikely to revert to public hospital care unless there are significant changes to the external environment (e.g., substantial reduction in uptake of private health insurance or reduced provision of TAVI in private hospitals).

A final point to note is that the patients currently receiving TAVI and SAVR do not necessarily represent the demand for procedures as it does not take into account waiting lists and any potential under-diagnosis of severe symptomatic aortic stenosis. The expansion of TAVI to patients at intermediate and low surgical risk would, of itself, not address any issues of capacity earlier in the system. However, conditional on sufficient catheterisation laboratory (cath lab) capacity, given the shorter length of stay associated with TAVI, increasing the proportion of AVR completed as TAVI may allow a higher volume of patients to be treated and thereby shorten waiting lists.

7.1.2 Estimation of patients in Ireland with severe symptomatic aortic stenosis eligible for TAVI

The prevalence of severe symptomatic aortic stenosis was addressed in Chapter 3. A systematic review aimed at identifying the number of patients eligible for TAVI estimated an incidence of 1.34% in people aged 65 years and older. [45] Prevalence was estimated at 3.4% in those aged greater than 75 years and 22.4% in those aged greater than 80 years. Between 68% and 76% of patients with severe aortic stenosis are symptomatic, therefore it is likely that 6,000-7,000 people have severe symptomatic aortic stenosis in Ireland. A 2018 review estimated that the annual number of patients eligible for TAVI would be 717 (95% CI: 435-1,073) based on current indications.[45] If the indications were expanded to include patients aged 75 years and older at low surgical risk, then the estimated demand in Ireland would be 1,106 per annum (95% CI: 701-1,610).

The demand estimates of Durko et al. are clearly well in excess of the AVR activity in the public system at present, so it is worth considering the plausibility of the estimates. In 2018 there were 595 AVRs in the public system across all ages and including both mechanical and bioprostheses. The combined total was 295 procedures in 2018 when restricted to TAVI and SAVR (with bioprosthesis) in

patients aged 70 years and over. As noted, these figures are an underestimate of total AVR activity in Ireland as it excludes procedures in the private hospitals. The figure of 295 does, however, include patients at low surgical risk undergoing SAVR who were assumed not to be eligible for TAVI in the estimate of 717 published by Durko et al.. The 95% confidence interval for estimate based on current indications includes the 2018 level of activity in the system, even if it was assumed that there were no procedures carried out in the private hospital system. However, there is a substantial difference in the estimated demand for TAVI (all levels of surgical risk) when compared with 2018 figures for TAVI and SAVR with bioprosthesis in those aged 70 years and older. That difference cannot be explained by the potential capacity of the private system and may reflect the use of prevalence estimates that are not applicable to Ireland. It is also worth highlighting that it is unclear if current activity in the Irish hospital system is reflective of true demand for AVR.

In accordance with current clinical guidelines and expert clinical opinion, in the absence of long term follow up data on the durability of TAVI valves and data supporting their use in younger patients, the use of TAVI in patients at low and intermediate risk of surgical complications is likely to be restricted to patients over the age of 70 years not undergoing other surgical procedures in the same episode of care. Those who require a surgical procedure such as coronary artery bypass graft are likely to continue to undergo SAVR in preference to TAVI. It was therefore estimated that the cohort of eligible patients will be approximately 100 per annum based on 2018 data. This cohort of patients therefore represents patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications and would translate to an additional nine patients undergoing TAVI every month, assuming that all cases would be treated using TAVI. It is not possible to disaggregate SAVR cases by level of surgical risk as this information is not recorded in the hospital discharge data, hence we cannot provide an accurate figure for demand in the event that TAVI is only extended to those at intermediate surgical risk. For the economic model, it was assumed that approximately one third of patients would be at intermediate surgical risk.

The mean age of patients in the intermediate surgical risk group trials was 80 to 81 years while the mean age in the low surgical risk groups trials was 74 years. By extending the indications for TAVI, the newly eligible patients will be a younger and possibly healthier cohort with a greater life expectancy. With the exception of the NOTION trial, follow-up was limited to two years and the majority of patients were fitted with first generation devices. Some of the registry data provides longer-term follow-up but that is also primarily for first generation devices. There is substantial uncertainty in relation to the durability of second and third generation devices as they are still relatively new and it is possible that patients will require further TAVI

procedures to replace valves due to valve failure. Over time the need to re-implant may contribute to increased demand, depending on device durability.

7.1.3 Indications for TAVI

In this HTA, and consistent with international clinical guidelines TAVI has been considered as treatment for those with severe symptomatic aortic stenosis. Trials are currently underway to evaluate the benefit of early valve replacement in those with asymptomatic disease.[130, 131] Similarly, while current guidelines suggest that it may be reasonable to perform AVR in patients with moderate aortic stenosis who are undergoing other cardiac surgeries, there are currently no recommendations for those in whom surgery is not otherwise indicated.[132] Emerging data suggest potential benefit of AVR over medical therapy, with trials of TAVI underway in patients with concomitant advanced heart failure and moderate aortic stenosis.[133] There is a risk that if capacity for TAVI is increased and the indications for it are widened that it may be offered to patients with indications other than those evaluated in this HTA. Indication creep occurs when an intervention programme to benefit patients with a specific health condition is expanded to either a broader patient population or to a different health condition.[134] An expansion of use gives rise to issues that should be considered. Firstly, the clinical and cost-effectiveness of TAVI for those with asymptomatic disease or those with moderate AS has not been assessed here. Secondly, an expansion of the indications for TAVI may greatly increase demand for procedures, thereby reducing access for those in whom it is indicated while creating access for those who may get limited clinical benefit.

The scope for indication creep depends on how clearly the appropriate patient population can be defined. Across the RCTs included in the review of clinical effectiveness, there was a lack of consistency in how surgical risk status was defined and exclusion or inclusion based on risk level was not always rigorously adhered to. In the OBSERVANT registry data, for example, 15.6% of patients treated with TAVI were at low surgical risk despite the devices not being CE marked at that time for use in that population.[135] Part of this may be down to the imprecise nature of risk assessment. Hence there is evidence of indication creep for this intervention and a further widening of the indications could have significant consequences for demand.

7.1.4 Pre-operative organisational considerations

The HSE TAVI pathway states that as part of the diagnostic work-up for TAVI patients must have an echocardiogram (not TOE), coronary angiogram and gated computed tomography (CT) TAVI. CT TAVI is a technique that takes an image of the aortic valve. Other routine diagnostic include carotid doppler, electrocardiogram (EBG), dental review and blood tests. Patients are then referred through the National TAVI Programme to one of four established cardiothoracic centres. There are four

established referral hospitals (Beaumont Hospital, St Vincent's University Hospital (SVUH), University Hospital Waterford (UHW) and University Hospital Limerick (UHL)) with the capability of providing suitable diagnostics required for TAVI. All four referral hospitals provide coronary angiograms and ECGs, however UHW and UHL do not have the capability to perform CT TAVI. The absence of this critical diagnostic test may increase waiting times and put the strain on centres that can provide this service. If demand for TAVI increases substantially then capital investment in CT TAVI may be required in hospitals that triage to the four main centres to ensure no increase in waiting times.

If TAVI is extended to low and intermediate risk patients, the increase in demand for diagnostics associated with TAVI will have to be assessed at a local and regional level to ensure adequate capacity is in place.

7.1.5 Procedure-related organisational considerations

Providing TAVI for patients at low and intermediate surgical risk will predominantly result in patients undergoing TAVI rather than SAVR. The increase in patients undergoing TAVI will have an impact on the cath lab at each of the four national centres. A TAVI procedure is usually performed in two hours although feedback from the centres suggest that up three hours are allocated for the procedure in case of complications and to allow for pre- and post-procedure care. This increase in cath lab activity may result in some centres reaching capacity and TAVI displacing other services such as PCI and angiography.

St. James's Hospital and Galway University Hospital each have two cath labs at present, Mater Misericordiae University Hospital has three and Cork University Hospital has three and one hybrid cath lab. The capacity at the four centres represents 48% (11 of 23) of cath lab capacity nationally. The centres represent four of the five primary percutaneous coronary intervention (PPCI) centres nationally, and have cath lab availability 24 hours a day. Depending on the extent to which additional TAVI activity can be supported within existing cath lab capacity, there is a possibility that capital investment may be required to increase cath lab availability at one or more of the four centres.

In regard to staffing, the HSE TAVI pathway gives details on the multidisciplinary team (MDT) required to provide TAVI:

- TAVI interventionist
- cardiac surgeon
- imaging/general cardiologist.

Input from other specialties (Elderly Care medicine, anaesthetics) will be required for some patients and local pathways should be developed for this input to be available

quickly. The MDT should meet at least weekly or sufficiently frequently to ensure that unnecessary delays do not occur. There should also be a system in place to organise the treatment of urgent cases that may arise between formal meetings. Adequate documentation with dissemination of decisions should be prioritised.

Broadly speaking, the following personnel are required to perform a TAVI procedure: two consultant (interventional) cardiologists, a registrar, three nurses (two pre- and post-procedure, three peri-procedure) a radiographer and a cardiac physiologist. The main difference in staffing compared to SAVR is that an interventional cardiologist rather than a cardiac surgeon performs the procedure, and the need for cath lab nurses rather than theatre nurses. This may put pressure on some centres if the volume of procedures increases, but the requisite number of experienced interventional cardiologists is not available. The other main staffing difference is that an anaesthetist is required for all SAVR procedures whereas in Ireland the majority of TAVI procedures are performed on consciously sedated patients.

Increasing the use of TAVI, and consequently reducing the use of SAVR, will represent a shift in the resources used to treat and manage the cohort of patients with severe symptomatic aortic stenosis. That shift will be in terms of staff, devices, accommodation and equipment. The steps required to manage such a shift efficiently and economically will require local and regional hospital-level planning.

7.1.6 Regional variation in capacity and demand

TAVI has been provided at six public acute hospitals, although activity is concentrated at four sites (Cork, Galway, and two in Dublin). There is variation in the ratio of TAVI to potentially TAVI-eligible SAVR cases. The centre that will potentially be impacted the most from extending TAVI to patients at low and intermediate risk of surgical complications is Cork University Hospital (CUH). In 2018, there were 53 episodes where SAVR with a bioprosthesis was carried out in a patients aged 70 years and over. If all of the SAVR cases switched to TAVI, there would be a 265% increase in demand for TAVI in CUH, reflecting one to two additional TAVI procedure per week. In contrast, the other national TAVI sites would experience increases in demand ranging from 17% to 34%.

As noted, an important consideration for the expansion of TAVI services is the availability of cath lab capacity. Centres that will experience the greatest increase in demand for TAVI are potentially most at risk in terms of being able to deliver the required capacity. A decision to extend TAVI to intermediate and low risk patients must be accompanied by an implementation plan that explicitly considers local and regional cath lab capacity and requirements in terms of both diagnostic and procedural activity. This would facilitate additional TAVI cases to be accommodated without undue risk from displaced patient care. Planning should also take

consideration of other national strategies and policies including the ongoing national review of specialist cardiac services and in particular any requirements for common support services.

7.1.7 Projected numbers of additional complications

Over the five year time horizon of the budget impact analysis (BIA) there was no difference in events of stroke, myocardial infarction or acute kidney injury between TAVI and SAVR for patients at intermediate risk of surgical complications.

In patients at low risk of surgical complications event rates were lower for all complications, for acute kidney injury as there were no data for this complication beyond 30 days. The BIA predicts that over the first five years there would be three additional strokes in the SAVR cohort and 17 more myocardial infarctions. The events of rehospitalisation were also lower in the TAVI cohort, with 13 fewer admissions forecast compared with the SAVR cohort.

7.1.8 Potential efficiency gains of extending TAVI

The economic analysis (Chapter 6) found that overall TAVI is highly cost-effective relative to SAVR. The potential for TAVI to be cost saving could be increased if a national tender process for TAVI devices is initiated. This process involves the HSE assuming responsibility for the procurement of TAVI devices which could facilitate a discount when purchasing a larger volume of devices, resulting in a reduction in the diagnosis-related group (DRG) cost associated with TAVI. However, it must be acknowledged that clinicians require access to a range of devices as no single device is appropriate in all circumstances.

An advantage of TAVI procedures is that the post-procedure length of stay is shorter than SAVR. [136] Based on a cohort of 100 patients and applying the results of the RCTs, there may be a reduction in hospital length of stay of between 300 and 400 days in one year. Based on HIPE data the reduction in length of stay could be more substantial, in the region of 500 bed days a year. Furthermore, post-procedure admission to the intensive care unit (ICU) is not routinely required following TAVI. There is likely to be reduced ICU usage of the order of 100 days a year. The costs associated with this are included in the economic analysis as the DRG takes these factors into account. However there are efficiency gains to the health system associated with this reduced length of stay and use of lower priority, specialised resources post procedure. It should be noted that while shorter length of stay results in a reduced cost for an episode, it facilitates a greater volume of episodes and therefore a net increase in budget albeit with a greater number of patients treated. By the same token, a greater use of TAVI in place of SAVR would decrease requirements for operating theatres and associated staff and anaesthetists, thereby freeing surgical capacity for other procedures. At a hospital level, expenditure on

devices will increase due to the higher device cost for TAVI. Service planning may need to take consideration of budget silos to ensure potential efficiency gains that can be gained by switching to SAVR can be achieved.

7.1.9 Volume-outcome and learning curve considerations

A number of have studies have investigated whether a volume-outcomes relationship exists for TAVI. These studies have generally capitalised on TAVI patient registry data to retrospectively assess the association between provider and surgeon volume on in-hospital mortality.

A US study compared mortality by hospital volume quartiles based on 1,481 TAVI cases.[137] After adjusting for TAVI access route (i.e., transfemoral versus transapical), patient age, sex and comorbidity, the odds of in-hospital mortality decreased with increasing hospital volume quartile. The difference was only statistically significantly different between the lowest and highest volume quartiles (odds ratio = 0.38; 95% CI: 0.27 to 0.54). The average number of operations per centre ranged from 10 in the lowest volume quartile to 150 in the highest volume quartile. Using the same dataset, a second study split the sample into high and low volume centres.[138] The second study demonstrated a volume-outcome relationship for mortality and a number of adverse events including bleeding, acute renal failure and pacemaker implantation. With the exception of acute renal failure, outcomes were better in high volume settings. The method for categorising hospitals and details of the volumes by group were not clearly reported in either study.

Registry data on 42,988 TAVI procedures in the US were used to investigate a volume-outcome relationship and whether outcomes improved over time.[139] Increasing hospital volume was associated with lower in-hospital risk-adjusted outcomes for mortality, vascular complications, and bleeding, but did not influence rates of stroke. The study also demonstrated evidence that increasing operator experience was associated with better outcomes. An Israeli study similarly showed that outcomes improved over time, although they noted that the results could be confounded by changing patient characteristics, such as increasing numbers of low surgical risk patients being treated.[140]

An analysis of a large German TVI registry found that risk-adjusted in-hospital mortality decreased over time and also decreased with increasing hospital volume.[141] The magnitude of the volume-outcome relationship decreased over time, which was interpreted as a ceiling effect. It was speculated that there could be a number of potential explanations for this, such as expertise sharing between high and low volume centres. In their analysis, low volume hospitals were those carrying out fewer than 50 TAVI procedures a year, while high volume carried out at least

100 procedures a year. Between 2008 and 2014, in-hospital mortality at the low volume centres decreased from 10.1% to 5.3% and from 6.6% to 3.7% at high volume centres. An international study produced similar findings, demonstrating the presence of both a learning curve effect and volume-outcome relationship.[142]

Finally, a recent US study based on balloon-expandable prostheses investigated both volume-outcome and learning curve relationships.[143] The analysis suggested a levelling off of the learning curve after 55 cases and termination of the learning curve at case 201. They did not find an association between volume and 30-day mortality.

Although not a universal finding, the published data suggest that there may be a volume-outcome relationship such that increasing volume is associated with lower mortality and improved outcomes for some safety endpoints. The published data do not facilitate an analysis to determine if there is a minimum safe volume. The four Irish centres had TAVI volumes ranging between 33 and 65 cases in the public system in 2018. As such, the Irish centres are at the upper end of what was defined as low volume in several studies. The addition of low and intermediate surgical risk patients to TAVI procedures would likely move all centres into the medium volume category. Studies have also shown that there may be a learning curve effect whereby outcomes improve with increasing experience of carrying out TAVI procedures. It is unclear if the learning curve applies to individuals or teams at treatment centres. Many of the analyses were based on first generation devices. However, an analysis restricted to second or third generation devices may be unlikely to observe a learning curve on the grounds that the included clinicians may have gone through the learning curve already using first generation devices.

7.2 Ethical and social considerations

The purpose of this section is to outline any potential ethical or social issues associated with extending TAVI to patients at low and intermediate risk of surgical complications. The framework for the ethical analysis is based on the EUnetHTA core model which has five main domains (Benefit-harm balance, autonomy, respect for persons, justice and equity, legislation and any ethical issues specific to the HTA process.) Ethical issues were identified from three of these domains:

7.2.1 Benefit-harm balance

Chapters 2, 3 and 4 have extensively discussed the burden of disease, treatments and the clinical effectiveness and safety. These have covered the potential benefits and harms of TAVI to the patient, health care system and society. However, the durability of the valves remains unknown as the technology has not been evaluated for a sufficiently long time horizon to accurately determine the lifespan of these

devices. Extending TAVI to a younger, healthier patient cohort (i.e., those at low surgical risk) will increase the time the valve must remain viable as the patient's life expectancy is longer. If device durability is an issue, then the increased use of TAVI could be associated with an increased need for a second or third AVR. As patients age, the surgical risk associated with implantation increases and therefore the risk of serious adverse events increases. Clinicians will have to consider, on an individual patient basis, whether TAVI is more appropriate than SAVR given the particular patient's circumstances. In this assessment, based on expert clinical opinion and current international clinical guidelines it was assumed that, until additional data are available, the use of TAVI in patients at low and intermediate surgical risk will generally be limited to those aged 70 years and older requiring an isolated AVR procedure.

The clinical effectiveness and safety of TAVI was considered in Chapter 4. There were limited RCTs available, and the evidence was mostly based on first generation devices and a number of the trials were powered for non-inferiority. In the event that existing TAVI devices become widely accepted for use in low and intermediate surgical risk patients, there will be little incentive for further trials to assess newer versions of the devices. As such it will be important that, in line with the HSE TAVI treatment pathway, a TAVI register is created and maintained so that the benefit-harm balance can be assessed over the longer term, particularly in relation to device durability. A registry should be adequately resourced to ensure sustainable implementation and long-term patient follow-up to capture clinical outcomes and device performance. In the interests of equity, any registry of TAVI patients should ideally include those who are treated through the private hospital system.

7.2.2 Respect for persons

An ethical consideration for some patients may relate to the fact that the valve is derived from an animal (bovine or porcine). This is an ethical issue for some religious and secular groups (vegetarians, vegans) who oppose the use of animal products.[144] For these patients, SAVR with a mechanical valve may continue to be the intervention of choice.

The TAVI procedure is percutaneous whereas SAVR is an open surgical technique. A patient undergoing TAVI will be left with minimal scarring compared with a patient undergoing SAVR. However, the scar location means that it may have limited impact on a patient's self-image.

7.2.3 Justice and equity

Section 7.1 indicates that TAVI could potentially lead to a reduction in complications compared to SAVR. Furthermore, fewer resources will be required due to the

reduction in overall bed days. However, an increase in the number of TAVI procedures might displace other healthcare activity. Competition for cath lab time will increase as the volume of TAVI procedures rises, which may require capital investment. There may also be an impact on patients downstream as more patients will require pre-procedure diagnostic tests. A lack of diagnostic resources in some regions is a concern as treatment may be delayed for some patients.

Patients can only access publicly-funded TAVI and SAVR procedures at four centres in Ireland. This has an impact on equity of access as the centres are located in three cities: Dublin, Cork and Galway. As TAVI and SAVR services are provided at the same locations, inequity will not be introduced or increased by switching from TAVI to SAVR unless there is regional variation in the ability to meet demand. The shorter hospital stay and faster recovery associated with TAVI should, in theory, reduce inequity as the burden on patients travelling long-distances will decrease. In the event that public hospitals are not able to meet increased demand for TAVI services, patients who are unable to access services at a private hospital will be at a disadvantage, creating an inequity between patients in the public and private systems.

The increased provision of TAVI may place a strain on cath lab capacity at some of the centres. In the event that cath lab activity is displaced by increased provision of TAVI, then displaced patients will experience inequity. Consideration should also be given as to whether the additional benefit to a patient undergoing TAVI rather than SAVR outweighs any disadvantage to a displaced patient. This is particularly the case when the evidence of clinical effectiveness of TAVI was primarily considered in terms of non-inferiority rather than superiority and that the benefits are primarily assessed in terms of reduced length of stay and short-term quality of life gains.

7.3 Discussion

Extending the availability of TAVI to patients at low and intermediate surgical risk will lead to an increased demand for TAVI procedures. The number of patients eligible for TAVI has been estimated using HIPE data and is based on patients aged 70 years or older undergoing an isolated AVR procedure using a bioprosthetic valve, although that does not include the number of TAVI procedures undertaken at private hospitals. The surgical risk associated with private patients and whether they would avail of TAVI publicly if it was extended to patients at low or intermediate surgical risk are unknown. Given the relatively stable proportion of patients that attend public hospitals as private patients, under current conditions it is likely that it is unlikely that there would be a substantial shift in demand from private to public hospitals.

By extending TAVI to low surgical risk patients in particular, the age profile of patients will be younger and potentially fewer comorbidities. As such, the patients will have a longer life expectancy than those included in the trials that estimated clinical effectiveness. A key issue will become the durability of the implanted valves, and whether patients will require further TAVI procedures to replace valves that have reached end of life. Little is known about the durability of second and third generation devices as they are still relatively new and the majority of longer term data collected by registries is specific to first generation devices.

The ability of the HSE to provide TAVI will be impacted by the availability of cath lab capacity. By extending TAVI to patients at low and intermediate surgical risk, it is likely that many patients aged 70 years and over currently undergoing SAVR with bioprosthesis will switch to TAVI. Based on 2018 data, the relative increase in TAVI activity will differ by TAVI centre. If the increased demand for cath lab capacity cannot be accommodated within existing resources then there will be consequences for displacement of care and or waiting times for TAVI. Service planning and an assessment of cath lab capacity will have to be carried out within each centre and at a regional level taking consideration of requirements for both diagnostic and procedural activity and where best to allocate this activity to ensure the most efficient use of available resources. Based on current activity levels additional cath lab capacity may be required at some locations.

This assessment was restricted to patients with severe symptomatic aortic stenosis that are considered at low and intermediate surgical risk. The five year budget impact analysis specifically identified the potential for 100 additional TAVI procedures per annum in patients aged 70 years and older. Spread across four sites nationally, this would suggest only approximately one additional procedure every two weeks at each site. However, as noted, there are existing cath lab constraints nationally, so that even small increases in TAVI numbers may be difficult to achieve in some centres. Furthermore, this relatively small increase for this cohort must be considered in the context of potential overall additional requirements for TAVI. As noted in Chapter 3, the majority of patients currently undergoing TAVI are aged 80 years and over, and would be considered high surgical risk. The numbers of people in Ireland aged 80 years and older is increasing at a faster rate than those aged 70 to 79 years, with predicted annual increases of between 6% and 7% in patients aged 80 years and older beyond 2026. Given the trend for population increases in those aged 80 years and over, demand for TAVI may increase substantially irrespective of whether it is formally extended to those at low and intermediate risk of surgical complications. These factors should therefore be considered in the planning of national cardiac services including cath lab capacity.

Although some ethical issues were identified, they were general in nature and could largely be addressed through the use of an informed consent process. The ethical considerations encompassed three domains in the EUnetHTA framework, and related to the long term durability of TAVI valves, the source of bioprosthesis valves from an animal and equity of access.

7.4 Key messages

- By extending TAVI to patients aged 70 years of older with severe aortic stenosis at low or intermediate surgical risk, an initial additional 100 procedures per annum will be required, with annual growth thereafter of five to six percent.
- An increase in TAVI procedures will require additional cath lab capacity and may displace other activity.
- The increased demand for TAVI will vary across the four treatment centres. Local-and regional-level service planning will be required to ensure efficient use and allocation of cath lab resources, so that adequate staff and cath lab capacity is in place to meet demand.
- By switching patients from SAVR to TAVI there will be reduced demand for ICU beds, patients will have shorter lengths of stay and there will be reduced demand for theatre time and associated staff.
- Although some potential ethical considerations related to the long term durability of TAVI valves, the source of bioprosthesis valves and equity of access associated with four centres providing care for the whole of Ireland were identified, they were largely general in nature and unlikely to be associated with any significant concerns.
- Although not part of this assessment, demographic changes mean that it is likely that there will be an increased demand for TAVI in older patients classified as high surgical risk. This must be taken into account in service planning if TAVI is extended to patients at low and intermediate surgical risk.
- Consistent with international best practice and as documented in the HSE TAVI care pathway, an essential part of any implementation plan should include data collection through an appropriately resourced national prospective TAVI registry to enable continuous monitoring of clinical outcomes and provider performance against agreed national standards.

8 Discussion & Conclusion

Health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions informed by evidence are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The purpose of this HTA was to examine the evidence for transcatheter aortic valve implantation (TAVI) as a treatment strategy for patients in Ireland with severe aortic stenosis at low or intermediate risk of surgical complications.

8.1 Indications for TAVI

TAVI devices were first CE-marked in 2007 for treatment of patients with severe symptomatic aortic stenosis for patients that were inoperable or at high risk of surgical complications. CE-marking for TAVI in patients at intermediate risk of surgical complications was first granted in 2016, while in November 2019 the first device was granted a CE-mark for use in those at low risk of complications. In August 2019, the Food and Drug Administration (FDA) approved an expanded indication for a number of devices marketed for use in patients at low risk of surgical complications.[21] A condition of their approval by the FDA was a requirement for continued follow up by manufacturers of patients enrolled in their RCTs for ten years to further monitor the safety and effectiveness of the devices, including their long term durability. Current (2017) guidelines from the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) recommend SAVR in patients at low surgical risk.[3] For patients at higher levels of surgical risk, they recommend that the decision between SAVR and TAVI be made by the Heart Team based on individual patient characteristics, with TAVI favoured in elderly patients suitable for transfemoral access. The initial lack of CE-marking has not prevented the use of TAVI in low surgical risk groups as evidenced by the trials, registry data, and Irish case series reports. However it is noted that these data typically categorise the level of surgical risk based on recognised scores (e.g., STS score <4% considered low risk) and do not capture additional risk factors such as frailty or porcelain aorta.

A consideration for future demand for TAVI is the extent to which it becomes an accepted or recommended treatment for a wider set of indications. Possible indications for which trials are planned or underway include the use of TAVI for the treatment of asymptomatic aortic stenosis [130, 131]) or for younger patients with bicuspid valve pathology.[145] The inclusion of additional indications could have very significant implications for demand for TAVI. This assessment was restricted to

patients with severe asymptomatic aortic stenosis at low and intermediate risk of surgical complications.

8.2 Applicability of international data

A systematic review was carried out to identify relevant studies of TAVI in the treatment of patients with severe symptomatic aortic stenosis at low and intermediate surgical risk.

It is worth emphasising that efficacy was largely determined based on non-inferiority trials with short-term follow-up based on first generation devices. All of the included trials were possibly underpowered to detect differences in safety outcomes. Due to important design differences, there are potentially different adverse event profiles between generations of valves and also between manufacturers, but the limited trial and registry data available constrain the potential for any detailed analysis. Furthermore, the devices are subject to iterative development, along with contemporary changes in the management of patients undergoing aortic valve replacement, which means that earlier trial data on TAVI may be of limited applicability.

For patient populations at intermediate or mixed low and intermediate surgical risk the available evidence is almost entirely based on first generation TAVI devices. For patients at low surgical risk, the available evidence was predominantly based on second generation TAVI devices. Even subtle changes to a device can have important consequences for clinical and safety outcomes. Most of the trials used a specific device from one manufacturer, which can also limit the applicability of the findings to a real-world setting, where clinicians may choose the most appropriate device given the clinical context of the presenting patient. However, the availability of registry data which is not device-specific supports the general finding that TAVI devices are non-inferior in terms of the main clinical effectiveness outcomes.

There were differences across trials not only in terms of the devices used, but also the profile of patients and potentially in terms of local clinical practice (e.g., rate of permanent pacemaker insertion). The presence of inter-trial variation is not surprising, but it does create challenges for generalising to an Irish setting. One example is in relation to length of hospital stay. Based on Irish data, the median length of stay is 12 days for SAVR and seven days for TAVI. Trial data suggest figures closer to 10 days for SAVR and six days for TAVI for intermediate surgical risk patients, and seven days for SAVR and three days for TAVI in low surgical risk patients. Making a direct comparison may not be appropriate as the mix of surgical risks is uncertain in the Irish patient population. Patients with a higher surgical risk

profile would be expected to have longer length of stay. However, the differences in length of stay highlight the challenges in interpreting the clinical effectiveness data.

Another important consideration in the clinical effectiveness data are the limited reports with longer-term follow up. The durability of TAVI devices is thus uncertain. At present the longest follow-up is six years, with the data suggesting that TAVI-inserted valves have equivalent durability to SAVR valves. By extending TAVI to lower surgical risk patients, the mean age of patients will become younger and valve durability will become a more important consideration. Valve deterioration or failure may require a further intervention, with important consequences for clinical outcomes and costs. The existing longer-term data are in relation to first generation devices, which may not be a good indicator of durability in second and third generation devices. Five year follow-up data on a second generation device has been published in abstract form, but full text has not been published as of November 2019. More comprehensive long-term follow-up data, particularly based on low and intermediate surgical risk patients, would help to determine whether the equivalence of durability of TAVI to SAVR valves persists.

8.3 Future demand for TAVI

This assessment was restricted to patients at low and intermediate surgical risk. It is acknowledged that some of these patients are currently undergoing TAVI in preference to SAVR. In the event that TAVI is formally extended to all patients at low and intermediate surgical risk, it was assumed that the additional cases would be generated by those aged 70 years and over currently undergoing SAVR as an isolated procedure. Based on clinical opinion, it was assumed that, in the absence of longer term follow-up data and acknowledging the limited data on TAVI in younger patients, those patients aged less than 70 years were likely to continue to be treated using SAVR. It was also assumed that only patients undergoing isolated SAVR would switch to TAVI as those requiring other surgical procedures in the same episode of care, such as coronary artery bypass grafting and mitral valve repair, would continue to be treated with SAVR.

Based on patients aged 70 years and over currently undergoing SAVR as an isolated procedure, demand for TAVI would increase by approximately 100 patients in the first year. That figure is likely to increase based on demographic changes. It should also be borne in mind that the four centres currently providing TAVI commenced their services at different time points, and have not all reached what might be considered a stable demand for TAVI.

The increase in numbers of AVR procedures nationally over the last 10 years is marginally above the rate of population increase, which may reflect changes in the

detection, diagnosis and management of severe aortic stenosis. The ageing population in Ireland means that demand for TAVI, particularly in patients aged 80 years and over, may increase at a greater rate over the next ten years than historically. While patients aged 80 years and older would not form part of the cohort at low and intermediate surgical risk, they form the majority of TAVI patients at present and increases in that population will have important consequences for capacity for TAVI services. The numbers of people in Ireland aged 80 years and older is expected to increase by 6 to 7% per annum in the coming decade.[58] TAVI service planning should take into account anticipated demographic changes to ensure that the service is able to meet demand, particularly if the service is to be extended to patients at low and intermediate surgical risk.

The key constraints to capacity are the availability of suitable beds, access to cath lab facilities, and the availability of operators. All three constraints are impacted by other activity taking place at the four centres. The benefits of TAVI are primarily observed in terms of improved efficiency without loss of clinical benefit. The efficiency gains are in terms of a shorter length of stay. Access to cath lab facilities is challenging, and many of the labs nationally are operating at or near capacity. The cost of cath lab facilities was included in the main economic analysis on the assumption that existing capacity could not meet demand for an additional 100 cases nationally. It is important to recognise that access to cath lab facilities includes the availability of the relevant staff to support carrying out TAVI procedures.

Just as demand will vary by location, so will the capacity constraints. Planning at a hospital level will be required which should be aligned with regional plans and, in turn, also take consideration of other national strategies and policies including the ongoing national review of specialist cardiac services and in particular any requirements for common support services. Consideration should also be given to where post-procedure telemetry monitoring can be provided to ensure that the lowest-necessary resource setting can be used.

8.4 Cost-effectiveness and budget impact

A systematic review was undertaken to assess the available evidence on the cost-effectiveness of TAVI versus SAVR among low or intermediate risk patients with severe symptomatic aortic stenosis. Seven studies[88-94] were identified that evaluated the cost-effectiveness of TAVI in intermediate risk patients, none of which were performed in Ireland. A number of concerns regarding the quality and credibility of the economic evaluations were identified, largely relating to model structure and choice of input parameters. Overall, the evidence base proved insufficient in determining the cost-effectiveness of TAVI among low or intermediate risk patients in Ireland. To address the question of cost-effectiveness and budget

impact, an economic model was developed specifically tailored to the Irish healthcare setting.

The economic model evaluated outcomes for patients aged 70 years and older at low or intermediate risk of surgical complications in Ireland. The model assumed a publicly funded health and social system perspective and evaluated costs and consequences over a 15-year time horizon, which is the expected lifespan of an artificial valve.[146] Any projection of costs and consequences beyond this time point would be speculative.

Although the model found TAVI was cost-effective in intermediate and low risk patient populations, some uncertainty was observed, particularly in relation to costs. The cost-effectiveness of TAVI was mainly affected by variations in the cost of the procedure. Although the estimated cost of the TAVI procedure likely reflects the national average cost of the procedure and all associated postoperative complications, the true cost of the procedure may be variable. A large proportion of the estimated cost is influenced by the cost of the TAVI valve, which varies by manufacturer. TAVI valves can range substantially in price from approximately €12,000 to just over €20,000. Depending on the choice of valve, the cost-effectiveness of TAVI compared with SAVR may be positively or adversely impacted. To mitigate against scenarios in which TAVI is not cost-effective, efforts could be made to minimise the proportion of the overall cost of the TAVI procedure that is attributable to the cost of the valve alone. Historically, individual hospitals secured privately negotiated contracts with manufacturers in an attempt to increase internal (budget) efficiencies. The same efficiencies could be achieved nationally with similarly negotiated contracts with manufacturers that could positively impact the cost-effectiveness of TAVI in Ireland. However, there remains the need to secure a wide range of valve types to ensure suitability to patients.

The economic model was also used to project the budget impact of implementing a TAVI care pathway in the Irish public health care system over a five-year time horizon. The model estimated the incremental cost of delivering TAVI relative to SAVR in patients at low and intermediate risk of surgical complications. Although the findings from the budget impact analysis suggest TAVI is likely budget neutral, the same uncertainty in the cost of the TAVI procedure was observed. The same budget efficiencies could be realised with favourably negotiated contracts with manufacturers.

The budget impact analysis also considered the impact of an ageing population on the demand for AVR. Increases in the proportion of the population aged 70 years or older will likely increase the demand for AVR, and associated budget impact of TAVI and SAVR. Although the incremental cost of providing TAVI relative to SAVR will

remain budget neutral, the impact of an ageing population on the health care budget is important. The efficiency advantage of providing TAVI instead of SAVR, however, is the procedure is associated with a shorter length of stay in hospital. As a consequence, fewer hospital and intensive care bed days would be required with TAVI than SAVR, which may release important resources to address other demands in the health care system arising from an ageing population, for example.

8.5 Conclusions

The extension of the TAVI care pathway to include patients with severe symptomatic aortic stenosis at low and intermediate surgical risk should be considered in the Irish public healthcare system. The current clinical evidence suggests TAVI is no less effective than SAVR in terms of cardiac and all-cause mortality. TAVI is associated with a shorter length of stay in hospital following the procedure than SAVR and, as a less invasive procedure, delivers additional health gains in terms of patients' health-related quality of life in the short-term.

Compared with SAVR, TAVI is considered a highly cost-effective treatment option for patients aged 70 years and over at low or intermediate surgical risk. The estimated five-year budget impact of extending the TAVI care pathway to include approximately 100 patients at low and intermediate surgical risk is likely to be budget neutral. This estimate incorporates the cost of additional catheterisation laboratory capacity. Greater use of TAVI as an alternative to SAVR will result in shorter length of hospital stay and a reduced demand for ICU beds and theatre time, which may release resources to address demands elsewhere in the system.

The uptake of TAVI will vary across each of the four designated centres in the TAVI model of care. Planning at a hospital level will be required which should be aligned with regional plans and, in turn, also take consideration of other national strategies and policies including the ongoing national review of specialist cardiac services and in particular any requirements for common support services. Planning considerations should include requirements for pre-procedural diagnostics, adequate catheterisation laboratory capacity and associated staff, and post-procedural beds with telemetry monitoring. TAVI service planning should take into account projected growth in the population aged over 80 years (a high surgical risk group) in addition to any requirements arising from an extension of the service to those at lower levels of surgical risk.

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Appendix A Search terms for systematic review of clinical effectiveness and safety

A systematic literature search was performed to identify randomised controlled trials (RCTs) published between 1 January 2016 and May 2019. The databases, results, search terms and methodology used for each database are outlined below.

Table A1 PICOS analysis for identification of relevant studies

Population	Patients with severe aortic stenosis (AS) at low or intermediate risk of death or complications associated with SAVR. The indication should at least be defined by NYHA class, and either STS-PROM score, EuroSCORE or EuroSCORE II
Intervention	TAVI as a therapeutic intervention for the defined target population. The assessment will be restricted to systems with a CE mark for the defined population. TAVI involves the insertion of a prosthetic valve, which functionally replaces the damaged aortic valve, using fluoroscopic and echographically-guided minimally invasive procedures. The prosthetic valve is compressed within a dedicated delivery system and, once in place within the diseased aortic valve, its deployment allows its expansion and the compression of the native diseased valve against the wall of the aorta. Depending on the anatomy of the patient and device characteristics, the procedure can be performed by one of four different approaches. The transfemoral (TF) route is the most common, whereas the others are performed when the anatomy of the patient precludes access via the TF route. These approaches are the subclavian/transaxillary (S/T) approach, the transapical (TA) approach, and the transaortic (TAo) approach. Subgroup analyses based on the risk assessment tool used, the TAVI system used (i.e., model dependent), and the procedural approach (i.e., TF, S/T, TA, and TAo) will be performed if there are sufficient data.
Comparator	SAVR can be performed using different approaches (full sternotomy and more minimally invasive procedures), different kinds of valves, and different kinds of valve-anchoring techniques (i.e., sutured and sutureless). Subgroup analyses based on these comparators will be performed if possible.
Outcomes	Clinical efficacy outcomes taken as surrogate markers of clinical effectiveness were: ▪ Mortality at 30-day follow-up and at the longest follow-up (all-cause mortality, cardiovascular mortality, and non-

	cardiovascular mortality) ▪ Improvement of symptoms (reduction in NYHA class) ▪ Improvement in health-related quality-of-life indicators [e.g., EQ-5D, SF-36 score, or KCCQ scores] ▪ Procedural success (i.e., successful valve implantation) ▪ Haemodynamic function of the valve ▪ Intensive care unit (ICU) length of stay (days) ▪ Hospital length of stay (days) ▪ Rehospitalisation for myocardial infarction (MI) (>72 hours following TAVI) Safety outcomes taken as surrogate markers of adverse events or outcomes were: ▪ Any major or minor adverse event (e.g. vascular complications; stroke; TIA; disabling or life-threatening bleeding; aortic valve reintervention; myocardial infarction ≤72 hours post procedure; new or worsening atrial fibrillation or atrial flutter; moderate or severe aortic valve regurgitation; acute kidney injury; pain; or need for permanent pacemaker implantation) ▪ Radiation causing harm to both patient and staff
Study design	Clinical efficacy ▪ Randomised controlled trials Safety ▪ Randomised controlled trials ▪ Real-world data derived from published studies from prospective national registries

Databases:

Embase (Ovid), Ovid MEDLINE(R),

Cochrane Library: Cochrane Database of Systematic Reviews (CDSR), Other Reviews, Cochrane Central Register of Controlled Trials (CENTRAL).

PubMed (publication status ahead of print publications).

Date Run: 17/05/2019

Overall Results (before removing duplicates across databases):

- 130 OVID (publication year 2016-2019)
- 109 Trials Cochrane Library (publication year 2016-2019)

- 273 Publication status ahead of print (non-indexed) publications (publication year 2016-2019)

Total RCTs (before duplicate removal) = 512

Embase and Medline [OVID]

Embase 1974 to 2019 Week 19
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date run: 17/05/2019

oemez – Embase specific (1974); ppez – Ovid MEDLINE specific

Searches Results:
1 heart valve prosthesis implantation/ use ppez 20366
2 heart valve replacement/ use ppez or aorta valve replacement/ use oemez or transcatheter aortic valve implantation/ use oemez or aorta valve prosthesis/ use oemez 36521
3 Aortic Valve/ use ppez or aorta valve/ use oemez or percutaneous aortic valve/ use oemez 51300
4 ((aortic valv* or aorta* valv* or heart valv*) adj4 (prosthe* or implant* or insert* or replac*)).ti,ab. 65487
5 or/1-4 115489
6 (percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR).ti,ab. 440180
7 5 and 6 32365
8 percutaneous aortic valve/ use oemez and (prosthe* or implant* or insert* or replac*).ti,ab. 2525
9 transcatheter aortic valve replacement/ use oemez 16485

10 or/7-9 34222

11 exp animals/ not humans.sh. 28635502
12 10 not 11 13120
19 (randomized controlled trial or controlled clinical trial).pt. or random*.mp. or placebo.ab. or double-blind*.ti,ab. or trial.ti. 3231952
20 12 and 19 1011
21 limit 20 to yr="2016 -Current" 485
22 remove duplicates from 21 477
23 ((low* or intermediate) adj2 risk).ti,ab.

24 22 and 23 130

Cochrane Library

Date run: 17/05/2019

Searches Results:

#1 MeSH descriptor: (Heart Valve Prosthesis Implantation) this term only 602
#2 MeSH descriptor: (Aortic Valve) this term only 409
#3 ((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)):ti,ab,kw in Cochrane Reviews (Reviews and Protocols) 23
#4 ((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)) in Trials and Clinical Answers 5066
(Other Reviews, Trials and Technology Assessments)
#5 #1 or #2 or #3 or #4 5143
#6 (percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR):ti,ab,kw in Cochrane Reviews (Reviews and Protocols) 191
#7 (percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR) in Trials and Clinical Answers 25594 (in Other Reviews, Trials and Technology Assessments)
#8 #6 or #7 25785
#9 MeSH descriptor: (Transcatheter Aortic Valve Replacement) this term only 120
#10 (#5 and #8) or #9 Publication Year from 2013 to 2019 1089
#11 (#5 and #8) or #9 Publication Year from 2016 to 2019 863
#17 ((low* or intermediate) near/2 (risk): ti,ab,kw in trials and clinical answers 16259

#18 #11 and #17 109

Medline Pub status ahead of print

Date run: 17/05/2019

Searches Results:

#1 Search (((((("heart valve prosthesis implantation"(MeSH Terms)) AND pubstatusaheadofprint)) OR ((("transcatheter aortic valve replacement"(MeSH Terms)) OR (TAVI[tiab] OR TAVR[tiab] OR "transcatheter aortic valve replacement"[tiab])) AND pubstatusaheadofprint))) 240

#2 Search (((((((percutaneous[tiab] OR transapical[tiab] OR transapical[tiab] OR transarterial[tiab] OR trans-arterial[tiab] OR transcatheter[tiab] OR trans-catheter[tiab] OR transcutaneous[tiab] OR trans-cutaneous[tiab] OR transfemoral[tiab] OR trans-femoral[tiab] OR transaxillary[tiab] OR trans-axillary[tiab] OR transluminal[tiab] OR trans-luminal[tiab] OR transaortic[tiab] OR trans-aortic[tiab] OR transcarotid[tiab] OR transcarotid[tiab] OR transsubclavian[tiab]OR transsubclavian[tiab] OR transiliac[tiab] OR trans-iliac[tiab] OR transiliofemoral[tiab] OR trans-iliofemoral[tiab])) AND (aortic valve Replace*[tiab] OR aortic valve implant*[tiab])) AND pubstatusaheadofprint))))) 255

#3 #1 OR #2 273

Identification of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference manager EndNote (version 7). For data management purposes, the results of the search were exported to Covidence (www.covidence.org) for title and abstract screening and full text review. Duplicates were removed and citations were screened by two reviewers to eliminate clearly irrelevant studies. Two reviewers independently screened the remaining citations. Full texts were obtained and reviewed as per the inclusion criteria.

Data extraction and management

Data extraction using a standardised data extraction form was performed independently by two reviewers, with any disagreements being resolved by discussion or inclusion of a third reviewer.

The following information was extracted from the included RCTs and their published supplementary materials:

- study author and year, study name (NCT if relevant), study design and length of follow up
- country, setting and number of centres
- inclusion and exclusion criteria, population surgical risk of mortality
- number of participants and non-respondents and/or loss to follow up
- population characteristics (that is, age and gender)
- intervention characteristics (type of device and access routes(s))
- comparator characteristics
- outcomes (see below)
- summary of results
- funding sources and potential sources of bias.

Where necessary, the study author was contacted to obtain available data already published, but not sufficiently detailed, and outcome data that were not reported.

Appendix B Studies excluded from systematic review of clinical effectiveness and safety

Study	Reason for exclusion
Amrane (2018)[147]	Post-hoc analysis
Amrane (2018)[147]	Duplicate study
Baron (2018)[100]	Wrong study design
Cremer (2017)[148]	Conference abstract/Supplement/Editorial
Daubert (2016)[149]	Wrong patient population
Durko (2018)[150]	Posthoc subgroup analysis
Kiaii (2018)[151]	Conference abstract/Supplement/Editorial
Kleiman (2019)[152]	Conference abstract/Supplement/Editorial
Kodali (2016)[153]	Wrong study design
Moriyama (2019)[128]	Data not in extractable form
NCT02675114 (2016)[154]	Emerging evidence/Ongoing clinical trial
NCT03112980 (2017)[155]	Emerging evidence/Ongoing clinical trial
NCT02701283 (2016)[156]	Emerging evidence/Ongoing clinical trial
NCT02825134 (2016)[157]	Emerging evidence/Ongoing clinical trial
Popma 2017[158]	Conference abstract/Supplement/Editorial
Serruys 2017[159]	Conference abstract/Supplement/Editorial
Serruys 2018[160]	Posthoc subgroup analysis
Sondergaard 2019[77]	Safety outcome – excluded from the efficacy review only
Thourani 2018[76]	Wrong intervention
Thyregod 2016[161]	Posthoc subgroup analysis
Vahanian 2016[162]	Wrong study design
Van Mieghem 2017[163]	Conference abstract/Supplement/Editorial
Waksman 2019[164]	Wrong study design
Yakubov 2019[165]	Conference abstract/Supplement/Editorial

Reason for exclusion from efficacy review	Study references
Conference abstract, supplement or editorial (n=7)	**(148, 151, 152, 158, 159, 163, 165)**
Emerging evidence or ongoing clinical trial (n=4)	**(154-157)**
Posthoc subgroup analysis (n=4)	**(147, 150, 160, 161)**
Inappropriate study design (n=4)	**(100, 153, 162, 164)**
Duplicate study (n=1)	**(147)**
Inappropriate intervention (n=1)	**(76)**
Safety outcome (n=1)	**(77)**
Inappropriate population (n=1)	**(149)**

Appendix C Characteristics of studies in systematic review of clinical effectiveness and safety

Characteristics of included studies on RCTs for assessment of clinical effectiveness and safety

Author (year)	Trial details (NCT) and funding	Country (no of centres)	Study duration	Risk profile and inclusion criteria	Age (yrs) and gender (% male)	Participant numbers	TAVI device (access route) vs. comparator	Outcomes (reporting intervals)
Nielsen (2012)	STACCATO (funded by two participating hospitals and Danish Heart Association)	Denmark (n=2)	2 years 7 months Nov 2008 – May 2011	Low and intermediate risk	Age: 81.0±4.2 Male: 30.0%	N=70 TAVI=34 SAVR=36	SAPIEN XT (TA) vs. SAVR	Primary (30d, 3m) Composite of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis Secondary (30d, 3m) all-cause death, cardiac death, stroke, myocardial infarction, New York Heart Association (NYHA), SF-36, aortic valve area, peak aortic valve gradient, aortic valve leakage, left ventricular ejection fraction, duration of hospital stay, operation for bleeding, and permanent pacemaker treatment.
Baron (2017)	PARTNER 2A (NCT01314313) non-inferiority RCT (funded by Edwards Lifesciences)	USA & Canada (n=57)	2 years Dec 2011 - Dec 2013	Intermediate risk patients with STS-PROM 4-8%	Age: 81.4±6.8 Male: 54.9%	N*=2,032 nΩ=1,833 (1,806) TAVI=950 (945) SAVR=883 (861)	SAPIEN XT (TF; TT) vs. SAVR	HRQoL: KCCQ-OS Score; EQ-5D; SF-36 (30d, 1y, 2y)

Leon (2016)	PARTNER 2 (NCT01314313) non-inferiority RCT (funded by Edwards Lifesciences)	USA & Canada (n=57)	2 years Dec 2011 - Dec 2013	Intermediate risk patients with STS-PROM 4-8%	TAVI 81.5±6.7y; male (54.2%) SAVR 81.7±6.7y; male (54.8%)	N*=2,032 TAVI=1011 (994)# SAVR=1021 (944)# TF ITT=775 TF AT=762	SAPIEN XT (TF-76.3% TT-23.7%) vs. SAVR	Primary (30d, 1y, 2y) Composite of death or disabling stroke; any stroke Secondary (30d, 1y, 2y) Major VC; LT/D bleed; new AF; new PP; AVR; AKI; PVR
Mack (2019)	PARTNER 3 (NCT02675114) non-inferiority & superiority RCT (funded by Edwards Lifesciences)	USA, Canada, Japan, Australia & New Zealand (n=71)	19 months Mar 2016-Oct 2017	Low risk patients with STS-PROM <4%	TAVI 73.3±5.8y; male (67.5%) SAVR 73.6±6.1y; male (71.1%)	N*=1,000 TAVI=503 (496)# SAVR=497 (454)#	SAPIEN 3 system (TF) vs. SAVR	Primary(30d, 1y) Composite of death, stroke, or rehospitalisation; Secondary (30d, 1y) CV death; stroke; death or stroke; MI; KCCQ-OS; rehospitalisation; change in NYHA; mean aortic gradient; LVEF; major VC; LT/D bleed; new AF; new PP; AVR; AKI; PVR
Popma (2019)	Evolut Low Risk (NCT02701283) non-inferiority & superiority RCT (funded by Medtronic)	USA, Canada, France, Netherlands Japan, Australia & New Zealand (n=86)	2 years 8 months Mar 2016-Nov 2018	Suitable anatomy for TAVI or SAVR Low risk patients with no more than a 3% risk of death by 30 days	TAVI 74.0±5.9y; male (63.8%) SAVR 73.8±6.0y; male (66.5%)	N*=1,468 TAVI=734 (725)# SAVR=734 (678)#	CoreValve (3.6%); Evolut R (74.1%); Evolut PRO (22.3%) (TF-99.0% TAo-0.4% S/T-0.6%) vs. SAVR	Primary (30d, 1y, 2y) Composite of death or disabling stroke; Secondary (30d, 1y, 2y) Death any cause; all and disabling stroke; TIA; MI; AVR; LT/D bleed; major VC; AKI, new AF; new PP
Reardon (2017)	SURTAVI (NCT01586910) non-inferiority RCT (funded by	USA, Canada & Europe (n=87)	4 years June 2012-June 2016	Intermediate risk patients with STS-PROM ≥3 to <15% as well as such	TAVI 79.9±6.2y; male (57.6%)** SAVR	N*=1,746 N=1,660 (mITT)** TAVI=864	CoreValve (84%); Evolut R (16%) (TF-93.6% TAo-4.1%	Primary (30d, 1y, 2y) Composite death and disabling stroke; Secondary (30d, 1y, 2y)

	Medtronic)			non-traditional factors as co-existing illness, frailty and disability	79.7±6.1y; male (55.0%)**	(863)# SAVR=796 (794)#	S/T-2.3%) vs. SAVR	Death (any cause/CV or valve related); stroke (all or disabling); LT/D bleed; AVR; major VC; AKI, new AF; new PP; PVR
Sondergaard (2016)	NOTION (NCT01057173) superiority RCT (grant funded by the Danish Heart Foundation) (statistician and medical writer of Medtronic)	Denmark & Sweden (n=3)	4 years 4 months Dec 2009-Apr 2013 (2 year outcomes)	Patients ≥70 years of age with severe degenerative aortic valve stenosis referred for SAVR and also candidates for TAVI regardless of their predicted risk of death after surgery. Low and intermediate risk with 81.8% considered low-risk patients (STS-PROM <4) mean/SD 3.0/1.7 Age & gender in Thyregod 2015		N*=280 TAVI=145 (142)# SAVR=135 (134)#	CoreValve (TF-96%; S/T-4%) vs. SAVR	Primary (3m, 1y, 2y) Composite rate of all-cause death, stroke, or MI; Secondary (3m, 1y, 2y) All-cause mortality; CV mortality; stroke; TIA; MI; change in NYHA; mean aortic gradient; new PP; AVR; total aortic valve regurgitation; valve endocarditis
Thyregod (2015)	NOTION (NCT01057173) superiority RCT (grant funded by the Danish Heart Foundation) (statistician and medical writer of Medtronic)	Denmark & Sweden (n=3)	4 years 4 months Dec 2009-Apr 2013 (1 year outcomes)	As reported in Sondergaard 2016	TAVI 79.2±4.9y; male (53.8%) SAVR 79.0±4.7y; male (52.6%)	N*=280 TAVI=145 (139)# SAVR=135 (135)#	CoreValve (TF-96%; S/T-4%) vs. SAVR	Primary (30d, 1y) Composite rate of all-cause death, stroke, or MI; all-cause mortality; CV mortality; stroke; TIA; MI; change in NYHA; mean aortic gradient; new AF; new PP; AVR; major VC; AKI; LT/D bleed; valve endocarditis

Thyregod (2019)	NOTION (NCT01057173) superiority RCT (grant funded by the Danish Heart Foundation) (statistician and medical writer of Medtronic)	Denmark & Sweden (n=3)	4 years 4 months Dec 2009-Apr 2013 (5 year outcomes)	As reported in Sondergaard 2016 & Thyregod 2015		N*=280 TAVI=145 (142)# SAVR=135 (134)#	CoreValve (TF-96%; S/T-4%) vs. SAVR	Primary (5y) Composite rate of all-cause death, stroke, or MI; Secondary (5y) All-cause mortality; CV mortality; stroke; TIA; MI; mean aortic gradient; new AF; new PP; total aortic valve regurgitation; AVR; valve endocarditis
Sondergaard (2019)	NOTION (NCT01057173) superiority RCT (grant funded by the Danish Heart Foundation) (statistician and medical writer of Medtronic)	Denmark & Sweden (n=3)	4 years 4 months Dec 2009-Apr 2013 (6 year outcomes)	As reported in Sondergaard 2016 & Thyregod 2015		TAVI=139 SAVR=135	CoreValve (TF-96%; S/T-4%) vs. SAVR	Primary (6y) Mortality Secondary (6y) Valve deterioration

Key: * number of participants randomised (intention-to treat population); Ω number of participants for primary analytic cohort (with baseline QoL characteristics) with per-protocol population in brackets; # as–treated population ** mITT. **Abbreviations**: AF – atrial fibrillation; AKI – acute kidney injury; AT – as-treated; AVR – aortic valve reintervention; CV – cardiovascular; ITT – intention-to-treat; LT/D – life-threatening or disabling; LVEF – left ventricular ejection fraction; MI – myocardial infarction; mITT – modified ITT; NOTION – NOrdic AorTic Valve InterventiON; PARTNER – Placement of AoRtic TraNscathetER valves; PP – permanent pacemaker; PVR – paravalvular aortic regurgitation; STS-PROM – Society of Thoracic Surgeons Predicted Risk Of Mortality; SURTAVI – SUrgical Replacement and Transcatheter Aortic Valve Implantation; TF – transfemoral; TIA – transient ischaemic attack; TT – transthoracic; TA – transapical; VC- vascular complication.

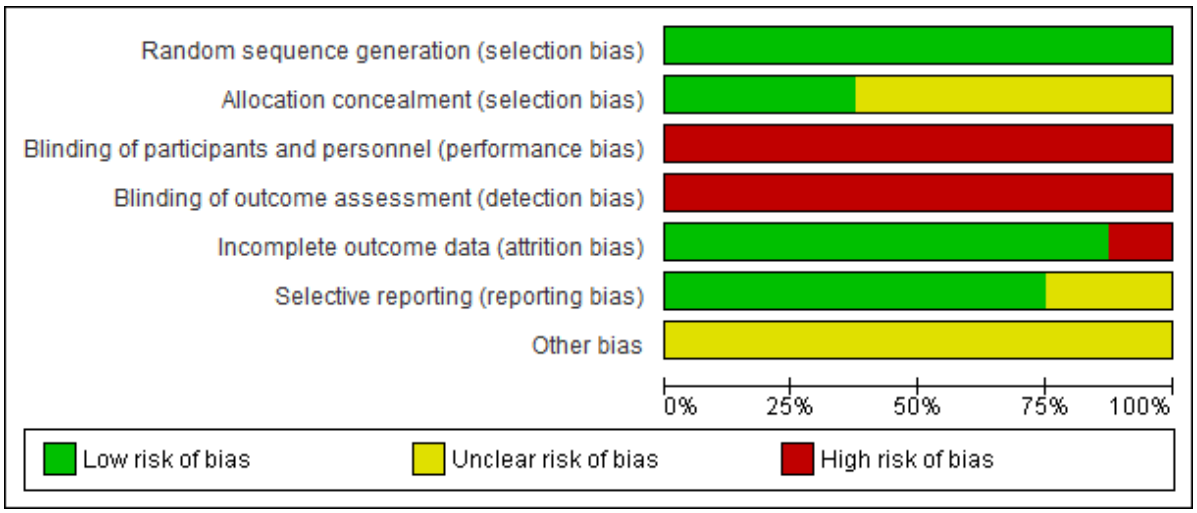
Characteristics of included studies using prospective national registry data for assessment of safety

Author (year)	Study details	Country (no of centres)	Study duration	Risk profile and inclusion criteria	Age and gender	Participant numbers	TAVI device (access route) vs. comparator	Safety outcomes (reporting intervals)
Fraccaro (2016)	Early and Midterm Outcome of Propensity-Matched Intermediate-Risk Patients Aged >80 Years with Aortic Stenosis Undergoing Surgical or Transcatheter Aortic Valve Replacement (from the Italian Multicenter OBSERVANT Study). Observational prospective multicenter cohort study supported by a Grant (Fasc.1M30) from Italian Ministry of Health and Instituto.	Italy (n=93)	18 months Dec 2010 – June 2012	Intermediate risk patients with mean logistic EuroSCORE of 8.0± 5.7% (SAVR) vs 14.9± 11.8% (TAVI) group	Age (years): 83.7± 2.9 TAVI 83.7± 2.6 SAVR Male (%): 158 (37%) TAVI 166 (40%) SAVR [matched pairs]	Enrolled population ≥80 yrs (N=2,820) to pre-matching population n=2,161 (1178 TAVI; 983 SAVR patients) Post-propensity score matched population n=830 patients (415 patients for each group)	Sapien XT 47%; CoreValve 53% vs. SAVR	MI; stroke; tamponade; shock; major vascular complications; NPMI; AKI, acute renal failure; infections; AVR (30 days)
Fujita (2019)	Impact of new pacemaker implantation following surgical and transcatheter aortic valve replacement on 1-year outcome.	Germany (German Aortic Valve Registry (GARY) – no details on the number of centres)	5 years Jan 2011 – Dec 2015	All comers registry – low-intermediate risk SAVR 1.8 (1.2–2.6) TAVI 4.4 (3.1–6.4)	Age (years): 81 (78–85) TAVI 72 (64–76) SAVR Male (%): 9442 (45%) TAVI 9699 (58%) SAVR	TAVI n=20,872* SAVR n=17,750 SAVR with conventional prosthesis n= 16,870* [*comparison cohorts]	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0% vs. SAVR	Disabling stroke, AVR, NPMI, new AF (in-hospital)
Werner	Patients at Intermediate	Germany	36	Intermedia	Age (years):	N=7,613 patients	SAPIEN XT	in-hospital

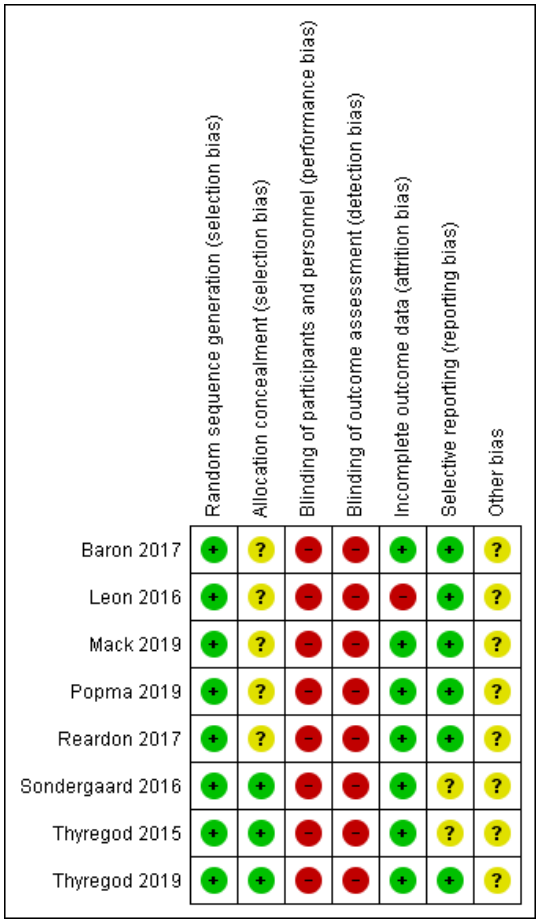
(2018)	Surgical Risk Undergoing Isolated Interventional or Surgical Aortic Valve Implantation for Severe Symptomatic Aortic Valve Stenosis-One-Year Results From the German Aortic Valve Registry.	(German Aortic Valve Registry (GARY)) (n=92 centres)	month s Jan 2012 – Dec 2014	te surgical risk (Society of Thoracic Surgeons score 4%–8%)	82.5±5.0 TAVI 76.6±6.7 SAVR Male (%): 2406 (37.2%) TAVI 405 (35.4%) SAVR	TAVI n=6,469 SAVR n=1,144	23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0% vs. SAVR	mortality, myocardial infarction, stroke, acute kidney injury, permanent pacemaker implantation, bleeding or vascular complications, and aortic valve regurgitation ≥ grade II (in-hospital; 1 year)

Risk of bias assessment

Summary risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Risk of bias by included studies: review authors' judgements



Appendix D Safety review of registry studies

Comparative safety review of registry studies - Intermediate Risk

Interval	Study	TAVI			SAVR		Effect
		TAVI devices	Total	Events	Total	Events	Risk Ratio [95% CI]
In-hospital mortality							
In-hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6469	233	1144	41	1.01 [0.73-1.39]
Stroke							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6469	93	1144	11	1.50 [0.80-2.78]
30 days	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	4	415	4	1.00 [0.25-3.97]
1 year	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	4145	73	821	13	1.11 [0.62-2.00]
MI							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6469	20	1144	9	0.39 [0.18-0.86]
30 days	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	4	415	4	1.00 [0.25-3.97]
1 year	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	4138	28	820	4	1.39 [0.49-3.94]

Interval	Study		TAVI		SAVR		Effect
		TAVI devices	Total	Events	Total	Events	Risk Ratio [95% CI]
TIA							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6469	59	1144	10	1.04 [0.54-2.03]
1 year	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	4145	59	821	15	0.78 [0.44-1.37]
Atrial Fibrillation							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	4239	239	842	71	0.67 [0.52-0.86]
Cardiac Tamponade							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6469	16	1144	20	0.14 [0.07-0.27]
30 days	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	17	415	10	1.70 [0.79-3.67]
Vascular complications							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6172	505	1055	5	17.26 [7.17-41.56]
30 days*	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	23	415	2	11.50 [2.73-48.47]

Interval	Study	TAVI			SAVR		Effect
		TAVI devices	Total	Events	Total	Events	Risk Ratio [95% CI]
NPMI							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	5606	1014	1043	42	4.49 [3.32-6.07]
30 days	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	54	415	15	3.60 [2.07-6.28]
1 year	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	3594	726	746	37	3.96 [2.88-5.46]
Aortic Valve Regurgitation^							
In hospital	Werner 2018	SAPIEN XT 23.9%; SAPIEN XT TA 11.7%; SAPIEN 3, 6.4%; CoreValve 30.0%	6172	236	1055	5	8.07 [3.34-19.52]
30 days	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	1	415	2	0.50 [0.05-5.49]
Acute Renal Failure							
In hospital	Fraccaro 2016	Sapien XT 47%; CoreValve 53%	415	14	415	37	0.38 [0.21-0.69]

Keys: *major vascular complications; ^ Werner (AVR >grade 2) and Fraccaro (severe AVR);

Comparative safety review of registry studies – Intermediate-Low Risk

Interval	Study	TAVI			SAVR		Effect
		TAVI devices	Total	Events	Total	Events	Risk Ratio [95% CI]
Stroke							
In-hospital	Fujita 2019	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0%	20872	264	16870	123	1.73 [1.40-2.15]
NPMI							
In hospital	Fujita 2019	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0%	20872	3459	16870	569	4.90 [4.51-5.36]
New AF							
In-hospital	Fujita 2019	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0%	15043	853	15513	751	1.17 [1.06-1.29]
AVR ≥2y							
In hospital	Fujita 2019	SAPIEN, SAPIEN XT or SAPIEN3 53.7% and CoreValve (CV) or CV Evolut 27.0%	20872	630	16870	39	13.06 [9.46-18.03]

Non-Comparative safety review of registry studies - Intermediate Risk

Interval	Study	TAVI			
		TAVI devices	Total	Events	Event rate (%)
Disabling Stroke					
30 days	Noble 2017	Evolut R	317	6	1.9%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	86	1.9%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	112	2.6%
Non-disabling Stroke					
30 days	Noble 2017	Evolut R	317	8	2.5%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	53	1.2%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	67	1.5%
MI					
30 days	Noble 2017	Evolut R	317	0	0%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	25	0.5%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	55	1.3%
TIA					
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	23	0.5%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	31	0.7%
Life Threatening Bleed					
30 days	Noble 2017	Evolut R	317	40	12.7%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	265	5.8%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	313	7.0%
Major vascular complications					
30 days	Noble 2017	Evolut R	317	31	9.8%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	442	9.6%

Interval	Study	TAVI			
		TAVI devices	Total	Events	Event rate (%)
NPMI					
30 days	Noble 2017	Evolut R	317	69	22.1%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	840	18.5%
1 year	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	905	22.0%
Aortic Valve Regurgitation^					
In hospital	Noble 2017	Evolut R	317	2	0.6%
Acute Kidney Injury					
30 days	Noble 2017	Evolut R	317	14	4.5%
30 days	Ferrari 2016	SAPIEN 49%; CV 19%; ER 13.3%	4599	216	4.7%

Non-Comparative safety review of registry studies – Low +/- Intermediate Risk

Finkelstein (2018) low risk STS score ≤4; Yu (2019) low-intermediate risk STS score 3.5 (2.4–5.0)

Interval	Study	TAVI			
		TAVI devices	Total	Events	Event rate (%)
Procedural mortality					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	7	0.6%
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	3	0.8%
Disabling Stroke					
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	4	1.1%
30 days	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	6	1.6%
1 year	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	10	2.8%
Stroke					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	23	1.9%
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	6	1.6%
30 days	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	8	2.1%
1 year	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	13	3.6%
Cardiac tamponade					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	24	2.0%
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	2	0.5%

Interval	Study	TAVI			
		TAVI devices	Total	Events	Event rate (%)
MI					
In hospital¥	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	7	0.6%
In hospital¥	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	3	0.8%
In hospitalΩ	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	1	0.3%
New AF					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	74	6.2%
Major Bleeding					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	69	5.8%
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	12	3.2%
30 days	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	12	3.2%
1 year	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	13	3.5%
Life Threatening Bleed					
30 days	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	28	2.3%
Major vascular complications					
30 days	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	50	4.2%
NPMI					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	216	18.0%
In hospital	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	26	6.9%
30 days	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	28	7.4%
1 year	Yu 2019	SAPIEN XT 20.7%; SAPIEN 3 35.9%; CV 11.7%; ER 22.6%; LOTUS 9%	376	29	7.7%

Interval	Study	TAVI			
		TAVI devices	Total	Events	Event rate (%)
Paravalvular Leakage (moderate)					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	62	5.2%
Acute Kidney Injury					
In hospital	Finkelstein 2018	SAPIEN 32%; CV 42%; ER 22%; other 4%	1198	132	11.0%

Keys: ¥ peri-procedural MI; Ω spontaneous MI

Appendix E Summary of outcomes tables

Table E1 Transcatheter Aortic Valve Implantation (TAVI) compared to Surgical Aortic Valve Replacement for Severe Aortic Stenosis in patients at intermediate surgical risk of death or complications

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (follow up: 30 days)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	not serious	none	39/1011 (3.9%) 18/879 (2.0%)	41/1021 (4.0%) 13/867 (1.5%)	**RR** 0.96 [0.63 to 1.48] **RR** 1.37 [0.67 to 2.77]	**2 less** per 1,000 **5 more** per 1,000	⨁⨁⨁◯ MODERATE
All-cause mortality (follow up: 2 years)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	not serious	none	123/1011 (12.2%) 55/879 (6.3%)	124/1021 (12.1%) 51/867 (5.9%)	**RR** 0.99 [0.81 to 1.20] **RR** 1.08 [0.80 to 1.48]	**1 more** per 1,000 **4 more** per 1,000	⨁⨁⨁◯ MODERATE
Cardiac mortality (follow up: 30 days)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	not serious	none	33/1011 (3.3%) 17/879 (1.9%)	32/1021 (3.1%) 13/867 (1.5%)	**RR** 1.04 [0.65 to 1.68] **RR** 1.29 [0.63 to 2.64]	**1 more** per 1,000 **4 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Cardiac mortality (follow up: 2 years)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	not serious	none	97/1011 (9.6%) 52/879 (5.9%)	104/1021 (10.2%) 51/867 (5.9%)	**RR** 0.94 [0.72 to 1.22] **RR** 1.01 [0.69 to 1.46]	**6 fewer** per 1,000 **0 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Improvement of symptoms (reduction in NYHA class) (follow up: 2 years)											
2[70, 72]	randomised trials	very serious [a,b]	not serious	not serious	not serious	none	PARTNER 2 trial: at baseline, 80% of patients were NYHA class III or higher; at 30 day follow-up, both groups had significant reduction of symptoms; at 2 year follow-up, 48% of patients in the TAVI group and 52% in the SAVR group maintained NYHA class I. There was no significant difference between the groups. SURTAVI trial: at baseline, 60% in the TAVI group and 58% in the SAVR group were NYHA class III or higher. After 2 year follow-up, there was a significant reduction to NYHA class II or I in the TAVI (63%) and SAVR (58%) groups. There was no significant difference between the groups.				⨁⨁◯◯ LOW
Aortic valve reintervention (follow up: 30 days)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	4/1011 (0.4%) 7/879 (0.8%)	0/1021 (0.0%) 1/867 (0.1%)	**RR** 17.36 [1.28 to 8772] **RR** 6.90 [0.85 to 56.00]	**4 more** per 1,000 **7 more** per 1,000	⨁⨁◯◯ LOW
Aortic valve reintervention (follow up: 2 years)											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	13/1011 (1.3%) 20/879 (2.3%)	5/1021 (0.5%) 3/867 (0.3%)	**RR** 2.63 [0.94 to 7.34] **RR** 6.58 [1.96 to 22.05]	**8 more** per 1,000 **19 more** per 1,000	⨁⨁◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Length of hospital stay											
2[70, 72]	randomised trials	serious [a]	not serious	not serious	not serious	none	Both trials reported significantly shorter durations of hospital stay in the TAVI group, but data could not be pooled. PARTNER 2 reported a median of 6 days for TAVI and 9 days for SAVR (p <0.001). In the SURTAVI trial, length of hospital stay was shorter by 4 days in the TAVI group than in the SAVR group (5.75±4.85 days versus 9.75±8.03 days)				⨁⨁⨁◯ MODERATE
Health related quality of life (follow up: up to 2 years)											
2[72, 76]	randomised trials	very serious [a,b]	not serious	not serious	not serious	none	PARTNER 2: KCCQ-OS: +14.3 (1m); 0 (1y); +1.8 (2y); SF-36(PS): +3.6 (1m); -0.7 (1y); +0.3 (2y); EQ-5D: +0.056 (1m); -0.022 (1y); -0.010 (2y) SURTAVI: KCCQ-OS: +12.5 (1m); SF-36(PS): +1.8 (3m); EQ-5D: +0.01 (3m); Overall; TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (1 to 3 months from baseline) for intermediate surgical risk patients, it is uncertain whether TAVI has any effect on improving HRQoL symptoms compared with SAVR at 1 or 2 year follow-up.				⨁⨁◯◯ LOW
Stroke (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	55/1011 (5.4%) 28/864 (3.2%)	61/1021 (6.0%) 43/796 (5.4%)	**RR** 0.91 [0.64 to 1.30] **RR** 0.60 [0.38 to 0.96]	**5 fewer** per 1,000 **22 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Stroke (follow up: 2 years)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	91/1011 (9.0%) 48/864 (5.6%)	85/1021 (8.3%) 58/796 (7.3%)	**RR** 1.08 [0.82 to 1.43] **RR** 0.76 [0.53 to 1.10]	**7 more** per 1,000 **17 fewer** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Disabling stroke (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	32/1011 (3.2%) 10/864 (1.2%)	43/1021 (4.2%) 19/796 (2.4%)	**RR** 0.75 [0.48 to 1.18] **RR** 0.48 [0.23 to 1.04]	**10 fewer** per 1,000 **12 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Disabling stroke (follow up: 2 years)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	59/1011 (5.8%) 19/864 (2.2%)	61/1021 (6.0%) 29/796 (3.6%)	**RR** 0.98 [0.69 to 1.38] **RR** 0.60 [0.34 to 1.07]	**1 fewer** per 1,000 **14 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Major vascular complications (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	80/1011 (7.9%) 51/864 (5.9%)	51/1021 (5.0%) 8/796 (1.0%)	**RR** 1.58 [1.13 to 2.23] **RR** 5.87 [2.80 to 12.30]	**29 more** per 1,000 **49 more** per 1,000	⨁⨁⨁◯ MODERATE
Major vascular complications (follow up: 2 years)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	86/1011 (8.5%) 54/864 (6.3%)	55/1021 (5.4%) 8/796 (1.0%)	**RR** 1.58 [1.14 to 2.19] **RR** 6.22 [2.98 to 12.99]	**31 more** per 1,000 **52 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Atrial fibrillation (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	91/1011 (9.0%) 113/879 (12.9%)	265/1021 (26.0%) 376/867 (43.4%)	**RR** 0.35 [0.28 to 0.43] **RR** 0.30 [0.25 to 0.36]	**170 fewer** per 1,000 **305 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Atrial fibrillation (follow up: 2 years)											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	110/1011 (10.9%)	273/1021 (26.7%)	**RR** 0.41 [0.33 to 0.50]	**159 fewer** per 1,000	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	85/1011 (8.4%) 217/864 (25.1%)	68/1021 (6.7%) 48/796 (6.0%)	**RR** 1.26 [0.93 to 1.72] **RR** 4.17 [3.09 to 5.61]	**17 more per 1,000** **191 more per 1,000**	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 2 years)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	114/1011 (11.3%) 253/864 (29.3%)	96/1021 (9.4%) 67/796 (8.4%)	**RR** 1.20 [0.93 to 1.55] **RR** 3.48 [2.71 to 4.47]	**19 more** per 1,000 **209 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Life threatening or disabling bleed (follow up: 30 days)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	105/1011 (10.4%) 49/864 (5.7%)	442/1021 (43.3%) 47/796 (5.9%)	**RR** 0.24 [0.20 to 0.29] **RR** 0.96 [0.65 to 1.42]	**329 fewer** per 1,000 **2 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Life threatening or disabling bleed (follow up: 2 years)											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	169/1011 (16.7%) 64/864 (7.4%)	471/1021 (46.1%) 63/796 (7.9%)	**RR** 0.36 [0.31 to 0.42] **RR** 0.94 [0.67 to 1.31]	**294 fewer** per 1,000 **5 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Transient ischaemic attack (TIA) (follow up: 30 days)											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	9/1011 (0.9%)	4/1021 (0.4%)	**RR 2.27** [0.70 to 7.35]	**5 more per 1,000**	⨁⨁◯◯ LOW
Transient ischaemic attack (TIA) (follow up: 2 years)											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	34/1011 (3.4%)	20/1021 (2.0%)	**RR 1.72** [1.00 to 2.96]	**14 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Myocardial infarction (MI) (follow up: 30 days)											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	12/1011 (1.2%) 7/864 (0.8%)	19/1021 (1.9%) 7/796 (0.9%)	**RR** 0.64 [0.31 to 1.31] **RR** 0.92 [0.32 to 2.61]	**7 fewer** per 1,000 **1 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Myocardial infarction (MI) (follow up: 2 years)											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	33/1011 (3.3%) 18/864 (2.1%)	37/1021 (3.6%) 13/796 (1.6%)	**RR** 0.90 [0.57 to 1.43] **RR** 1.28 [0.62 to 2.59]	**4 fewer** per 1,000 **5 more** per 1,000	⨁⨁⨁◯ MODERATE

GRADE Working Group grades of evidence: High evidence: we are very confident that the true effect lies close to that of the estimate of the effect; **Moderate evidence:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low evidence:** our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect; **Very low evidence:** we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias.

b. Downgraded by another level because unblinded assessment of subjective outcomes may be prone to detection bias

c. Downgraded one level because of few event rates in one or both cohorts

Table E2 Transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis in patients at low surgical risk of death or complications

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/496 (0.4%) 4/734 (0.50%)	5/454 (1.1%) 6/734 (0.80%)	**RR 0.37** [0.07-1.88] **RR 0.67** [0.25-1.77]	**7 fewer** per 1,000 **3 fewer** per 1,000	⨁⨁◯◯ LOW
All-cause mortality (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	5/496 (1.0%) 18/734 (2.40%)	11/454 (2.4%) 21/734 (2.90%)	**RR 0.42** [0.15-1.19] **RR 0.86** [0.54-1.35]	**14 fewer** per 1,000 **5 fewer** per 1,000	⨁⨁◯◯ LOW
Cardiac mortality (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/496 (0.4%) 4/734 (0.50%)	4/454 (0.9%) 4/734 (0.60%)	**RR 0.46** [0.08-2.49] **RR 1.00** [0.38-2.66]	**5 fewer** per 1,000 **1 fewer** per 1,000	⨁⨁◯◯ LOW
Cardiac mortality (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	4/496 (0.8%) 12/725 (1.70%)	9/454 (2.0%) 18/678 (2.60%)	**RR 0.41** [0.13-1.31] **RR 0.62** [0.36-1.09]	**12 fewer** per 1,000 **9 fewer** per 1,000	⨁⨁◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Improvement of symptoms (reduction in NYHA class) (follow up: up to 1 year)											
2[19, 20]	randomised trials	very serious [c,d]	not serious	not serious	not serious	none	PARTNER 3 trial: 28% of all patients were NYHA class III or higher at baseline; however these consisted of 31% in the TAVI and 24% in the SAVR groups. The investigators reported 20% of TAVI patients were NYHA class II, III or IV at 30-day follow-up. The SAVR group had 33% of patients with this functional status classification. At 1 year follow-up, both groups had comparable percentages (17-18%) remained in NYHA class II, III or IV. Given the differences at baseline and change in classification grouping from NYHA class III or higher to NYHA class II or higher, it is impossible to draw conclusions from the evidence. Evolut Low Risk trial: 25% of the TAVI group and 28% of the SAVR group were NYHA class III or higher at baseline. After 30 day follow-up, there was a significant reduction in these classifications, with 2% NYHA class III or higher in the TAVI and 5% in the SAVR group. The majority of patients for each intervention were now classified as NYHA class I (TAVI 77% and SAVR 67%) at 30 days. No differences in effect were observed between the two groups at 1 year follow-up.				⨁⨁◯◯ LOW
Aortic valve reintervention (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0/496 (0.0%) 1/734 (0.20%)	0/454 (0.0%) 3/734 (0.40%)	**RR 1.10** [0.00-833.4] **RR 0.33** [0.05-2.36]	**0 difference** per 1,000 **2 fewer** per 1,000	⨁⨁◯◯ LOW
Aortic valve reintervention (follow up: 1 year)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/496 (0.6%) 5/725 (0.70%)	2/454 (0.4%) 4/678 (0.60%)	**RR 1.37** [0.23-8.18] **RR 1.17** [0.49-2.80]	**2 more** per 1,000 **1 more** per 1,000	⨁⨁◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Hospital length of stay											
1[19]	randomised trials	not serious	not serious	not serious	not serious	none	PARTNER 3 trial: patients in the TAVI group had a significantly shorter index hospitalisation than the SAVR group (median, 3±1 versus 7±1 days; p <0.001) as well as a shorter duration of stay in the intensive care unit than those in the surgery group (median, 2±1 versus 3±1 days).				⊕⊕⊕⊕ HIGH
Health related quality of life (follow up: 1 year)											
2[19, 20]	randomised trials	serious [c]	not serious	not serious	not serious	none	PARTNER 3 trial: the KCCQ-OS score change from baseline was 18.5±0.83 (TAVI) and 2.5±1.05 (SAVR) at 30 days, and 19.4±0.87 (TAVI) and 17.4±0.99 (SAVR) at 1 year. Evolut Low Risk trial: the mean KCCQ change from baseline was 20.0±21.1 (TAVI) and 9.1±22.3 (SAVR) at 30 days. Again, TAVI appears to have a superior effect on HRQoL outcomes compared with SAVR in the short-term (30 days from baseline) for low surgical risk patients, while it is uncertain whether TAVI has any effect on improving HRQoL symptoms compared with SAVR at 1 year follow-up.				⊕⊕⊕◯ MODERATE
Stroke (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/496 (0.6%) 15/734 (2.10%)	11/454 (2.4%) 14/734 (1.90%)	**RR 0.25** [0.07-0.89] **RR 1.07** [0.65-1.77]	**18 fewer** per 1,000 **2 more** per 1,000	⊕⊕◯◯ LOW
Stroke (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	6/496 (1.2%) 29/734 (4.00%)	14/454 (3.1%) 31/734 (4.20%)	**RR 0.39** [0.15-1.01] **RR 0.94** [0.65-1.34]	**19 fewer** per 1,000 **2 fewer** per 1,000	⊕⊕⊕◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Disabling stroke (follow up: 30 days)											
1[19]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0/496 (0.0%) 3/734 (0.40%)	2/454 (0.4%) 7/734 (0.90%)	**RR 0.18** [0.01-3.80] **RR 0.43** [0.14-1.33]	**4 fewer** per 1,000 **5 fewer** per 1,000	⨁⨁◯◯ LOW
Disabling stroke (follow up: 1 years)											
1[19]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1/496 (0.2%) 6/734 (0.80%)	4/454 (0.9%) 15/734 (2.10%)	**RR 0.27** [0.03-2.45] **RR 0.40** [0.18-0.89]	**7 fewer** per 1,000 **13 fewer** per 1,000	⨁⨁◯◯ LOW
Major vascular complications (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	11/496 (2.2%) 28/725 (3.80%)	7/454 (1.5%) 22/678 (3.20%)	**RR 1.44** [0.56-3.68] **RR 1.19** [0.83-1.71]	**7 more** per 1,000 **6 more** per 1,000	⨁⨁⨁◯ MODERATE
Major vascular complications (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	14/496 (2.8%) 28/725 (3.80%)	7/454 (1.5%) 24/678 (3.50%)	**RR 1.83** [0.75-4.50] **RR 1.09** [0.76-1.57]	**13 more** per 1,000 **3 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Atrial fibrillation (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	21/496 (4.2%) 56/725 (7.70%)	145/454 (31.9%) 240/678 (35.40%)	**RR 0.13** [0.09-0.21] **RR 0.22** [0.17-0.28]	**277 fewer** per 1,000 **277 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Atrial fibrillation (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	29/496 (5.8%) 71/725 (9.80%)	150/454 (33.0%) 260/678 (38.30%)	**RR 0.18** [0.12-0.26] **RR 0.26** [0.20-0.32]	**272 fewer** per 1,000 **285 fewer** per 1,000	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	32/496 (6.5%) 126/725 (17.40%)	18/454 (4.0%) 41/678 (6.10%)	**RR 1.56** [0.89-2.75] **RR 2.87** [2.45-3.38]	**25 more** per 1,000 **113 more** per 1,000	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	36/496 (7.3%) 141/725 (19.40%)	24/454 (5.3%) 45/678 (6.70%)	**RR 1.32** [0.80-2.18] **RR 2.93** [2.52-3.41]	**20 more** per 1,000 **127 more** per 1,000	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Life threatening or disabling bleed (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	18/496 (3.6%) 17/725 (2.40%)	111/454 (24.4%) 51/678 (7.50%)	**RR 0.15** [0.09-0.24] **RR 0.31** [0.19-0.50]	**208 fewer** per 1,000 **51 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Life threatening or disabling bleed (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	38/496 (7.7%) 23/725 (3.20%)	117/454 (25.8%) 60/678 (8.90%)	**RR 0.30** [0.21-0.42] **RR 0.36** [0.24-0.54]	**181 fewer** per 1,000 **57 fewer** per 1,000	⨁⨁⨁◯ MODERATE
Transient ischaemic attack (TIA) (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0/496 (0.0%) 4/734 (0.50%)	3/454 (0.7%) 1/734 (0.20%)	**RR 0.13** [0.00-2.53] **RR 4.00** [1.51-10.63]	**7 fewer** per 1,000 **3 more** per 1,000	⨁⨁◯◯ LOW
Transient ischaemic attack (TIA) (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	5/496 (1.0%) 12/734 (1.60%)	5/454 (1.1%) 14/734 (1.90%)	**RR 0.92** [0.27-3.14] **RR 0.86** [0.49-1.50]	**1 fewer** per 1,000 **3 fewer** per 1,000	⨁⨁◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Myocardial infarction (MI) (follow up: 30 days)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	5/496 (1.0%) 7/734 (0.90%)	6/454 (1.3%) 4/734 (0.60%)	**RR 0.76** [0.23-2.48] **RR 1.75** [0.84-3.66]	**3 fewer** per 1,000 **3 more** per 1,000	⨁⨁◯◯ LOW
Myocardial infarction (MI) (follow up: 1 years)											
2[19, 20]	randomised trials	serious [a]	not serious	not serious	not serious	none	6/496 (1.2%) 12/734 (1.70%)	10/454 (2.2%) 12/734 (1.60%)	**RR 0.54** [0.20-1.50] **RR 1.00** [0.57-1.75]	**10 fewer** per 1,000 **1 more** per 1,000	⨁⨁⨁◯ MODERATE

GRADE Working Group grades of evidence: definitions as outlined for table 4.12.

Explanations

a. Downgraded one level because one study is based on the interim results of the Evolut Low Risk trial

b. Downgraded one level because of few event rates in one or both cohorts

c. Downgraded one level because unblinded assessment of subjective outcomes may be prone to detection bias

d. Downgraded another level because of inability to interpret results due to difference in NYHA classification combinations at baseline versus 1 year follow-up in PARTNER 3 trial.

Table E3 Transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis in patients at low and intermediate surgical risk (mixed-risk population) of death or complications

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	3/142 (2.1%)	5/134 (3.7%)	**RR 0.57** (0.14 to 2.32)	**16 fewer per 1,000** (from 32 fewer to 49 more)	⨁⨁⨁◯ MODERATE
All-cause mortality (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	7/142 (4.9%)	10/134 (7.5%)	**RR 0.66** (0.26 to 1.69)	**25 fewer per 1,000** (from 55 fewer to 51 more)	⨁⨁⨁◯ MODERATE
All-cause mortality (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	11/142 (7.7%)	13/134 (9.7%)	**RR 0.80** (0.37 to 1.72)	**19 fewer per 1,000** (from 61 fewer to 70 more)	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	39/142 (27.5%)	37/134 (27.6%)	**RR 0.99** (0.68 to 1.46)	**3 fewer per 1,000** (from 88 fewer to 127 more)	⨁⨁⨁◯ MODERATE
Cardiac mortality (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	3/142 (2.1%)	5/134 (3.7%)	**RR 0.57** (0.14 to 2.32)	**16 fewer per 1,000** (from 32 fewer to 49 more)	⨁⨁⨁◯ MODERATE
Cardiac mortality (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	6/142 (4.2%)	10/134 (7.5%)	**RR 0.57** (0.21 to 1.52)	**32 fewer per 1,000** (from 59 fewer to 39 more)	⨁⨁⨁◯ MODERATE
Cardiac mortality (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	9/142 (6.3%)	12/134 (9.0%)	**RR 0.71** (0.31 to 1.63)	**26 fewer per 1,000** (from 62 fewer to 56 more)	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Cardiac mortality (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	29/142 (20.4%)	29/134 (21.6%)	**RR 0.94** (0.60 to 1.49)	**13 fewer per 1,000** (from 87 fewer to 106 more)	⨁⨁⨁◯ MODERATE
Improvement of symptoms (reduction in NYHA class) (follow up: 2 years)											
1[73]	randomised trials	serious [b]	not serious	not serious	serious [a]	none	NOTION trial: 48% of the TAVI group and 45% of the SAVR group were NYHA class III or higher at baseline. After 30 day follow-up, there was a significant reduction in these classifications, with 5% NYHA class III or higher in the TAVI and 4% in the SAVR group. No differences in effect for this functional status classification were observed between the two groups at 1 and 2 year follow-up.				⨁⨁◯◯ LOW
Length of hospital stay											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	NOTION trial: the mean in-hospital time after the index procedure was shorter for TAVI (8.9±6.2 days versus 12.9±11.6 days; p <0.001).				⨁⨁⨁◯ MODERATE
Stroke (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	2/142 (1.4%)	4/134 (3.0%)	**RR 0.47** (0.09 to 2.53)	**16 fewer per 1,000**	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Stroke (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	4/142 (2.8%)	6/134 (4.5%)	**RR 0.63** (0.18 to 2.18)	**17 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Stroke (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	5/142 (3.5%)	7/134 (5.2%)	**RR 0.67** (0.22 to 2.07)	**17 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Stroke (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	13/142 (9.2%)	10/134 (7.4%)	**RR 1.23** (0.56 to 2.70)	**18 more per 1,000**	⨁⨁⨁◯ MODERATE
Major vascular complications (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	8/142 (5.6%)	2/134 (1.5%)	**RR 3.72** (0.80 to 17.22)	**41 more per 1,000**	⨁⨁⨁◯ MODERATE
Atrial fibrillation (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	24/142 (16.9%)	77/134 (57.5%)	**RR 0.29** (0.20 to 0.44)	**406 fewer per 1,000**	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Atrial fibrillation (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	30/142 (21.1%)	79/134 (59%)	**RR 0.36** (0.20 to 0.44)	**379 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Atrial fibrillation (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	32/142 (22.5%)	80/134 (59.7%)	**RR 0.38** (0.27 to 0.53)	**372 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Atrial fibrillation (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	35/142 (24.6%)	82/134 (61.2%)	**RR 0.40** (0.29 to 0.55)	**366 fewer per 1,000**	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	46/142 (32.4%)	2/134 (1.5%)	**RR 21.7** (5.37 to 87.66)	**309 more per 1,000**	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	51/142 (35.9%)	3/134 (2.2%)	**RR 16.04** (5.13 to 50.17)	**337 more per 1,000**	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
New permanent pacemaker implantation (NPMI) (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	55/142 (38.7%)	5/134 (3.7%)	**RR 10.38** (4.29 to 25.14)	**350 more per 1,000**	⨁⨁⨁◯ MODERATE
New permanent pacemaker implantation (NPMI) (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	58/142 (40.8%)	10/134 (7.5%)	**RR 10.38** (4.29 to 25.14)	**333 more per 1,000**	⨁⨁⨁◯ MODERATE
Life threatening or disabling bleed (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	16/142 (11.3%)	28/134 (20.9%)	**RR 0.54** (0.31 to 0.95)	**96 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Transient ischaemic attack (TIA) (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	2/142 (1.4%)	2/134 (1.5%)	**RR 0.94** (0.13 to 6.60)	**1 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Transient ischaemic attack (TIA) (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	3/142 (2.1%)	2/134 (1.5%)	**RR 1.42** (0.24 to 8.34)	**6 more per 1,000**	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Transient ischaemic attack (TIA) (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	8/142 (5.6%)	4/134 (3.0%)	**RR 1.86** (0.57 to 6.04)	**26 more per 1,000**	⨁⨁⨁◯ MODERATE
Transient ischaemic attack (TIA) (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	9/142 (6.3%)	5/134 (3.7%)	**RR 1.70** (0.58 to 4.94)	**26 more per 1,000**	⨁⨁⨁◯ MODERATE
Myocardial infarction (MI) (follow up: 30 days)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	4/142 (2.8%)	8/134 (6.0%)	**RR 0.47** (0.15 to 1.53)	**32 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Myocardial infarction (MI) (follow up: 1 years)											
1[75]	randomised trials	not serious	not serious	not serious	serious [a]	none	5/142 (3.5%)	8/134 (6.0%)	**RR 0.59** (0.20 to 1.76)	**25 fewer per 1,000**	⨁⨁⨁◯ MODERATE
Myocardial infarction (MI) (follow up: 2 years)											
1[73]	randomised trials	not serious	not serious	not serious	serious [a]	none	7/142 (4.9%)	8/134 (6.0%)	**RR 0.83** (0.31 to 2.21)	**11 fewer per 1,000**	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter Aortic Valve Implantation (TAVI)	Surgical Aortic Valve Replacement	Relative (95% CI)	Absolute (95% CI)	
Myocardial infarction (MI) (follow up: 5 years)											
1[74]	randomised trials	not serious	not serious	not serious	serious [a]	none	11/142 (7.7%)	11/134 (8.2%)	**RR 0.94** (0.42 to 2.10)	**5 fewer per 1,000**	⨁⨁⨁◯ MODERATE

GRADE Working Group grades of evidence: definitions as outlined for table 4.12.

Explanations

a. Downgraded one level because of small sample sizes (<400)

b. Downgraded by another level because unblinded assessment of subjective outcomes may be prone to detection bias

Appendix F Systematic review of cost-effectiveness studies: search terms

PubMed

	Search Terms	Results
#1	TAVI	3994
#2	TAVR	2794
#3	"transcatheter aortic valve implantation"	4802
#4	“transcatheter aortic valve replacement”	6228
#5	SAVR	777
#6	“surgical aortic valve replacement”	1675
#7	“aortic valve replacement”	18309
#8	“aortic valve stenosis”	24885
#9	“heart valve prosthesis”	47970
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	49,585
#11	"cost effectiveness analysis"	9570
#12	economics	761140
#13	“cost analysis”	9570
#14	“economic model”	2043
#15	“quality adjusted life year”	4880
#16	QALY	17175
#17	“cost utility analysis”	2362
#18	“incremental cost effectiveness ratio”	4936
#19	ICER	3737
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	498,954
#21	#10 AND #20	657

Embase

	Search Terms	Results
#1	TAVI	9540
#2	TAVR	5577
#3	‘Transcatheter aortic valve implantation’	19280
#4	‘Transcatheter aortic valve replacement’	6394
#5	SAVR	1486
#6	‘Surgical aortic valve replacement’	3031
#7	‘aortic valve replacement’	33366
#8	‘aortic valve stenosis’	17340
#9	‘heart valve prosthesis’	24046
#10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	74123
#11	‘cost effectiveness analysis’	144956
#12	‘cost utility analysis’	9875
#13	‘cost analysis’	12399

#14	'economics'	375484
#15	'economic model'	3924
#16	'quality adjusted life year'	25343
#17	QALY	15078
#18	'incremental cost effectiveness ratio'	8145
#19	ICER	8512
#20	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19	519437
#21	#10 AND #20	416

Cochrane

	Search Terms	**Results**
#1	TAVI	404
#2	TAVR	388
#3	'Transcatheter aortic valve implantation'	715
#4	'Transcatheter aortic valve replacement'	619
#5	SAVR	172
#6	'Surgical aortic valve replacement'	674
#7	'aortic valve replacement'	1630
#8	'aortic valve stenosis'	1304
#9	'heart valve prosthesis'	1328
#10	OR #1-#9	2880
#11	'cost effectiveness analysis'	20897
#12	'cost utility analysis'	3515
#13	'cost analysis'	33807
#14	'economic model'	4984
#15	'quality adjusted life year'	9600
#16	QALY	2676
#17	'incremental cost effectiveness ratio'	2244
#18	ICER	1299
#19	OR #11-#19	42599
#20	#10 AND #19	41

Appendix G Assessment of included studies in the systematic review of cost-effectiveness

Table G.1: Assessment of included studies using the Consensus on Health Economic Criteria (CHEC) list

Item	Baron et al. (2019)	Goodall et al. (2019)	Kaier et al. (2019)	Kodera et al. (2018)	Tam et al. (2018a)	Tam et al. (2018b)	Zhou et al. (2019)
Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are competing alternatives clearly described?	Yes	No	Yes	Yes	Yes	Yes	Yes
Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the economic study design appropriate to the stated objective?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant costs for each alternative identified?	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
Are all costs measured appropriately in physical units?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Are costs valued appropriately?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant outcomes for each alternative identified?	Unclear	Yes	Yes	No	No	No	Yes
Are all outcomes measured appropriately?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Are outcomes valued appropriately?	Unclear	Yes	Yes	No	No	No	Yes
Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are all future costs and outcomes discounted appropriately?	Yes	Yes	N/A	Yes	Yes	Yes	Yes

Table G.1: Assessment of included studies using the Consensus on Health Economic Criteria (CHEC) list

Item	Baron et al. (2019)	Goodall et al. (2019)	Kaier et al. (2019)	Kodera et al. (2018)	Tam et al. (2018a)	Tam et al. (2018b)	Zhou et al. (2019)
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	No	Yes	Yes	Yes	Yes
Do the conclusions follow from the data reported?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	Yes	No	No	No	Yes	Yes	Yes
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	No	Yes	Yes	No	No	No
Are ethical and distributional issues discussed appropriately?	No	No	No	No	No	No	No
Outcome	**Low**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**High**

Appendix H Relevance and credibility of included studies in the systematic review of cost-effectiveness

Table H.1: Assessment of included studies using the ISPOR questionnaire on relevance and credibility

Item	Baron et al. (2019)	Goodall et al. (2019)	Kodera et al. (2018)	Tam et al. (2018a)	Tam et al. (2018b)	Zhou et al. (2019)
Is the population relevant?	Yes	Yes	Yes	Yes	Yes	Yes
Are any critical interventions missing?	No	No	No	No	No	No
Are any relevant outcomes missing?	Unclear	No	Yes	No	No	No
Is the context applicable?	Yes	Yes	Yes	Yes	Yes	Yes
Is external validation of the model sufficient?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Is internal validation of the model sufficient?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Does the model have sufficient face validity?	Unclear	No	Yes	Yes	Yes	Yes
Is the design of the model adequate?	Unclear	No	No	No	Yes	Yes
Are the data used in populating the model suitable?	Unclear	No	No	No	No	Yes
Were the analyses adequate?	Unclear	Yes	Yes	Yes	Yes	Yes
Was the adequate assessment of uncertainty?	Yes	Yes	Yes	Yes	Yes	Yes
Was the reporting adequate?	No	No	No	Yes	Yes	Yes
Was interpretation fair and balanced?	Unclear	Yes	Yes	Yes	Yes	Yes
Were there any potential conflicts of interest?	Yes	Yes	No	Yes	Yes	Yes
Were steps taken to address conflicts?	No	No	NA	No	No	No
Outcome	**Not applicable**	**Partially applicable**	**Partially applicable**	**Partially applicable**	**Partially applicable**	**Partially applicable**