Transcatheter Aortic Valve Implantation –

Tier 3 Assessment

National Health Committee (NHC)

The National Health Committee (NHC) is an independent statutory body charged with prioritising new and existing health technologies and making recommendations to the Minister of Health.

It was re-formed in 2011 to establish evaluation systems that would provide the New Zealand people and the health sector with greater value for money invested in health.

The NHC executive is the secretariat that supports the committee. The NHC executive's primary objective is to provide the committee with sufficient information for it to make decisions regarding prioritisation and reprioritisation of interventions and services. They do this through a range of evidence-based products chosen according to the nature of the decision required and timeframe within which decisions need to be made.

The New Zealand Government has asked that all new diagnostic and treatment (non-pharmaceutical) services, and significant expansions of existing services, are to be referred to the NHC.

In August 2011 the NHC was appointed with new terms of reference and a mandate to establish the capacity to assess new and existing health technologies. Its objectives (under Section 4.2 of its terms of reference – www.nhc.health.govt.nz) include contributing to improved value for money and fiscal sustainability in the health and disability sector by:

- providing timely advice and recommendations about relative cost-effectiveness based on the best available evidence;
- providing advice and recommendations which influence the behaviour of decision-makers, including clinicians and other health professionals;
- providing advice and recommendations which are reflected in resource allocation at national, regional and local levels; and
- contributing to tangible reductions in the use of ineffective interventions and improved targeting to those most likely to benefit.

In order to achieve its objectives under Section 4.2 and to achieve 'value for money', the NHC has adopted a framework of four assessment domains – clinical safety and effectiveness; economic; societal and ethical; and feasibility of adoption – in order that assessments cover the range of potential considerations and that the recommendations made are reasonable.

It is intended that the research questions asked will fall across these domains to ensure that when the committee comes to apply its decision-making criteria, it has a balanced range of information available to it. When the NHC is setting those questions, they will have the decision-making criteria in mind.

The 11 decision-making criteria will assist in the determination of the NHC work programme and in the appraisal and prioritisation of assessments.

Executive summary

This report synthesises current evidence about the use of transcatheter aortic valve implantation (TAVI) for the treatment of severe aortic stenosis in New Zealand. Its purpose is to enable the National Health Committee to make recommendations on the role and value of TAVI in the model of care for severe aortic stenosis that ensure that the New Zealand public get the highest quality care, and that as a nation we can afford that care.

TAVI is a novel technology that is changing treatment choices for aortic stenosis internationally. It allows for the replacement of the aortic valve, without the need to open the chest cavity or to use cardiopulmonary bypass (a machine that takes over the role of the heart and lungs) as is the case with conventional surgical valve replacement.[1] This assessment reviews the current evidence and model of care to assess which patients may benefit from the use of TAVI within current New Zealand cardiovascular budgets.

Internationally, there are many different TAVI devices available and in development. The two most commonly used valves are the Medtronic CoreValve and Edwards Lifesciences Sapien valve. TAVI can be delivered via percutaneous access (transfemoral delivery), or via minimally invasive surgical access (transapical, transaortic/direct aortic or subclavian delivery).[2] Different access routes may be appropriate for different patients, but the two main access routes are the transfemoral (TF) retrograde (against normal blood flow) approach and the transapical (TA) antegrade (in the direction of normal blood flow) approach. The transfemoral approach is the dominant approach used in New Zealand.

Initial trial data for TAVI were centred on 'inoperable' patients, and 'high surgical risk' patients. Inoperable patients are patients who are considered too high risk for surgery, who without TAVI would receive limited intervention to relieve symptoms variously referred to in the literature as 'medical management' or 'standard therapy'. More recently, inoperable patients have been subdivided into patients who are inoperable due to significant comorbidities such as cancer, end-stage renal failure or diabetes; and those who are inoperable for technical reasons such as having a porcelain aorta or a significantly deformed chest. The first group of patients are referred to as being 'clinically inoperable', and while they may survive the TAVI procedure, they have a limited capacity to benefit due to their poor life expectancy. The second group of patients are referred to as being 'technically inoperable'. These patients have fewer comorbidities to limit their capacity to benefit from TAVI. High-risk patients are eligible for surgery, but carry a high risk of mortality. In the absence of TAVI, these patients are likely to undergo surgical AVR. At least 100 trials, including 24 randomised controlled trials, are planned or underway internationally. These include trials of moderate and low-risk patients. However, at this time, surgical AVR remains the gold standard intervention for moderate and low-risk patients.

In cardiac surgery and interventional cardiology, operative risk is defined by algorithms, some of which are more accurate than others. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons Predicted Risk of Mortality Score (STS-PROM) are the most widely used risk scores to predict operative mortality in cardiac surgery.[3, 4] The Logistic

EuroSCORE significantly overestimates the high-risk population pool. STS-PROM is a better fit and is advocated by international and New Zealand-specific research. Using the STS-PROM, about 5% of surgical AVR patients can be classed as high-risk, 15% as moderate or intermediate-risk, and 80% as low-risk. In New Zealand, TAVI is only supported in surgical candidates at high surgical risk. TAVI has not received Ministerial approval for moderate-risk, low-risk, or inoperable patients.

Internationally, TAVI is supported by health technology assessment agencies and professional bodies for inoperable patients or patients at high risk of mortality from surgical AVR – where surgical AVR remains the gold standard treatment for low and moderate-risk patients.[5-15] That includes current professional guidance from the American College of Cardiology/American Heart Association (2014), and the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (2012). In practice, however, it appears that TAVI is already being performed in moderate and low-risk populations in some countries, particularly Germany.[16-25]

Safety and effectiveness

Safety and effectiveness evidence was reviewed from randomised controlled trials, large international registries, and systematic reviews. Follow-up now extends to five years in randomised controlled trials and international registries.

Compared with surgical AVR in high-risk patients, TAVI appears to have similar survival and lower rates of major bleeding events; but is associated with higher rates of aortic regurgitation and major vascular complications. TAVI is also associated with higher rates of pacemaker implantation with the CoreValve but not the Edwards Sapien valve. Permanent pacemaker insertion is three to four times greater using the CoreValve than the Edwards valve. Renal complications appear to be similar between TAVI and surgical AVR, but elevated using the transapical approach.

Among high-risk TAVI patients, those who receive the transfemoral approach appear to have better survival, though this may reflect patient selection. Moderate or severe aortic regurgitation is more common using the CoreValve than the Edwards Sapien valve. Vascular complications are more likely in patients who receive the transfemoral, rather than the transapical approach.

Early concerns about stroke in high-risk patients have not played out in subsequent randomised control data or meta analyses. In the Placement of Aortic Transcatheter Valves (PARTNER) randomised controlled trial, stroke was elevated at one and two years for high-risk TAVI patients, but did not reach statistical significance. The more recent high risk CoreValve study demonstrated significantly lower total stroke (major and minor) for TAVI compared with surgery at two years.

For inoperable patients, compared with medical management, TAVI is associated with superior survival and reduced hospital readmissions, but higher rates of aortic regurgitation, vascular complications, stroke, and major bleeding events. All-cause mortality for inoperable TAVI patients is still very high in randomised evidence; where it was 43% at two years in the PARTNER trial.

Survival and complication rates are generally similar or better in large international registries compared with randomised controlled trials (RCTs) for high-risk and inoperable patients. Registry data also show that TAVI is being undertaken in moderate-risk patients in Australasia.

Health technology assessment agencies

Earlier health technology assessments (HTAs) of TAVI led to recommendations that TAVI be funded for use in inoperable patients only, but later HTAs have expanded indications to include high-risk patients. TAVI is not supported in moderate and low-risk patients.

UK commissioning guidelines stipulate that only high-risk or inoperable patients are eligible for publicly funded TAVI, where 'inoperability is primarily the result of anatomical limitations' [26] Inoperable patients who are inoperable primarily due to comorbidities have poor outcomes post TAVI. Patients who are inoperable primarily due to technical (anatomical) reasons such as porcelain aorta, previous mediastinal radiation, and chest wall deformity, may gain similar survival benefit from TAVI as high-risk patients. However, prospective evidence (preferably RCT evidence) is required to confirm this result.

Economic

Aortic valve replacement is a high-cost procedure, whether undertaken with conventional surgical AVR or TAVI. The lifetime cost of isolated TAVI ranges from $84,000 to $98,000, for high-risk and technically inoperable patients respectively. The lifetime cost of isolated surgery ranges from $90,000 to $101,000. Medical management is relatively inexpensive, costing about $15,000 per patient over their remaining lifetime.

Cost-effectiveness

TAVI appears to be highly cost-effective, but only in a very small group of patients, namely those patients who are at high risk from surgery. The high-risk AVR patient population in New Zealand (STS>8%) is relatively small, probably less than 30 patients per annum based on current AVR volumes. For these patients, TAVI appears to be cost-saving compared with surgery, largely due to the reduced length of stay associated with percutaneous intervention.

Our cost-saving finding in high-risk patients is consistent with a recent UK analysis sponsored by the British Heart Foundation which found TAVI had an incremental saving of $3,000 (£1,300) per patient compared with surgical AVR in high-risk patients. A 2013 economic assessment by the Ontario Health Technology Assessment Committee (OHTAC) also found TAVI had an incremental cost saving of $5,000 (C$4,600) per procedure compared with surgery in high-risk patients.

For the inoperable patient population, TAVI does not appear to be cost-effective, where the cost per quality adjusted life years is about $74,000. In the subgroup of 'technically inoperable' patients, patients who have fewer comorbidities and tend to be younger, the cost per QALY is $40,000, due to vastly better life expectancy. The evidence for this patient population is, however, limited to a secondary analysis of a single randomised controlled trial and registry. Sensitivity analysis shows that cost-effectiveness is most sensitive to the relative efficacy of TAVI compared with surgical AVR and medical management.

Budgetary impact

The projected potential budgetary impact of TAVI depends on the population for whom TAVI is funded. On the basis of population growth in people over 65 years of age, TAVI volumes are expected to expand from 66 procedures in 2012/13 to about 84 procedures in 2019/20. For this base case scenario, we project a cost profile of about $4.4 million (confidence interval: $3.5m, $5.3m) in 2015/16, increasing to $6.7 million ($5.3m, $8.0m) in 2019/20, accounting for both the index admission cost and attributable follow-up costs.

If TAVI is expanded to inoperable patients, including patients with significant comorbidities, intervention rates could grow to 210 procedures in 2019/20. For this scenario, the additional cost (beyond the base case) would be $6.2 million ($5.0m, $7.5m) in 2015/16, increasing to $7.5 million ($6.2m, $9.3m) in 2019/20. That is, the total cost of TAVI would be approximately $14.2 million in 2019/20 if expanded to inoperable patients.

If TAVI is expanded to 'technically inoperable' patients only, the intervention rate could grow to 113 procedures by 2019/20. Under this scenario, the additional cost (compared with our base case) would

be about $1.5 million ($1.2m, $1.8m), increasing to $2.0 million ($1.6m, $2.4m) over the same time period.

These scenarios assume an expansion of TAVI volumes. There is, however, little doubt that current volumes are well in excess of what would be expected if only high-risk patients were receiving TAVI in New Zealand. Sixty-six TAVI procedures were undertaken in 2012/13, whereas, on the basis of current AVR volumes, high-risk volumes should account for no more than 20 to 30 patients annually in New Zealand. This finding is corroborated by a recent retrospective study of all TAVI undertaken in New Zealand between 2008 and 2014 that found TAVI had been performed in moderate and high-risk patients.[27, 28] Two substitution scenarios are thus suggested: either TAVI should be limited to high-risk patients only, with moderate-risk patients converting to surgical AVR; or TAVI should be limited to high-risk patients with moderate-risk patients converted to AVR, and remaining TAVI volumes taken up by technically inoperable patients.

Under the first scenario, TAVI volumes would be reduced to 20 to 30 patients per annum. With a proficiency requirement of at least 20 TAVI operations per annum,[29] the scenario implicitly assumes a reduction of three TAVI centres to one. As surgical AVR does not appear to be significantly less costly compared with TAVI in moderate-risk patients, we do not project any savings through this scenario. The second substitution scenario assumes maintenance of current TAVI volumes with allowance for population growth. Under the scenario, any shift to technically inoperable cases would be consequent to moderate risk TAVI volumes being converted to surgical AVR. Under this scenario we project an additional cost of $1 million ($0.8m, $1.2m), increasing to $1.7 million ($1.4m, $2.1m) over five years. This is less than the prior scenario, where technically inoperable volumes were in addition to base volumes, but not significantly less due to the implied conversion of moderate-risk TAVI patients to surgical AVR.

Societal and ethical

The Midland region appears to have a higher TAVI intervention rate than other regions (by DHB of domicile), most likely owing to the high volume of TAVI undertaken at Waikato DHB. Patients with severe aortic stenosis tend to be elderly and can have significant morbidities. Mid-term outcomes, even with a successful procedure can be very poor for some patients. Hence appropriate patient selection is imperative to avoid futile outcomes. In technically inoperable patients, TAVI is a substitution for medical management, rather than surgical AVR, and thus raises issues of equity of access that would need to be worked through with the sector.

Feasibility of adoption

New Zealand guidance for TAVI patient selection is dated and has not achieved its stated intention of constraining TAVI to high-risk patients. Following two joint meetings with key stakeholders, it became apparent that the current model of care required revision. A number of elements are suggested for inclusion in the revised model including:

- An evidence-based definition of ‘high risk’ – New Zealand and International research suggests that the STS-PROM should be used to define operative risk.
- Consideration of other factors not included in the STS such as frailty, ‘hostile chest’ and the presence of a porcelain aorta are also important considerations.
- Data collection on patient quality of life to provide feedback to clinicians on the value of intervention, and provide the evidence for any indication expansion.
- A greater role for geriatricians in the heart team used to prioritise interventions.

Neither the clinical nor the economic evidence reviewed in this report suggests significant expansion in TAVI is warranted. For patient safety, it is imperative that TAVI is undertaken in centres with

sufficient volume and experience. As volumes are not expected to expand significantly in the foreseeable future, TAVI should be limited to the current three centres in Auckland, Waikato and Canterbury District Health Boards.

Though there remain complex issues regarding workforce and capital planning, TAVI is not expected to significantly impact on either workforce or capital in the foreseeable future. While TAVI appears to be undertaken in moderate-risk patients, the current reimbursement regime, which reimburses TAVI at the same rate as conventional AVR, sets broadly the right incentive for DHBs to fund the procedure when it makes financial sense. No change to the reimbursement of TAVI is proposed.

Purpose

This report synthesises current evidence about the use of transcatheter aortic valve implantation (TAVI) for the treatment of severe aortic stenosis in New Zealand. Its purpose is to enable the National Health Committee to make recommendations on the role and value of TAVI in the model of care for severe aortic stenosis that ensure that the New Zealand public get the highest quality care, and that as a nation we can afford that care.

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2 Introduction and context for NHC involvement

Transcatheter aortic valve implantation (TAVI) is a novel technology that is changing treatment choices for aortic stenosis internationally. It allows for the replacement of the aortic valve, without the need for a median sternotomy (incision that separates the sternum to open the chest cavity) or cardiopulmonary bypass (a machine that takes over the role of the heart and lungs) that accompanies conventional surgical valve replacement.[1] The introduction of TAVI has caused much controversy amongst policy makers and medical practitioners, due to the high cost of the valve and the difficulty in defining its precise role within current models of care for aortic stenosis**.** The large volume of published research is such that it has been difficult for governing agencies to position the technology in the sector without recommendations becoming obsolete.

TAVI was first introduced in New Zealand at Waikato Hospital in 2008. Following sanctioning by the Auckland Clinical Practice Committee (CPC) in 2011, public funding of TAVI in New Zealand was approved by the Minister of Health for high-risk surgical candidates subject to a national review.

TAVI was first added to the NHC reactive work programme in August 2012 following discussions between the NHC, the National Health Board, and the chairs of the New Zealand Cardiac Network and the National Cardiac Surgery Clinical Network. The NHC published a briefing report in September 2012.[30]

A literature review was then undertaken and a draft review presented to the NHC in May 2013, alongside a proposed engagement process with key stakeholders. The report highlighted the need for a stakeholder workshop to address issues around the cost-effectiveness and sustainability of TAVI. Consequently, two joint meetings with key stakeholders took place, contributing to this assessment of TAVI.

The NHC reviews health technologies using four assessment domains: clinical safety and effectiveness; economic; societal and ethical; and feasibility of adoption. This report presents the evidence for TAVI across these four domains, where the broad research questions for each domain are presented in Section 3. Addressing the first domain, the report outlines the clinical safety and effectiveness evidence for TAVI gathered from clinical trials. The economic domain builds on the clinical review, incorporating cost and quality of life data to undertake cost-utility analysis and a cost impact assessment of various diffusion scenarios. The societal and ethical section reviews available literature on ethical and social issues that may arise in relation to TAVI. Lastly, the feasibility of adoption section outlines the practical concerns that face the health sector, including workforce and infrastructure constraints that may confront the delivery and sustainability of TAVI in New Zealand.

The research questions are outlined next in Section 3. Section 4 provides background on aortic stenosis and its treatment options. A brief outline of the burden of disease is given, followed by a description of alternative treatments – including TAVI and its multiple technical approaches. Section 5, the Technology Status, outlines the regulatory status of competing TAVI valves and delivery systems. The section summarises New Zealand's current policy setting for TAVI including the patient selection pathway. Section 6 assesses the clinical safety and effectiveness evidence for TAVI. Likewise sections 7, 8 and 9 summarise available evidence for the economic, societal and ethical, and feasibility of adoption domains, respectively.

3 Research questions

A series of research questions across the NHC's four domains were formulated to gather the necessary evidence for the committee to evaluate the intervention against its 11 decision-making criteria.[1] These are detailed below and are followed by information on aortic stenosis, including prognosis, epidemiology, and current treatment options.

Clinical safety and effectiveness	• For what patient groups is TAVI a clinically safe and effective treatment for aortic stenosis compared with current alternative interventions in terms of adverse effects (eg death, major stroke and vascular complications) and outcomes?
Economic	• What is the cost and cost-effectiveness of TAVI in the New Zealand environment?
Feasibility of adoption within the system	• What are the feasibility of adoption issues relating to TAVI in New Zealand when budget impact, workforce, policy congruence and any legal issues are taken into account? • Is the establishment of a national registry necessary for consistent collection of data appropriate?
Societal and ethical considerations	• What are the potential social and ethical implications that need to be considered?

[1] http://nhc.health.govt.nz/about-us/decision-making-criteria

4 Background

Condition description

Aortic stenosis (AS) is a pathological narrowing of the aortic valve, which reduces blood flow from the heart to the rest of the body via the aorta. In the early stages of the disease, people with AS are asymptomatic without an increased risk of death or decrease in quality of life.[31, 32] Initially, the left ventricle compensates through a process of left ventricular hypertrophy (thickening of the heart muscle) to maintain adequate blood flow. However, over time, and with progressive worsening of the obstruction, this response becomes maladaptive; resulting in excessive left ventricular hypertrophy and dysfunction. Symptoms include fatigue, angina (chest pain caused by inadequate blood flow to the heart muscle), dyspnoea (shortness of breath) and syncope (fainting or loss of consciousness caused by inadequate blood flow to the brain).[31]

The natural history of AS is such that patients face a bleak prognosis once the disease becomes clinically evident, either with the onset of symptoms or with a deterioration of left ventricular function. The life expectancy of patients with clinically evident AS is two to three years without intervention, and quality of life is often poor due to the burden of symptoms and multiple admissions to hospital for heart failure.[33, 34] However, when symptomatic AS is successfully treated with valve replacement, age-adjusted survival is close to that for individuals without aortic stenosis, especially among older patients.[35]

In adults, AS is most commonly caused by age-related progressive calcification of the aortic valve, although it can also be the result of a congenital heart defect or rheumatic heart disease. Age-related calcification of the normal tri-leaflet valve typically presents in those aged ≥70 years, whereas stenosis of a congenital bicuspid valve or that due to previous rheumatic fever may present earlier.[34]

The diagnosis of severe AS is made via transthoracic echocardiography, with occasional requirement for stress echocardiography and cardiac catheterisation. The European Association of Echocardiography/American Society of Echocardiography have published guidelines for quantifying the severity of AS and reiteration of these are beyond the scope of this document.[35] However, it should be mentioned that in the vast majority of patients, Doppler and transthoracic echocardiography data are sufficient for determining the severity of AS.

The 2014 American College of Cardiology/American Heart Association practice guideline for the management of patients with valvular heart disease clearly provides direction around the optimum timing of intervention.[36] There is a class 1 recommendation for aortic valve replacement (AVR) in patients with severe AS with decreased systolic opening of a calcified aortic valve; and an aortic velocity of 4.0 m/sec or greater or mean pressure gradient across the valve of 40 mmHg or higher; and symptoms of heart failure, syncope, exertional dyspnoea, or angina on history or on exercise testing. Exercise testing and biomarkers such as NT-proBNP (indicative of heart failure) may be helpful in determining optimal timing of intervention in patients who are asymptomatic or have equivocal symptoms.[36, 37] Although valve replacement in asymptomatic AS is more contentious, valve replacement is appropriate if the patient has a decreased left ventricular function, and at least moderate AS on transthoracic echocardiography and is undergoing other cardiac surgery where valve replacement can be carried out simultaneously. Also, if other high-risk factors are present, such as a high degree of calcification of the valves, rapidly progressive disease, or bicuspid valve disease with aneurysmal or expanding aortic root, then AVR may be reasonable.[36]

Many patients are unsuitable for AVR due to comorbidities (other medical conditions that the patient may have) and general frailty. These patients are medically managed and have a poor outlook as described above.

4.1.1 Prevalence and incidence

In the absence of published data, the NHC used the New Zealand National Minimum Dataset (NMDS)[2] to estimate the prevalence and incidence of hospital diagnosed AS. In 2012/13, the prevalence of any hospital diagnoses of AS was 103 per 100,000 population or approximately 4,700 patients. Patients were recorded as having AS if they were still living in 20012/13 and had received any hospital diagnosis of AS since 2005/06 but not an aortic valve replacement[3]. Detail on our methodology is contained within *National Health Committee Aortic Stenosis Overview Tier 2 (2015).*Incidence was 36 cases per 100,000 population, counting any patient who received a new hospital diagnosis of AS in 2012/13 not previously present.

Just over a third of all patients with a hospital diagnosis of AS in 2012/13 had AS recorded as a primary diagnosis. A primary hospital diagnosis is assumed to represent a more severe and symptomatic population, as it is more likely to represent symptomatic admission rather than as a secondary condition. The prevalence of a severe hospital diagnoses of AS is estimated at 38 per 100,000 population or approximately 1,703 patients. Of these patients, 23 were recorded as having rheumatic AS. Incidence of AS was 19 cases per 100,000 population, ranging from one patient per 100,000 population for those aged under 50, to 145 per 100,000 population for those aged over 70. There were 860 new cases of severe AS in 2012/13. As prevalence and incidence of AS are greatest in older age groups, population ageing can be expected to increase the incidence of AS.

4.1.2 Mortality

In 2011, there were 295 deaths attributed to AS in New Zealand.[(38)] The age-standardised mortality rate was three per 100,000 population, with only four deaths recoded for Māori. Eighty-two percent of all deaths occurred over the age of 80.

Current treatment

Traditional treatment options for AS include medical therapy, balloon aortic valvuloplasty (BAV), and surgical aortic valve replacement. TAVI and sutureless surgical valve replacement are alternatives to conventional surgical AVR.

4.1.3 Medical management

Medical management's role in AS is for symptomatic relief and in particular treatment of heart failure. Medical treatments do not prevent or delay the disease progression. Nevertheless, palliative medical management of symptomatic AS is appropriate for patients who are either not candidates for surgical AVR due to frailty, have poor life expectancy or significant comorbidity, or do not wish to have interventional treatment.[(39, 40)]

4.1.4 Balloon aortic valvuloplasty

Percutaneous balloon aortic valvuloplasty (BAV), whereby a balloon is inflated within the aortic valve to release the stenosis, results in immediate hemodynamic improvement in adult patients with calcific aortic stenosis. However, the clinical improvement is not sustained due to the high rate of restenosis.[(41)] Therefore, prognosis remains poor in these patients. There has been no significant difference in long-term survival demonstrated between patients undergoing BAV and those undergoing medical therapy alone. It has been recommended that BAV should not be used as a substitute for AVR in patients who are candidates for surgery [(42)] BAV may be used to bridge patients until definitive treatment can be carried out (this is now given a Class 2B recommendation in the 2014

[2] The NMDS records all publically funded inpatient events.

AHA/ACC guidelines) or as a palliative measure.[36] However, the BAV procedure is not without risks, and given its temporary benefits, the procedure is done relatively infrequently in New Zealand.

4.1.5 Aortic valve replacement

Surgical aortic valve replacement prolongs life in patients with aortic stenosis and improves quality of life.[36] There are two types of prosthetic valve: mechanical valves that may last up to 25 years but require the recipient to take anticoagulants to prevent stroke, and bioprosthetic ('tissue') valves that last 10 to 15 years but do not require anticoagulation.[43-45] Anticoagulants such as warfarin can cause bleeding, requiring regular monitoring with blood tests, and may interact with certain foods and other medications. There is a worldwide trend toward using more bioprosthetic valves, partly due to data suggesting comparable survival despite increased need for surgery.[46]

AVR has traditionally involved open heart surgery with full sternotomy (incision that separates the sternum to open the chest cavity). However, given that the majority of patients requiring valve replacement are elderly, a significant proportion of patients with aortic stenosis are too high-risk for surgery and are therefore not suitable candidates for traditional surgical valve replacement. This may be due to significant comorbidity, frailty or anatomical limitations to sternotomy (eg scarring from previous surgery).[40] A Waikato study found that among patients with symptomatic severe aortic stenosis, only about half were offered surgical AVR, and international data suggest that between 30% and 50% of severe symptomatic AS patients are considered ineligible for traditional open heart surgery.[47] Mortality rates were significantly higher in those who did not undergo surgical AVR; however, this in part reflects the characteristics of the patients that were not offered surgery. For some of these patients, surgical AVR would offer little benefit because of poor life expectancy or operative mortality. For the remaining high surgical risk group who would benefit from AVR, less invasive techniques may have advantages over standard surgical AVR. Less invasive alternatives to conventional surgical AVR include TAVI and sutureless AVR, with or without minimally invasive approaches.

In a report from the Society of Thoracic Surgeons (STS) database published in 2015, operative mortality was 3.0% in the 141,905 patients who underwent isolated valve replacement between 2002 and 2010.[48] Operative risk can be estimated with online risk calculators from the STS (STS-PROM) and the European System for Cardiac Operative Risk Evaluation (EuroSCORE). In patients with minimal comorbidity, mortality and major morbidity is as low as 1.0% in many centres, perioperative stroke rates are 1.5% (with major life-debilitating stroke being somewhat less) and other major complications are relatively rare. However, as older, more frail patients with extensive comorbidities undergo surgical AVR, the risk of death and morbidity, as well as length of hospitalisation and cost increases significantly. [49]

4.1.6 Sutureless aortic valve replacement

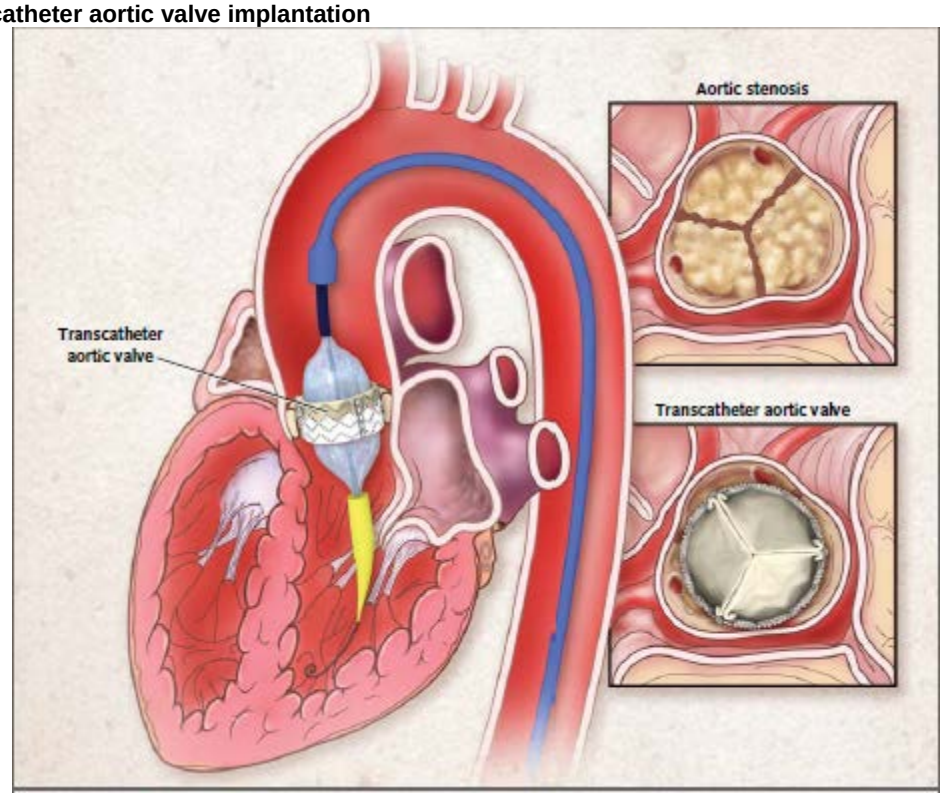
Sutureless AVR involves the surgical replacement of a diseased aortic valve with a bioprosthetic valve that requires no or very few stiches to keep in place. It allows the stenosed valve to be completely removed with decalcification of the annulus, unlike TAVI where the native valve remains in situ. By removing the need for sutures, operative and cardiopulmonary bypass times may be reduced compared with conventional surgery. This may enable high-risk surgical patients with concomitant cardiac surgery to undergo long cardiac procedures.[50] It should be noted that sutureless AVR does not obviate the need for cardiopulmonary bypass, unlike TAVI. Sutureless AVR can be undertaken using conventional open heart surgery or minimally invasive surgery. Minimally invasive aortic valve surgery involves smaller incisions allowing patients to recover more rapidly, and is associated with reduced hospital and intensive care length of stay without elevated risk of death.[51, 52] It is still uncertain, however, if these benefits are applicable to minimally invasive sutureless AVR.

Internationally the procedure is often undertaken minimally invasively but this is not currently the case in New Zealand.[50, 53] As part of the NHC's assessment of aortic stenosis an accompanying report has been undertaken for sutureless AVR: *National Health Committee, Sutureless Aortic Valve Replacement: Assessment Report Tier 3 (2015).*

4.1.7 Transcatheter aortic valve implantation

TAVI is a percutaneous intervention (delivered through a small incision in the skin) that allows a new aortic valve to be implanted in the heart through a catheter. It avoids major surgery and was first performed in 2002 in France by Alain Cribier.[54] During the procedure, the heart remains beating and a cardiopulmonary bypass machine is not needed. When TAVI is performed via a peripheral approach, it does not always require general anaesthesia and can be performed using sedation only. The transcatheter valve is positioned at the level of the native aortic valve during the final step of valve replacement; the balloon is then inflated within the native valve during a brief period of rapid ventricular pacing. In Figure 1 the delivery system is shown after it has traversed the aorta over a guide wire from its point of insertion in the femoral artery (transfemoral access route).

Figure 1: Transcatheter aortic valve implantation



Source: Smith et al (2011), p 2187 [24]

Before balloon inflation, the valve and balloon are collapsed on the catheter (dark blue) and fit within the sheath (blue). After inflation, the function of the calcified native valve (upper panel) is replaced by the expanded transcatheter valve (lower panel, shown short-axis view from the aortic side of the valve), but the native valve remains where it is, pressed flat against the walls of the aorta. Prior to the procedure, the position of the coronary artery origins are checked on computed tomographic (CT) imaging to make sure the new valve or the native valve leaflets will not obstruct the coronary circulation. CT imaging allows for improved valve sizing, as under sizing results in paravalvular aortic regurgitation, which is associated with an increased mortality.[55, 56]

4.1.7.1 TAVI approaches

TAVI can be delivered via percutaneous peripheral access (transfemoral delivery), or via minimally invasive surgical access (transapical, transaortic/direct aortic or subclavian delivery).[2] Different access routes may be appropriate for different patients, but the two main access routes are the transfemoral (TF) retrograde (against normal blood flow) approach and the transapical (TA) antegrade (in the direction of normal blood flow) approach.[57]

The transfemoral approach, also referred to as the iliofemoral approach, is the least invasive and most commonly used technique. The TF approach is performed via the femoral artery using fluoroscopic and transoesophageal echocardiographic guidance without cardiopulmonary bypass.[58] The technique has procedural similarity to coronary angiography, a commonly-used technology for evaluating coronary artery disease. Records provided to the NHC show that approximately 90% of TAVI undertaken in New Zealand (with known access route) were performed using the transfemoral approach. Likewise, the transfemoral approach appears to be the preferred approach internationally (Table 1).

The transapical approach is the most commonly used technique employing minimally invasive surgery. Access to the aortic valve is achieved via mini-thoracotomy, transaortic/direct aortic and subclavian procedures are alternative surgical approaches if the patient's anatomy prevents a transapical approach.[58-60]

The Medtronic CoreValve can be implanted via a transfemoral, subclavian or transaortic approach. The Edwards Sapien XT valve can be implanted via a transfemoral or transapical approach. [61]

Despite rapid advances, anatomical constraints remain, particularly with regard to the diameter of the aortic annulus (for all approaches) and of the iliofemoral arteries (for the transfemoral approach), which limits patient access to TAVI.[61]

Table 1: TAVI approaches used in NZ and recorded in major international registries

Study	TF	TA	TS	TV	DA	Other	Unknown
NZ 2008-2014 records (n=229)	154	13	1		4		57
	67%	5.7%	0.4%		1.8%		25%
SOURCE –EU (n=1038)	463	575					
	45%	55%					
FRANCE 2 (n=3195)	2361	567	184				83
	74%	18%	5.8%				2.6%
Spanish National Registry (n=1416)	1114	302					
	79%	21%					
TCVT-EU (n=4571)	3390	749				432	
	74%	16%				9.5%	
UK TAVI (n=870)	599					271	
	69%					31%	
GARY-Germany (n=3876)		1181		2695			
		30.5%		69.5%			
TVT-US High Risk (n=6151)	3833					2318	
	62%					38%	
TVT-US Inoperable (n=1559)	1139					420	
	73%					27%	

Approaches TF: transfemoral, TA: transapical, TS: trans-subclavian, TV: transvascular (transfemoral, direct aortic and trans-subclavian access), DA: direct aortic, Other: either specified as 'other' or non-TF. Source:[18, 20, 62-67]

5 Technology status TAVI

The increased mortality and morbidity of surgical AVR for high-risk patients and the poor long-term results of BAV and medical therapy has promoted interest in the development and use of TAVI, resulting in a plethora of new devices and innovation in technique that has improved outcomes for patients undergoing this procedure.[68]

Internationally, there are many different TAVI valve devices available. The main differences between first generation and new devices are that the newer devices are often repositionable, have profiles that minimise the risk of coronary obstruction and conduction disturbances, and often include a cuff or skirt that decreases para-valvular aortic regurgitation (Figure 2). Medtronic (CoreValve device) and Edwards Lifesciences (Sapien device) currently hold the largest market share.

Figure 2: TAVI valves and delivery systems

First generation

- CoreValve® (Medtronic Inc.; Minneapolis, MN);
- Edwards Sapien® Transcatheter Heart Valve (Edwards Lifesciences LLC; Irvine, CA);

Second and third generation

- Edwards Sapien XT™ (Edwards Lifesciences LLC; Irvine, CA);
- Sapien III™ (Edwards Lifesciences LLC; Irvine, CA);
- CoreValve evolut R™ (Medtronic, Inc.; Minneapolis, MN);
- JenaValve™ (JenaValve Technology, Munich, Germany);
- Acurate TA™ valve (Symetis, Ecublens, Switzerland).
- Lotus™ valve (Boston Scientific, Marlborough, MA)
- Direct flow medical® (Direct Flow Medical Inc, Santa Rosa, CA)
- Engager™ (Medtronic Inc.; Minneapolis, MN)
- Portico™ (St Jude Medical; St Paul, MN)
- Centera™ (Edwards Lifesciences LLC; Irvine, CA);
- Heart Leaflet Technology® (HLT Inc, maple Grove, MN)
- Colibri ™ (Colibi Broomfield, BO)*
- TBD ™ (Endocor, Hamburg, Germany)*
- AorTXTM ™ (Hansen medical, Mountain View, CA)*

**These devices have not been approved by the FDA, CE, or the Australian Therapeutic Goods Administration*

Source: NHC

Regulatory status

A table summarising the regulatory status of various TAVI valves and delivery systems is contained in Appendix 1.

5.1.1 *Europe*

The CoreValve, Sapien, Sapien XT, JenaValve, Direct flow medical and Acurate TA valve devices all have the CE (European Conformity) mark of approval. There is also separate CE marking for the different catheter delivery approaches. The Sapien device is approved in Europe for implantation via the transfemoral and transapical approaches, whereas the CoreValve device can also be implanted via a subclavian approach or by direct puncture of the aorta.[69]

5.1.2 United States

The Sapien device was given Food and Drug Administration (FDA) approval in November 2011 for a transfemoral approach in non-surgical patients; in October 2012 FDA approval was expanded to high-risk surgical candidates and to transapical device delivery.[70, 71] The Sapien XT valve was granted FDA approval in June 2014 for a similar indication to the original Sapien device. The CoreValve received FDA approval in June 2014 for high-risk patients after receiving approval for extreme-risk patients in January that year.[72, 73] The FDA further expanded the use of the CoreValve system for aortic valve-in-valve replacement in March 2015. The approval means the CoreValve can be marketed to patients requiring valve replacement for dysfunctional bioprosthetic aortic valves.[74] The CoreValve system also has conditional FDA (IDE) approval for study in patients at intermediate risk from surgical AVR.

In March 2015 the St Jude valve received Investigational Device Exemption from the FDA to resume its US Portico trial (PORTICO-IDE, clinical trials number NCT02000115) originally launched in May 2014.[75] The study was halted in September 2014 due to reports of reduced leaflet motion observations in patients implanted with the Portico valve within the trial.

5.1.3 Australia

The Sapien TAVI device was approved for inclusion on the Australian Register of Therapeutic Goods (ARTG) in 2013, allowing it to be supplied in Australia. The Medtronic CoreValve system (models P130021/S010 & P130021/S002) were given ARTG approval in May 2015. For other TAVI devices that are not on the ARTG, use in Australia is currently confined to specific circumstances that allow lawful supply, such as a clinical trial.

5.1.4 New Zealand

There is currently no regulatory approval process for the use of medical devices in New Zealand. However, for a medical device to be legally supplied in New Zealand it must be notified to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) Web Assisted Notification of Devices (WAND) database within 30 days of a person or organisation becoming the sponsor of the device. A sponsor may import, export, manufacture or arrange the manufacture of a device and must meet all the requirements of the Medicines Act 1981, the Medicines Regulations 1984 and the Medicines (Database of Medical Devices) Regulations 2003. The CoreValve and Sapien devices were originally notified to WAND in 2008 and the Sapien XT device in 2010.

New Zealand policy setting

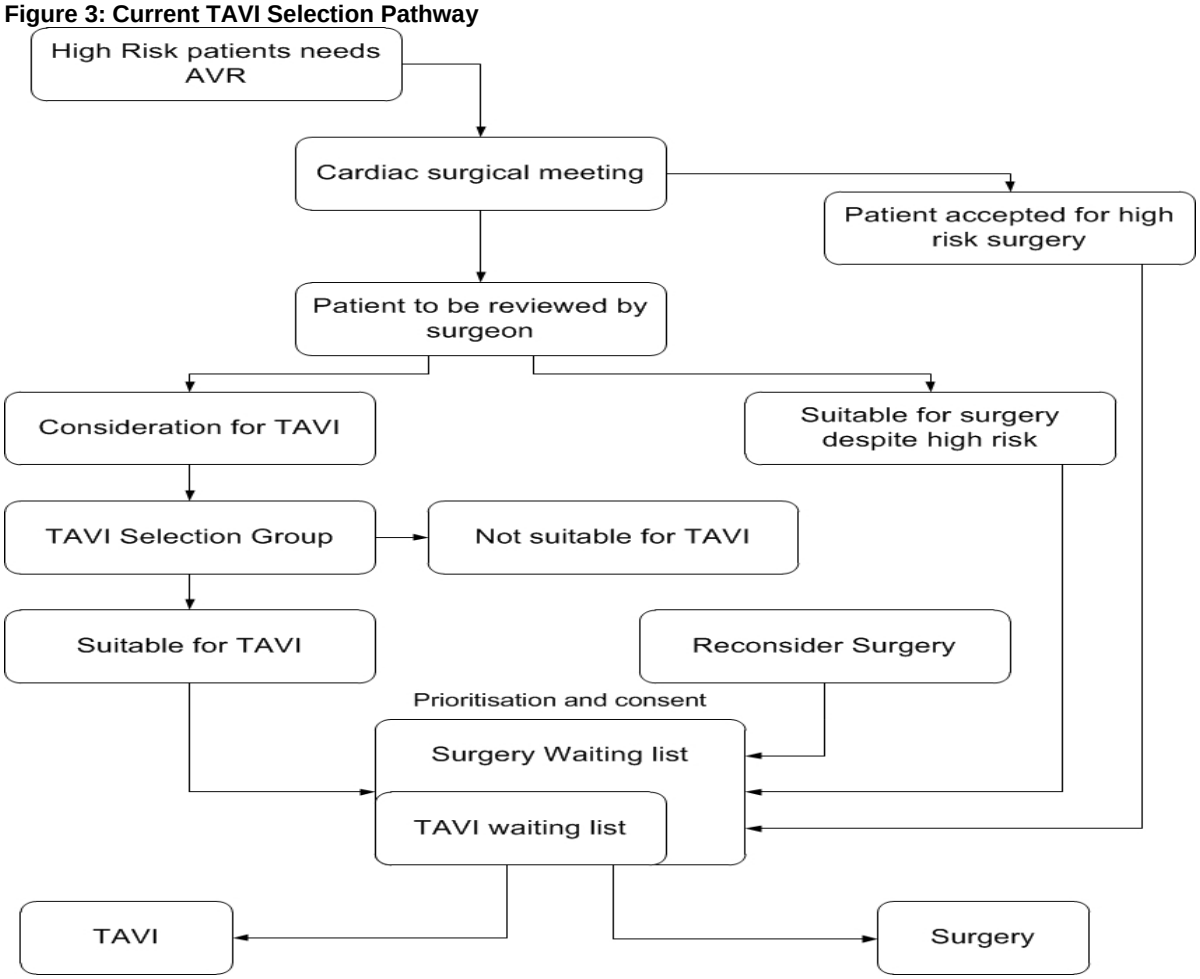
In New Zealand, Ministerial approval of public funding for TAVI was provided in April 2011 with approval granted for high-risk surgical candidates, subject to nationally consistent criteria and patient prioritisation, including regional multidisciplinary patient review committees. Approval was not granted for inoperable patients, moderate-risk patients or low-risk patients and has not subsequently been granted. High-risk surgical cases were to be identified by having one or more of the following high risk features:

- Advanced age
- Previous coronary artery bypass graft (CABG)
- Heavily calcified aorta
- High-risk Logistic EuroSCORE or STS score
- Previous chest irradiation
- Previous coronary artery bypass graft (CABG)
- Sum of comorbidities (such as renal, pulmonary, hepatic and cerebrovascular), severe pulmonary hypertension, previous chest radiation.

TAVI patients were/are expected to benefit from the procedure in terms of quality of life improvement, with an estimated life expectancy greater than two years. The guidance stated that eligibility creep, using TAVI for non-high-risk patients, should be avoided. Here it was recommended that clear documentation of the patient selection processes and outcomes followed by regular audit were undertaken. A pathway of care for TAVI patients, Figure 3, was documented highlighting four important steps:

1. A clinical decision that the patient would benefit from a surgical valve replacement.
2. A clinical review by a cardiac surgeon to evaluate risk benefit for AVR versus TAVI.
3. Selection for TAVI is made by a TAVI selection group.
4. Prioritised for access and informed patient consent.

Figure 3: Current TAVI Selection Pathway



Source: National Health Board Communication to Chief Executive Officers 7 October 2011

Selection for TAVI is made by a TAVI selection group comprising at least one interventional cardiologist, non-interventional cardiologist, cardiac anaesthetist (or cardiac intensivist) and a non-cardiac physician, alongside two cardiac surgeons. As an alternative to conventional surgical aortic valve replacement, TAVI is included within the cardiac surgery targets.

6 Clinical safety and effectiveness of TAVI

This section addresses the research question:

For what patient groups is TAVI a clinically safe and effective treatment for aortic stenosis compared with current alternative interventions in terms of adverse effects (eg death, major stroke and vascular complications) and outcomes?

At the outset it is important to distinguish between different patient populations according to preoperative risk. The initial trial data for TAVI was centred on 'inoperable' patients, and 'high surgical risk' patients. Inoperable patients are patients who are considered too high-risk for surgery, who without TAVI would receive limited intervention, mostly palliative care, variously referred to in the literature as 'medical management' or 'standard therapy'. High-risk patients are eligible for surgery, but carry a high risk of mortality. In the absence of TAVI, these patients are likely to undergo surgical AVR. Data of variable quality is now emerging for 'moderate-risk' and 'low-risk' patients. In the absence of TAVI, these patient populations would receive surgical AVR. Throughout this assessment we distinguish between these different risk-stratified patient populations (inoperable, high-risk, moderate-risk and low-risk).

Internationally, TAVI is supported by health technology assessment agencies for inoperable patients or patients at high risk of mortality from surgical AVR – where surgical AVR remains the gold standard treatment for low and moderate risk patients.[5-15] In practice, however, it appears that TAVI is already being performed in moderate and low-risk populations in some countries, particularly Germany.[16-25] In New Zealand, TAVI is only supported in surgical candidates at high surgical risk. This implies the first hurdle in determining eligibility for TAVI is whether or not a patient is genuinely high-risk for surgery.

In the first part of this section, therefore, we discuss the main algorithms used to risk stratify cardiac surgery. This is followed by an assessment of the clinical safety and effectiveness evidence in randomised controlled trials, major international registries, and systematic reviews. We conclude with a summary of recommendations from other health technology assessment agencies, recommendations from United States and European professional body guidelines, and briefly outline the large volume of international trials currently underway for TAVI.

Risk stratification

Key points

- In cardiac surgery and interventional cardiology, operative risk is defined by algorithms, some of which are more accurate than others.
- Logistic EuroSCORE significantly overestimates the high-risk population pool. STS-PROM is a better fit and is advocated by international and New Zealand-specific research.
- Using the STS-PROM, about 5% of surgical AVR patients can be classed as high-risk, 15% as moderate or intermediate-risk, and 80% as low-risk.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons Predicted Risk of Mortality Score (STS-PROM) are the most widely used risk scores to predict operative mortality in cardiac surgery.[3, 4] The Aus-AVR score, an algorithm based on the Australasian population, is also being used in New Zealand.[76]

High risk is most often defined as an STS-PROM ≥ 8%[36, 48] or STS-PROM ≥ 10%[3, 77-79] or a logistic EuroSCORE ≥20.[78] EuroSCORE has been shown to significantly and markedly over-predict operative risk,[4, 36, 80] resulting in estimates of the high-risk population pool (EuroSCORE >20) as much as three times those derived using the STS score.[21, 47, 81, 82] A revised EuroSCORE II was published in 2012 to better fit contemporary outcomes.[83]

New Zealand and international evidence indicates STS-PROM is an accurate predicator of operative mortality while EuroSCORE II may be an improvement on EuroSCORE.[4, 48, 80, 84] STS-PROM and EuroSCORE II may also have utility in stratifying long-term mortality.[4, 85, 86] A study of 142,000 first-time isolated surgical aortic valve replacements performed in the United States between 2002 and 2010 found higher preoperative risk (STS-PROM) was significantly associated with higher postoperative mortality, complications, and length of stay.[48] Actual mortality versus predicted mean mortality was 1.4% vs 1.7% for low-risk patients (STS <4%), 5.1% vs 5.5% for intermediate-risk patients (STS 4%≤ 8%), and 11.8% vs 13.7% for high-risk patients (STS >8%), p<0.0001. Eighty percent of patients were low-risk, 14% intermediate-risk, and 6% high-risk.

Isolated AVR accounts for about 60% of aortic valve replacements, where nearly 40% of cases are undertaken in combination with coronary artery bypass surgery. A small portion of patients (<5%) may have also have concomitant mitral valve surgery.[87] Generally surgical AVR, rather than TAVI, is recommended if patients require concomitant valve procedures.[36, 88] The STS score has been adapted for non-isolated AVR, with excellent calibration for surgical AVR plus CABG.[89] In a study of 9,200 patients receiving surgical AVR + CABG, 84% were low-risk (STS<5%), 12% were moderate-risk (STS 5≤ 10%), and 4% were high-risk (STS>10%).[79]

A meta analysis of ten studies involving 13,856 patients who underwent either TAVI or surgical AVR found both EuroSCORE II and STS-PROM had good predicative value in estimating operative (30 day) mortality for aortic valve replacement – though they tended to underestimate mortality for TAVI and overestimate mortality for surgical AVR (Table 2).[80]

Table 2: Utility of STS and ESII for TAVI and AVR

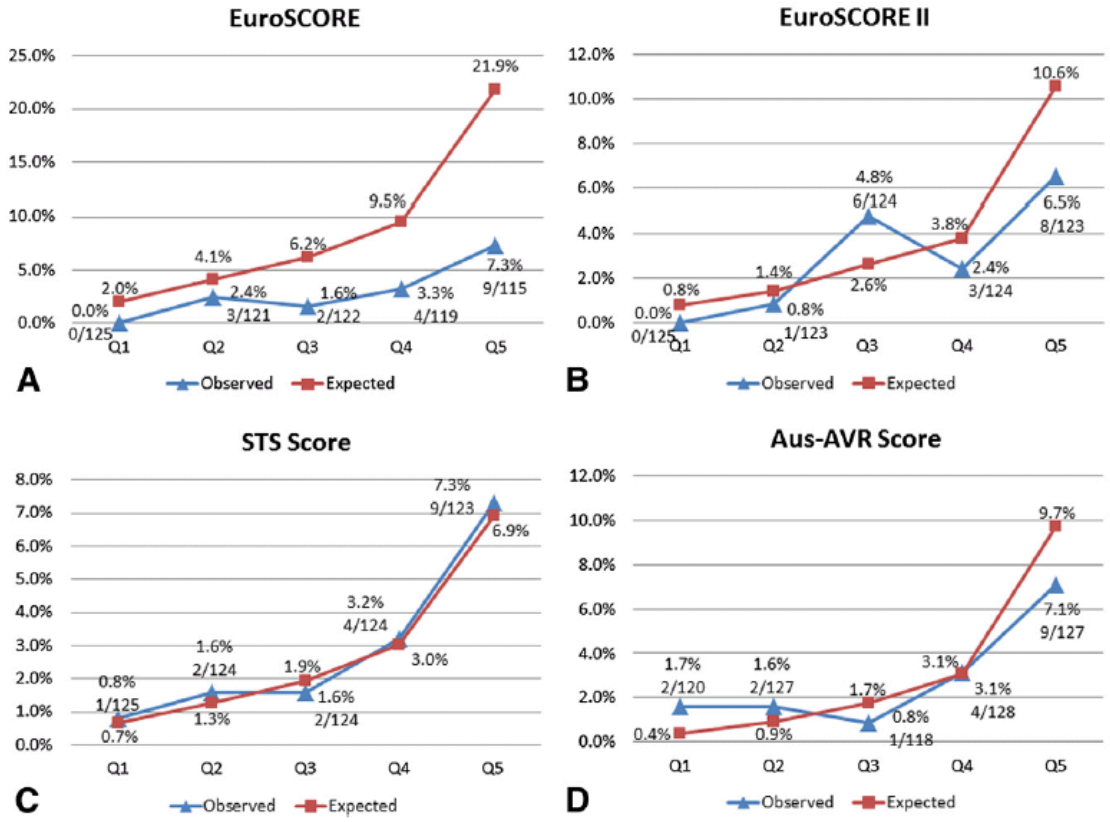
	Mortality (%)	Mean Predicted Mortality (%)		Observed-Expected Ratio	
		ESII	STS	ESII	STS
All AVR	6.1	5.1 (4.0-6.2)	6.3 (4.5-7.5)	1.2	0.98
TAVI (6 Studies, n= 2,065)	9.6	7.8(7.2-8.3)	8.5 (7.3-9.6)	1.23	1.13
Surgical AVR (5 Studies, n=11,791)	3.1	3.3 (2.1-4.4)	3.7 (2.4-5.0)	0.94	0.84

Source: [80]

The meta analysis was limited by moderate to high heterogeneity between the included studies; all studies were retrospective introducing potential bias; and data was taken from multiple years – potentially ignoring any learning curve in TAVI or surgical AVR.

A retrospective study of 620 patients who underwent isolated surgical AVR at Auckland City Hospital, from January 2005 to December 2012, compared the prognostic utility of the EuroSCORE, EuroSCORE II, STS score, and Aus-AVR score.[4] The STS score was found to be the best calibrated score in high-risk patients, with expected mortality closely tracking observed mortality across all risk quintiles (Table 3).

Table 3: Calibration of operative mortality and predicted quintiles of each risk model. NZ experience



The expected line (red) is the mean score for that quintile, and the observed line (blue) is the proportion of patients with operative mortality in that quintile. Source:[4]

The authors of the Auckland study recommended the score for the risk stratification of patients referred for TAVI. They considered the 'influence of STS ethnicity likely to be limited' in generalising their results, as the Aus-AVR score was not superior to the other scores. Likewise the STS score is favoured by the Valve Academic Research Consortium (VARC) – a body of representatives from several independent academic research organisations, several surgery and cardiology societies, members of the US Food and Drug Administration (FDA), and several independent experts.[3]

With the introduction of TAVI, commentators have noted the need for additional studies to assess the value of including parameters not traditionally incorporated into risk scores, such as the assessment of frailty, porcelain aorta, liver disease, right ventricular dysfunction, and prior cardiac surgery.[3, 4, 78, 90] The Society of Thoracic Surgeons and the American College of Cardiology (ACC) launched the STS/ACC TVT Registry in 2011. The data from more than 13,000 TAVI patients is now being used to develop several risk models to better predict operative and one-year mortality in TAVI.[91]

Randomised controlled trials

Key points

- RCT evidence shows TAVI is generally safe and effective for high-risk and inoperable patients.
- Safety issues include paravalvular regurgitation, major bleeding, major vascular complications, and in the case of the CoreValve, electrical conduction abnormalities.
- Early concerns about stroke have not played out in subsequent randomised control data.
- 30-day outcomes in the head-to-head trial of the CoreValve and Edwards Sapien valve favour the Edwards valve.
- The STACCATO trial of low-risk patients was terminated early due to adverse outcomes for TAVI.

Following the first-in-man experience of TAVI in 2002 reported by Cribier[54], there were several feasibility studies performed using both the balloon-expandable Edwards valve and the self-expanding Medtronic CoreValve system. In these early studies, it was established that TAVI could be safely performed through the trans-femoral and transapical approaches.[92-96]

Since these early trials, the principal randomised data has come from two multicentre trials.[97] These are the CoreValve high risk randomised controlled trial (RCT) for patients eligible for but at high risk from surgical AVR; and the Placement of Aortic Transcatheter Valves (PARTNER) RCT. The PARTNER trial is split into two subgroups, A and B. PARTNER A compared the safety and effectiveness of the Edwards Sapien transcatheter heart valve to surgical AVR in high-risk patients with severe AS. PARTNER B compared the safety and effectiveness of the Edwards valve to best medical management in inoperable patients with severe AS.

Two further randomised controlled trials were identified. The STACCATO trial is the only RCT to have trialled TAVI in a low-risk population, and the CHOICE trial is the only head-to-head RCT of the CoreValve and Sapien valve. Each study is discussed in turn below.

The PARTNER and CoreValve high risk RCTs

Key points

- In PARTNER, TAVI was non-inferior to surgical AVR with five years of follow up.
- In the CoreValve study, TAVI was superior to surgical AVR at two years.
- Rates of moderate or severe paravalvular regurgitation, and major vascular complications were higher for TAVI than surgical AVR in both studies.
- Rates of major bleeding were lower for TAVI than surgical AVR in both studies.
- Rates of new pacemaker insertion, reflecting electrical conduction disorders, were higher for TAVI than surgical AVR in the CoreValve study but not PARTNER.

The PARTNER trial evaluated TAVI using the Sapien valve in patients with severe aortic stenosis, with 12 month results for the inoperable and high-risk subgroups published in 2010 and 2011, respectively.[98, 99] Amongst high-risk surgical patients (n = 699, cohort A), TAVI was compared with conventional surgical AVR.[99] Three hundred and forty-eight patients were randomly allocated to the TAVI arm, and 351 patients to the surgical arm. In those who were deemed 'inoperable patients' (n = 358, cohort B), TAVI was compared with palliative management, often involving balloon aortic valvuloplasty (64% within 30 days of randomisation) which is not commonly used in New Zealand.[98] One hundred and seventy-nine patients were randomly allocated to each arm of the trial.

The PARTNER trial distinguished high-risk patients from inoperable patients as follows:

High-risk surgical patients – PARTNER A	- STS score of ≥ 10%, **or** - Coexisting condition/s that result in ≥15% predicted probability of death 30 days after surgery.
Inoperable patients – PARTNER B	- Coexisting conditions that would be associated with a EuroSCORE I predicted probability of ≥50% of either death by 30 days after surgery or a serious irreversible condition, **and** - Two surgeon investigators had to agree that the patient was not a suitable candidate for surgery.

The first results from the US CoreValve trial were published in mid-2014.[100] The RCT compared TAVI (using the self-expanding CoreValve) with surgical AVR in high-risk patients. A total of 795 high-risk patients with severe symptomatic AS were randomised – 394 to the TAVI arm and 401 to the surgical arm.

6.1.1 Patient characteristics for the high risk PARTNER A and CoreValve trials

Key points

- Both studies aimed to have trial populations with at least a 15% chance of operative mortality from conventional surgery.
- PARTNER appears to have a higher risk population than the CoreValve study.
- The mean STS score in the CoreValve study (<7.5%) is indicative of the inclusion of moderate-risk patients.

The patient characteristics of the high risk PARTNER and CoreValve trials are presented in Table 4. The analysis presents results on an intention-to-treat basis. The CoreValve study also presents patient characteristics for the 'as-treated' patient pool (which are very similar). Patient characteristics were well matched between the TAVI and surgical AVR arms within both studies. There were no significant between-group differences in baseline characteristics in either trial, with the exception of diabetes mellitus in the CoreValve study, where the rate was 34.5% vs 42.9% for the TAVI and surgical AVR arms, respectively (P = 0.02 in the intention-to-treat population).

Patient characteristics are broadly similar between the trials, with the exception of the preoperative risk scores (STS-PROM and logistic EuroSCORE), the New York Heart Association Class for categorising heart failure, moderate or severe mitral regurgitation, and previous coronary artery bypass graft, though prevalence of ischaemic heart disease appears equivalent. On all these measures the CoreValve patient population appears to be lower risk than the patient population in the PARTNER trial.

The PARTNER and CoreValve trial protocols pre-specified similar patient populations, where enrolled patients were expected to have symptomatic severe aortic stenosis with a predicted risk of operative mortality ≥ 15% < 50%. In PARTNER, a patient was deemed to be at high risk if they had an STS-PROM ≥ 10%. Patients with an STS-PROM less than 10 could be included provided there was peer reviewed documentation of comorbidities such that at least two surgeons (not including the enrolling surgeon) agreed a patient's predicted risk of operative mortality was ≥15%. Likewise for the CoreValve trial, preoperative mortality risk was based on investigator-estimated mortality or an STS score >10%. One cardiologist and two cardiac surgeons had to agree that predicted risk of operative mortality was ≥15%.

Patients in the CoreValve study had a mean STS-PROM of just over 7 in both arms. By comparison, the mean STS-PROM in the PARTNER trial was nearly 12 for TAVI and surgical AVR patients. Whilst the exact distribution of scores was not reported, 87% of patients in the CoreValve trial had an STS-PROM ≤ 10%, whereas about half the patients in the PARTNER trial had an STS-PROM > 11%.

Table 4: Patient characteristics for the high risk PARTNER A and CoreValve studies

Characteristic	PARTNER		COREVALVE	
	TAVI	Surgery	TAVI	Surgery
Age year	84.5±6.4	84.5±6.4	83.2±7.1	83.2±6.4
Male sex	56.7%	56.70%	53.6%	52.9%
Society of Thoracic Surgeons score	11.7±3.5	11.7±3.5	7.3±3.0	7.5±3.2
Logistic euroSCORE	29.2±15.6	29.2±15.6	17.6±13.0	18.4±12.8
New York Heart Association class				
II	5.7%	6.00%	14.2%	13.2%
III or IV	94.3%	94%	85.8%	86.8%
Coronary artery disease — no./total no.	74.9%	76.90%	75.4%	76.3%
Previous myocardial infarction	26.8%	30%	25.6%	24.4%
Previous CABG	42.6%	44.2%	29.7%	30.2%
Previous PCI	34%	32.5%	33.8%	37.9%
Congestive heart failure	nr	nr	95.4%	96.4%
Previous balloon aortic valvuloplasty	13.4%	10.2%	Nr	Nr
Cerebral vascular disease	29.3%	27.4%	Nr	Nr
Prior stroke			12.9%	13.2%
Prior transient ischaemic attack			12.7%	12.8%
Peripheral vascular disease	43%	41.6%	41.7%	42.5%
COPD — no./total no				
Any	43.4%	43%	Nr	Nr
Oxygen-dependent	9.2%	7.1%	Nr	Nr
Diabetes mellitus				
All	nr	nr	34.5%	42.9%
Controlled by insulin	nr	nr	10.9%	12.2%
Creatinine level >2 mg/dl (177 µmol/liter)	11.1%	7%	Nr	Nr
Chronic kidney disease stage 4 or 5			12.3%	13.1%
Atrial fibrillation	40.8%	42.7%	41% †	47.5% †
Permanent pacemaker	20%	21.9%	23.4% ‡	20.7% ‡
Pulmonary hypertension	42.4%	36.4%		
History of hypertension			95.2%	96.3%
Frail condition	15.6%	17.6%	nr ţ	nr ţ
Extensively calcified aorta	0.6%	1.1%	Nr	Nr
Deleterious effects of chest-wall irradiation	0.9%	0.9%	Nr	Nr
Chest-wall deformity	0.0%	0.3%	Nr	Nr
Liver disease	2.0%	2.6%	Nr	Nr
Aortic-valve area — cm2	0.7±0.2	0.6±0.2	0.72±0.23	0.73±0.24
Aortic-valve gradient — mm Hg	42.7±14.6	43.5±14.3	48.27±15.31	47.65±13.85
Left ventricular ejection fraction	52.5±13.5	53.3±12.8	Nr	Nr
Moderate or severe mitral regurgitation	19.8	21.3%	5.2%	6.1%

Source:[99, 100]

† Defined as prior atrial fibrillation or atrial flutter. ‡ Defined as pre-existing pacemaker or defibrillator ţ Summary statistic not provided. PARTNER and COREVALVE used different measures of frailty. Plus-minus values are means ± Standard deviations

6.1.2 Patient characteristics in the PARTNER B trial for inoperable patients

Key points

- Anatomical features including the presence of a heavily calcified aorta, chest-wall deformity, and issues arising from chest-wall irradiation play heavily in defining inoperability.

Table 5 presents the patient characteristics for both subgroups of the PARTNER trial. The inoperable subgroup compared TAVI with standard treatment – medical management with some patients receiving additional symptomatic relief through balloon aortic valvuloplasty. Compared with standard treatment, patients randomised to the TAVI arm had a lower logistic EuroSCORE (26.4 vs 30.4, p=0.04), lower prevalence of COPD (41.3% vs 52.5%, p=0.04), and atrial fibrillation (32.9% vs 48.8%, p=0.04), but higher prevalence of extensive aortic calcification (19% vs 11.2%, p=0.05).

It appears that anatomical reasons played heavily in determining the 'inoperable' status of patients. Compared with the high-risk arm (PARTNER A), inoperable patients had less peripheral vascular disease (30.3% vs 25.1% compared with 43% vs 41.6%) but greater oxygen dependent COPD (21.2% vs 25.7% compared with 9.2% vs 7.1%), extensively calcified aorta (19.0% vs 11% compared with 0.6% vs 1.1%), deleterious effects of chest-wall irradiation (8.9% vs 8.4% compared with 0.9% vs 0.9%) and chest-wall deformity (8.4% vs 5% compared with 0% vs 0.3%). STS-PROM, and NYHA class were similar between the inoperable and high-risk patient groups. Despite being unsuitable for surgery, 10% of patients in the standard care group underwent surgical AVR, suggesting some patients may have been high-risk but not strictly inoperable.

Table 5: PARTNER patient characteristics – inoperable (B) vs high risk patients (A)

Characteristic	Inoperable		High risk	
	TAVI	Standard therapy	TAVI	Surgery
Age year	83.1±8.6	83.2±8.3	84.5±6.4	84.5±6.4
Male sex	45.8%	46.9%	56.70%	56.70%
STS score	11.2±5.8	12.1±6.1	11.7±3.5	11.7±3.5
Logistic EuroSCORE	26.4±17.2*	30.4±19.1	29.2±15.6	29.2±15.6
NYHA class				
II	7.8%	6.1%	5.70%	6.00%
III or IV	92.2%	93.9%	94.30%	94%
Coronary artery disease	67.6%	74.3%	74.90%	76.9%
Previous myocardial infarction	18.6%	26.4%	26.80%	30%
Previous intervention				
CABG	37.4%	45.6%	42.60%	44.2%
PCI	30.5%	24.8%	34%	32.5%
Balloon aortic valvuloplasty	16.2%	24.4%	13.40%	10.2%
Cerebral vascular disease	27.4%	27.5%	29.30%	27.4%
Peripheral vascular disease	30.3%	25.1%	43%	41.6%
COPD				
Any	41.3%*	52.5%	43.4%	43%
Oxygen-dependent	21.2%	25.7%	9.2%	7.1%
Creatinine >2 mg/dl (177µmol/liter)	5.6%	9.6%	11.1%	7%
Atrial fibrillation	32.9%*	48.8%	40.8%	42.7%
Permanent pacemaker	22.9%	19.5%	20%	21.9%
Pulmonary hypertension	42.4%	43.8%	42.4%	36.4%
Frailty	18.1%	28.0%	15.6%	17.6%
Extensively calcified aorta	19%*	11.2%	0.6%	1.1%
Deleterious effects of chest-wall irradiation	8.9%	8.4%	0.9%	0.9%
Chest-wall deformity	8.4%	5.0%	0.0%	0.3%
Liver disease	3.4%	3.4%	2.0%	2.6%
Aortic-valve area — cm2	0.6±0.2	0.6±0.2	0.7±0.2	0.6±0.2
Mean aortic-valve gradient — mm Hg	44.5±15.7	43.0±15.3	42.7±14.6	43.5±14.3
Mean LVEF	53.9±13.1	51.1±14.3	52.5±13.5	53.3±12.8
Moderate or severe mitral regurgitation	22.2%	23.0%	19.8	21.3%

Source: [98, 99] * P≤ 0.05. Plus-minus values are means ± Standard deviations

6.1.3 Outcomes for high-risk patients PARTNER A and CoreValve

Key points

- PARTNER was analysed on an intention-to-treat basis for non-inferiority. This creates a potential issue if significant crossover occurs. Crossover was not permitted other than for exceptional circumstances.
- The results of the CoreValve study were analysed on an 'as-treated basis'. The CoreValve study undertook a superiority analysis for all-cause mortality.
- All-cause mortality was non-inferior with five years of follow-up in PARTNER.
- All-cause mortality was superior in CoreValve at two years.
- In PARTNER, stroke was elevated at one and two years in the TAVI arm, but did not reach statistical significance. The CoreValve study demonstrated significantly lower total stroke for TAVI compared with surgery at two years.
- Aortic regurgitation and vascular complications were significantly elevated in both studies in all years of follow-up. New pacemaker implantation rates for electrical conduction abnormalities were elevated in the CoreValve study. Major bleeding events were higher for surgery compared with TAVI.

The primary end-point for both trials was all-cause mortality at 12 months. Clinical outcomes for the high risk PARTNER and CoreValve trials are presented in Table 6. The trials differ in that PARTNER was analysed on an intention-to-treat basis, whereas CoreValve used an 'as treated' approach for the primary analysis. Though not reported in full, the authors of the CoreValve study note that the results were similar in their intention-to-treat analysis. An intention-to-treat analysis reports the outcomes for patients as per their randomisation to treatment or control arms, regardless of the treatment patients actually receive. This is done to address the issues of non-compliance to treatment and missing data.[(101)] On the other hand, if there is a lot of crossover in a trial, where a patient receives the control intervention rather than the investigational intervention, then results may be averaged across the two arms and understate any difference. This is a particular issue if the trial is set up to prove the non-inferiority of a new intervention against an existing intervention. In this case crossover makes the two trial arms more similar and makes the demonstration of non-inferiority easier. The PARTNER trial analysis did not allow for crossover from one assignment group to another, except for medical reasons during the assigned procedure.

In the high risk PARTNER trial, all-cause mortality was tested using a non-inferiority analysis, where it was predetermined that superiority was unlikely to be proven. A superiority analysis was used in the inoperable arm of the trial. The CoreValve study undertook both superiority and inferiority analysis of all-cause mortality and MACCE (major adverse cardiovascular or cerebrovascular events and includes all-cause death, stroke, myocardial infarction and reintervention). Table 6 reports results from the non-inferiority analysis for both trials. The exception is all-cause mortality, where the CoreValve results are reported from the superiority analysis. At the time of writing, not all two-year outcomes data had been realised.

6.1.3.1 Mortality

The PARTNER trial reported similar all-cause and cardiovascular mortality for TAVI and surgical AVR patients over five years. TAVI and surgical AVR patients in the CoreValve study show lower rates of all-cause mortality compared with the PARTNER trial, possibly reflective of a lower risk population. In

the CoreValve trial, all-cause mortality at one and two years was significantly lower in the TAVI group compared with the surgical group. The absolute one year survival advantage of TAVI over surgical AVR was 4.9%, and 6.4% at two years (P = 0.04 for superiority in both years). At one year, results were similar in the intention-to-treat analysis; all-cause mortality was 13.9% in the TAVI group, as compared with 18.7% in the surgical group (an absolute risk reduction, 4.8%, P = 0.04 for superiority).

In the high-risk CoreValve trial, 83% of patients received transfemoral TAVI (with the remaining patients receiving the subclavian artery or direct aortic approach) compared with 70% of patient receiving transfemoral TAVI in PARTNER, where 30% received transapical TAVI. All-cause mortality tends to be lower using the transfemoral approach (discussed in the systematic review section below). Any impact from the differential mix of approaches between the studies is likely to be small, however; one and two year all-cause mortality using the transfemoral approach in the PARTNER trial were 22.2% and 30.9%, respectively.

Table 6: Clinical outcomes of PARTNER and CoreValve high risk trials

	PARTNER (intention to treat)								CoreValve (as treated)					
	30-day		1 year		2 years		5 years		30-day		1 Year		2 years	
Outcomes	TAVI	Surgery	TAVI	Surgery	TAVI	Surgery	TAVI	Surgery	TAVI	Surgery	TAVI	Surgery	TAVI	Surgery
All-cause mortality	3.4%	6.5%	24.3%	26.8%	33.9%	35.0%	67·8%	62·4%	3.3%	4.5%	14.2%* †	19.1%	22.2%* †	28.6%
Cardiovascular death	3.2%	3.0%	14.3%	13.0%	21.4%	20.5%	53·1%	47·6%	3.1%	4.5%	10.4%	12.8%	nr	Nr
Stroke	4.7%	2.4%	6.0%	3.2%	7.7%	4.9%	10·4%	11·3%	4.9%	6.2%	8.8%	12.6%	10.9%*	16.6%
Major stroke	3.8%	2.1%	5.1%	2.4%	Nr	nr	nr	Nr	3.9%	3.1%	5.8%	7.0%	6.8%	9.8%
Stroke or TIA	5.5%*	2.4%	8.7%*	4.3%	11.2%*	6.5%	15·9%	14·7%	5.6%	6.4%	10.0%	7.8%	nr	Nr
Myocardial infarction	0.0%	0.6%	0.0%	0.6%	0%*	1.5%	2·9%	5·9%	0.8%	0.8%	1.9%	1.5%	nr	Nr
All-cause mortality or major stroke									5.9%	6.7%	16.3%*	22.5%	24.2%*	32.5%
MACCE									7.7%	10.4%	20.4%*	27.3%	29.7%*	38.6%
Moderate or severe paravalvular aortic regurgitation	12.2%**	0.9%	6.8%**	1.9%	6.9%**	0.9%	nr	Nr	9.0%**	1.0%	6.1%**	0.5%	6.1%	Nr
Major vascular complications	11.0%**	3.2%	11.3%**	3.8%	11.6%**	3.8%	11·9%**	4·7%	5.9%*	1.7%	6.2%*	2.0%	nr	Nr
Renal dialysis	2.9%	3.0%	5.4%	6.5%	6.2%	6.9%	8·6%	8·5%						
Acute kidney injury									6.0%**	15.1%	6.0%**	15.1%	nr	Nr
Major bleeding	9.3%**	19.5%	15.7%**	26.7%	19.0%**	29.5%	26·6%*	34·4%	28.1%*	34.5%	29.5%*	36.7%	nr	Nr
Life-threatening or disabling bleeding									13.6%**	35.0%	16.6%**	38.4%	nr	Nr
Endocarditis	0.0%	0.3%	0.6%	1.0%	1.5%	1.0%	2·0%	2·5%						Nr
Cardiogenic shock									2.3%	3.1%	2.3%	3.1%	nr	Nr
Cardiac perforation									1.3%*	0.0%	1.3%*	0.0%	nr	Nr
New onset atrial fibrillation	8.6%*	16.0%	12.1%	17.1%	Nr	nr	nr	Nr	11.7%**	30.5%	15.9%**	32.7%	nr	Nr
New pacemaker	3.8%	3.6%	6.4%	5.0%	7.2%	6.4%	9·7%	9·1%	19.8%**	7.1%	22.3%**	11.3%	nr	Nr
Repeat hospitalisation	4.4%	3.7%	18.6%	17.7%	24.7%	21.7%	42·3%	34·2%						
Re-intervention									0.8%	0.0%	1.9%*	0.0%	nr	Nr

Source: [99, 100, 102] * P ≤ 0.05, ** P < 0.001, nr = not reported; TIA = transient ischaemic attack. † = result for superiority analysis, all other figures for non-superiority analysis

6.1.3.2 Stroke

In the PARTNER trial, major strokes were observed more frequently in the TAVI group compared to the surgical group at 30 days (3.8% vs 2.1%, p= 0.2) and one year (5.1% vs 2.4%, p = 0.07).[99] Although not statistically significant, the results have raised concern as stroke is associated with significant morbidity, long-term disability and mortality. The 30-day rate of stroke in high-risk patients (STS-PROM >8%) undergoing isolated surgical AVR is 3.5% according to the Society of Thoracic Surgeons database, and 1.9% for transient ischaemic attack.[48] Major stroke was not reported in subsequent year's analyses of the PARTNER trial.

In PARTNER, total stroke was greater for TAVI than surgery at one and two years but not five years. Differences were not statistically significant. Total stroke or transient ischaemic attack was higher for TAVI compared with surgery at 30 days (5.5% vs 2.4% p=0.04), one year (8.7% vs 4.3%, p=0.03), and two years (11.2% versus 6.5%, p=0.05), but similar at five years (15.9% vs 14.7%, p=0.35).

By contrast, the CoreValve study reported lower rates of total stroke for TAVI compared with surgical AVR. At two years, stroke was significantly lower for TAVI (10.9% vs 16.6%, p=0.05). But lower rates of 'major stroke' in the TAVI arm were not statistically significant.

Compared with PARTNER, the CoreValve study reported similar stroke rates for TAVI but higher rates for surgical AVR. In counting strokes, the CoreValve study followed the Value Academic Research Consortium-2 consensus (VARC-2) guideline using the Modified Rankin scale.[3] The PARTNER trial predates VARC-2 guidelines and used the National Institutes of Health (NIH) Stroke Scale. Compared with the NIH stroke scale, the Modified Rankin scale is weighted toward physical function and particularly a patient's ability to walk. It is not known if the use of different scales had any influence on the results.

Concomitant atrial fibrillation, has been reported to increase the risk of stroke four-fold.[103, 104] New onset atrial fibrillation was lower in the TAVI group compared with the surgical group at 30 days (8.6% vs 16.0%, p=0.006; 11.7% vs 30.5%, p<0.001) and one year (12.1% vs 17.1%, p=0.07; 15.9% vs 32.7%, p<0.001) in the PARTNER and CoreValve trials, respectively. AF rates may be higher in the CoreValve study compared with PARTNER due to a broader definition of AF which also includes 'worsening existing AF'.

6.1.3.3 Paravalvular aortic regurgitation

During conventional surgical AVR, the heavily calcified valve is excised and a new prosthesis is sutured to the annulus, resulting in a better seal and low incidence of leaking or regurgitation around the valve (paravalvular AR) (4.2%).[105] Generally, paravalvular AR is associated with increased mortality.[55] TAVI has been associated with higher rates of moderate or severe AR due to the fact that the valve is not sutured to the annulus.

The PARTNER and CoreValve trials show significant increased incidence of moderate or severe paravalvular AR. Rates remain above 6% in both studies at two years, compared with 0.9% in the surgical group for PARTNER (P<0.001) (comparator not yet reported in CoreValve).

6.1.3.4 Conduction abnormalities

Abnormalities of electrical conduction in the heart have always been a problem with aortic valve replacement due to the extremely close anatomic relationship (2-3 mm) between the aortic valve and the branching atrioventricular bundle of conducting tissue. These abnormalities are generally treated

with implantation of a pacemaker. In PARTNER, new pacemaker insertion rates were similar in the TAVI and surgical AVR groups over five years of follow-up. The insertion rates were 6.4% vs 5.0% at one year in addition to baseline rates of 20% and 22% for TAVI and surgical AVR, respectively. In the CoreValve trial, the rates of new pacemaker insertion were significantly higher. Rates were 22.3% and 11.3% at one year in addition to baseline rates of 23.4% and 20.7% for TAVI and surgical AVR, respectively.

6.1.3.5 Vascular complications and bleeding

Vascular complications and bleeding are important barriers to good patient outcomes after TAVI; this commonly includes vascular dissection, perforation and access site haematoma.[106] With smaller delivery systems, this is an area that shows significant improvement. Major vascular complications at 30 days for TAVI in the PARTNER trial occurred in 11% compared to 5.9% in the US CoreValve trial. While vascular complications at one year remained more frequent in TAVI patients (6.2%) than in the surgical AVR group (2.0%), life-threatening bleeding was significantly more common in the surgical group (38.4%) vs the TAVI group (16.6%), as might be expected with a more invasive procedure. The CoreValve study also reported lower incidence of acute kidney injury at 30 days and one year.

6.1.4 Outcomes for inoperable patients PARTNER

Key points

- All-cause mortality is significantly reduced for TAVI in all years of follow-up compared with standard therapy.
- All-cause mortality remains very high for TAVI patients, 43% at two years.
- Aortic regurgitation, vascular complications and bleeding events are significantly elevated for TAVI.
- Repeat hospitalisations are significantly lower for TAVI compared with standard therapy.

All-cause and cardiovascular mortality in all five years of follow-up was significantly lower for TAVI compared with standard therapy. Repeat hospitalisations were also significantly lower in the TAVI group compared with standard treatment. The TAVI group also demonstrated improved functional status compared with standard treatment two years post-intervention. At two years, 86% of survivors in the TAVI group had NYHA class 1 or 2 symptoms compared with 40% in the standard treatment group ($p<0.0001$).[107] At baseline 92.2% of patients assigned to undergo TAVI, and 93.9% of patients on standard treatment had NYHA grade III or IV symptoms, representing significant heart failure. Both groups witnessed a mean improvement in functional status from baseline, possibly reflecting attrition of the sickest patients. Differences in functional status were not statistically significant at three or five years.[108]

At 30 days and one year, the TAVI group had higher rates of stroke or transient ischaemic attacks, major vascular complications, and major bleeding. At two years, the TAVI group had a significantly higher rate of stoke (13.8% vs 5.5%, $p=0.01$).

Table 7: PARTNER B outcomes

	30-days		1 year		2 years		5 years	
Outcomes	TAVI	Standard	TAVI	Standard	TAVI	Standard	TAVI	Standard
Death any cause	5.0%	2.8%	30.7%**	50.7%	43.3%**	68.0%	71.8%**	93.6%
Cardiovascular death	4.5%	1.7%	20.5%**	44.6%	31%**	62.4%	nr	Nr
Stroke	6.7%	1.7%	11.2%	5.5%	13.8%*	5.5%	16.0%	18.2%
Stroke or TIA	6.7%*	1.7%	10.6%*	4.5%	nr	nr	nr	Nr
Myocardial infarction	0.0%	0.0%	0.8%	0.7%	1.6%	2.5%	nr	Nr
Major vascular complications	16.2%**	1.1%	16.8%**	2.2%	nr	nr	nr	Nr
Renal dialysis	1.1%	1.7%	2.3%	4.7%	3.2%	7.6%	nr	Nr
Major bleeding	16.8%**	3.9%	24.2%*	14.9%	28.9%	20.1%	nr	Nr
Endocarditis	0.0%	0.0%	1.4%	0.8%	2.3%	0.8%	nr	nr
New onset atrial fibrillation	0.6%	1.1%	0.6%	1.7%	nr	nr	nr	Nr
New pacemaker	3.4%	5.0%	4.7%	8.6%	6.4%	8.6%	nr	Nr
Repeat hospitalisation	5.6%	10.1%	27.0%**	53.9%	35.0%**	72.5%	47.6%**	87.3%
Moderate or severe paravalvular aortic regurgitation	11.8%		10.5%		4.5%		Not measured	

*** P ≤ 0.05; ** P < 0.001; nr = not reported; TIA = transient ischaemic attack**

Source:[98, 108]

The STACCATO trial

The STACCATO RCT (n=70) compared TAVI with surgical AVR in low-risk elderly patients, ≥75 years, using the Edwards Sapien valve.[109] Patients were enrolled in the trial from November 2008 to May 2011. At baseline, the mean STS was 3.1±1.5, and 3.4±1.2, p=0.43, for the TAVI and surgical groups, respectively. The primary endpoint was a composite of all-cause mortality, major stroke, and/or renal failure at 30 days. The trial was terminated early following the death of two TAVI patients, two suffering a stroke, and another developing renal failure. In the surgical arm, just one stroke occurred (p=0.07). The investigators considered that the transapical approach was not responsible for the poor outcomes.

The CHOICE trial

The CHOICE trial compared the short-term success rate of the Edwards Sapien XT valve with Medtronic's CoreValve.[110] In the study 'success' was defined as a composite end point including:

"successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only one valve implanted in the proper anatomical location."

Across five German centres, 121 patients were randomly allocated to receive the CoreValve and 120, the Sapien XT valve. Patients were well matched in baseline characteristics. Patients had moderate preoperative risk with a mean STS score of 5.6% and 6.2% for patients receiving the CoreValve and Sapien XT valves, respectively. The composite measure of success was met in 77.5% of patients who received the CoreValve compared with 95.9% of patients who received the Sapien XT valve (relative risk, 1.24, $p < 0.001$). The greater success rate in the Edwards Sapien XT valve appears to be mostly due to lower rates of severe aortic regurgitation (4.1% vs 18.3%, $p < .001$) and lower rates of pacemaker implantation (17.3% vs 37.6%, $p = 0.001$). 30 day all-cause mortality was 4.1% and 5.1% for the Sapien XT valve and CoreValve, respectively ($p=0.77$).

TAVI registry data

Key points

- Survival and stroke rates are generally similar or better in registry data compared with RCTs for high-risk and inoperable patients.
- High rates of moderate or severe paravalvular aortic regurgitation, and major vascular complications are maintained in registry data for high-risk and inoperable populations.
- Studies using standardised VARC definitions appear to report higher rates of paravalvular aortic regurgitation and major vascular complications.
- The CoreValve has consistently higher rates of new pacemaker insertion compared with the Edwards Sapien valve.
- Registry data shows that TAVI is being undertaken in moderate-risk patients in Australasia.

Much of the published data on TAVI comes from large international registries. We summarise below some of the key data from these registries. Registry data shows how a technology performs outside the confines of a controlled trial, and with much larger patient numbers can highlight infrequent but serious safety concerns. Data is, however, uncontrolled, often with no comparator, and open to significant selection bias, where it is unclear how well patients might have done under an alternative treatment regime. Table 8 summarises outcomes data from 15 multicentre registries including two Australasian registries. We report on all-cause mortality, aortic regurgitation, major vascular complications, permanent pacemaker implantation, stroke and major stroke. We separate outcomes by access route and valve type (Edwards Sapien or CoreValve) but not by valve generation, as that data is scantly reported.

Most of the registries are industry sponsored or have lead investigators with financial links to industry. FRANCE 2, UK TAVI, The Spanish National Registry, the US Transcatheter Valve Therapy (TVT)

registry, and the German Aortic Valve Registry (GARY) are national registries recording outcomes from competing TAVI valves. There is probably crossover in the data collected by the national registries and the multinational registries sponsored by industry. Medtronic's ADVANCE and Edward Lifescience's SOURCE registries report data from France, the UK and Germany, which may also be recorded in the countries respective national registries. The SOURCE registry also includes data from Spain that may be recorded in the Spanish national registry. The European Transcatheter Valve Treatment Sentinel Pilot Registry is a prospective European independent registry of 10 European countries, including data from Spain, France, the UK, and Germany. Again this data may also appear in the respective national registries. SOURCE-EU includes European data only, so does not cross over with SOURCE-ANZ. The ANZ CoreValve registry also appears to be independent from other CoreValve studies. Further detail on the registries is contained in Appendix 2.

6.1.5 All-cause mortality

Of the registries, the CoreValve Australia and New Zealand study has reported the lowest all-cause mortality rate at 4.1% and 11.9% for 30 days and 12 months, respectively. The highest recorded are for the FRANCE 2 registry, where the corresponding rates are 13.9% and 32.3%. The favourable results in the CoreValve ANZ study likely reflect relatively low preoperative risk, STS 5.7 ± 3.9, compared with the FRANCE 2 registry with a very high STS 15.1±13.8.

Of the studies in Table 8, only the GARY registry has compared TAVI with surgical AVR. All-cause mortality was reported for transvascular TAVI (transfemoral or direct aortic and trans-subclavian access) and transapical TAVI, where 30 day and 12 month mortality were 5.6% and 20.7%, and 9.0% and 28.0%, respectively. All-cause mortality for surgical AVR without coronary artery bypass grafting was 2.4% and 6.7% (30 days and 12 months) (not reported in Table 8). And all-cause mortality for surgical AVR with CABG was 4.5% and 11.0% (30 days and 12 months). Lower mortality rates among surgical patients appear to reflect their lower preoperative risk status. When patients were stratified into risk groups using the logistic EuroSCORE or the German AV Score, survival was comparable for conventional AVR and TV-TAVI in high-risk patients.[21]

In registries for very high risk or inoperable patients, all-cause mortality exceeds one in five patients at 12 months. FRANCE 2 has the highest preoperative risk score reflecting the French National Authority for Health's recommendation that TAVI be limited to patients with a contraindication to surgical valve replacement.[7] Enrolled patients in the registry are either at very high risk of operative mortality or are inoperable. Compared with the PARTNER-B RCT, where inoperable patients underwent transfemoral access TAVI, transfemoral patients in FRANCE 2 had higher preoperative risk, STS 14.5% vs 11.2%, higher 30 day mortality, 8.5% vs 5%, but lower 12 month mortality, 21.7% vs 30.7%. In the US, TVT registry 30 day mortality for inoperable transfemoral TAVI patients (n=1139) was 6.7%, reflecting a median STS of 7% (not reported in Table 8).[18] The CoreValve Extreme risk study, a single arm observational study of the CoreValve delivery system, reported all-cause mortality of 8.4% and 24.3% at 30 days and 12 months, respectively.[111]

6.1.6 Moderate or severe paravalvular aortic regurgitation

In general studies using the Valve Academic Research Consortium definitions of valvular regurgitation recorded relatively high aortic regurgitation estimates, including the ADVANCE study, ANZ CoreValve, and the CoreValve Extreme Risk study, with 30 day rates of 13.3%, 20.1%, and 15.3%, respectively.[3, 112] The FRANCE 2 registry is an exception with moderate or severe aortic valve regurgitation below 2% at 30 days. The VARC definition combines the measure of both central and paravalvular regurgitation. By comparison the CoreValve high risk RCT, which also used VARC definitions, reported a 30 day rate of 9%.[100] Paravalvular aortic regurgitation in the PARTNER RCT, which predates VARC definitions, was about 12% at 30 days in both the inoperable and high-risk

arms.[98, 99] The PARTNER trial protocol defined a major paravalvular leak as grade ≥3+ aortic insufficiency or a paravalvular leak requiring surgical intervention. The US TVT and UK TAVI registries also record relatively high AR rates, but neither used VARC definitions, with rates of 8.5% and 9.1%-17.3%, respectively.[3] The UK TAVI registry is moving toward adopting VARC definitions.[113]

6.1.7 Major vascular complications

Registries using VARC definitions tend to report higher rates of major vascular complications. Compared with the randomised controlled trial data registries are reporting similar or lower rates of major vascular complication using an Edwards Sapien valve, ranging from 0.3% in the Spanish National Registry for transapical TAVI (in hospital rate), to 12.3% at 30 days in the PRAGMATIC registry. By comparison PARTNER recorded rates of 11% and 16.8% in the high-risk and inoperable arms respectively.[98, 99] Major vascular complication reported for Medtronic's CoreValve range from 3% or less in the Spanish National Registry and the TCVT Registry to 10.9% in the ADVANCE study at 30 days. The high risk CoreValve study reported a 30 day rate of 5.9%.

6.1.8 Permanent pacemaker insertion

Consistent with the RCT evidence, higher rates of pacemaker insertion are observed in the registry data for the CoreValve compared with the Edwards Sapien valve. Thirty day rates of new pacemaker insertion range from 16.6% to 28.4% for the CoreValve, whereas rates are typically much less than 10% for the Edwards Sapien valve.

6.1.9 Stroke

Relatively low rates of stroke and major stroke are observed in the registry data compared with the randomised data. Rates of stroke and major stroke using the Edwards Sapien valve are as good or better in the registry data compared with PARTNER. For the Edwards valve, short-run stroke rates ranged from an in-hospital rate of 1% in the Spanish National Registry, to a 30 day rate of 4.8% in SOURCE ANZ trial, both figures being for transapical TAVI. Major stroke ranges from 1% to 2.9%, in the SPANISH and PRAGMATIC registries, respectively. By comparison, the PARTNER A trial reported 30 day total and major stroke rates of 4.7% and 3.8%, respectively. Twelve-month stroke rates are generally as good or favourable in the registry data compared with the randomised trial data. The SOURCE ANZ study reported an elevated 12-month total stroke rate for transapical TAVI of 8.3% vs 6.8% in PARTNER,[99] but the rate was derived from a comparatively small sample (n=60).

Stroke rates also appear similar or better for the CoreValve compared with RCT data. Thirty-day total stroke ranges from an in-hospital rate of 1.2% in a multicentre Italian registry to 5.3% in the ANZ CoreValve registry. Major stroke ranges from an in-hospital rate of 1% in the Spanish National Registry to 2.9% in the PRAGMATIC registry at 30 days. Thirty-day stroke and major stroke in the high risk CoreValve RCT were 4.9% and 3.9%, respectively.[111]

6.1.10 Other complications

Valve embolisation (migration of the valve away from its original site where it was positioned to begin with) is a rare but serious complication of TAVI, with a reported incidence of 0.3% in the SOURCE Registry and is usually related to technical factors or anatomical factors.[63] Embolisation to the aorta is generally well tolerated as the valve can often be snared but embolisation to the ventricle requires surgical removal. The newer generation of TAVI valves are more easily repositionable, although the Lotus valve is the only valve that can be repositioned fully after deployment.

Table 8: Short-term and mid-term results of the main multicentre registries and Australasian registries

Study	VARC	Valve	Access	n	STS	All-cause mortality		AR (moderate or Severe) >2		Major Vascular complications		Permanent Pacemaker		Stroke		Stroke-major	
						30 days	1 Year	30 days	1 Year	30 days	1 Year	30 days	1 Year	30 days	1 Year	30 days	1 Year
ADVANCE[16]	VARC-1	CV	TAVI	996	5.3%	4.5%	17.9%	13.3%	10.8%	10.9%	12.0%	26.3%	29.2%	3.0%	4.5%	1.2%	2.2%
ANZ CoreValve[17]	VARC-1†	CV	TAVI	540	5.7%	4.1%	11.9%	20.1%	18.5%	7.6%*		28.4%	29.1%	5.3%	8.2%		
COREVALVE Extreme Risk[111]	VARC-1	CV	TAVI	506	10.3%	8.4%	24.3%	15.3%	6.4%	8.2%	8.4%	21.6%	26.2%	4.0%	7.0%	2.3%	4.3%
FRANCE 2[64]	VARC-1	Mix	TAVI	3195	14.4%	9.7%	24.0%	0.8%			4.7%	15.6%		3.4%	4.1%	1.9%	2.3%
			TAVI-TS	184	16.6%	10.1%	25.1%	1.8%			4.3%	25.5%			7.0%		2.7%
			TAVI-TA	567	15.1%	13.9%	32.3%	0%			1.9%	13.6%			4.4%		2.1%
			TAVI-TF	2361	14.5%	8.5%	21.7%	0.9%			5.5%	15.2%			3.7%		2.2%
		CV	TAVI	1043	14.2%	9.4%	23.7%	1.6%			4.5%	24.2%			4.3%		2.6%
		ES	TAVI	2107	15.6%	9.6%	24.0%	0.4%			2.7%	11.5%			3.8%		1.9%
GARY[20, 21]	No	Mix	TAVI -TV	2695		5.6%	20.7%	0.3%*				24.2%*	26.2%	2.7%*	4.8%		2.0%
			TAVI-TA	1181		9.0%	28.0%	0.6%*				11%*	14.1%	1.5%*	3.6%		1.8%
Multicentre Canadian registry[114]	No	ES	TAVI	345	9.8%	10.4%	24.0%			0.6%*		4.9%		2.3%			
			TAVI-TA	177	10.5%	11.3%	22.0%					6.2%		1.7%			
			TAVI-TF	168	9.0%	9.5%	25.0%					9.5%		3.0%			
Multicentre Italian registry[115]	No	CV	TAVI	663		5.4%	15.0%	<2%*		2.0%*		16.6%	19.1%	1.2%*	2.5%		
NRCA [116]	No	ES	TAVI-TF	1039	10.9%	4.3%	19.0%			8.0%	8.4%			3.7%	5.0%	2.4%	3.6%
PRAGMATIC[117]	VARC-1	CV	TAVI-TF	453	8.1%	8.8%	16.2%		5.2%	9.3%		22.5%				2.9%	
		ES	TAVI-TF	340	8.9%	6.4%	12.3%		2.8%	12.3%		5.9%				1.0%	
SOURCE-ANZ[118]	VARC-2	ES	TAVI-TA	62		9.7%	23.3%			3.2%	5.0%	8.1%	8.3%	4.8%	8.3%		
			TAVI-TF	67		6.0%	13.6%			4.5%	4.6%	1.5%	4.6%	3.0%	3.0%		
SOURCE-EU[63]	No	ES	TAVI	1038		8.5%	23.9%	1.9%		7.0%		7.0%	8.5%	2.5%			
			TAVI-TA	575		10.3%	27.9%	2.3%		2.4%		7.3%		2.6%			
			TAVI-TF	463		6.3%	18.9%	1.5%		10.6%		6.7%		2.4%			
Spanish National Registry[65]	VARC-1†	Mix	TAVI-TF	504		9.0%		4%*		5%*		5%*		3%*		1%*	
			TAVI	1416		9.0%		6%*		3%*		10%*		3%*		1%*	
		CV	TAVI	610		7.0%		8%*		3%*		17%*		3%*		1%*	
		ES	TAVI-TA	302		11.0%		6%*		0.3%*		4%*		1%*		1%*	
TCVT - EU[66]	VARC-1†	Mix	TAVI	4571				1.3%*		3.1%		13.2%*		1.8%*			
			TAVI-other	432						5.1%		10.7%*		1.4%*			
			TAVI-TA	749						2.2%		4.5%*		1.6%*			
			TAVI-TF	3390						2.9%		15.5%*		1.9%*			
		CV	TAVI	1943				2.3%*		2.8%		23.4%*		2.1%*			
		ES	TAVI	2604				0.6%*		3.3%		6%*		1.7%*			
TVT - US[18, 19]	VARC-1†	Mix	TAVI	12182	7.1%	7.0%	23.7%	8.5%*		6.4%*		6.6%*		2.5%	4.1%		
UK TAVI[67]	No	Mix	TAVI	870		7.1%	21.4%	13.5%		6.3%	6.4%	16.3%	16.3%	4.1%*			
			TAVI-other	271		10.7%	27.7%	9.1%		1.9%				4.1%*			
			TAVI-TF	599		5.5%	18.5%	15.6%		8.4%				4%*			
		CV	TAVI	452		5.8%	21.7%	17.3%		6.2%		24.4%		4%*			
		ES	TAVI	410		8.5%	20.6%	9.6%		6.3%		7.4%		4.2%*			

CV: CoreValve; ES: Edwards Sapien; Mix: ES & CV; TF: transfemoral, TA: transapical, TS: trans-subclavian, TV: Transvascular (transfemoral, direct aortic and trans-subclavian access) *: In-hospital rate. VARC: Valve Academic Research Consortium definitions, VARC-1 and VARC-2 represent the first and second versions; †: Partial compliance with VARC definitions

6.1.11 Australasian registries

Of the two Australasian studies, the CoreValve Australia and New Zealand (n=540) study, sponsored by Medtronic, is the largest. Data from the single arm study is for patients enrolled between August 2008 and July 2013 in 10 centres across Australia and New Zealand. New Zealand data came from Waikato Hospital, and Mercy Hospital in Auckland.[17] Patients had a mean logistic EuroSCORE of 17.3% and an STS score of 5.7%, representing moderate preoperative risk. Patients were evaluated by a multidisciplinary heart team to establish eligibility. All-cause mortality rates were 4.1%, 11.9% and 21.2% at 30 days, one year and two years, respectively. At 30 days, all deaths were for cardiovascular causes (4.1%); MACCE (comprising all-cause death, MI, stroke, and re-intervention at 30 days) was 11.5%. At one and two years, cardiovascular mortality was 9.9% and 15.2%; and stroke, 8.2% and 10.1%, respectively. The overall Kaplan-Meier rate of new permanent pacemaker implantation was 28.4% at 30 days, and 29.4% at two years, reflective of the high rates of insertion seen in other studies of the CoreValve implant. Pacemaker insertion rates were in addition to 12.6% of patients having pacemakers at baseline. Three-quarters of patients had significant symptoms of heart failure at baseline – New York Heart Association class III/IV. The corresponding rates at 30 days, one year and two years were 12.2% (n=506), 10.8% (n=397) and 9.7% (n=272), respectively.

The SOURCE-ANZ registry is a single arm industry sponsored registry assessing the outcomes of the Edwards Sapien valve.[118] A total of 132 high-risk patients were enrolled between December 2008 and December 2010 from eight centres in Australia and New Zealand. Sixty-three patients were treated transfemorally, 56 treated transapically, and two patients were withdrawn from the study. The study included 17 patients from Waikato Hospital. A mean logistic EuroSCORE was recorded of 26.8% in patients and 28.8% in transapical (TA) patients. Outcomes were not significantly different between TF and TA implants. All-cause mortality rates at 30 days were 5.97% for transfemoral (TF) patients compared to 9.67% for TA patients. Mortality rates after one year were 13.6% for TF patients and 21.7% for TA patients. MACCE was 16.7% (TF) and 28.3% (TA) (p = 0.12), pacemaker requirement was 4.6% (TF) and 8.3% (TA) (p = 0.39), and VARC major vascular complication occurred in 4.6% (TF) and 5.0% (TA) (p = 0.91).

6.1.12 A secondary analysis of the PARTNER B and non-randomised continued access registry

Key points

- Inoperable patients who are inoperable primarily due to comorbidities have poor outcomes post-TAVI.
- Patients who are inoperable primarily due to technical reasons such as porcelain aorta, previous mediastinal radiation, and chest-wall deformity, may gain similar survival benefit from TAVI as high-risk patients. However, prospective evidence (preferably RCT evidence) is required to confirm the result.

A secondary analysis of the PARTNER B trial for inoperable patients and the Non-randomised Continued Access Registry (n=369) found that two-year mortality was significantly reduced for the 23% of patients deemed 'technically' inoperable compared with the 77% considered 'clinically' inoperable. Two-year mortality was 23.3% and 43.8% for the technically inoperable and clinically inoperable patient groups, respectively (p <0.001).**[119]** In total, a third of patients had technical reasons for inoperability. For most of these patients (71%) this was the primary reason for inoperability and they were accordingly classified as technically inoperable patients. Of the clinically inoperable patients, 12% also had technical reasons for inoperability, but were classified as 'clinically

inoperable' nonetheless. Three causes accounted for more than three-quarters of technically inoperable patients: porcelain aorta (42%), previous mediastinal radiation (25%), and chest-wall deformity (6%). An additional 10% of patients had multiple technical causes for inoperability with roughly three-quarters of these patients having some combination of the preceding three causes. Patients were 'clinically' inoperable due to comorbidities or frailty: 48% had multiple comorbidities, 31% were considered too frail for surgical AVR, 16% had severe lung disease, 2% had liver disease, and 3% had other comorbidities.

The secondary analysis has a number of important limitations. Firstly, the measurement of differential outcomes between technically inoperable and clinically inoperable patients was not pre-specified in either the PARTNER B or NCAR trial protocols, so reported results are better regarded as 'exploratory' rather than conclusive. Statistical significance can arise as a matter of chance if sufficient secondary analyses are undertaken. Secondly, the analysis mixes randomised evidence with non-randomised evidence. Non-randomised evidence is subject to multiple biases including selection bias where positive outcomes can result due to selection of less complex cases. Thirdly, authors conclude that there is substantial survival benefit for both technically inoperable and clinically inoperable patients compared with standard therapy (medical management). The comparator in the analysis, patients undergoing medical management, came from the PARTNER B trial (NCAR is single arm). The control group was not subdivided into technically inoperable or clinically inoperable groups. Clinically inoperable TAVI patients matched the control group in terms of age and preoperative risk and other characteristics. But technically inoperable TAVI patients were ten years younger than the control (73 vs 83 years), and had an STS-score less than half (5.4 vs 12). A more appropriate comparison would match technically inoperable TAVI patients with a control group with similar baseline characteristics. The current analysis risks overstating the survival benefit of technically inoperable patients compared with standard therapy. Lastly, not all patients were strictly inoperable; some patients had conversions to open heart surgery – 5.9% for those with (combined) clinical and technical reasons for inoperability.

Long-term mortality after TAVI

Mid and long-term all-cause mortality after TAVI has been reported in the ANZ CoreValve, UK TAVI and multicentre Canadian registries (Table 9). Results compare favourably with the PARTNER A trial at two years in the ANZ CoreValve and UK TAVI registry, probably reflecting lower preoperative risk status in these studies; whereas the multicentre Canadian registry recorded comparable mortality at 12 months and two years. Compared with the PARTNER A, mortality rates remain favourable in UK TAVI registry at three and five years.

Table 9: Mid and long-term mortality after TAVI

Study	n	Device	1 Year	2 years	3 years	5 years
ANZ CoreValve[17]	540	CV	11.9%	21.2%		
Multicentre Canadian registry[114]	345	ES	24.0%	36.0%		
UK TAVI [120]	870	Mix	21.4%	26.3%	38.8%	54.5%

Source: NHC analysis, CV: CoreValve; ES: Edwards Sapien

Systematic reviews

Key points

- Meta analyses report comparable survival for TAVI and surgical AVR in high-risk patients. Survival rates appear similar between the CoreValve and the Edwards Sapien valve. Survival tends to be better for the transfemoral approach compared with the transapical approach, but this may reflect patient selection.
- Pooled results of early studies report elevated stroke and TIA rates for TAVI compared with surgery. Differences are non-statistically significant in more current meta analyses. Rates are comparable between valves and approaches.
- Pooled results report higher rates of moderate or severe aortic regurgitation in TAVI compared with surgery. Rates appear to be less using the Edwards Sapien valve, but comparable between approaches.
- Pooled results report higher rates of vascular complications compared with surgery, with greater rates for the transfemoral approach compared with the transapical approach.
- Renal complications appear to be similar between TAVI and surgery, but elevated using the transapical approach.
- Permanent pacemaker insertion is greater using the CoreValve than the Edwards valve, typically three or four times higher using the CoreValve.

There are a large number of systematic reviews on TAVI, employing various methodologies, where most have compared TAVI with surgical AVR or compared different approaches or types of valve. Very few reviews have focused specifically on inoperable patients. These reviews combine the data of multiple studies, essentially that seen in the prior sections, to form an overall estimate of the effectiveness of TAVI.

6.1.13 All-cause mortality

Biondi-Zoccai et al (2014) undertook a systematic review of randomised controlled trials comparing TAVI with surgery (n=1,805).[121] The meta nalysis included data from four RCTs published between 2011 and 2014 including the PARTNER A (12-month results), high risk CoreValve, CHOICE and STACCATO trials. Differences in one-year all-cause mortality between TAVI and surgical AVR were not statistically significant by valve type (Edwards Sapien vs CoreValve) or approach (transfemoral or transapical). Compared with surgical AVR, the odds ratio for all-cause mortality was 0.82 (95% CI, 0.55, 1.23) for the Edwards Sapien valve, using the transfemoral approach. The corresponding rate for the CoreValve was 0.72 (95% CI, 0.50, 1.05). The odds ratio for transfemoral vs transapical TAVI using the Sapien valve was 0.61 (95% CI, 0.30, 1.26).

The authors reported following Cochrane Collaboration guidelines when screening studies for bias. Valve Academic Research Consortium endpoint definitions were used and imputed if not available. Risk estimates were obtained using Bayesian network meta analytic methods. The study did not report on the level of heterogeneity in the included data.

Earlier meta analyses of randomised and non-randomised data reported similar short and mid-term all-cause mortality for TAVI and surgical AVR in high-risk patients.[122-125] Meta analyses of randomised and non-randomised studies published prior to 2013 show greater 30-day mortality using the transapical approach compared with the transfemoral approach.[123, 126-129]

Nagaraja et al (2014) undertook a meta analysis of 14 studies comprising 6,965 patients comparing the two approaches. Study data was from randomised and non-randomised trials published prior to 2013. The review found 30-day (OR: 0.70, 95% CI, 0.53-0.92, I^2 28%) and one-year mortality (OR: 0.72, 95% CI, 0.56-0.93, I^2 58%) lower in transfemoral patients compared with transapical patients. The authors did not consider the evidence sufficient, however, to support for the superiority of the transfemoral approach, citing a lack of randomised controlled evidence.[123]

Nagaraja et al's (2014) review used a regression model to determine the risk of publication bias, none was detected. A qualitative review of bias (eg allocation concealment, selective outcomes reporting, patient selection bias) appears not to have been undertaken. Valve Academic Research Consortium endpoints were not explicitly used. Reporting on baseline patient characteristics was limited and did not include risk status.

The tendency for the transapical approach to report higher all-cause mortality compared with the transfemoral approach may be influenced by the selection strategy of patients with transapical patients potentially burdened by more comorbidities.[130]

6.1.14 Stroke

Contrasting with meta analyses of observational data, early meta analyses of the STACCATO and PARTNER A randomised controlled trials reported elevated (and statistically significant) stroke rates (or stroke and transient ischaemic attack rates) for TAVI compared with surgical AVR.[122, 124] Later meta analyses, including results from the high risk CoreValve RCT, report elevated but non-statistically significant stroke rates.[121, 131]

Biondi-Zoccai et al's (2014) meta analysis of randomised controlled trials reported lower incidence of stroke at 12 months using the CoreValve compared with surgical AVR, though the results were not statistically significant (OR 0.7, 95% CI 0.44, 1.06).[121] Greater incidence was reported for the Edwards Sapien valve compared with surgery, but again the result was not statistically significant (OR 2.2, 0.95 5.34 in TF and OR 2.12, 0.80-6.08 in TA).

Nagaraja et al (2014a) undertook a meta analysis of randomised and non-randomised data. In their analysis of randomised controlled trials they pooled data from the PARTNER A (two-year results), STACCATO and CoreValve high risk studies. They reported an elevated but non-statistically significant risk of stroke for TAVI compared with surgical AVR (OR1.94, 95% CI 0.81, 4.6).[131] Similar limitations in methodology apply as reported above for Nagaraja et al (2014).

Cao et al's (2013) meta analysis of 14 studies found the incidence of stroke was not significantly different between TAVI and surgical AVR during the peri-procedural period (2.6% vs. 2.3%; P=0.54; I^2=0%), at 12 months (4.5% vs. 3.4%; P=0.46; I^2=29%) or beyond 12 months (5.8% vs. 4.1%; P=0.21; I^2=5%).[122] The meta analysis included randomised and non-randomised data. The review process for omitting potentially bias publications was not outlined. Some endpoints were reportedly measured according to Valve Academic Research Consortium definitions, but were not clearly marked. Baseline patient characteristics indicate the study combined patients of low to high preoperative risk, with mean STS scores ranging from 3% to 12%.

Athappan et al's (2014) systematic review of randomised and non-randomised trials, published between 2006 and 2013, found no significant difference in the 30-day stroke rate between TAVI and surgical aortic valve replacement. [68] Compared with surgical AVR, the odds ratio was 1.24 (p=0.58) in high-risk patients, and 1.7 (p=0.52) in intermediate-risk patients. The review process for omitting potentially biased publications was not outlined. Valve Academic Research Consortium endpoint definitions were used in sensitivity analysis, with exclusion of non-VARC compliant studies. VARC only results were not reported for TAVI vs surgery. The study included records for 29,000 patients from multicentre studies and 7,100 patients from single centre studies.

Biondi-Zoccai et al's (2014) meta analysis found strokes at 12 months were less frequent with the CoreValve than the Edwards Sapien valve for both the transfemoral (odds ratio =0.32 [0.13-0.73]) and transapical approaches (odds ratio =0.33 [0.10-0.93]). It is not clear, however, to what extent differences in underlying patient characteristics may have influenced the finding.[121]

Eggebrecht et al reported similar 30-day major stroke rates for the CoreValve (n=1795, 2.5% ± SD 1.8%) and the Edwards valve (n= 1190, 3.0 % ± SD 2.0%).[132] Their meta analysis combined the data of 10,000 patients from randomised and non-randomised studies published prior to 2012, a result consistent with findings by Athappan et al (2014).[68]

Nagaraja et al (2014) found stroke rates similar at 30 days for transfemoral and transapical approaches (OR 0.95, 95% CI 0.7 1.3, I^2= 0%),[123] a result consistent with findings by Athappan et al (2014).[68] Athappan et al also reported a decline in stroke rate over time, possibly reflecting improvement in technology and patient selection and operator experience.

6.1.15 Aortic regurgitation

Compared with surgical AVR Biondi-Zoccai et al reported significantly elevated moderate or severe aortic regurgitation using both the CoreValve (OR 15.9, 95% CI 3.76, 123) and the Sapien valve (OR 5.91, 95% CI 1.31, 57.4). The Sapien valve had lower reported aortic regurgitation compared with the CoreValve but the difference was not statistically significant (OR 0.39, 95% CI 0.09,1.31).[121]

Meta analyses including observational data report significantly elevated moderate or severe aortic regurgitation for the CoreValve compared with the Sapien valve.[133, 134] Athappan et al (2013) reported higher rates of moderate or severe aortic regurgitation using the CoreValve compared with the Sapien valve (16% vs 9.1%, p=0.005). They also reported increased risk of mortality in the presence of moderate or severe aortic regurgitation at 30 days (OR 2.95 95% CI 1.73, 5.02) and one year (Hazard Ratio 2.27 95% CI 1.84, 2.81).[133] Their review of aortic regurgitation after TAVI (n=12,926) was methodologically similar to their 2014 review relating to stroke discussed above.

Nagaraja et al (2014) reported comparable incidence of aortic regurgitation between the transfemoral and transapical approaches (OR 1.25, 95% CI 0.84 1.86).[123]

6.1.16 Permanent pacemaker insertion

In Cao et al (2013) patients required permanent pacemaker insertion significantly more frequently after TAVI compared to AVR (13.2% vs. 3.0%; P<0.001 I^2=68%).[122] Multiple meta analyses have found pacemaker insertion rates higher in the CoreValve compared with the Sapien valve.[121, 135-137] Rates are typically three or four times higher using the CoreValve. Nagaraja et al (2014) found the need for pacemaker at 30 days comparable between transfemoral and transapical TAVI,[123] as did Garcia et al (2013).[127]

6.1.17 Vascular complications

Nagaraja et al's (2014) meta analysis of non-randomised data reported a seven-fold increase in the odds of major vascular complications following TAVI compared with surgery (OR=7.117, 95% CI=2.287 to 22.149).[131]

Multiple meta analyses have reported significantly higher rates of vascular complications in TAVI using transarterial approaches (including transfemoral) compared with the transapical approach. [123, 126, 127, 135] Khatri et al (2013) reported vascular complications following TAVI were significantly more frequent with transarterial procedures than with transapical procedures (14.2% vs. 3.4%; P < 0.001).[135]

6.1.18 Renal complications

Nagaraja et al (2014) reported comparable rates of acute renal failure requiring haemodialysis for TAVI and surgical AVR (OR 0.94, 95% CI 0.28 to 3.2),[131] as did Wu et al (2013).[138]

Khatri et al (2013) found the overall rate of renal replacement therapy for acute renal failure was 4.9% in TAVI (time period unclear – likely 30 days). Higher rates were observed with transapical procedures than transarterial procedures (8.2% vs. 2.8%; P <0.001).[135] Garcia et al (2013) reported a 0.3-fold increase in the odds of renal dialysis with transapical compared with the transfemoral approach (p<0.01).[127]

6.1.19 Cochrane reviews

In 2013 the Cochrane Collaboration issued two protocols for systematic reviews of TAVI in patients with severe aortic stenosis.[139, 140] The protocols overlap in comparing TAVI with surgical AVR, though one also compares TAVI with optimal medical therapy. When published, the reviews are likely to provide further clarity on treatment effect in terms of all-cause mortality, major adverse events, and quality of life improvement. Lead authors were contacted, but it is not known when the publications are expected.

New Zealand experience

236 records of TAVI were identified in the national minimum dataset and confirmed with DHBs. The procedures, performed between 2008 and 2014, were matched to mortality records using encrypted national health index numbers. Records show relatively low mortality following TAVI, though as there is no prospective control, relative efficacy compared with surgical AVR is not known (Table 10).

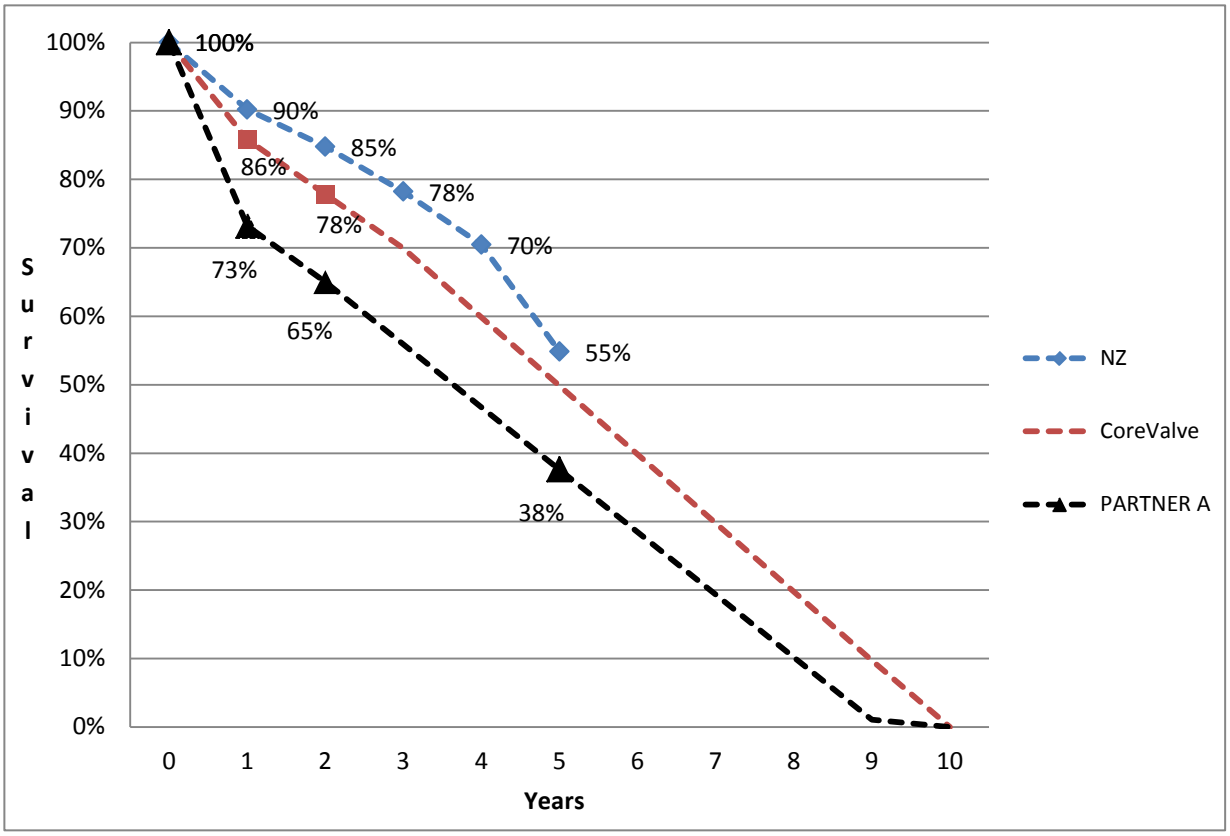
Table 10: Mid-term mortality of TAVI patients in New Zealand

	30 days	1 year	2 year	3 year	4 year	5 years
Follow up	236	204	137	78	44	31
Alive	227	184	116	61	31	17
Survival	96.2%	90.2%	84.7%	78.2%	70.5%	54.8%
Mortality	3.8%	9.8%	15.3%	21.8%	29.5%	45.2%

Source: NHC analysis of NMDS

A likely influence on the result is the inclusion of moderate-risk patients, who can be expected to have better survival than high-risk patients.[27] Figure 4 presents the inferred survival curves for the high risk CoreValve trial, the PARTNER A trial, and the New Zealand experience, where actual data is clearly marked. We calculated the New Zealand rate of mortality following TAVI as a simple frequency of deaths to potential survivors at time periods 30 days to five years.

Figure 4: Survival curves for TAVI in high and moderate-risk patients



Source: [100, 141] NHC analysis

Health technology assessments of TAVI

Key points

- Health technology agencies support the use of TAVI in high-risk and inoperable patients, but not in lower risk populations.
- UK commissioning guidelines stipulate that only high-risk or inoperable patients are eligible for publicly funded TAVI, where 'inoperability is primarily the result of anatomical limitations'.[26]
- Earlier health technology assessments of TAVI led to recommendations that TAVI be funded for use in inoperable patients only, but later HTAs have expanded indications to include high-risk patients.

Earlier health technology assessments of TAVI led to recommendations that TAVI be funded for use in 'inoperable patients', but not funded for high-risk patients. More recent health technology assessments have led to recommendations that TAVI also be funded for high-risk patients.

In April 2015, the Australian Medical Services Advisory Committee (MSAC) considered an application from Edwards LifeSciences for Medicare Benefit Schedule (MBS) listing of TAVI for use in patients with symptomatic severe AS and who are determined to be at high risk for surgical AVR or non-operable.[58] An MBS listing enables public funding of a procedure in Australia. TAVI is currently not funded under the MBS, though legal access is available under the Therapeutic Goods Administrations special access scheme or for clinical trials and clinical registries. MSAC deferred the application to its 30-31 July meeting to allow the applicant to re-present its economic model. MSAC published a public summary document for its April meeting, noting that:

- current treatments for severe AS include medical management or an aortic valve replacement.
- there are two main comparators for TAVI: as an alternative to surgical AVR in high operative-risk patients; and as an alternative to medical management with or without balloon valvuloplasty in inoperable patients.
- they considered restricting TAVI to transfemoral delivery only due to the weak evidential support for the safety and effectiveness of TAVI via transapical delivery or other minimally invasive surgical approaches, but concluded this would be too restrictive.
- the existing evidence does not justify discriminating against any particular device on clinical grounds.
- five-year results from PARTNER demonstrated a continued superior all-cause mortality for TAVI via transfemoral delivery over medical management, and non-inferior all-cause mortality between transfemoral delivery and surgical AVR.
- there was insufficient evidence to draw conclusions on the safety and effectiveness of any approach other than the transfemoral delivery where the PARTNER trial was under-powered to assess the comparative effectiveness or safety of TAVI via transapical delivery.
- compared with medical management, TAVI via transfemoral delivery had increased risk of stroke, vascular complications, and major bleeding at one year.
- compared with surgical AVR TAVI via transfemoral delivery had decreased risk of major bleeding, but higher rates of paravalvular leak, vascular complications and permanent pacemaker implantation and a (non-increasing) trend towards increased stroke.
- five-year results from PARTNER showed that the risk of stroke did not increase over time for inoperable patients and diminished over time for high-risk patients receiving TAVI.
- TAVI via transfemoral delivery had a lower use of associated procedural healthcare resources than surgical AVR.

The Australia and New Zealand Health Policy Advisory Committee on Technology (HealthPACT) reviewed TAVI (using the Sapien valve) in 2012. They concluded that ‘the Sapien device appears preferable to standard care [medical management] for patients ineligible for surgery’. They noted that TAVI should only be performed for patients in whom existing comorbidities would not prevent the expected benefit from correction of aortic stenosis.[142] Subsequently HealthPACT commissioned work lead by DLA Piper giving a brief overview of TAVI,[143] and supporting a workshop on TAVI,[144] concluding that TAVI should only be made available through three avenues:

- The Commonwealth’s Special Access Scheme, where the importation of an approved therapeutic good is assessed on a case-by-case basis for 'persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment'.
- Via importation for personal use.
- Under the auspices of a clinical trial.

And proposing two actions:

- Joint development, by the Cardiac Society of Australia and New Zealand and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons, of patient referral and selection criteria, including articulation of criteria for patients deemed suitable for TAVI and to be cared for by a multidisciplinary heart team; and
- Development of an Australian/New Zealand TAVI Registry (ANZTAVIR) as a means of tracking procedure numbers and, more importantly, short and long-term outcomes.

The National Institute for Health and Care Excellence (NICE) published guidelines on TAVI in 2012 finding the evidence for the efficacy of TAVI in inoperable patients 'adequate', but 'inadequate' for high surgical risk patients.[145] For inoperable patients, NICE recommended that TAVI may be used with normal arrangements for clinical governance, consent and audit. For high-risk patients, NICE recommended that TAVI should only be used with special arrangements for clinical governance, consent and data collection or research. They recommended that the details of all TAVI patients should be entered into the UK Central Cardiac Audit Database.

Subsequent UK commissioning guidelines (2013) outline criteria for TAVI as "an alternative to standard surgical AVR" and for inoperable patients where "inoperability is primarily the result of anatomical limitations, such as extensive aortic calcification".[26] The key criterion for deciding which patients should have TAVI is that patients who are potential candidates are considered by an appropriate multidisciplinary team. The governance arrangements for the multidisciplinary team are based on the consensus statement of the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (2009).[146] These arrangements specify (among other requirements) that TAVI should be reserved for patients who have been considered by a multidisciplinary team (including two surgeons and two interventional cardiologists) who consider the risk/benefit ratio of open heart surgery and TAVI to favour TAVI. The usual 'high-risk' patient will have a logistic EuroSCORE of >20 or an STS score of >10.

HTAs published in 2012 or earlier by Ontario Health Technology Advisory Committee (2012),[13, 14] the French National Authority for Health (2011),[7] the Belgian Health Care Knowledge Centre (2011),[147] the Norwegian Knowledge Centre for the Health Services (2012),[12] the Austrian Ludwig Boltzmann Institute for Health Technology Assessment (2012),[6] and The National Institute for Excellence in Health and Social Services in Quebec Canada (2012),[15] also supported TAVI's use in inoperable patients but found inadequate clinical evidence to support TAVI use in high-risk patients.

Ontario Health Technology Advisory Committee OHTAC recommended that TAVI not be used for patients with severe aortic valve stenosis who are candidates for surgery due to high complication rates, similar effectiveness and unfavourable cost-effectiveness compared with surgery.[13, 14] In patients with severe aortic valve stenosis who are not candidates for open heart surgery, they recommended a field evaluation with follow-up on patient resource use, quality of life preference information, and clinical outcome data.

The French National Authority for Health (HAS) published an assessment in 2011 recommending that TAVI be limited to patients with a contraindication to surgical valve replacement following assessment by a multidisciplinary team.[7] HAS recommended, however, that "TAVI must not be used on compassionate grounds in patients with a life expectancy of less than one year with regard to the associated comorbidities, or in patients who are eligible for surgery but refuse it." They emphasised "that surgical aortic valve replacement remained the standard treatment irrespective of the surgical risk."

More recent reviews by the Canadian Agency for Drugs and Technology in Health (CADTH) (2013),[5] Health Improvement Scotland (2014),[10, 11] and The California Technology Assessment Forum (2012/13),[8, 9] echo previous findings for TAVI in inoperable patients, but also lend support for TAVI in high surgical risk patients.

CADTH concluded that long-term outcomes support the use of TAVI as an alternative to AVR in selected high-risk patients with aortic stenosis. Health Improvement Scotland found rapid progress being made in TAVI device modification and patient selection such that the published evidence may not fully capture the emergent evidence for the latest generation of TAVI devices. Their report, whilst not making specific recommendations, focused on the findings of the PARTNER trial noting its findings of non-inferiority for TAVI compared with AVR (in all-cause mortality) at one and two year follow-up for high surgical risk patients.

The California Technology Assessment Forum, a core programme of the American Institute for Clinical and Economic review, has issued two reports supportive of TAVI in inoperable and high surgical risk patients. They noted FDA approval for TAVI valves in both inoperable and operable patient groups; found sufficient quality evidence that TAVI improves net health outcomes at least as well as established technologies; and considered that improvement was attainable in usual use. It was noted, however, that patient selection was essential to ensure that the results of the PARTNER trial apply to patients treated in the community. The Forum also noted the need for a multidisciplinary team that includes at a minimum one cardiac surgeon, a general cardiologist, and an interventional cardiologist who should agree that a patient is high risk before offering TAVI.

International professional guidelines

The 2014 American College of Cardiology/American Heart Association practice guideline for the management of patients with valvular heart disease includes TAVI under “choice of intervention” in aortic stenosis.[36] These are summarised in Table 11.

A class I recommendation is given for patients to receive TAVI who have a prohibitive surgical risk with a life expectancy of greater than 12 months. A Class IIa recommendation is given to those who are at high risk of poor outcome with surgery. High risk is defined as an STS-PROM >8 in these guidelines, which is in line with the updated Valve Academic Research Consortium (VARC-2) consensus document.[3] Specifically, TAVI is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of the AS, and this could be extrapolated to include those with high frailty indices also.

Table 11: Summary of recommendations for aortic stenosis: Surgical vs Transcatheter Intervention

Recommendations	COR	LOE
Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.2.3) with low or intermediate surgical risk	I	A
For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care	I	C
TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 mo	I	B
TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.2.3) and who have high surgical risk (Section 2.5)	IIa	B
Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS	IIb	C
TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS	III: No Benefit	B

Source: Adapted from Nishimura et al. 2014 AHA/ACC Valvular Heart Disease Guideline [36]

Earlier European Guidelines, published 2012, by *The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS),* concluded that:

- TAVI is recommended in patients with severe symptomatic AS who are, according to the 'heart team', considered unsuitable for conventional surgery because of severe comorbidities.
- TAVI is recommended in patients with severe symptomatic AS who are, according to the 'heart team', considered unsuitable for conventional surgery because of severe comorbidities. Here they noted that the STS scoring system >10% may result in a more realistic assessment of operative risk than a logistic EuroSCORE ≥20%, but noted that 'frailty and conditions such as porcelain aorta, history of chest radiation or coronary bypass grafts may make patients less suitable for AVR despite a logistic EuroSCORE >20%/STS score >10%.'
- TAVI should not be performed in patients at intermediate risk for surgery and trials are required in this population.[88]

Ongoing and future trials

The Australian and New Zealand Clinical Trials Registry, and United States Institute of Health's clinical trial registry, ClinicalTrials.gov, were utilised to identify ongoing and planned trials relating to TAVI. More than 100 trials, including 24 randomised controlled trials (Table 40 Appendix 3) and two small observational studies planned or underway at Waikato Hospital were identified.

Planned and ongoing trials in New Zealand

Waikato Hospital is listed as the sole participant in a phase one study of Vascular Innovations limited, a Thailand-based company, HYDRA self expanding TAVI valve (Clinical trial ID NCT02434263). The primary endpoint for the single arm study (n=70) is 30 day all-cause mortality. The proposed start date is November 2015 with a primary completion date of January 2017 (final data for collection of primary outcome measure). The study is reported to be for high-risk patients, though an STS threshold is not reported. Waikato Hospital is also involved in a small multicentre multinational (including Australia and the UK) evaluation of the Medtronic CoreValve Evolut R delivery system (Clinical trial ID NCT01876420). The primary endpoints for the single arm study (n=60) are 30 day all-cause mortality and stroke and the one to seven-day device success rate. Enrolled patients are to have an estimated 30 day mortality risk of > 15% by study centre heart team assessment or be inoperable (confirmed by two surgeons). The Evolut R delivery system is designed to better deliver the CoreValve and reduce paravalvular leak. The study commenced in October 2013 with the study expected to be complete in September 2016. In addition, the aforementioned CoreValve Australia and New Zealand registry (Clinical trial ID NCT01015612) and the Source ANZ registry (Clinical trial ID ACTRN12611001026910) appear to be ongoing.

Planned and ongoing observational studies

Of the observational studies, the largest studies are the ongoing German GARY registry (Clinical trial ID NCT01165827) with estimated enrolment of 100,000 patients for TAVI and surgical AVR, the US TVT registry (Clinical trial ID NCT01737528) with an estimated enrolment of 15,000 TAVI patients, and FRANCE 2, n=5,000, (Clinical trial ID NCT01777828). These have all been previously described above. Other large observational studies include: The PARTNER Post Approval Study Part II (PASII) (n=5,000) (Clinical trial ID CT02184442), a post-market approval study to determine the learning curve for iterations of Sapien valve and delivery system; the AVIATOR study an independent German study to evaluate the intraoperative anesthesiologic characteristics faced during TAVI (n=5,000)

(Clinical trial ID NCT01390675); the continued access study for Medtronic's CoreValve system in high-risk patients (n=4,500) (NCT01531374), a post-market approval study for ongoing evaluation of safety and effectiveness; the SOURCE XT REGISTRY (Clinical trial ID NCT01238497), a post-market approval study of the Edwards Sapien XT valve to monitor safety and identify patient characteristics and indicators related to complications and clinical benefits for patients with severe AS (n=3,000).

Planned and ongoing randomised controlled trials

Considering the large randomised controlled trials; the PARTNER II trial is designed to compare surgical AVR with the second generation valve (SAPIEN-XT) and two delivery systems (Novoflex for transfemoral TAVI and Ascendra 2 for transapical TAVI).[148] It is attempting to expand the indication to lower risk patients and thus intermediate-risk patients are being recruited in Cohort A. In Cohort B (inoperable group) of this trial, the first generation Sapien valve is being compared to the second generation Sapien XT valve. The SURTAVI trial is Medtronic's competing study – comparing surgical AVR with the Medtronic CoreValve in intermediate-risk patients. Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial (PORTICO-IDE) is designed to evaluate the safety and effectiveness of St Jude Medical's Portico TAVI valve and delivery system in high-risk patients, STS score ≥8%. While the study is reported to be recruiting patients, the company's five-year observational study of the TAVI valve (PORTICO-1) has been suspended due to the need to evaluate reports of reduced leaflet mobility (Clinical Trial ID NCT02000115). REPRISE III compares the safety and effectiveness of Boston Scientific's Lotus TAVI valve and delivery system with Medtronic's CoreValve system in high-risk patients, STS score ≥8%, with severe AS.

To further reduce cerebrovascular events, three mechanical cerebral protection devices are being tested; the Claret Pro™, the TriGuard® and the Embrella® device.[149-151] Of these devices, two are currently subject to randomised controlled trials, namely the Claret Pro™ system (n=359, Clinical Trial ID NCT02214277), and the TriGuard® system (n=86, Clinical Trial ID NCT02070731).There are also several studies underway to determine optimal antiplatelet therapy following TAVI including: REAC-TAVI (n=60 Clinical Trial ID NCT02224066) ARTE Trial (n=200, Clinical Trial ID NCT01559298) and BRAVO-2/3 (n=870, Clinical Trial ID NCT01651780).

Suspended studies

Several TAVI studies have been suspended or terminated. Where an explanation was not provided we contacted the principal investigators or companies concerned. Suspended or terminated studies include the aforementioned PORTICO-1 observational study and the:

- HLT transfemoral Replacement of Aortic Valve via Transcatherterision (HORIZON) observational study (Clinical Trial ID NCT02157142); HLT Medical determined that design changes were necessary before reopening the study.
- Safety and Efficacy Study of the Cardiapex Percutaneous Transapical Access and Closure System observational study (Clinical Trial ID NCT01722591); the study was to trial the Cardiapex Percutaneous Transapical Access and Closure System. The company has gone into voluntary liquidation.
- Use of Cardiac-MRI to Predict Results for People With Severe Aortic Stenosis observational study (Clinical Trial ID NCT01905852). The study was to assess the ability of cardiac MRI measurement of extracellular volume fraction to predict short and long-term LV function post-TAVI. The study was closed as a key staff member left.

7 Economics

This section addresses the research question:

What is the cost and cost effectiveness of TAVI in the New Zealand environment?

The cost, budgetary impact, and cost-effectiveness of four policy options is investigated, namely:

- Continuation of the current level of TAVI provision: TAVI versus surgical AVR in a mixed group of high and moderate-risk patients.
- Limitation of TAVI to high-risk patients only: TAVI versus surgical AVR in high-risk patients.
- Expansion of TAVI to inoperable patients: TAVI versus medical management for inoperable patients.
- Expansion of TAVI to 'technically' inoperable patients only: TAVI versus medical management for 'technically inoperable' patients.

Firstly, we estimate the current and future pool of TAVI patients under these policy options. Secondly, we estimate the cost of TAVI, surgical AVR, and medical management. From these two estimates we derive the potential budgetary impact of the policy options. Lastly, we model the cost-effectiveness of TAVI for the policy options with a concluding overview of the international economic literature for TAVI. The analysis is undertaken from a health funder's perspective.

Patient numbers

Key points

- The high-risk AVR patient population in New Zealand (STS>8%) is relatively small, probably less than 30 patients per annum, whereas 66 TAVI procedures were undertaken in 2012/13. TAVI is most likely being undertaken in moderate-risk patients in addition to high-risk patients in New Zealand.
- On the basis of 65+ population growth, TAVI volumes are expected to expand from 66 procedures in 2012/13 to about 84 procedures in 2019/20.
- If TAVI were expanded to inoperable patients, including patients with significant comorbidities, intervention rates could grow to 210 procedures in 2019/20.
- IF TAVI were expanded to 'technically inoperable' patients only, the intervention rate could grow to 113 procedures by 2019/20.

The number of patients receiving TAVI in the year 2012/13 was 66. We have used international evidence to estimate the number of TAVIs that would be performed under the three other policy options.

At the time of analysis no specific code (Diagnostic Related Group code or ICD-10 procedure code) existed to identify TAVI in the national minimum dataset. To identify TAVI, we searched the free text field within the national minimum dataset. We then asked DHBs to confirm or amend our records. Sixty-six records of TAVI were confirmed by DHBs for the 2012/13 financial year, the latest year for which cost data was available in the National Costing Collection and Pricing Programme dataset.

In 2012/13, about 21 (95% CI, 20, 22) patients nationally could be defined as surgically operable but with a high risk of mortality, and TAVI feasible. In the same year, we estimate that TAVI was feasible

in about 100 (95% CI 80,121) inoperable patients; where about 23 (95% CI 12, 35) were technically inoperable and 77 (95% CI 39, 116) clinically inoperable (Table 12).

Table 12: Estimated TAVI feasible population for publicly funded high-risk and inoperable patients

		2012/13	2013/14	2015/16	2016/17	2017/18	2018/19	2019/20
Estimated population with severe symptomatic aortic stenosis	Total pool	860	895	931	968	1008	1048	1091
	Operable patients	511	532	553	575	599	623	648
	Inoperable patients	349	363	378	393	409	425	443
TAVI feasible								
High-risk (4.2% of operable patients)		21 (20,22)	22 (21,23)	23 (22,24)	24 (23,25)	25 (23,26)	26 (24,27)	27 (25,28)
Inoperable (29% of inoperable patients)		100 (80,121)	104 (83,126)	108 (86,131)	113 (90,136)	117, (93,142)	122 (97,147)	127 (101,153)
	Technically inoperable (23%)	23 (12,35)	24 (12,36)	25 (12,37)	26 (13,39)	27 (13,40)	28 (14,42)	29 (15,44)
	Clinically inoperable (77%)	77 (39,116)	80 (40,120)	83 (42,125)	87 (44,131)	90 (45,135)	94 (47,141)	98 (49,147)

Source: NHC analysis using population forecasts provided to the NHC by Statistics New Zealand. Numbers in brackets = approximated 95% confidence intervals

Five-year demand for TAVI is projected under the four alternative policy settings (base case, high risk, inoperable, technically inoperable); the projections are reported in Table 13 below. The methods for the estimates under each policy option are detailed in the following sections. The number of TAVIs performed in the year 2019/20 ranges from 27 if restricted to high-risk patients only and 210 if access is widened to include all inoperable patients where the procedure may be feasible. The inoperable and technically inoperable scenarios are split according to whether the additional cases are additive to the base case (+ base case) or additive to the high surgical risk population.

Table 13: Projected demand for publicly funded TAVI

	2012/13	2013/14	2015/16	2016/17	2017/18	2018/19	2019/20
Base case	66	69	71	74	77	80	84
High risk only	21 (20,22)	22 (21,23)	23 (22,24)	24 (23,25)	25 (23,26)	26 (24,27)	27 (25,28)
Inoperable							
+ base case	166 (146,187)	173 (152, 195)	180 (157,202)	187 (164,210)	194 (170,219)	202 (177,227)	211 (185,237)
+ high risk	121 (100,143)	126 (104,149)	131 (108,155)	137 (113,161)	142 (116,168)	148 (121,174)	154 (126,181)
Technically inoperable							
+ base case	89 (78,101)	93 (81,105)	96 (83,108)	100 (87,113)	104 (90,117)	109 (94,122)	113 (99,128)
+ high risk	44 (32,57)	46 (33,59)	48 (34,61)	50 (36,64)	52 (36,66)	54 (38,69)	56 (40,72)

Source: NHC analysis using population forecasts provided to the NHC by Statistics New Zealand. Numbers in brackets = 95% confidence intervals

The base case

In 2012/13, 860 patients received a primary hospital diagnosis of aortic stenosis. In the same year, 511 patients with a primary diagnosis of aortic stenosis underwent publicly funded aortic valve replacement including TAVI. Hence we estimate that about two in five patients with a primary diagnosis of AS are inoperable – consistent with international experience.[77, 152, 153] The incidence of aortic stenosis, and the associated number of operable and inoperable patients, is modelled to grow at the same rate as the 65 and over population at about 4% per annum. The base case is a straight-line extrapolation of the 2012/13 intervention rate, assuming a 4% growth rate. The financial year 2012/13 was chosen as the base year as it is the most recent year for which we have cost data.

TAVI for high-risk patients only

In the TAVI for high-risk patients only scenario, just 21 cases are estimated to be undertaken in 2015/16, increasing to 27 cases in 2019/20. With a proficiency requirement of at least 20 TAVI operations per annum,[29] the scenario implicitly assumes a reduction of three centres to one.

This estimate is based on the assumption that 4.2% of operable cases are high-risk, with high-risk being defined as a STS-PROM of ≥ 10%. The proportion of cases deemed high risk differs depending on the scoring tool used and the cut-off value used.

The New Zealand usage data, of 71 cases predicted for 2015/16, infers that two-thirds of TAVIs currently done are outside of the high-risk patient group.

7.1.1 Rationale

Estimated number of patients: About 5.2% of operable patients are high risk, of which 80% may be eligible for TAVI 511*5.2%*80%= 21

In one randomised controlled trial, TAVI has demonstrated non-inferiority to surgical AVR in high-risk patients with five years of follow-up;[141] in another RCT with two years of follow-up, TAVI was superior.[102] This scenario assumes 4.2% of operable patients are high-risk and candidates for TAVI. The figure of 4.2% was derived from a 2013 meta analysis of United States and European data.[77] The meta analysis found 5.2% (95% CI: 4.9-5.4%) of surgical candidates in Europe and the United States were high risk, based on an STS Predicted Risk of Mortality Score >10% – with 80% of these high-risk patients assumed to be eligible for TAVI. Consistent with the estimate of the high-risk population pool, less than 5% of patients in the population from which the STS algorithm was derived had a predicted operative risk of more than 10%.[99, 154]

Accurate risk stratification is very important in selecting patients for TAVI, surgical AVR or medical management. The STS score is an accurate predicator of AVR operative mortality and has recently been corroborated with New Zealand specific evidence (discussed below).

Is TAVI only going to high-risk patients in New Zealand?

Projected supply in the high-risk scenario is a third of what is currently being observed (ie the base case). Yet TAVI has only been approved for high-risk surgical patients in New Zealand. With TAVI only being performed in three of five cardiac centres nationally, it is likely that some high-risk patients are still undergoing conventional surgery. Thus it appears that TAVI is currently being performed on roughly three times as many patients as would be defined as 'high risk' using the STS score. We think this is most likely due to some moderate-risk patients receiving the intervention in addition to high-risk patients. It is possible that the use of outdated and inaccurate risk scores, such as the logistic EuroSCORE, may have led to an overestimation of the size of the high-risk population in New Zealand.

A retrospective study of all TAVI undertaken in New Zealand between 2008 and 2014 found TAVI had been performed in a moderate and high-risk population in New Zealand.[27, 28] The study risk stratified TAVI using EuroSCORE II. It reported a mean EuroSCORE II of 10.2% with a standard deviation of 7.7.[27] EuroSCORE II is a relatively new risk score and it is not clear precisely how it maps to the STS score. A recent meta analysis of the two scores in surgical AVR and TAVI patients reported similar observed/expected mortality ratios for the two instruments (outlined above), indicating that an STS score of 10% may roughly map to a EuroSCORE II of 9%.[80] In the absence of a precise guide, we imputed a moderate risk range for EuroSCORE II of 4.5 ≤ 9%, and low risk EuroSCORE II < 4.5%. A mean EuroSCORE II of 10.2% approximates the preoperative risk in the PARTNER high risk RCT, where the mean STS score was 11.8±3.3. [99] But the population appears higher risk than that enrolled in the CoreValve high risk study, STS 7.3±3.0.[100] Compared with the PARTNER high risk study, there is far greater variation in the distribution of risk scores in the New Zealand data, where the standard deviation is 7.7 compared with 3.3 in PARTNER. The median EuroSCORE II in the New Zealand data is 7.7%, representing moderate preoperative risk, suggesting the data is skewed by a few very high risk cases.

The NHC were provided with the (anonymised) data from the New Zealand TAVI study.[27] The data shows that between financial years 2008/09 and 2013/14 nearly two-thirds of TAVI patients had a EuroSCORE II less than 9%, with a mean and median EuroSCORE II of 9.6%, and 7.5% across the dataset respectively. By comparison, 58% of TAVI patients in the PARTNER high risk study had an STS >11.[99] No discernible trend in risk scores is observable over time (Table 14).

Table 14: Preoperative risk (EuroSCORE II) of TAVI patients in New Zealand

Date	Median ESII	Mean ESII	Count	ESII < 9	ESII < 4.5
2008/09	7.4	9.6	20	65%	15%
2009/10	6.6	10.2	21	57%	19%
2010/11	7.8	8.7	14	64%	7%
2011/12	7.3	8.4	47	64%	32%
2012/13	8.4	12.4	59	54%	17%
2013/14	7.8	8.1	54	67%	31%
Average	7.5	9.6	215	62%	20%

Mean and median risk scores vary slightly from those reported in the published study. This may be due to marginally different reporting periods; the data in the study reportedly ends in March 2014, whereas the data in the table above goes through to the end of June 2014. Compared with NHC estimates the study identified seven fewer TAVI in 2012/13 and 13 fewer in 2013/14. NHC estimates have been confirmed by DHBs. As estimates are drawn from a dynamic database they are subject to change as data is updated by DHBs.

Source: NHC analysis

The New Zealand TAVI study is limited by its retrospective nature. The risk threshold was not explicitly defined. A single cardiologist retrospectively assessed patient notes to determine the EuroSCORE II of TAVI patients introducing potential bias in the scoring of patients.

TAVI expanded to inoperable patients

Estimated number of patients:

About 350 patients presenting at hospital with severe symptomatic AS patients in 2012/13 were inoperable. TAVI may be feasible in about 29% of these patients.

349*28.7%= 100; + 66 (base-case) =166; +21 (high-risk) =121

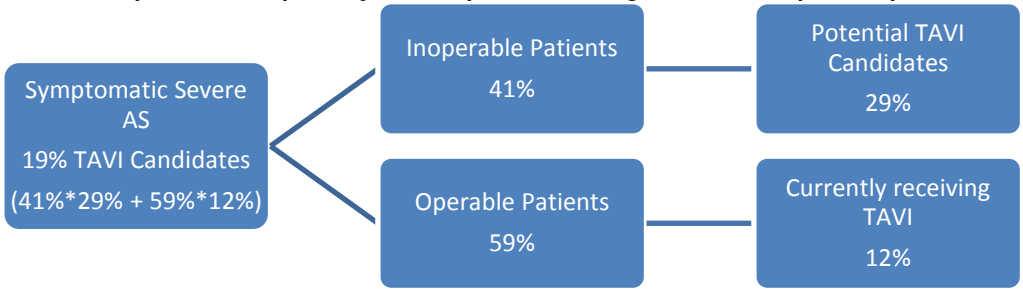
The inoperable + base case scenario represents a pure expansion on the status quo level of intervention. The inoperable + high risk scenario represents an expansion and shift towards higher risk patients, where moderate risk patients currently receiving TAVI would instead receive surgical AVR. The NHC has been told that there may have been some expansion into the inoperable pool in New Zealand; we are unable to quantify any such indication creep, but do not have cause to assume it material for our analysis.

The inoperable + base case scenario projects 166 cases in 2015/16, increasing to 210 cases in 2019/20. That is roughly two and a-half times the status quo intervention volume – with the addition of 100 inoperable cases in 2015/16, increasing to an additional 127 cases in the 2019/20. The inoperable + high-risk scenario projects 131 cases increasing to 154 over the same time period.

7.1.2 Rationale

One randomised controlled trial has shown TAVI is superior to medical management in inoperable patients out to five years.[108] In addition to current volume, the scenario assumes 29% of inoperable patients are candidates for TAVI – again derived from the aforementioned meta analysis of United States and European data.[77] Under this scenario, 19% of symptomatic aortic stenosis patients are eligible for TAVI, ie 29% of inoperable patients and the 12% of operable patients currently receiving TAVI (Figure 5). Of note, the meta analyses mean estimate of inoperable patient population, aligns almost exactly with New Zealand data at 40.5%. Confidence intervals 95%, as illustrated in Table 12, were derived from this study.

Figure 5: Estimated pool of TAVI publicly funded patients for high-risk and inoperable patients



Source: NHC analysis

TAVI expanded to technically inoperable patients only

Estimated number of patients:

Of the inoperable patients in which TAVI may be feasible, about 23% are technically inoperable.

100*23%= 23; + 66 (base case) =89; + 21 (high-risk)=43

This scenario assumes that TAVI is expanded to patients who are inoperable for technical reasons only, rather than to patients who are inoperable due to comorbidities. This scenario projects 96 cases in 2015/16, increasing to 113 cases in 2019/20. Compared with the base case, there are less than an additional 30 cases per annum.

The technically inoperable + base case scenario is a pure expansion, whilst the technically inoperable + high risk scenario requires reprioritisation towards higher risk patients. Of note, the latter scenario is still one-third less than current volumes.

The additional cases are a subset of the inoperable patients identified in the previous section. Trials suggest that 23% of inoperable patients receiving TAVI are inoperable for technical reasons, rather than clinical reasons.

7.1.3 Rationale

A secondary analysis of the PARTNER B trial for inoperable patients and the Non-randomised Continued Access Registry found two-year mortality was 23.3% and 43.8% for the technically inoperable and clinically inoperable patient groups, respectively (p <0.001).[119] (See section 6.1.12)

This scenario assumes 23% of inoperable patients are eligible for TAVI in addition to the patients eligible for TAVI under the base case scenario. We do not know precisely how many inoperable patients in New Zealand are technically inoperable as opposed to clinically inoperable, but expect that it is a small fraction of the total pool of inoperable patients. Table 15 reports on prevalence of these anatomical and technical features in international registries. 'Hostile chest' (also included in Table 15**)**, has been defined as a combination of chest radiation or chest-wall deformities.[155] Rates may not be independent, and hence should not be assumed to be additive.

All studies report relatively low proportions of patients with anatomical issues (Table 15). In ANZ-SOURCE 17% and 3% of high risk TAVI patients had porcelain aorta, for transapical and transfemoral TAVI, respectively. In the few studies reporting on inoperable patients, hostile chest was reported in about 20% of TAVI patients in the United States TVT registry. In the same study porcelain aorta was reported in 10% and 20% of inoperable transfemoral and non-transfemoral patients, respectively. In the COREVALVE extreme risk study 5.5% of patients had chest-wall deformation, with a similar proportion having a porcelain aorta. 11.9% were reported to have a hostile mediastinum. The multicentre Canadian registry, for very high or prohibitive surgical risk patients, has reported a similar incidence of porcelain aorta to PARTNER B. By contrast, the rates of anatomical issues are relatively low in the FRANCE 2 registry. Whilst not all patients may be strictly inoperable in the registry, mean preoperative risk was very high (STS 15%) consequent to the French National Authority for Health (HAS) recommending that TAVI be limited to patients with a contraindication to surgical AVR.[7]

In the absence of better evidence, we estimated the 95% confidence interval for the proportion of technically inoperable patients as 23% ± 11.5% (ie 11.5%-34.5%).

Table 15: Rates of porcelain aorta, chest radiation and chest-wall deformity and hostile chest observed in TAVI international registries

Study	Risk	Valve	N	Access	Chest-wall deformation	Chest radiation	Hostile chest	Porcelain aorta
ADVANCE (16)	High risk	CV	996	TAVI				4.1%
COREVALVE Extreme Risk (111)	Inoperable	CV	506	TAVI	5.5%		11.9%	4.9%
FRANCE 2 (64)	High risk or Inoperable	Mix	184	TAVI-Subclavian	3.4%	1.7%		11.9%
			567	TAVI-TA	1.1%	5.2%		1.8%
			2361	TAVI-TF	2.7%	6.2%		5.5%
Multicentre Italian registry (115)	High risk	CV	663	TAVI				10.9%
Multicentre Canadian registry (114)	High risk or Inoperable	ES	168	TAVI-TF				17.3%
			177	TAVI-TA				18.6%
			345	TAVI				17.9%
PARTNER B (98)	Inoperable	ES	179	MM-TF	5.0%	8.4%		11.2%
			179	TAVI-TF	8.4%	8.9%		19.0%
SOURCE (63)	High risk	ES	463	TAVI-TF				4.5%
			575	TAVI-TA				11.3%
			1038	TAVI				8.3%
SOURCE-ANZ (118)	High risk	ES	62	TAVI-TA				17.5%
			67	TAVI-TF				3.0%
TCVT – EU (66)	High risk	Mix	4571	TAVI	2.9%			22.4%
TVT – US – 30 day results (18)	Overall	Mix	7710	TAVI			10.0%	8.0%
	High risk	Mix	2318	TAVI-Non TF			7.0%	9.0%
			3833	TAVI-TF			7.0%	5.0%
	Inoperable	Mix	420	TAVI-Non TF			19.0%	20.0%
			1139	TAVI-TF			19.0%	10.0%
TVT - US -1 year results (19)	High risk	Mix	12182	TAVI			8.2%	6.8%

TF: transfemoral, TA: transapical , CV: CoreValve; ES: Edwards Sapien

Expansion into lower risk patient groups

The expansion of TAVI has not been explicitly modelled into lower risk groups because there is currently insufficient evidence to suggest TAVI is a feasible option for the 80% of patients who have low preoperative risk. Indeed, the only randomised controlled trial in low-risk patients was discontinued due to safety concerns.[(109)] Trial evidence is beginning to materialise for TAVI in moderate-risk patients, arguably the CoreValve high risk trial is the first RCT to report results on moderate and high-risk patients. At least three randomised controlled trials are underway to measure the effectiveness of TAVI in moderate-risk patients. These include:

- The PARTNER II RCT (Clinical Trial ID: NCT01314313), n= 6650, Edwards Lifesciences, Sapien XT valve vs surgical AVR, primary completion date July 2020.
- The SURTAVI RCT(Clinical Trial ID: NCT01586910), n=2500, Medtronic, CoreValve vs surgical AVR, primary completion date August 2016.
- The REPRISE III RCT (Clinical Trial ID: NCT02202434), n=1032, Boston Scientific, Lotus valve vs surgical AVR, primary completion date January 2021.[4]

The approximate size of the moderate-risk patient population in New Zealand (with reference to Table 13 based on 2012/13 data) is 77 patients. This assumes about 15% of operable patients are classed as moderate risk.[(48)] Not all of these patients would be suitable for TAVI. Assuming 80% (or 61 patients) were suitable, we estimate the maximum operable patient population for TAVI (moderate and high-risk patients only) is about 82 patients per annum (61 moderate-risk, 21 high-risk). That assumes surgical AVR is almost exclusively provided to low-risk patients.

7.1.4 Limitations

The preceding analysis is dependent on the precision of the estimated operable and inoperable populations for severe symptomatic AS. In the absence of echocardiographic records, we estimated the annual incidence of severe AS counting patient presentations with a (new) primary hospital diagnosis of AS. Likewise, patients with aortic valve replacement were limited to patients with a primary diagnosis of AS (except for TAVI and sutureless AVR patients where we were reliant on DHB records and assumed all patients to have severe symptomatic AS). Our methods are described in more depth in *National Health Committee Aortic Stenosis Overview Tier Two (2015).* The overview also presents a sensitivity analysis around the estimation of the high-risk and inoperable patient populations.

Arguably, the primary diagnosis AS filter on aortic valve replacement is too conservative. It might reasonably be contended that all patients with any diagnosis of AS undergoing AVR most likely have severe symptomatic AS, and hence should be counted. The effect for operable patients is relatively immaterial, as about 90% of all patients undergoing aortic valve replacement with a diagnosis of AS, have a primary diagnosis of AS. For the high-risk population, that translates through to an estimated 24 high-risk patients eligible for TAVI (30* 80%) in 2012/13 (rather than 21 patients), still significantly less than the 66 patients who underwent TAVI in that year. Again, the Tier 2 AS overview presents further detail on alternative scenarios for estimating the high-risk and inoperable patient populations.

Increasing the count of aortic valve replacements (to include any diagnosis of AS) would marginally reduce the count of inoperable patients eligible for TAVI, assuming no change in the estimate of severe symptomatic AS. The change in the estimate for the inoperable population is still within the 95% confidence interval of the original estimate (Table 12).

[4] As listed on the US National Institute of Health trial registry – ClinicalTrials.gov

If TAVI were expanded into the inoperable population, there may be a greater demand in the one or two years than is illustrated by a projected demand based on AS incidence. Given the short life expectancy of symptomatic severe AS patients, prevalent cases are unlikely to weight on overall demand in the medium-term.

Cost of TAVI, surgical AVR and medical management

Key points

- If preoperative risk is not accounted for, the index admission cost of TAVI is about $9,000 more than surgical AVR using a bioprosthetic valve.
- Accounting for preoperative risk, TAVI appears significantly less costly than surgical AVR in high-risk patients ($18,000) with comparable cost in moderate-risk patients. Combined, these populations account for about 20% of AVR patients.
- In low-risk patients, representing 80% of all AVR, TAVI is significantly cost-increasing ($18,000).
- Follow-up costs do not appear to significantly vary between surgical AVR and TAVI.
- Medical management is relatively inexpensive, due to the low cost of pharmaceuticals in New Zealand, and the short life expectancy of patients.

In this section we estimate the costs of TAVI, surgical AVR and medical management for patients who have similar characteristics. The relative cost of the interventions informs the budgetary impact and cost-utility analysis in the next sections.

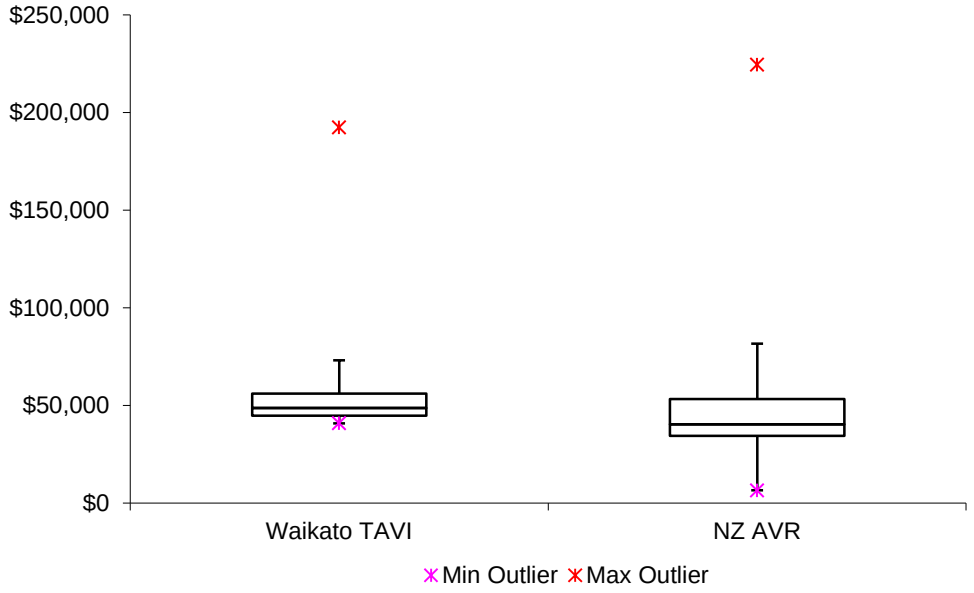
Comparison of all patients treated with TAVI or surgical AVR

The average cost of TAVI is estimated to be $55,000, with an average length of hospital stay of seven days. This estimate is based on the cost of 35 TAVIs performed at Waikato hospital in the year ending June 2013, this includes moderate to high-risk patients. In the same year, the average cost of a surgical AVR nationally using a bioprosthetic valve was $46,000 (n=331), with an average length of hospital stay of 12 days. This includes low to high-risk patients.

We include only Waikato TAVI data, as the data for Auckland and Canterbury DHBs showed implausible variation in the cost of the valve. In 2012/13 the average cost per surgical bioprosthetic AVR in Waikato was $44,500; where the cost per index admission ranged nationally from an average of $45,000 per patient in Wellington Hospital, to $52,000 per patient in Christchurch Hospital. We compare TAVI with bioprosthetic AVR, rather than AVR using mechanical valves, as TAVI also employs a bioprosthetic valve. The average cost of a mechanical valve was $41,000 in the same year. Since comparatively few mechanical valve implants are undertaken (just 100 for AS in 2012/13), the mean cost of all AVR, $45,000, is similar to that of bioprosthetic AVR.

Both TAVI and surgical AVR cost estimates are skewed upwards by high cost outliers; the median cost of TAVI was $49,000 in Waikato DHB, while the median cost of surgical bioprosthetic AVR was $40,000 nationally. The distribution of costs is summarised in Table 16 below. These estimates are based on data sourced from the National Costing Collection and Pricing Programme. The costs are for the entire index hospital admission, and in some instances include the costs of other procedures.

Table 16: Cost of TAVI and bioprosthetic AVR 2012/13



	Minimum	25th Percentile	Median	Mean	75th Percentile	Interquartile range	Maximum
Waikato TAVI	$41,000	$45,000	$49,000	$55,000	$56,000	$11,000	$192,000
NZ bioprosthetic AVR	**$7,000**	**$34,000**	**$40,000**	**$46,000**	**$53,000**	**$19,000**	**$225,000**

Source: NHC analysis of NCCP

Both mean and median estimates in Table 16 suggest TAVI is about $9,000 more costly than surgical AVR. The largest driver of the cost of TAVI is the valve cost (and associated consumables), costing about $34,000. By contrast a surgical bioprosthetic valve costs about $5,000, where the cost of surgical AVR is driven primarily by the cost of theatre and inpatient stay.[5] A full breakdown of the cost of TAVI and surgical AVR is contained in Appendix 4 alongside cost data provided in analysis provided by Auckland DHB. Note that the breakdown of costs is for TAVI patients of high and moderate-risk, whereas most of the surgical AVR patients will be of low-risk.

The TAVI cost estimate is limited by a relatively small sample size. NCCP data shows, however, that the average cost of TAVI has been reasonably consistent at Waikato DHB with an average cost of $58,500 (n=16) in 2010/11, and $57,000 (n=26) in 2011/12. Costs in earlier years show implausible variation which we understand may be due to external charitable funding of the valves not accounted for in the national records.

As a further check on costs, we asked Auckland DHB to undertake an assessment of the cost of TAVI and Surgical AVR using a bioprosthetic valve. The DHB reported a mean cost of $56,000 for TAVI and $42,000 for isolated bioprosthetic AVR (excluding cases with concomitant coronary bypass surgery or other valve procedures).

[5] TAVI valves are likely to be less expensive in the future due to competition from new valves and competitive procurement consequent to PHARMAC's initiation (from 1st December 2014) of a nationalised procurement process for TAVI valves.

Comparison of isolated AVR and TAVI

Key points

- There is a positive correlation between preoperative surgical risk, hospital length of stay, and the cost of surgical AVR.
- The index admission cost of isolated TAVI is about $55,000, based on Waikato DHB cost data.
- High-risk surgical isolated AVR (comprising about 5% of volume) has an index admission cost of about $73,000 – equivalent to the average cost of the most costly 15% of isolated surgical AVR cases.
- Moderate-risk isolated surgical AVR (comprising about 15% of volume) has an index admission cost of about $54,000 – equivalent to the average cost of the top third of isolated surgical AVR by cost.

Patients undergoing AVR with other cardiac procedures are known to be at higher risk of mortality than patients undergoing isolated AVR.[156, 157] All 35 records of TAVI where without concurrent angioplasty or other valve procedures, which would otherwise increases cost. The average cost of isolated bioprosthetic surgical AVR, excluding cases with concomitant coronary bypass surgery or other valve procedures, was $41,200 (n=176), with an average length of hospital stay of 11.5 days. On this basis isolated admission (ie no other major cardiac procedures), AVR appears $14,000 less costly than isolated TAVI ($55k). However, this does not account for preoperative surgical risk. TAVI has been targeted at patients at elevated risk of surgical mortality in New Zealand and internationally.[21, 27, 158] Preoperative surgical risk is positively correlated with patient length of stay and cost in AVR patients.[49, 82] A positive correlation between preoperative risk, length of stay and cost has also been evidenced in coronary artery bypass graft surgery and mitral valve surgery.[159, 160]

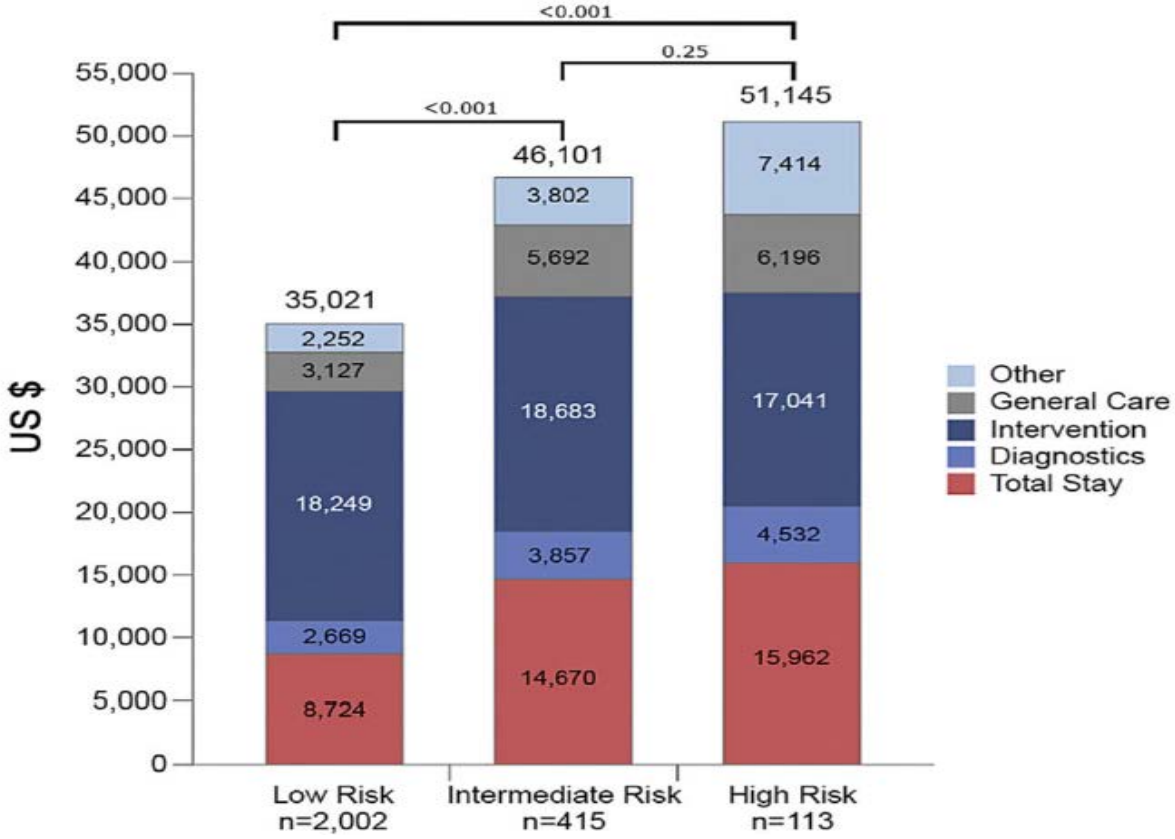
In 2012/13, the national average age of a patient receiving an isolated bioprosthetic (surgical) valve was 74, compared with an average age of 80 for TAVI patients (in Waikato DHB and nationally). National data collections, however, do not record preoperative surgical risk so we cannot directly control for it. Nevertheless, international evidence, discussed below, enables the estimation of comparative costs accounting for preoperative surgical risk.

Comparison of costs in patients with similar preoperative surgical risk

A study of all first-time isolated surgical AVR performed in Virginia State between 2003 and 2012 (n=2,530), found higher preoperative risk (STS-PROM) was significantly associated with higher postoperative mortality, complications, length of stay, and costs.[49] Compared with low-risk patients, the cost of AVR at 30 days in high and moderate-risk patients was 46% and 32% greater respectively ($p<0.001$). Just under half of the additional cost was attributable to increased length of stay (Figure 6).

Clinical data was matched with cost data from a state-wide multi-institutional database comprised of all cardiac surgical procedures in the Commonwealth of Virginia. The study classified 4.5% of AVR patients as high risk with a mean STS-PROM of 12.6 ± 4.3 and an average cost of $68,400 (US$ 51,145± $32K). 16.4% of patients were moderate risk with a mean STS PROM of 5.4 ± 1.1 and an average cost of $62,000 (US$ 46,101± $42K). And 79.1% of patients were low risk with a mean STS-PROM of 1.8± 0.9 and an average cost of $47,000 (US$ 35, 0210 ± 22K). Overall, the average cost of AVR patients was $50,200 (US$ 37,559± $28K), with a mean STS-PROM of 2.9± 2.8.

Figure 6: Cost of isolated AVR predicted by risk: Virginia state-wide registry



Source: [49] Reproduced in [161]

A study of 142,000 first-time isolated surgical AVR performed in the United States between 2002 and 2010, found higher preoperative risk (STS-PROM) was significantly associated with higher postoperative mortality, complications, and length of stay.[48] The study classified 6% of AVR patients as high risk with a mean STS-PROM of 13.8, operative mortality of 12.9%, an average length of stay of 13.3 days, of which 6.9 were spent in intensive care. 14% of patients were moderate risk with a mean STS PROM of 5.48, operative mortality of 5.8%, an average length of stay of 10.4 days, of which 4.6 days were spent in intensive care. 80% of patients were low risk with[84] an average length of stay of seven days, of which 2.5 days were spent in intensive care. Overall, the average length of stay was 7.9 days, with 3.1 days in intensive care, mean STS-PROM of 2.95 and operative mortality of 3%. As would be expected with such a large sample, differences between groups were highly significant ($p < 0.0001$).

Table 17 extrapolates the two studies findings to estimate the index admission cost of surgical AVR in low, moderate, and high-risk patients in New Zealand. We also estimate the cost of AVR in a population of high and moderate-risk patients. The risk multipliers used to derive the cost estimates compare the average cost of AVR with the cost of AVR in each of the four risk categories. The cost stratification is indicative only, and has significant limitations, which are discussed below. Nevertheless, the analysis suggests TAVI is likely to be cost-increasing, compared with surgical AVR, for low-risk operable patients. The incremental cost of TAVI in low-risk patients is $18,000 (-$12,500, -$23,500), where the 95% confidence interval is estimated to be ±15% reflecting significant uncertainty in our estimate. Nearly 80% of patients are low-risk. The index admission cost is similar in moderate-risk patients for TAVI and surgical AVR, with a small incremental saving of $1,000 (-$7,000, $9,000) indicated for TAVI. High-risk patients have an incremental saving of $18,000 (-$7,000, -$29,000) per

patient, but this represents just five to six percent of AVR patients. Lastly, the mixed moderate and high-risk patient group, perhaps most indicative of the TAVI population in New Zealand, shows an incremental cost-saving of $4,000 per patient.

Table 17: Estimated cost of isolated surgical AVR accounting for preoperative risk 2012/13

	TAVI	Bioprosthetic AVR	Preoperative surgical risk			
			Low	**Moderate**	**Moderate and high**	**High**
STS-PROM			1.7	5.5	8.0	13.7
Total cost	$55,000	$41,000				
Risk multiplier			0.89	1.30	1.44	1.78
Cost estimate for AVR			$37,000 ($31,500, $42,500)	$54,000 ($46,000, $62,000)	$59,000 ($50,000, $68,000)	$73,000 ($62,000, $84,000)
Incremental cost of TAVI			$18,000 ($12,500, $23,500)	$1,000 (-$7,000, $9,000)	-$4,000 (-$13,000, $5,000)	-$18,000 (-$7,000, -$29,000)
Length of stay (days)	7	11	7	10	11	13
Age	80	74	68	77	77	77
Proportion of operable patients			80%	14%	20%	6.2%
Operable patient pool			409	72	102	32

Source: NHC analysis of NCCP, and based on cost schedule seven cost fields. The estimated cost of the TAVI and surgical AVR bioprosthetic valves is based on DHB feedback to NHC. Estimates for TAVI are limited to Waikato DHB, while surgical AVR estimates are national.

US utilisation differentials between risk stratified groups were applied to New Zealand cost data to derive the estimates in Table 17. Nearly half the cost differential between groups was driven by hospital length of stay, as suggested by the Virginia State study. The larger US study (n=142,000) recorded length of stay by general ward and intensive care for the risk stratified groups.

To illustrate with an example, the average cost of isolated bioprosthetic AVR is $41,000. For high-risk patients we added to this $14,000 which is the average cost of an additional 3.8 days in intensive care at $3,500 per day and 1.6 days on the general ward at $650 per day.[162] The difference in additional length of stay for high-risk patients, compared with the population mean was derived from the aforementioned US national study of 140,000 surgical AVR patients. So accounting for additional inpatient stay, we estimate that high-risk AVR patients cost about $55,000. However, additional inpatient stay is not the only added resource that comes with being a high-risk patient. The Virginia State study showed that just over half the short-term additional cost attributable to patient risk comes from increased use of diagnostics and other interventions such as respiratory therapy, rehabilitation, and dialysis. Compared with all patients these other costs accounted for 56% of the additional cost

accumulated for high-risk patients. To account for this additional cost we multiplied the cost attributable to increased length of stay by 2.3 [1 / (1-.0.56)]. Accordingly the full estimated cost differential between the average isolated bioprosthetic surgical AVR patient ($41,000) and isolated high risk bioprosthetic surgical AVR is $32,000 ($14,000 * 2.3); with a total estimated cost of $73,000 ($41,000 + $32,000).

7.1.5 Limitations

Our comparative cost estimates are retrospective and drawn from non-randomised data. As such, patient characteristics may vary significantly between TAVI and surgical AVR patients. We have based our estimates on New Zealand cost data, but have assumed a resource utilisation differential between risk stratified groups that is equivalent to that observed in the US data. The elasticity of cost to preoperative risk may be significantly different in New Zealand compared with the United States. Resource utilisation between high and lower risk groups is likely to depend on institutional settings, clinician behaviour, patient characteristics, and patient pathways, all of which may vary considerably between the US and New Zealand.

Average patient length of stay appears to be less in the United States than New Zealand, at about eight days and 11 days respectively. Limited information is available on patient characteristics in national datasets. The two patient populations appear comparable with regards to age. The average age of patients in both US studies was 67 compared with an average age of 70 for all isolated surgical AVR patients in New Zealand, and 74 for isolated bioprosthetic AVR patients. The average age of high-risk patients was 79.5 and 77 in the Virginia State study and the broader US study, respectively. The average age of TAVI patients in New Zealand is about 80.

Little has been published on the risk stratification of AVR patients in New Zealand. A small Waikato study found 68% of 39 consecutive AVR patients were low risk with a logistic EuroSCORE <10%; while 17% had a score between 10%-20%, and 15% had a score >20%.[47] As discussed previously, however, EuroSCORE tends to overestimate risk. Extensive international evidence suggests that the proportion of surgical AVR patients at high risk of operative mortality is in the range of five to six percent.[48, 77] Although it cannot be ruled out entirely that New Zealand is a special case, it seems unlikely. The unique ethnic makeup of New Zealand may be less important for aortic stenosis than it is for other health conditions, where Māori have relative low incidence of AS (Section 8.1.2). A recent study found a preoperative risk score for surgical AVR based in part on New Zealand population data, underperformed the STS score, based on US population data. [4]

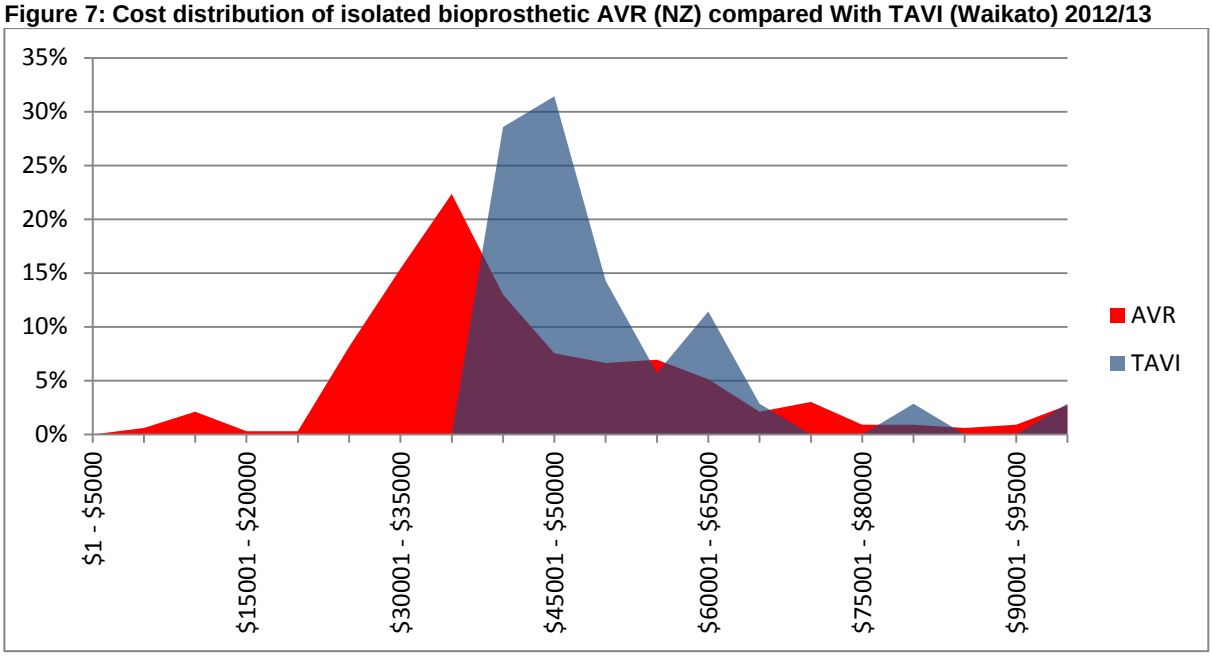
Waikato DHB data, as with national data, suggests a mix of high and moderate-risk patients. The aforementioned retrospective study of New Zealand TAVI procedures reported a mean EuroSCORE II of 10.8 with a standard deviation of 8.2 for 127 cases undertaken at Waikato DHB between 2011 and 2014.[27] Just as moderate risk surgical AVR patients appear to be lower cost than high-risk patients, moderate-risk TAVI patients may be lower cost than high-risk patients.[163, 164] Thus the incremental saving of TAVI in high-risk patients may be less than is implied in Table 17. Likewise, the incremental cost of TAVI in low-risk patients may also be overstated if low-risk TAVI patients have lower cost than is illustrated by the data we have from Waikato DHB. The relative mix of valves used in the United States compared with New Zealand might have some impact on the cost estimate. However, costs do not differ significantly enough between mechanical and bioprosthetic AVR valves to have a material impact. Bioprosthetic valves dominate in both settings, comprising a little less than 80% of procedures in the US data.

Our cost estimates for surgical AVR and TAVI are comparable with a recent analysis of Auckland DHB data. The study retrospectively risk stratified TAVI and surgical AVR procedures undertaken within Auckland DHB up to 2014, comparing 40 TAVI (ESII 9.8 ± 5.4) cases with 72 surgical AVR

cases (ESII: 7.3 ±3.4). Average costs was $53,000 ± 16,000 and $70,000 ± $43,000, for TAVI and surgical AVR, respectively.[27] It is unclear, however, if the study was restricted to isolated cases of AVR, where isolated AVR is less costly than AVR with concomitant cardiac surgery. A similar result was reported in an Australian cost analysis of TAVI compared with surgical AVR in high-risk patients, though limited information was reported on patient characteristics and comparability of groups.[165]

Patients with high preoperative risk tend to be resource-intensive. But not all patients with high preoperative risk are high cost, as is evident in the Virginia State study where the standard deviation for high-risk patients was $US32,000, or 62% of the mean cost of high-risk patients. Thus we would not expect the five or six percent of patients with the highest preoperative risk scores to exclusively occupy the top five or six percent of the AVR cost distribution. Some high-risk patients will turn out to be relatively low cost, whilst some low-risk patients may turn out to be relatively high cost. Figure 7 shows the cost distribution of 176 isolated bioprosthetic AVR undertaken nationally compared with 35 TAVI in Waikato in 2012/13. Here, the mean cost of TAVI is $55,000 compared with a mean cost of $41,000 for bioprosthetic AVR. As is evident, there is greater spread in the cost of surgical AVR with a large proportion of cases less than $40,000, about the minimum cost of TAVI in our records. There are a very few outlier bioprosthetic AVR records at less than $15,000, these may represent aborted procedures or false records. As there are relatively few, we did not investigate further.

Figure 7: Cost distribution of isolated bioprosthetic AVR (NZ) compared With TAVI (Waikato) 2012/13



Source: NHC analysis of NCCP data

Our estimated cost for high-risk surgical AVR patients in 2012/13 is $73,000 (Table 17). That is equivalent to the mean cost of the top 15% of patients in the cost distribution. Our estimate for the moderate and high-risk AVR population, $59,000, is equivalent to the top third of AVR patients by cost.

Follow-up costs of TAVI, medical management and surgical AVR

Key points

- Follow-up costs add about $14,000-$15,000 in the first two years to the cost of TAVI and $13,000-$14,000 to the cost of surgical AVR, comprising hospital readmission costs, GP costs, pharmaceutical costs, need for new pacemaker insertion, repeat intervention, and blood tests. The cost of medical management appears relatively low, at about $18,000 over two years.
- As mortality, quality of life, and functional status appear similar for surgery and TAVI, follow-up costs are broadly similar.

Table 18 presents expected two-year costs for TAVI, surgical AVR and medical management including follow-up costs. Costs are modelled on estimated resource use, using New Zealand costs and probabilities where available. Each cost and probability is justified below. We assume a relatively wide confidence interval of ±25% for follow-up costs reflecting a high degree of uncertainty, and ±15% for index admission cost.

Table 18 is based on a cost analysis undertaken by DLA Piper for the Australian health system. Two-year costs of TAVI were compared to the cost of medical management based on the two-year results of the PARTNER B trial and estimated Australian health system costs.[143] DLA Piper made the simplifying assumption that costs were applied according to two-year survival rates. This underestimates costs as survival rates in the first year are higher than the second. Whilst still a simplification, we took the midpoint of two-year survival and 30 day survival to approximate follow-up costs. We also added the cost of repeat admissions for a second procedure and the cost of receiving a pacemaker as described below. Costs are undiscounted, and the two-year time horizon is limiting in scenarios where patients are expected to live for significantly more years.

Two-year costs are similar across risk stratified classes of TAVI patients, costing about $68,000 to $70,000 on average per patient. Two-year cost is similar for the moderate to high-risk surgical patients $72,500 ($60,500-$85,000) compared with TAVI. Cost appears greater for high-risk surgical patients compared with TAVI $86,000 ($72,000, $100,000) but confidence intervals overlap reflecting significant uncertainty in the relative cost of the two modalities over the two-year time frame. Medical management is clearly less costly than all other options, $18,200 ($14,000, $23,000), but patient outcomes are also very poor.

Table 18: Two-year costs for TAVI, surgical AVR and medical management

	TAVI				Surgery		Medical management
	Moderate and high risk	High risk	Inoperable	Technically inoperable	Moderate and high risk	High risk	Inoperable
Index admission cost	$55,000 (47,000,$63,000)				$59,000 ($50,000, $68,000)	$73,000 ($62,000, $84,000)	NA
Two-year survival	78% (CoreVALVE high risk)[102]	66% (PARTNER A) [166]	57% (PARTNER B) [18]	77% (Secondary analysis PARTNER B and Canadian Registry)[119]	71% (Core Valve High Risk)	65% (PARTNER A)	32% (PARTNER B)
Midpoint survival	87%	81%	76%	86%	83%	79%	65%
Follow-up costs							
Repeat intervention	$1,100	$1,100	$1,100	$1,100	$590	$730	
New pacemaker	$500	$500	$500	$500	$200	$200	$200
Readmission	$5,300	$5,000	$4,600	$5,200	$5,100	$4,800	$12,100
Pharmaceuticals	$130	$120	$110	$130	$130	$120	$100
Bloods	$360	$330	$310	$350	$340	$320	$260
Cardiology outpatients	$5,800	$5,400	$5,100	$5,800	$5,600	$5,300	$4,300
Echocardiograph	$990	$920	$860	$980	$950	$900	$730
GP	$660	$620	$580	$650	$630	$600	$490
Total follow-up	$14,800 ($11,200, $18,600)	$14,000 ($10,500, $17,500)	$13,200 ($10,000, $16,500)	$14,700 ($11,000, $18,400)	$13,500 ($10,200,$17,000)	$13,000 ($9,800, $16,300)	$18,200 ($14,000, $23,000)
Total cost	$69,800 ($58,000, $82,000)	$69,000 ($57,000, $81,000)	$68,200 ($57,000, $80,000)	$69,700 ($58,000, $82,000)	$72,500 ($60,500, $85,000)	$86,000 ($72,000, $100,000)	$18,200 ($14,000, $23,000)

The Australian analysis did not extend to the other categories of patients (high-risk or technically inoperable). Although we used New Zealand cost data and slightly amended the analysis, as described, overall costs for medically managed and inoperable TAVI patients were similar in our analysis to the Australian analysis (Table 19). The Australian analysis did not extend to the other categories of patients (high-risk or technically inoperable).

Table 19: Comparison of NHC and DLA-Piper estimates of two-year costs for TAVI and medical management

	DLA Piper Australian estimate				NHC New Zealand estimate	
	AUD$	AUD$	NZD$	NZD$	NZD$	NZD$
	TAVI	MM	TAVI	MM	TAVI	MM
Index admission cost	$49,485		$54,434		$55,000	
GP	$944	$530	$1,038	$583		
Bloods	$244	$137	$268	$151		
Pharmaceuticals	$1,231	$691	$1,354	$760		
Cardiology outpatients	$3,052	$1,966	$3,357	$2,163		
Echocardiograph	$526	$295	$579	$325		
Readmission	$4,534	$9,392	$4,988	$10,331		
Total follow-up cost	$10,531	$13,011	$11,584	$14,312	$13,200	$18,200
Total cost	$60,016	$13,011	$66,018	$14,312	$68,200	$18,200
Exchange rate (NZD:AUD)			1.1	1.1		

Source: NHC analysis

7.1.6 Cost of repeat intervention

Key points

- Trial and registry data shows repeat valve intervention is very infrequent for TAVI and surgical AVR.
- Long-term data is lacking for TAVI, but bioprosthetic valves tend not to fail before 10 to 15 years of use.

The index admission cost of TAVI was outlined in the previous section. There is no specific interventional cost associated with medical management. In some hospitals, balloon aortic valvuloplasty may be used to relieve symptoms of heart failure, although the practice is understood to be uncommon in New Zealand. For TAVI, we multiplied costs by 2% to reflect the probability of repeat intervention. The probability assumes a small increment to observed 12-month reintervention rates in the high-risk CoreValve trial and the PARTNER B trial for inoperable patients to account for reintervention in out-years. We have assumed a 1% reintervention for surgical AVR, though 12-month

results of the high risk CoreValve study show no reintervention, longer-term studies show low (non-zero) rates of reintervention. As discussed below, reintervention rates appear to be very low for both surgical AVR and TAVI, suggesting repeat intervention is not a significant driver of cost or incremental cost.

In the PARTNER trial for inoperable patients, the rate of repeat TAVI was 1.7% at 30 days and 12 months.[98] In the CoreValve extreme risk study, the rate of reintervention (including any surgical or percutaneous intervention that repaired, adjusted, or replaced the implanted valve), was 1.1% at 30 days and 1.8% at 12 months.[111] In the CoreValve high risk study, the rate of re-intervention was 0.8% at 30 days and 1.9% at one year, with no intervention required for surgical AVR.[100] In the United States-based Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapies (TVT) Registry (n=12,182) the rate of reintervention for TAVI was 1.4% at 12 months.[19] Similarly, in the German Aortic Valve Registry (n=16,680) 1-year reintervention was 0.7% for transvascular TAVI and 0.3% for the transapical approach.[21] A second intervention was required in 1.5% of conventional surgical patients, including patients undergoing subsequent CABG. In a single centre study of 70 consecutive patients undergoing TAVI between January 2005 and December 2006 (with an average length of follow-up of 3.7 years) . One patient required reoperation.[167]

For surgical AVR, using a bioprosthetic valve, freedom from reoperation at five years is typically > 95%.[168, 169] Bioprosthestic valves tend to fail 10 to 15 years after implantation because of factors such as leaflet calcification or tearing, which leads to either stenosis or regurgitation.[168, 170, 171] This is likely to be an issue for both surgical AVR and TAVI. For the high-risk and elderly patient pool, the majority of whom would not be expected to live longer than five years, the cost of reintervention is relatively small.

7.1.7 Readmission cost

Key points

- Readmission rates are high for elderly patients who receive aortic valve replacement.
- New Zealand data shows (attributable) readmission rates (for valve related problems or cardiac causes) of 37% in the first year following TAVI. Rates average about 16% in out-years.
- The average cost of readmission was about $12,800 per admitted patient in the first year, declining to about $7,000 per admitted patient in out-years. Hence we assume a cost per patient of about $4,700 ($3,500-$5,900) in the first year, declining to $1,100 ($840-$1,400) in out-years (±25% for the confidence interval).
- International trials suggest similar readmission rates for TAVI and surgical AVR for patients of comparable risk. We assume, therefore, that the cost of readmission for surgical AVR and TAVI are equivalent.
- Technically inoperable patients appear to have a similar readmission rate to high-risk patients; hence we also assume an equivalent readmission cost for technically inoperable TAVI patients as for high-risk TAVI patients.
- The broader inoperable TAVI group (predominantly clinically inoperable patients) appear to experience higher rates of readmission compared with high-risk TAVI patients. Comparing PARTNER A and B arms, we assume a 50% greater rate of readmission for inoperable TAVI, resulting in an average readmission cost of $7,100 ($5,300 - $8,900) declining to $1,700 ($1,300 - $2,100) in out-years.

- A flat readmission rate of 50% is assumed for medically managed patients, based on New Zealand and international trial data for medically managed heart failure and aortic stenosis patients.
- The cost of a readmission for medically managed patients is estimated as the cost of catastrophic heart failure at about $9,400, implying an annual readmission cost of $4,700 ($3,500-$5,900).

We tracked the hospitalisation costs of all patients who received TAVI between 2008 and 2014 using the National Minimum Dataset. Primary cause readmissions data for these patients was assessed with a view to capturing all complications possibly related to aortic stenosis or the procedure. Table 20 reports our findings. 37% of patients were readmitted to hospital within the first year of receiving TAVI, spending on average 16 days in hospital at an average cost of $12,800 per admitted patient per annum. Readmission rates declined to less than 20% in years two to five, with an average length of stay a week or less per annum.

Table 20: Probability and cost of readmission for TAVI patients in New Zealand

Year	1	2	3	4	5
Number of patients followed (dead or alive)	204	137	78	44	31
Number of readmitted patients	75	23	15	4	6
Probability of readmission	37%	17%	19%	9%	19%
Average length of stay per patient per annum (days)	16	6	7	4	7
Average cost per admitted patient per annum	$12,800	$8,500	$7,700	$5,500	$6,400
Average cost per patient per annum	$4,700	$1,400	$1,500	$500	$1,200

Source: NHC analysis of NMDS records

The probabilities and costs presented in Table 20 were used in the simple cost analysis presented in Table 18 (above) where readmission costs were applied to two-year survival rates. For the purposes of cost-utility analysis, discussed below, we slightly modified the readmission input parameters. In the cost-utility analysis, the Markov model automatically applies costs to surviving patients, so the input required is the cost and probability of readmissions for surviving patients.

Table 21: Probability and cost of readmission of surviving TAVI patients in New Zealand

Year	1	2	3	4	5
Number alive (start of period)	227	184	116	61	31
Number of admitted patients (end of period)	75	23	15	4	6
Probability of hospitalisation	33%	13%	13%	7%	19%
Average length of stay per patient per annum	16	6	7	4	7
Average cost per admitted patient per annum	$12,800	$8,500	$7,700	$5,500	$6,400
Average cost per patient per annum	$4,200	$1,100	$1,000	$400	$1,200

Source: NHC analysis of NMDS records

Table 20 attempts to catch readmissions attributable to TAVI or aortic stenosis post the procedure. Cost was estimated using an average caseweight of 1.65 and a cost weight price of $4,600 (2012/13 cost weight price). We excluded readmissions where the primary diagnosis was non-attributable. We took a deliberately broad view in assigning attribution to ensure we did not miss significant costs. Across all years post TAVI the major causes of readmission were heart failure, myocardial infarction, sepsis, stroke, and other cardiac conditions (Table 22).

Table 22: Cause of readmission post TAVI

Condition	Count	Percentage of readmissions
Heart failure	57	37%
MI	25	16%
Sepsis	23	15%
Stroke	17	11%
Other cardiac	17	11%
Arrhythmia	8	5%
Valvular (aortic valve)	8	5%
Total	155	100%

Note: the count of readmissions is greater than in Table 20 due to this table include admissions beyond five years of follow up. Source: NHC analysis

The analysis was retrospective and patient notes were not reviewed (or centrally available) to better estimate readmission costs. Our readmission estimate is higher than that indicated in the literature (below) possibly because we erred on the side of including admissions that were potentially casually related to AS or the TAVI procedure.

7.1.7.1 International evidence on readmission rates and cost

Readmission rates are primarily reported in the literature as a secondary clinical endpoint not as a measure of cost. Record of readmissions is usually limited to cardiac causes or valve related issues. Cumulative length of stay is often not reported at all. The trial evidence indicates that TAVI may reduce hospital readmissions compared with medical management, and TAVI appears to have a similar readmission rate compared with surgical AVR. Readmission rates from the PARTNER trial and several large registry studies are present in Table 23.

Readmission rates for surgical candidates appear broadly consistent across studies, with less than one in five patients being readmitted for cardiac reasons in the first year following TAVI or surgical AVR. This increases to a cumulative rate of one in four patients at two years and one in three patients at five years. Readmission rates may be higher in inoperable patients. In PARTNER B, about one in four TAVI patients were readmitted in the first year, increasing to about one in two patients by year five. By comparison, over half of all conservatively managed patients were readmitted for cardiac causes in the first year, with nearly all surviving patients having been admitted by the fifth year.

Table 23: Hospital readmission rates for TAVI, surgical AVR, and medical management

Study	Valve	Intervention	N	STS	Logistic EuroSCORE	Cause of readmission	30 days (%)	1 year (%)	2 years (%)	3 years (%)	5 years (%)
GARY	2,061 ES	AVR	6523		8.8	Complications from the procedure, or cardiovascular problems		17.8			
	1,614 CV	AVR+CABG	3464		11			18.8			
		TAVI -TV	2695		25.9			19.8			
		TAVI-TA	1181		24.5			25.2			
PARTNER A	ES	TAVI	348	11.8	29.3	Valve-related or AS	4.4	18.6	24.7		42.3
		TAVI-TA	104				3.9	18.6	29		
		TAVI-TF	244				4.6	18.5	23		
		AVR	351	11.7	29.2		3.7	17.7	21.7		34.2
		AVR-TA	103				5.1	16.1	23.9		
		AVR-TF	248				3.1	18.3	20.9		
PARTNER B	ES	MM-TF	179	12.1	30.4	Valve-related or AS	10.1	53.9	72.5	75.7	87.3
		TAVI-TF	179	11.2	26.4		5.6	27	35	43.1	47.6
PARTNER B / NRCA	ES	TAVI -TI	85	5.4	14.5	Valve-related or AS		~13	20.3		
		TAVI -CLI	284	12	26.9			~20	29		
PRAGMATIC	453 CV	CV	204	8.9	23	Valve-related symptoms or Congestive Heart Failure		18.8			
	340 ES	ES	204	8.1	21.4			13.2			
TVT - US	Mix not specified	TAVI	12,182	7.1		Any	17.4	53.2			
						Stroke/heart failure or repeat aortic valve intervention	6.7	18.6			

ES = Edward Sapien valve; CV = CoreValve; TA= transaortic; TF= transfemoral; TI = technically inoperable; CLI = clinically Inoperable; CABG = Coronary artery bypass graft surgery; TV= transfemoral, direct aortic, and Transsubclavian access

Source:[19, 21, 98, 99, 107, 108, 117, 119, 141, 166]

In the PARTNER high risk trial, the cumulative (Kaplan-Meier) probability of repeat hospital admission for the TAVI arm was 18.6% at one year, which increased to 42.3% at five years.[141] Repeat hospitalisation was similar for surgical AVR with a hazard ratio of 1.22 at five years (95% CI, 0.92, 1.63, p=0.17). Repeat hospitalisations in the PARTNER trial were included if they were due to aortic stenosis or complications of the valve procedure. In the PARTNER trial of non-surgical candidates, the probability of repeat hospital admission in the TAVI arm was 27% at one year, which increased to 47.6% at five years.[108] Repeat hospitalisation was significantly higher in the medical management arm, increasing from 53.9% at one year to 87.3% at five years. In the secondary analysis of the PARTNER B trial and the Non-randomised Continued Access Registry, readmission rates for inoperable patients, and technically inoperable patients in particular, appear similar to high-risk patients.[119]

High rates of repeat hospitalisation have also been reported in observational studies. In the German Aortic Valve Registry (GARY). Readmission due to cardiovascular problems or complications from the procedure at 12 months was 25.2% and 19.8% for transaortic and transvascular TAVI, respectively (n=1,181, and 2,695).[21] Readmission for surgical AVR was 18.8% and 17.8% for surgical AVR with coronary artery bypass graft (CABG) and surgical AVR without CABG, respectively (n=3464, and 6523). Any-cause readmission at 12 months was 45.5% for TAVI-transapical, 40.2% for TAVI-transvascular, 29.6% for surgical AVR, and 34.4% for surgical AVR + CABG. TAVI patients had a higher mean preoperative risk compared with surgical AVR patients (70% of AVR patients had EuroScore <10 vs 16% for TAVI), hence rates cannot be directly compared.

The US Transcatheter Valve Therapies Registry reported any-cause readmission for TAVI of 53.2% at 1 year (n= 12 182).[19] Of these patients, just under half had two or more admissions. Heart failure was the leading cause for rehospitalisation with 14.3% (95% CI 13.6, 15.0) of all TAVI patients being readmitted for heart failure within a year of their procedure. Readmission for a composite of stroke, heart failure, or repeat aortic valve intervention was 18.6%, accounting for less than half of readmissions.

The PRAGMATIC registry, a collaboration of four European institutions, compares outcomes after TAVI between the CoreValve and Edwards Sapien/ Sapien XT valves. The propensity matched study reported a 12-month readmission rate for congestive heart failure or valve related symptoms of 18.5% and 13.2 % for the CoreValve and Edwards Sapien delivery systems respectively (p=0.2).[117]

7.1.7.2 Length of stay for readmitted patients

Readmission rates give some indication of a patient's health status and quality of life post-intervention, but without length of stay data they are of limited valve for cost-utility analysis. Few studies have addressed health resource utilisation after TAVI. Table 24 presents data indicating that most readmissions post TAVI are for non-cardiac causes. Two studies report a cumulative length of stay for readmitted patients of 15 days for any-cause readmission, at six months in one study and 12 months in the other.

Table 24: Readmission and length of stay post TAVI and surgical AVR

Study	Hammerer et al (2011)		Altisent et al (2012)		Stortecky et al (2014)		Perera et al (2011)	
Country	Austria		Spain		Switzerland		Waikato NZ	
Intervention	TAVI		TAVI	MM	TAVI		AVR	MM
Valve	CV		NA	NA	NA		NA	NA
N	50		86		579		39	42
Mean follow-up	9.9 months		499 days		12 months			
STS	6.2							
Logistic EuroSCORE			16.8				10	26
Cause of readmission	Any	Cardiac	Cardiac	Cardiac	Any	Cardiac	Cardiac	Cardiac
Readmission rate at 6 months	53.90%	10.30%						
Readmission rate at 12 months			0.3	4.2	26.10%	10.80%		
Annual mean LOS (days) (relates to all patients)	13.2	3.1	14.4* days (annual)	8.2* days (annual)	5.2	2.2	0.06	0.1
Annual ICU LOS (days)			1	3				
Cumulative mean LOS for readmitted patients	15.4 days (6 months)				15.6 days (annual)			

Source: [47, 172-174] * In-hospital length of stay per patient year / number of admissions per patient year

An Austrian single centre prospective study of 50 moderate to high-risk TAVI (CoreValve) patients (STS 6.2± 3.8) reported any-cause readmission at six months at 53.9% (21/39), where 10.3% of surviving patients experienced readmissions for cardiac causes.[174] From six months to a mean follow-up of 9.9 months, the rate of readmission fell by half, from 1.54 hospital days per month per patient to 0.74 days. The change was driven by a reduction in non-cardiac admissions. For comparative purposes we annualised the study's length of stay data in Table 24.

A prospective Spanish (single centre) study of 86 non-surgical TAVI patients followed patients for an average of 499 days comparing resource use before and after TAVI.[173] 83 patients survived the operation. After TAVI there were significant reductions in cardiac admissions (4.2 per patient-year vs.

0.3; p<0.001), in hospital length of stay (2.87 per patient-month vs. 0.36; p<0.001); intensive care unit length of stay (0.25 per patient-month vs. 0.08; p=0.004), and in the number of outpatient clinical visits (0.433 per patient-year vs. 0.29; p<0.001). There was no significant difference in emergency room visits (1.03 per patient-year vs. 0.33; p=0.179). While average length of stay for admitted patients was lower prior to TAVI than with TAVI (8.2 days vs 14.4), there was 14 times as many readmissions prior to intervention than post TAVI (4.2 annual cardiac admissions vs 0.3). The net effect is likely to be lower readmission cost.

A prospective Swiss registry of 549 consecutive TAVI patients found one in four patients were readmitted to hospital for any cause within the first year after TAVI, and one in ten patients were readmitted for cardiac causes. There were 529 patients (96.4%) who survived the procedure; 138 patients were readmitted within one year of discharge, accumulating 176 readmissions with a cumulative mean hospital length of stay of 15.6±16 days.[172] Among readmitted patients, 73 patients (41.5%) were re-evaluated for cardiovascular causes (heart failure 17%, peripheral vascular disease 15%, 2% for valvular heart disease), 22 (13%) for gastrointestinal, 12 (7%) for respiratory and eight patients (5%) for chronic kidney disease. Twenty-two patients (13%) received non-cardiac surgery and eight patients (5%) were found to have a malignant tumour.

Readmission rates may vary among different health care systems depending on reimbursement policies, availability of specialist outpatient care, quality of primary health care and many other factors.[174] Readmission rates might be lower in New Zealand than suggested by international data. A Waikato study of patients with symptomatic severe aortic stenosis showed patients who did not undergo AVR (n=41) had significantly more recurrent hospitalisations related to cardiovascular causes compared to patients who underwent surgical valve replacement (n=39).[47] The data from 2005 to 2009 did not include TAVI but showed very low hospitalisation rates for surgical AVR patients and medically managed patients – just 10.1 days per 100 patient years for medically managed patients (0.1 days per year) versus 6.4 days/100 patient years for surgical AVR 0.064 days per year). Such low readmission rates, if true, suggest readmission costs could be immaterial in New Zealand. We think it is more likely that the study is at error.

Readmission rates may be higher in high-risk patients compared with low-risk patients. A United States retrospective study tracked the resource use of 252 high-risk surgical AVR patients, mean logistic EuroSCORE 17.5%, compared with 1,223 non-high-risk patients, mean logistic EuroSCORE 7.4%, for five years from 2003 to 2008 using Medicare records.[82] Over five years, non-high-risk patients experienced an average of 3.9 inpatient hospitalisations per patient, including the index hospitalisation, versus 4.7 hospitalisation for high-risk patients, p=0.003. Cumulative length of stay, including index admission, was 46.6 days and 29 days for high-risk and non-high-risk groups, respectively, p<0.0001.

7.1.7.3 Cost of readmission for TAVI and surgical AVR patients

The proceeding discussion suggests:

- Rates of readmissions appear similar for TAVI and surgical AVR in patients of similar preoperative risk.
- Rates of readmissions may be greater for inoperable compared with high-risk patients (PARTNER B vs PARTNER A). At two years, the rate of readmission for inoperable TAVI patients was just over 50% greater than in the high-risk arm (35% vs 23%). But this does not appear to be the case for technically inoperable patients (PARTNER B/NRCA study).

- Most readmissions post-TAVI are for non-cardiac causes, typically much less than half. While any-cause readmission may capture the full readmission cost, the cost attributable to the valve intervention is better caught by limiting readmission costs to cardiac or procedure related causes.

Uncertainty remains around the appropriate readmission cost, for the purpose of our economic model we assume:

- A probability of readmission for TAVI patients of 37% in the first year with an associated cost of $12,800 (Table 26). In out-years we assume a 16% probability of readmission with an associated cost of $7,000 per admitted patient per annum, representing the average of cost and readmission rate in years two to five. These probabilities are at the higher end of readmission rates seen in the literature (Table 23 and Table 24), but they fit with the evidence that readmission rates are highest in the first year post-procedure.
- Equivalent cost of readmission for TAVI and surgical AVR.
- Equivalent cost of readmission for moderate, high-risk and technically inoperable TAVI patients.
- 50% higher cost of readmission for TAVI in the broader (mostly clinically) inoperable population.
- A relatively wide range of ± 25% to account for uncertainty in the cost assumption.

This implies:

- A cost of readmission in the first year following TAVI of about $4,700 ($12,800 *37%) with a range of $3,500 to $5,900 declining to $1,100 in out-years ($7,000 * 16%) with a range of $840 to $1,400. Where these cost apply to moderate and high-risk TAVI and surgical AVR patients and technically inoperable TAVI patients.
- In the broader inoperable patient population a cost of readmission in the first year following TAVI of about $7,100 with a range of $5,300 to $8,900 declining to $1,700 in out-years with a range $1,300 to $2,100.

7.1.7.4 Cost of readmission for medically managed patients

We have relatively little information on readmission rates for medically managed patients. In the PARTNER B trial, the Kaplan-Meier readmissions rate for standard therapy was 54% at 12 months, increasing to 87% at five years.[108] In a before and after study of intermediate-risk TAVI patients in Spain, hospital admissions for cardiac causes declined from 4.2 per annum before TAVI to 0.3 per annum after TAVI, with annual length of stay declining from 34 days to 4.3 days per annum.[173] High rates of readmission have also been observed in single arm studies. A five-year US retrospective study of 2,150 medically managed patients with severe AS found patients had a high rate of readmission with 1.9 admissions per patient year with an average length of stay of 11.5 days per patient-year.[175]

The PARTNER B probability of readmission for medically managed patients was applied in an Australian cost analysis of TAVI for inoperable patients.[143] As indicated in the PARTNER B study, the analysis applied a probability of readmission of 72.5% and 35%, for medical management and TAVI, at two years respectively. The cost of heart failure as reflected by the diagnostic related group (DRG - F62A) cost for 'heart failure with shock and catastrophic complications' was applied to these probabilities. DRG F62A has an average cost of $9,400 in New Zealand with an average length of stay of nine days (from the National Costing Collection and Pricing Programme for 2013/14). In TAVI

patients, heart failure was the largest single cause of readmission in the US TVT registry (n= 12,182) accounting for 77% of its composite readmission measure (including stroke, heart failure, or aortic valve intervention) at 12 months.[19] It was also the largest single cause of readmission, accounted for 41% of cardiac readmissions, in the aforementioned prospective Swiss TAVI registry (n=549) at 12 months.[172]

The Auckland Heart Failure Management Study (n=197) reported an annual readmission rate for heart failure of 51% (101 readmissions) with an average length of stay per admission of nine days (919 hospital days). Surgical candidates were excluded from the analysis.[176] A similar readmission rate was observed in a recent large US study. In a retrospective study of 47,000 Medicare patients with heart failure aged 65 years or older who had been discharged for heart failure between 2005 and 2011, annual cardiovascular readmission rates ranged from 41% in white Americans, to 49 % in African Americans.[177] Readmission rates for heart failure may be health system-specific. A French retrospective study of the national health insurance information system study of 70,000 patients with heart failure in 2009, found nearly half 46.3%, were readmitted for cardiovascular disease, including 24.5% for heart failure, within two years of a first hospitalisation for heart failure.[178] A single centre Japanese study of 282 patients discharged with acute heart failure, reported readmission rates of 17.5% at one year, 21.4% at two years, and 25.5% at three years.[179]

In our analysis, we assume a flat cardiac readmission rate of 50% per year for medically managed patients. This roughly corresponds to the rate of readmission observed in the Auckland Heart Failure Management Study, and is broadly consistent with the readmission rate observed in the PARTNER B study at one year. We make the simplifying assumption that the cost of readmission is given by DRG F62A for heart failure at $9,400 with an average length of stay of nine days. This implies:

- The cost of readmission for medically managed patients is about $4,700 in all years with a range of $3,500 to $5,900.
- The cost of readmissions for medically managed patients is less than TAVI for inoperable patients in the first year following TAVI ($4,700 vs $7,100), accounting for potential procedural complications, but greater in out-years ($4,700 vs $1,700), accounting for reduced readmissions for TAVI patients consequent to the treatment of AS.

7.1.8 Cost of a pacemaker

Key points

- The rate of new pacemaker insertion for TAVI depends on the valve used. The CoreValve has a higher rate of insertion than the Edwards Sapien valve.
- The current mix of valve use in New Zealand is not very dissimilar to the UK, where the rate of pacemaker insertion is about 16%. Thus we assume an insertion rate of 16%.
- For medical management and surgical AVR, we assume a uniform insertion rate of 7%, where interventions rates at 12 months range from 5% in PARTNER A to 11.3% in CoreValve high risk, with a rate of 7.7% in GARY for isolated AVR.
- New pacemaker insertion typically occurs soon after TAVI. Hence we assume a one-off up-front cost.
- The cost of a pacemaker is about $3,200.

Pacemaker insertion consequent to surgical AVR is relatively infrequent, and rates of pacemaker insertion are similar for the Edwards Sapien TAVI valve and surgical AVR.[99, 141, 166] An (unpublished) meta analysis of 93 non-overlapping studies including 37,836 patients found the CoreValve was associated with a more frequent need for pacemaker implantation than the Edwards valve, with insertion rates of 6.5% (95% CI 5.7%-7.4%) and 22.5% (95% CI 19.4%-25.9%) for the Edwards valve and CoreValve respectively, p<0.01.[180] This differential between the valves is plainly seen in the major trials and registries in Table 26 below.

Our base case assumption is that the insertion rate for new pacemakers post-TAVI is equivalent to that illustrated in the UK through the UK TAVI registry. That is, a rate of 16.3% in the first year, not changing in subsequent years. We assume the rate is the same for all TAVI patients regardless of risk. The CoreValve may have been used a little more frequently in the UK than in New Zealand historically. Table 25 presents data provided to the NHC on valve use from a recent study of TAVI in New Zealand.[27]

Table 25: Valve type in use in New Zealand 2008:2014

Valve	Count	Percentage of use
Edwards valve	109	47%
CoreValve	79	34.5%
Unknown	42	18%
Total	229	100%

Source: NHC analysis

For medical management and surgical AVR, we assume a uniform insertion rate of 7%, where interventions rates at 12 months range from 5% in PARTNER A to 11.3% in CoreValve, with a rate of 7.7% in GARY for isolated AVR. Across studies in Table 26, the majority of new pacemaker insertion occurs in the first 30 days or year post-intervention. Accordingly, we make the simplifying assumption when modelling cost that the cost of pacemaker insertion is incurred upfront, where additional cost in out-years is only incurred if patients have a repeat procedure.

Table 26: New pacemaker insertion rates following TAVI, surgical AVR and medical management

Study	Access	n	Device	In-hospital	30 days	1 Year	2 years	3 years	5 years
ADVANCE [16]	TAVI	996	CV		26.3%	29.2%			
ANZ CoreValve [17]	TAVI	540	CV		28.4%	29.1%	29.4%		
SOURCE [63]	TAVI	1038	ES		7.0%	8.5%			
	TAVI-TF	463	ES		6.7%				
	TAVI-TA	575	ES		7.3%				
SOURCE ANZ [118]	TAVI-TF	67	ES		1.49%	4.55%			
	TAVI-TA	62	ES		8.06%	8.33%			
UK TAVI [67]	TAVI	870	Mix		16.3%	16.3%		16.3%	16.3%
	TAVI	410	ES		24.4%				
	TAVI	452	CV		7.4%				
Italian registry [115]	TAVI	663	CV		16.6%	19.1%			
GARY [20, 21]	TAVI –TV	2695	Mix	24.2%		26.2%			
	TAVI-TA	1181	Mix	11.0%		14.1%			
	AVR	6523	Mix	5.1%		7.7%			
	AVR+CABG	3464	Mix	4.5%		7.3%			
FRANCE 2 [64]	TAVI	3,195	Mix		15.6%				
	TAVI	2107	ES		11.5%				
	TAVI	1043	CV		24.2%				
	TAVI-TF	2361	Mix		15.2%				
	TAVI-TA	567	Mix		13.6%				
	TAVI-TS	184	Mix		25.5%				
Spanish National registry [65]	TAVI	1,416	Mix	10.0%					
	TAVI	610	CV	17.0%					
	TAVI-TF	504	ES	5.0%					
	TAVI-TA	302	ES	4.0%					
TCVT – EU [66]	TAVI	4,571	Mix	13.2%					
	TAVI	2604	ES	6.0%					
	TAVI	1943	CV	23.4%					
	TAVI-TF	3390	Mix	15.5%					
	TAVI-TA	749	Mix	4.5%					
	TAVI-Other	432	Mix	3.6%					
TVT – US[18]	TAVI	7,710	Mix		6.6%				
	TAVI-TF	3,833	Mix		5.8%				
	TAVI-Non TF	2,318	Mix		7.8%				
	TAVI-TF (Inoperable arm)	1,139	Mix		6.9%				
	TAVI-TF (Inoperable arm)	420	Mix		6.4%				
PRAGMATIC [117]	TAVI-TF	453	CV		22.5%				
	TAVI-TF	340	ES		5.9%				
PARTNER A[99, 141, 166]	TAVI	348	ES		3.80%	6.40%	7.20%		9.70%
	AVR	351	ES		3.6%	5.0%	6.4%		9.1%
	TAVI-TF	244	ES		3.7%	6.0%	7.2%		
	AVR-TF	248	ES		3.4%	3.8%	5.8%		
	TAVI-TA	104	ES		3.9%	7.1%	7.1%		
	AVR-TA	103	ES		4.1%	7.7%	7.7%		
PARTNER B[98, 107]	TAVI-TF	179	ES		3.4%	4.7%	6.4%		
	MM-TF	179	ES		5.0%	8.6%	8.6%		
COREVALVE [100]	TAVI	390	CV		19.80%	22.30%			
	AVR	357	CV		7.10%	11.30%			
COREVALVE Extreme Risk [111]	TAVI	506	CV		21.6%	26.2%			
Multicentre Canadian registry [114]	TAVI	345	ES		4.9%				
	TAVI-TF	168	ES		9.5%				
	TAVI-TA	177	ES		6.2%				

CV: CoreValve; ES: Edwards SAPIEN; Mix: ES & CV; TF: transfemoral, TA: transapical, TS: trans-subclavian, TV: Transvascular (transfemoral, direct aortic and trans-subclavian access)

Pacemakers may be inserted during the same admission as a valve replacement or in a separate admission. In our cost data there were no pacemakers inserted during the same TAVI or surgical AVR admission. The cost of a pacemaker was derived from NCCP data using ICD-10 procedure code 382-8100, Insertion of cardiac pacemaker generator, where the average cost of the implant is $3,200. The Average cost of the event, including hospital stay and associated interventions, is $10,300. Our base case models only the implant cost to avoid double counting the cost of re-admission. As most pacemakers are inserted shortly after aortic valve replacement, we make the simplifying assumption that the cost is born upfront, and do not make the probability of pacemaker insertion time dependent.

7.1.9 Cost of pharmaceuticals

The cost of pharmaceuticals is applied annually. No medical therapy is able to improve outcomes other than temporary relief of symptoms.[88] US and European guidance for valvular disease note that coronary artery disease and hypertension are common in patients with AS and should be treated according to standard guidelines.[36, 88] Statins and beta blockers are recommended for patients with hypertension and concurrent coronary artery disease. Digoxin, Diuretics, Angiotensin-Converting-Enzyme (ACE) Inhibitors, or Angiotensin ii Receptor Blockers (ARBs) are recommended to relieve the symptoms of heart failure.

The cost of medical therapy was derived from PHARMAC's pharmaceutical schedule for the following medications:

- Cilazapril 5mg 1 daily (ACE inhibitor)
- Frusemide 40mg 2 daily (diuretic)
- Simvastatin 40mg 1 daily (statin)
- Bisoprolol 10mg 1 daily (beta blocker)
- Digoxin 125mcg 1 daily (antiarrhythmic).

The net annual cost to government of the above five pharmaceuticals is about $75 per patient. While medical therapy will vary from patient to patient, these pharmaceuticals are so inexpensive that greater precision is highly unlikely to have a material impact on overall cost. Indeed accounting for patient co-payments of $5 per script, most of the above pharmaceuticals have no (or next to no) net-cost to government. We make the simplifying assumption that pharmaceutical cost remains constant across patient groups.

7.1.10 Cost of bloods

The cost of bloods is applied annually. The cost of bloods was based on published costs data from Canterbury Health Laboratories, and Labtests Auckland for a monthly full blood count, creatine count, and electrolyte blood test. Like pharmaceuticals, the cost of monthly routine blood tests is inexpensive, at $204 per annum, and immaterial to the total cost of treatment; we have assumed that the cost is uniform across patient groups.

7.1.11 Cost of cardiology outpatients

The cost of cardiology outpatient visits is applied annually. In our base case it is assumed that patients have monthly visits to cardiology outpatients costing $279 each (Purchase unit M10003). We assume the rate is constant across patient groups, where total attributable cost depends on survival. This is based on a 2013 Australian cost analysis of TAVI in inoperable patients, which was informed by clinical advice.[143] A recent Spanish economic evaluation suggests a lower rate of use in Spain, with about two annual visits to a cardiologist in operable patients and a similar rate for surgical AVR patients.[181]

7.1.12 Cost echocardiograph

The cost of echocardiograph is applied annually. In our base case it is assumed that patients have six-monthly echocardiograms costing $284 (Purchase unit code: CS04001) again based on an Australian cost analysis of TAVI in inoperable patients.[143] We have assumed the cost of echocardiograph is uniform across patient groups in the base case.

7.1.13 Cost of general practice

The cost of general practice is based on a monthly visit to a GP for all patients. We assume a uniform cost across patient groups in the base case. The Pharmac Cost Resource Manual reports an average consult fee of $65 including patient co-payment (2009 dollars).[162] The University of Otago Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE^3) costing protocol reports a mean cost of $57 per GP visit for those 65 years or older, including a mean patient co-payment of $25.45 (2011 dollars).[182] The average cost to government including of a GP visit overhead is $31.58, which is used in our model. We assume monthly visits to the GP are sustained for all patients. [143] Limited data is held centrally on primary care, the Auckland Heart Failure Management Study found heart failure patients had a median 14 GP visits per annum.[183]

Limitations and discussion

In the absence of prospective New Zealand specific data, we have estimated follow-up costs for TAVI, surgical AVR, and medical management from multiple international and local sources. As a retrospective analyses the risk of bias is high, including exclusion of significant attributable cost data, selection bias in the populations used to measure costs, and measurement error.

The proceeding analysis of follow-up costs used as its starting point work by DLA-Piper. We expanded this analysis to consider TAVI compared with surgical AVR and include the cost of repeat intervention and new pacemaker insertion. As noted, total two-year follow-up costs are similar between the DLA-Piper analysis and our analysis for medically managed patients and inoperable TAVI patients. Whilst reasonably comprehensive, the DLA-Piper analysis did exclude a number of costs including:

- **Pre-operative costs** – some preoperative costs, including preadmission anaesthetist and nurse consultation are already built into the index admission cost for TAVI and surgical AVR. Other preadmission costs, specifically diagnostic costs, will not be accounted for within the index-admission cost for surgical AVR or TAVI.
- **Cost of rehabilitation** – regarding in-hospital rehabilitation – the index admission cost for TAVI and surgical AVR include transfer to other hospitals and facilities. The cost of outpatient rehabilitation (an up to 12-week group-based programme focused on education and exercise) is about $250 per patient (Purchase unit code: M10004).
- **Cost of aged care** (discussed p.106).
- **Cost of palliative care** (discussed p.110).

7.1.14 Preoperative costs

We contacted representatives at Auckland, Waikato, and Canterbury DHBs to get an approximation of preoperative costs. Overall it appears that preoperative costs are similar between TAVI and surgical AVR, at about $4000 per patient, although TAVI may make greater use of computed tomography (CT) for patient screening than for surgical AVR (Table 27). There appears to be some variation in

preoperative practice across centres. Auckland and Canterbury DHB reported that the use of balloon valvuloplasty (as a bridge to surgery or TAVI or as a preoperative test) was very infrequent. The technology appears to be used more frequently in Waikato DHB, though still fairly infrequently. The DHB reported a rate of less than 10% for TAVI, and suggested that the rate may be similar for surgery. We were unable to get confirmation of its relative use or cost at Waikato DHB, though it was suggested to us that valvuloplasty was undertaken as a day case at a cost of about $3,000. Hence its overall cost is likely to be very small nationally. We have not included balloon valvuloplasty as a preoperative cost.

We also received conflicting evidence on the relative use of CT, where Waikato DHB suggested an equivalent use in TAVI and surgical AVR patients. We received contrary clinical advice that CT may be used almost universally for TAVI but infrequently for surgical AVR. The cost of CT was reported to be $450 in Auckland DHB and Canterbury DHB reported a similar cost. Some concern has been expressed in Auckland DHB that the cost may be too low. As a check, we reviewed private sector radiology costs where chest CT scans are priced between $500 and $900.[6] Thus, although we do not know the precise frequency of use or cost of CT, its overall cost impact is likely to be relatively small.

Echocardiography is the primary diagnostic test for AS and is thus assumed to be undertaken for all patients. We also assume that all patients will be assessed for concurrent ischaemic heart disease using coronary angiography. We assume all patients will have at least one outpatient appointment with a cardiologist, two if undergoing TAVI, and an outpatient appointment with a cardiothoracic surgeon if undergoing surgery.

[6] The cost of CT scans were taken from Auckland XRAY services: (http://www.aucklandxray.co.nz/Home+Links/Price+List.html) Pacific Radiology: (http://pacificradiology.co.nz/services/prices/) Broadway Radiology: (http://broadwayradiology.co.nz/service-fees.html) and Christchurch Radiology group: (http://www.christchurchradiology.co.nz/fees/)

Table 27: Preadmission costs for TAVI and surgical AVR

Intervention	Cost	Reference	TAVI (moderate/ high risk)		Surgical AVR (moderate/ high risk)	
			Frequency	Average cost	Frequency	Average cost
CT	$450	Estimate provided by Auckland DHB	1	$450	0.5	$225
Echo	$284	Purchase unit code CS04001	1	$284	1	$284
Coronary Angiogram	$2,634	Estimate provided by Auckland DHB	1	$2,634	1	$2,634
Cardiology 1st attendance	$449	Purchase unit code M10002	1	$449	1	$449
Cardiology 2nd attendance	$289	Purchase unit code M10003	1	$289	0	$0
Cardiothoracic 1st attendance	$445	Purchase unit code S15002	0	$0	1	$445
Total cost				**$4,106**		**$4,037**

Source: NHC analysis

7.1.15 The costs of complications

As discussed in the clinical safety and effectiveness section, TAVI, surgical AVR and medical management are associated with specific complications. Compared with surgical AVR in high-risk patients, TAVI is associated with higher rates of aortic regurgitation and major vascular complications. TAVI is also associated with higher rates of pacemaker implantation with the CoreValve but not the Edwards Sapien valve. TAVI is associated with lower rates of major bleeding events compared with surgical AVR, and it is associated with higher rates of aortic regurgitation, vascular complications, stroke, and major bleeding events compared with medical management.

We have not reported the excess costs associated with specific complications other than pacemaker insertion (for electrical conduction abnormalities) and repeat intervention (for failed procedure/ prosthesis). Rather adverse outcomes have been indirectly modelled through readmissions rates, and index admission costs (for short-term complications). An indirect approach was undertaken as a pragmatic response to a lack of specific data on the translation of specific complications to health system costs over the mid to long-term. Mid-term data was available and used for pacemaker insertion rates, repeat intervention and readmission rates. Modelling health system costs associated with aortic regurgitation, stroke, major bleeding events, and major vascular complications would require further extrapolation, and we expect that it is broadly captured in the index admission, readmission, and other follow-up costs specified above.

7.1.15.1 Adverse events and their short-run costs

Costs of adverse events associated with TAVI have been studied in the short-run, but we are unaware of any long-run trial data costing adverse events. In the PARTNER trial (A and B arms), seven complications were independently associated with increased index admission costs including death, major stroke, major bleeding, renal failure, arrhythmia, repeat TAVI, and conversion to surgical AVR. Complications accounted for about 25% of non-implant related costs or, 16% of the total index admission cost (including the cost of the valve). The largest attributable costs were major bleeding (5% of average cost), arrhythmia (3.5% of average cost), and death (2.6% of average cost).[(184)]

Whilst associated with increased cost:

- Renal dialysis and new onset arrhythmia were not greater for TAVI compared with surgical AVR or medical management in PARTNER.
- All-cause mortality was similar (non-inferior) in TAVI compared with surgical AVR and superior compared with medical management in PARTNER.
- Rates of repeat TAVI, and conversion to surgical AVR, were low at 0.6% and 1.5%, respectively in PARTNER.

Such short-term costs should be broadly accounted for within the index admission cost of TAVI.

7.1.15.2 Adverse events and follow-up readmissions

As illustrated in Table 23, above, readmissions consequent to TAVI do not appear to be greater than for surgical AVR. In GARY, 17.8% of surgical AVR patients compared with 19.8% of transvascular TAVI were readmitted for cardiovascular problems or complications 12 months following the procedure. Though TAVI readmission rates are slightly higher these patients also had significantly higher preoperative risk than surgical AVR patients (logistic EuroSCORE 25.9 vs 8.8%, TAVI vs surgical AVR). In PARTNER, readmission rates were similar between TAVI and surgical AVR and significantly lower for TAVI compared with medical management.

Higher specific complication rates for TAVI do not appear to play through to higher readmission rates (compared with surgical AVR or medical management). This may in part be due to complications being addressed in the initial hospital admission, particularly with respect to major vascular complications (Table 6 Table 7). For high-risk patients, higher rates of aortic regurgitation and vascular complications may be partly offset by lower major bleeding events. For inoperable patients, higher rates of stroke, major bleeding events, and major vascular complications may be offset by lower rates of heart failure and death.

While TAVI appears to significantly reduce follow-up costs compared with medical management, the difference in complication rates between TAVI and surgical AVR may not be sufficiently large to detect a difference in follow-up costs. For example, two-year PARTNER data illustrated a non-increasing trend toward higher stroke rates for TAVI compared with surgical AVR. But the cumulative differential in stroke rates, 2.8% at two years (7.7% vs 4.9%, TAVI vs Surgery, p=0.17) was reversed to -0.9% at five years (10.4% vs 11.3%, TAVI vs Surgery, p=0.61). Thus while health system costs will be incurred consequent to stroke for both TAVI and surgical AVR, the difference in cost may be relatively small.

7.1.16 Follow-up costs in other economic analyses

Follow-up costs are not always clearly specified in economic assessments. Follow-up costs including readmission costs appear to be similar or marginally higher in TAVI compared with surgical AVR, and significantly less in TAVI compared with medical management. A recent systematic review of economic analyses reported wide variation in follow-up costs for TAVI, surgical AVR, and medical management. Of 16 assessments mean annual follow-up costs were USD$18,476 ($336-$52,536) for TAVI, USD$ 15,819 ($217-$51,992) for surgical AVR and USD$25,094($1,086-$53,621) for medical management (minimum-maximum values in brackets).[185]

A 2013 cost-utility analysis of TAVI in high-risk patients compared with surgical AVR (funded by the British Heart Foundation) reported almost equivalent 10-year readmission and long-term care costs for TAVI and surgical AVR (about £31,000). Long-term costs were driven by the New York Heart Association (NYHA) classification of heart failure, which was observed to be equivalent between modalities in the PARTNER two-year results and assumed to be equivalent in out-years .[186] Costs included readmissions for adverse events including an additional valve replacement.

The cost-utility analysis of the PARTNER A trial, using patient level cost data, reported similar total follow-up costs for TAVI and surgical AVR at one year. Average per patient readmission costs were USD$18,122 and $15,645 for transfemoral TAVI and surgical AVR, respectively p=0.7. Total one year follow-up costs were USD$24,787 for TF-TAVI and $23,540 for surgical AVR, p=0.88.[147] In the analysis of the inoperable PARTNER B cohort, one year follow-up hospitalisation costs were $USD 18,074±35,320 and $USD 45,093 ± 46,943 for TAVI and medically managed patients, respectively (± standard deviation in brackets).[187]

Budgetary impact

Table 28 presents the expected budgetary impact of the four policy options outlined above, namely, continuation of the current level of TAVI provision, limitation of TAVI to high-risk patients only, expansion of TAVI to inoperable patients or, expansion of TAVI to ‘technically’ inoperable patients only. The analysis assumes the demand projections outlined in Table 13 and the index admission costs outlined in Table 17 and follow up costs outlined in the previous section.

Table 28: Budgetary impact of policy options

		2015/16	2016/17	2017/18	2018/19	2019/20
Base case		71	74	77	80	84
	First year cost of TAVI	$4.4m	$4.6m	$4.8m	$5.0m	$5.2m
	Follow-up cost of TAVI		$0.4m	$0.8m	$1.2m	$1.5m
	Total	$4.4m ($3.5m,$5.3m)	$5.0m ($4.0m,$6.0m)	$5.6m ($4.5m,$6.7m)	$6.1m ($4.9m, $7.4m)	$6.7m ($5.3m,$8.0m)
High-risk only		23 (22,24)	24 (23,25)	25 (23,26)	26 (24,27)	27 (25,28)
	First year cost of TAVI	$1.4m	$1.5m	$1.5m	$1.6m	$1.7m
	Follow-up cost of TAVI		$0.1m	$0.2m	$0.3m	$0.4m
	Total	$1.4m	$1.6m	$1.8m	$1.9m	$2.1m
	Cost of surgical AVR substitution	$3.0m	$3.4m	$3.8m	$4.2m	$4.6m
	Net cost	$4.4m	$5.0m	$5.6m	$6.1m	$6.7m
	Additional cost (relative to base)	$0.0m	$0.0m	$0.0m	$0.0m	$0.0m
TAVI inoperable		108 (86,131)	113 (90,136)	117, (93,142)	122 (97,147)	127 (101,153)
	First year cost of TAVI	$6.7m	$7.0m	$7.2m	$7.5m	$7.8m

	Follow-up cost of TAVI		$0.6m	$1.0m	$1.4m	$1.7m
	Total cost	$6.7m	$7.5m	$8.2m	$8.9m	$9.5m
	Cost of medical management	$0.5m	$1.0m	$1.4m	$1.6m	$1.8m
	Additional cost (relative to base)	$6.2m ($5.0m, $7.5m)	$6.5m ($5.2m,$7.8m)	$6.9m ($5.5m,$8.3m)	$7.2m ($5.8m,$8.8m)	$7.5m ($6.2m,$9.3m)
TAVI technically inoperable		25 (12,37)	26 (13,39)	27 (13,40)	28 (14,42)	29 (15,44)
	First year cost of TAVI	$1.6m	$1.7m	$1.7m	$1.8m	$1.9m
	Follow-up cost of TAVI		$0.2m	$0.3m	$0.4m	$0.6m
	Total cost	$1.6m	$1.8m	$2.0m	$2.2m	$2.4m
	Cost of medical management	$0.1m	$0.2m	$0.3m	$0.4m	$0.4m
	Additional cost (relative to base)	$1.5m ($1.2m,$1.8m)	$1.6m ($1.3m,$1.9m)	$1.7m ($1.4m,$2.1m)	$1.9m ($1.5m,$2.2m)	$2.0m ($1.6m,$2.4m)

Source: NHC analysis

7.1.17 Budget impact of base case

In the base case, the cost of TAVI is expected to increase from $4.4 million ($3.5m, $5.3m) in 2015/16 to $6.7 million ($5.3m, $8.0m) in 2019/20 due purely to demographic growth. Follow-up costs grow over the five-year period as more patients accumulate. Costs are discounted at a rate of 3.5%.

7.1.18 Budget impact of high-risk patients only

Targeting TAVI exclusively to high-risk patients is not expected to generate significant savings. TAVIs currently undertaken in moderate-risk patients would be replaced by surgical AVR, where surgical AVR is expected to be only marginally less costly (Table 17).

7.1.19 Budget impact of inoperable patients

Expanding TAVI to inoperable patients increases cost by $6.2 million ($5.0m, $7.5m) to $7.5 million ($6.2m, $9.3m) annually over five years compared with the status quo. As these patients would have otherwise been medically managed, we subtracted the discounted cost of medical management.

7.1.20 Budget impact of technically inoperable patients

If expansion is limited to technically inoperable patients, the added cost is roughly $1.5 million ($1.2m, $1.8m) - $2.0 million ($1.6m, $2.4m).

7.1.21 Budget impact of low risk patients not estimated

We have not considered expansion of TAVI into low-risk patients as good quality clinical trial evidence does not exist in this population pool. However, for low-risk patients (representing about 80 percent of all patients), TAVI is likely to be significantly cost-increasing relative to surgical AVR, as documented in Table 17.

7.1.22 Budget impact of technically inoperable patients if substituted for moderate-risk patients.

The high-risk only scenario assumes a substitution of TAVI patients to surgical AVR. An alternative scenario is a substitution to technically inoperable patients. Under this scenario, the volume of TAVI patients would not change from the base case scenario. Instead there would just be a reprioritisation of patients away from moderate-risk towards technically inoperable patients. The scenario is relatively less costly than the expansion option as no additional TAVI valves are purchased for technically inoperable patients. There is a small additional cost incurred for bioprosthetic valves for the moderate risk patients receive surgical valve replacement instead of TAVI. Under this scenario, overall costs would be expected to increase from about $1 million ($0.8m, $1.2m) to $1.7million ($1.4m, $2.1m) between 2015 and 2020 (Table 29). Of note, supply is still expected to be in excess of demand from high-risk and inoperable patients. This would remain the case if we took a prevalence view, where prevalence of technically inoperable patients is roughly twice incidence *(see National Health Committee Aortic Stenosis Overview Tier Two (2015)*.

Table 29: Cost of substituting moderate risk TAVI patients for inoperable patients

		2015/16	2016/17	2017/18	2018/19	2019/20
Base case		71	74	77	80	84
High-risk only		23 (22,24)	24 (23,25)	25 (23,26)	26 (24,27)	27 (25,28)
Excess to high-risk demand		48	50	52	54	57
Technically inoperable demand		25 (12,37)	26 (13,39)	27 (13,40)	28 (14,42)	29 (15,44)
Excess to high-risk and technically inoperable demand		23	24	25	26	28
Cost of TAVI if expanded to TI		$1.5m ($1.2m,$1.8m)	$1.6m ($1.3m,$1.9m)	$1.7m ($1.4m,$2.1m)	$1.9m ($1.5m,$2.2m)	$2.0m ($1.6m,$2.4m)
Cost of valve substitution (substitution vs expansion)						
	Cost of Bioprosthetic valve	$115,000	$120,000	$125,000	$130,000	$140,000
	Saving on TAVI valve	$690,000	$720,000	$750,000	$780,000	$840,000
	Net saving	$575,000	$600,000	$625,000	$650,000	$700,000
Net cost of substitution		$1.0m ($0.8m,$1.2m)	$1.2m ($1.0m,$1.5m)	$1.4m ($1.1m,$1.7m)	$1.6m ($1.3m,$1.9m)	$1.7m ($1.4m, $2.1m)

Source: NHC analysis

Cost-utility analysis

Key points

- TAVI is cost-effective and cost-saving in high-risk patients, but this represents a small population, <30 patients per annum.
- TAVI appears to be equivalently cost-effective to surgical AVR in New Zealand, where it is being performed in a mix of high and moderate-risk patients.
- For technically inoperable patients, TAVI has a cost per QALY of about $40,000.
- In the broader inoperable patient population, the cost per QALY is about $74,000.
- The CUA model was most sensitive to the relative efficacy of TAVI.

A Markov model was developed to estimate the cost-effectiveness of TAVI under the four policy options described above, namely:

1. TAVI vs surgery in a mixed pool of high and moderate-risk patients (status quo).
2. TAVI vs surgery in high-risk surgical patients (contraction to high-risk patients only).
3. TAVI vs medical management in inoperable patients (expansion to inoperable patients).
4. TAVI vs medical management for technically inoperable patients (expansion to technically inoperable patients only).

The model developed uses a lifetime horizon, starting from when patients receive treatment until all patients are assumed to be dead. Though life expectancy with or without aortic valve replacement may be no more than one or two years for some patients, it is important to attribute the cost and benefit of those patients with longer life expectancy to get a fairer measure the technologies value. All patients start in the model in the health state 'severe aortic stenosis'; following treatment, patients are either dead or alive at the end of each annual cycle. In each cycle the follow-up costs and utility value (outlined below) are applied. All costs and benefits are half-cycle corrected. That is, in the year of death only half the annual cost and half the annual utility are computed. This is done to account for the likelihood that deaths occur gradually throughout the year (on average, half-way) rather than strictly at the end of each year.

The model includes two arms – treatment with TAVI, or an alternative treatment, either surgical AVR or medical management. The appropriate costs, utilities, and survival probabilities are applied to each arm. The same Markov model is used to determine the cost effectiveness of TAVI vs medical management in inoperable patients and TAVI vs surgical AVR in operable patients. The difference in the probability of survival, cost, and utility between the two arms generates the incremental cost-effectiveness ratio (ICER) for the respective strategies.

7.1.23 Estimated efficacy of TAVI

Key points

- Mid-term RCT data shows TAVI has similar efficacy to surgical AVR in high-risk patients, and moderate to high-risk patients.
- Mid-term RCT data shows TAVI has superior efficacy to medical management in inoperable patients.
- A secondary analysis indicates that TAVI may have similar efficacy in 'technically

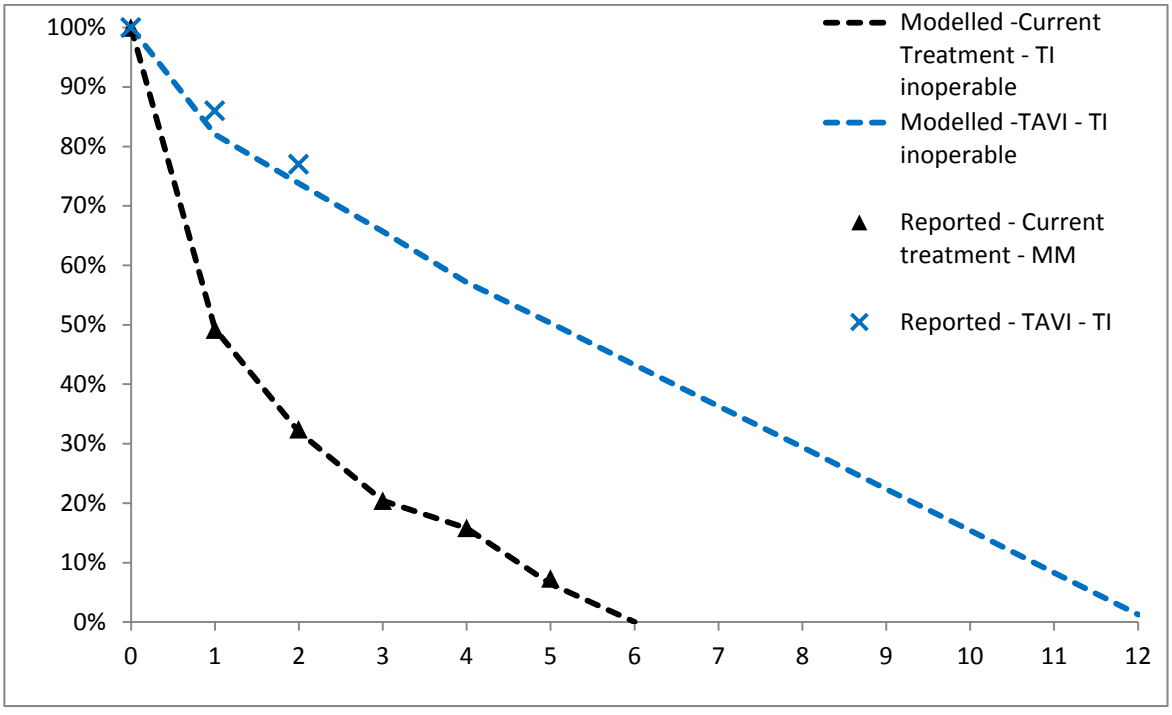
inoperable' patients as it does in moderate to high-risk patients, however, the evidence is of limited quality.

One randomised controlled trial has shown TAVI is superior to medical management in inoperable patients out to five years.[108] One randomised controlled trial has demonstrated non-inferiority of TAVI compared with surgical AVR in high-risk patients with five years of follow-up,[141] and another RCT has shown superiority with two years of follow-up.[102] Data from international registries, discussed earlier, generally demonstrates similar or better mid-term survival to that demonstrated in the randomised data in both high-risk and inoperable patients. Outcomes are generally better using the transfemoral approach compared with the transapical approach, where the transfemoral approach is the most commonly used internationally, and the predominant approach in New Zealand.

7.1.23.1 Survival curves for inoperable patients

For inoperable patients, we used the five-year results from the PARTBNER B trial. In this trial all TAVI were performed using the transfemoral approach. Survival curves were extrapolated beyond five years, until no patients were assumed to be alive, with a linear trend from the last two years of data. The survival curve for technically inoperable patients was derived from the two-year mortality data in the secondary analysis of the PARTNER B and NRCA studies,[119] where survival in out-years was extrapolated based on the longer-term data observed in the PARTNER B trial (Figure 8).

Figure 8: Survival curves for technically inoperable patients compared with medical management



Source: NHC analysis [108, 119]

The mortality rate of the technically inoperable patients is roughly half that illustrated in PARTNER B – where patients are predominantly clinically inoperable (Table 15). Indeed one and two-year survival is better than that observed in the PARTNER A trial for high-risk patients, and roughly equivalent to that

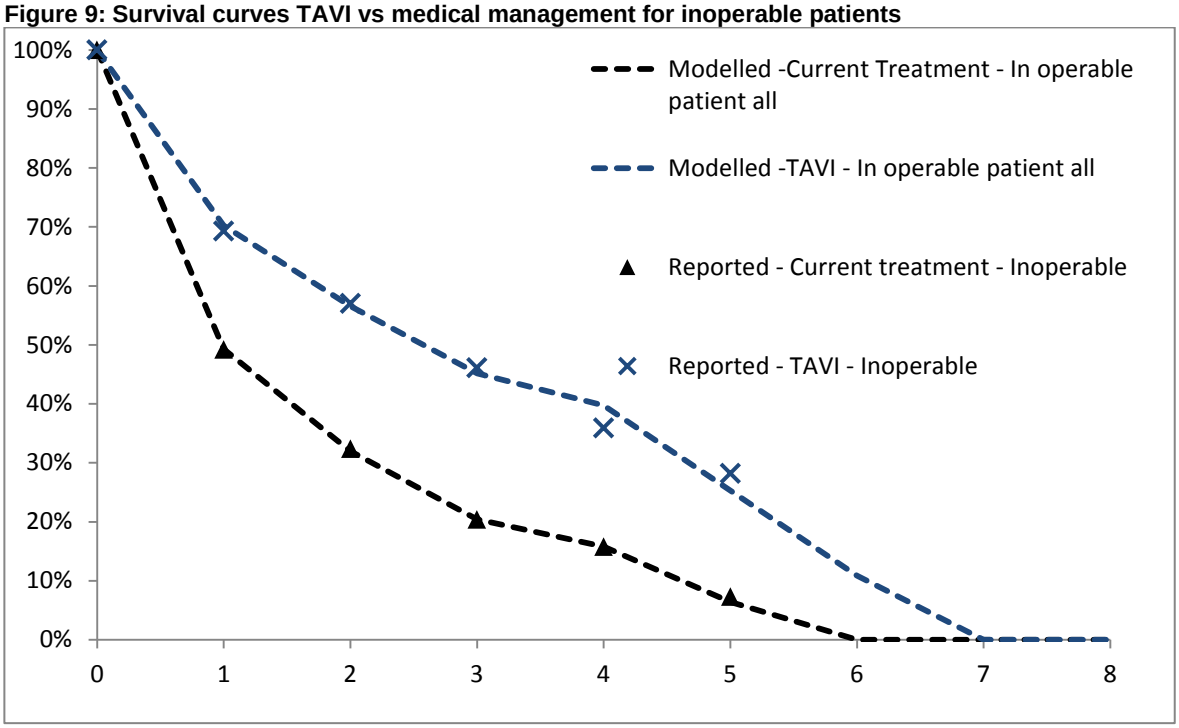
observed in the high risk CoreValve study. This technically inoperable subgroup of patients is about 10 years younger, with less than half the preoperative risk score (STS 5 vs 12) shown in both PARTNER A and PARTNER B.

The secondary analysis of the PARTNER B and NRCA studies reported a hazard ratio for all-cause mortality of 0.54 – favouring technically inoperable patients compared with clinically inoperable patients. It did not report a hazard ratio for technically inoperable patients compared with medically managed patients. However, all-cause mortality is roughly equivalent for clinically inoperable TAVI patients in the secondary analysis as it is for TAVI patients in the broader PARTNER B cohort at one year (30.7% vs 32%) and two years (43.3% vs 43.8%), respectively. We imputed the long-run efficacy of technically inoperable TAVI by applying the hazard ratio for technically inoperable TAVI vs clinically inoperable TAVI, HR= 0.54, to the long-run data from the PARTNER-B study. Three qualifications are required:

- The secondary analysis compared technically inoperable patients directly with the medically managed (standard treatment) arm of the PARTNER B study. As previously mentioned the control group was not stratified by technically and clinically inoperability, so there is some risk of favourable efficacy bias for the technically inoperable group compared with medical management (the TI patients are younger and lower risk compared with the control).
- The PARTNER B results are broadly reflective of clinically inoperable patients, as appears to be the case from two years of data. Baseline characteristics suggest about three quarters of patients in PARTNER B may be clinically inoperable (Table 15). Nevertheless, as PARTNER B includes some technically inoperable patients, our survival curve for technically inoperable patients may be optimistic.
- The hazard ratio is not a point in time measure; rather it includes all data in the survival curve. In extrapolating the survival curves from the hazard ratio we are assuming proportional hazards over time. That is, the relative effectiveness of TAVI vs medical management is constant over time – the survival curves fitted to each treatment have a similar shape.[188]

In both inoperability scenarios we compared TAVI against the survival curve for medically managed patients in the PARTNER B study. The survival curve for the broader inoperable patient population derived from the PARTNER B trial is depicted in Figure 9.

Figure 9: Survival curves TAVI vs medical management for inoperable patients



Source: NHC analysis [108]

7.1.23.2 Survival curves for surgical candidates

For high-risk patients, we took the headline mortality results reported in the PARTNER A trial over five years, predominantly adopting the transfemoral approach (70%), and continued the linear trend line until no patients were assumed to be alive. For the mixed moderate and high-risk population we took the headline results from the CoreValve study, where there is two years of follow up data. Here the survival curve was extrapolated beyond two years by assuming an equivalent trend in mortality to that demonstrated in the PARTNER A trial in out-years.

7.1.24 Quality of life values

Key points

- Health related quality of life is similar in short-term studies between TAVI and surgical AVR.
- Health related quality of life is significantly improved for TAVI compared with medical management.
- Baseline health related quality of life is greater in the CoreValve high-risk study than the PARTNER high-risk study – indicating (alongside a lower STS) a lower risk patient population.
- Functional status (NYHA class) improvement is sustained in mid-term results for both high-risk and inoperable patients suggesting that improved quality of life is sustained.

Each health state in the model is assigned a quality of life (QoL) value. The quality of life values and the number of years spent in each health state determine the quality of life years (QALYs) attributed

to TAVI. The duration of increased QoL following an AVR (either TAVI or surgical AVR) is uncertain; the base case estimate is two years of increased QoL following AVR.

A recent systematic review of 60 observational studies and two randomised controlled trials involving 11,205 patients focused on functional status and quality of life measures after TAVI.[189] Most of the studies found that there was an average improvement of 1 in NYHA class. Improvements in disease specific measures were noted but differences were small in more general health measures such as EQ5D and in psychological dimensions. Few of the studies evaluated patients beyond 12 months. The authors conclude that future prospective research should consider individual frailty status and that evaluation of longer-term functional outcomes and quality of life measures is required. The quality of life values used in the model are shown in Table 30.

Table 30; Quality of life values used in the cost-utility analysis

Patient population With severe AS	Quality of life value base-value	Post-treatment value at 12 months	Increment	Study
High risk TAVI and surgical AVR	0.67	0.76	0.09	PARTNER A[190]
Moderate and high risk TAVI and surgical AVR	0.75	0.79	0.04	CoreValve High Risk[191]
Inoperable TAVI	0.59	0.72	0.13	PARTNER B[187]
Technically inoperable TAVI	0.59	0.72	0.13	PARTNER B[187]
Medical management	0.59	0.59	0	PARTNER B [187]

All quality of life values were derived from randomised controlled trials using the EQ5D health questionnaire. Quality of life is measured in utility weights on a scale of 0 to 1, where 0 represents the worst possible health state, usually death, and 1 represents perfect health. Note that the reported mean utility scores take account of comorbidities and complications such as stroke and heart failure post procedure, hence separate calculation of utilities has not been performed for patients transitioning into differential health states.

7.1.24.1 Quality of life for high and moderate risk patients

Quality of life values did not significantly differ between TAVI and surgical AVR being approximately equivalent at baseline and 12 months. Quality of life values are reported for the transfemoral approach, the main approach used in New Zealand. Baseline and 12-month quality of life values were also similar between TAVI and surgical AVR in the transapical cohort of the PARTNER A trial.[190]

The CoreValve high risk population had higher baseline quality of life compared with the PARTNER A trial, consistent with the baseline patient characteristics of the two trials (Table 4) suggesting the trial contains a mix of high and moderate-risk patients. The incremental improvement in quality of life post-TAVI is also less in the CoreValve trial compared with the PARTNER A trial (0.04 vs 0.09). Again, quality of life is similar at baseline and 12 months for TAVI and surgical AVR in the CoreValve study. In both the PARTNER A and high risk CoreValve studies there appears to be a short-term gain in utility at 30 days for TAVI compared with surgery, as might be expected for a percutaneous procedure compared with open chest surgery. The very small gain in quality of life, equivalent to less than 0.01 QALYs, is not sustained at six months in either trial and is not included in our base case analysis.

There is limited information on the long-term durability of quality of life improvements, ie 12 months' follow-up data. In the PARTNER A trial, the TAVI group showed a sustained reduction in symptoms of heart failure over five years, as measured by New York Heart Association functional class, that was comparable with surgical AVR (Table 31); this infers there may be QoL gains beyond 12 months.

Table 31: NHYA class II or II (mild or no symptoms) PARTNER A

Intervention	Baseline	1 year	2 years	5 years
TAVI	5.7%	84.8%	83.9%	85%
Surgical AVR	6.0%	86.7%	85.2%	81.4%

Source:[141]

In the base case, we assume no difference in quality of life between TAVI and surgical AVR for high-risk and moderate and high-risk populations.

7.1.24.2 Quality of life for inoperable patients

The PARTNER B trial demonstrated a large and statistically significant ($p<0.05$) improvement in quality of life for TAVI patients compared with medically managed patients over 12 months. Of note, the medically managed patient group also reported an increase in quality of life at 12 months of 0.05 units, possibly a chance finding or due to the study environment. We assume no change in utility for the medically managed patient group over time.

The secondary analysis of the PARTNER B and NRCA studies reported higher mean quality of life at baseline for technically inoperable patients, compared with clinically inoperable patients.[119] Using the Kansas City Cardiomyopathy Questionnaire, scale 0-100, there were small but no significant differences between mean quality of life scores between technically inoperable patients and clinically inoperable patients at baseline and 12 months of follow-up. At baseline, the mean utility score for technically inoperable patients was 35.6 ± 19.5 vs 33.2 ± 21.3 for clinically inoperable patients, $p=0.35$. At 12 months the respective scores were 78.6 (95% CI, 72.1, 85.1) versus 72.7 (95% CI 68.5, 76.9), $p=0.14$. We assume no difference between inoperable groups and use the utility scores from the PARTNER B study as our baseline assumption of quality of life for both inoperable patient groups.

There is limited information on the long-term durability of quality of life improvements in inoperable patients, ie 12 months of follow-up data. In the PARTNER B trial, the TAVI group showed a sustained reduction in symptoms of heart failure over five years (as measured by New York Heart Association functional class); this infers there may be QoL gains beyond 12 months. Of note, mean functional class also improved in the medically managed group, indicating that part of the observed improvement is a consequence of attrition.[141, 166]

Table 32: NHYA class II or II (mild or no symptoms) PARTNER B

Intervention	Baseline	1 year	3 years	5 years
TAVI	7.8%	76.3%	70.0%	85.7%
MM	6.1%	50.0%	50.0%	60.0%

Source:[108]

Between group differences in functional class lost statistical significance at three years. At two years of follow-up, 83.1% in the TAVI cohort had mild or no symptoms of heart failure compared with 42.5% in the standard therapy cohort (p<0.001).[166] At three years, the respective rates were 70% and 50% (p=0.245).[141] While the lack of statistical significance in functional class post-two years may be a power issue, in the absence of utility evidence with more than 12 months of follow-up, we assume in our base case that there is no additional utility benefit attributable to TAVI after two years compared with medical management.

7.1.25 Model parameters

An annual discount rate of 3.5% was used to discount future costs and benefits, based on the real risk-free long-term government bond rate, representing the government's opportunity cost of borrowing money.**[192]** The model length was 18 years to account for the maximum life expectancy of any patient in the sensitivity analysis of technically inoperable patients.

7.1.26 Cost-effectiveness results

Table 33 presents the results of the cost-utility analysis for TAVI under four scenarios. In high-risk patients, TAVI is cost-saving compared with surgical AVR, a consequence of equivalent efficacy and utility combined with lower patient cost. This is, however, a small patient pool – estimated to be less than 25 patients in 2015/16 (Table 13). The moderate and high-risk scenario attempts to capture the status quo and the shift to lower risk populations seen in recent literature including the high risk CoreValve study. Again, the scenario appears cost saving. Disaggregating the result, moderate-risk patients are reducing the cost-effectiveness of the whole – as we estimate it is still less costly to perform surgical AVR in moderate risk patients (Table 17). The maximum population pool for moderate and high-risk patients is estimated to be about 80 patients per annum. This assumes surgical AVR is almost exclusively confined to low-risk patients. Current TAVI volumes, 66 patients in 2012/13, suggest there is little room for growth in this patient population.

The cost-effectiveness of TAVI, compared with medical management in inoperable patients, is estimated to be $74,000 per QALY. This ratio is based on an increased cost of $63,000 and a QALY gain of 0.85. The increased cost is made of $55,000 for the procedure and an average $8,000 of additional cost over the patient's lifetime (discounted at 3.5% per annum).

The cost-effectiveness of TAVI, compared with medical management in technically inoperable patients, is estimated to be $40,000 per QALY. Cost-effectiveness in the technically inoperable subgroup is almost twice as favourable compared with the broader inoperable population; the improvement in cost-effectiveness is due to improved survival. This plays out with an incremental QALY gain of 2.04 vs 0.85 for technically inoperable and inoperable patients, respectively; while incremental cost is also increased owing to increased survival. The technically inoperable patient pool is small – estimated to be about 25 patients in 2014/15 (Table 13).

In the budget impact analysis, we used a five-year time horizon (p.115). This captures most but not all the follow-up costs associated with TAVI and surgical AVR, as some patients can be expected to live for more than five years. The full cost of TAVI, surgical AVR and medical management is best expressed as a lifetime cost. The lifetime cost of intervention, discounted at 3.5%, is given in (Table 33). The lifetime cost of TAVI ranges from $84,000 to $98,000, for high-risk and technically inoperable patients respectively. The lifetime cost of surgery ranges from $90,000 to $101,000, while medical management is relatively inexpensive, costing about $15,000 per patient over their remaining lifetime.

Table 33: Cost-effectiveness of TAVI, base case results

Scenario	Estimated maximum population pool	Intervention	Life time cost	Incremental cost	QALYs	Incremental effect	Cost per QALY
High risk	~ 25 patients	TAVI	$84,000		2.53		
		Surgical AVR	$101,000	-$16,500	2.53	0	TAVI dominates*
Moderate and high risk	~ 80 patients	TAVI	$88,000		3.06		
		Surgical AVR	$90,000	-$2,000	3.06	0	TAVI dominates*
Inoperable	~ 110 patients	TAVI	$78,000		1.84		
		Medical management	$15,000	$63,000	0.99	0.85	$74,000
Technically inoperable	~ 25 patients	TAVI	$98,000		3.03		
		Medical management	$15,000	$82,000	0.99	2.04	$40,000

*TAVI dominates means that TAVI is less expensive and has the same health outcomes.

Source: NHC

Modelled and actual data for the technically inoperable scenario is presented in Figure 9. Using PARTNER B as our index, and an imputed hazard ratio of 0.28 (TAVI vs medical management), we modelled slightly lower survival for technically inoperable patients at one and two years compared with reported survival in the secondary analysis of the PARTNER B and NCRA studies.

7.1.27 Sensitivity analysis

Sensitivity analysis was undertaken to determine the effect of different assumptions in the model. The results of the sensitivity analysis for the technically inoperable scenario are presented in Table 34.

Table 34: Sensitivity analysis

Variable	Base case	Updated	Cost Per QALY
Base case			**$40,000**
Hazard ratio TAVI vs MM	**0.28**	**0.16**	**$30,000**
		0.46	**$60,000**
Duration of utility gain for TAVI, years	**2**	**0**	**$45,000**
		Lifetime	**$34,000**
Cost of TAVI	**100%**	**85%**	**$36,000**
		115%	**$44,000**
Annual cost follow-up costs excluding readmissions	**100%**	**75%**	**$37,000**
		125%	**$44,000**
Annual cost of readmissions	**100%**	**75%**	**$39,000**
		125%	**$42,000**
Discount rate	**3.5%**	**0%**	**$37,000**
		10%	**$47,000**
Inclusion of aged care	**Excluded**	**Included**	**$44,000**
Measure of benefit	**Utility**	**Life years**	**$27,000**

Despite the fairly wide range in the values used for each variable in the model, the cost-effectiveness does not improve beyond $30,000 per QALY – largely due to the low cost of medical management. The model was most sensitive to the relative efficacy of TAVI compared with medical management. Cost-effectiveness of TAVI ranged from $30,000 to $60,000 per QALY with hazard ratios of 0.16 and 0.46, respectively. The HR range was imputed from the 95% confidence interval for the hazard ratio for clinically inoperable vs technically inoperable patients given in the secondary analysis of the PARTNER B and NRCA studies.[119] The model is relatively sensitive to the cost of TAVI and duration of utility benefit. The incremental cost-effectiveness of TAVI ranges from $36,000 to $44,000 per QALY with an index admission cost of TAVI 85% ($47,000) and 115% ($63,000) of the base case, respectively. Varying the duration of the utility benefit (the quality of life improvement compared with medical management) from zero years to the patient's remaining lifetime, improves cost-effectiveness from $44,000 to $33,000 per QALY. The model was relatively insensitive to follow-up costs. A 50% variation in follow-up cost resulted in a cost per QALY range of $37,000 to $44,000.

International cost-effectiveness analyses

The cost effectiveness of TAVI compared with medical management ranged from about NZ$30,000 [193, 194] to NZ$180,000 [195] per QALY in a recent systematic review.[185] The cost-effectiveness of TAVI compared with surgical AVR ranged from TAVI being the dominant strategy[147, 186] (costing less than surgery and generating more QALYs) to TAVI being dominated by surgical AVR (costing more than surgery and generating less QALYs).[147, 193, 196, 197] Table 44 (Appendix 5) summarises international economic evaluations of TAVI in operable and inoperable patients. Whilst there have been multiple evaluations of TAVI in inoperable patients, we are unaware of any cost-effectiveness evaluations in technically inoperable patients specifically.

7.1.28 Economic evaluations by heath technology assessment agencies

Table 44 illustrates a very wide range of cost-effectiveness values for inoperable and operable patients, often driven off the same baseline efficacy data. We focus on the evaluations reported by other heath technology assessment agencies. Of note, all these economic evaluations were published prior to the five-year results from the PARTNER trials or the publication of the CoreValve high risk study.

A 2013 economic assessment by the Ontario Health Technology Assessment Committee (OHTAC) found TAVI had an incremental cost saving of $5,000 (C$4,600) per procedure compared with surgery in high-risk patients. Costs were estimated based on the two-year results of the PARTNER A trial, other medical literature and health system costs in Ontario.[194] The assessment assumed a 20-year time horizon, effectively a lifetime horizon. A previous assessment in 2012 by OHTAC reported an incremental cost of $12,000 per procedure (C$12,000).[14] The improvement in cost was largely due to a $14,000 reduction in the cost of the TAVI valve ($38,000 to $25,000). The study reported a small increment in life years for TAVI patients of 0.012 years, but also reported a small decrement in utility resulting in a net QALY decrement of -0.069 QALY per TAVI compared with surgical AVR in high-risk patients. Consequently TAVI was the dominant strategy on a life years analysis, but had an incremental cost-effectiveness of $80,000 (C$67,000) per QALY (-C$4642/-0.069). It is unclear how the negative utility value was derived. For inoperable patients, the study reported a cost-effectiveness ratio $29,000 (C$24,257) per QALY from an incremental cost of $18,000 (C$15,233) and incremental effectiveness of 0.628 QALYs.

A 2011 evaluation by the Belgian Health Care Knowledge Centre reported TAVI having an incremental cost of $30,000 (€20,000) per procedure compared with surgery in high-risk patients.[198]

They assumed a marginally lower valve cost than indicated by New Zealand data at NZ$26,000 (€18,000). Costs were estimated based on parameters from the PARTNER A trial and direct costs from a Belgium healthcare payers perspective. The assessment was for a one year time horizon, where 12-month follow-up costs were relatively low in both AVR and TAVI patients (<€1,000). Insufficient detail was reported to understand the large incremental cost of TAVI. The study reported an incremental cost-effectiveness ratio of $124,000 (€750,000) per QALY in high-risk patients (compared with surgical AVR) and $74,000 (€44,900) per QALY in inoperable patients, compared with medical management.

Another early economic assessment by the Scottish Health Technology Group in 2010 reported an incremental cost of $10,000 (£4,859) in high-risk patients compared with surgery, and $34,000 (£14,680) compared with medical management.[199] The study modelled a small incremental effect of 0.06 QALYs for TAVI compared with surgery and 0.65 QALYs compared with medical management. The resulting cost-effectiveness ratios were $200,000 (£87,293) and $53,000 (£22,600) per QALY for high-risk and inoperable patients, respectively.

A 2013 evaluation by the National Institute for Health Research in England reported an incremental cost of $16,000 (£7,983), with a time horizon of 25 years, for TAVI compared with surgery.[193] For inoperable patients the incremental cost was $56,000 (£24,147) compared with medical management. The incremental effect was -0.60 and 1.87 QALYs in high-risk and inoperable patients, respectively. Consequently, TAVI was dominated by surgical AVR in high-risk patients, with an incremental cost-effectiveness ratio of $30,000 (£12,900) per QALY in inoperable patients. Of note, the analysis compared the cost and outcomes for TAVI with moderate-risk surgical AVR (EuroSCORE between 10 and 20) rather than high-risk surgical AVR. The authors did not differentiate the total cost of TAVI between high-risk and inoperable patients. Results for the high-risk PARTNER A trial were not publicly available at the time the report was produced, and accordingly it relied on non-randomised data. The mean EuroSCORE of surgical AVR and TAVI patients in the PARTNER trial was 29, significantly higher than modelled in the NIHR study, suggesting an overstatement of incremental cost for TAVI in operable patients.[99]

A more recent UK analysis undertaken at Leeds University, and sponsored by the British Heart Foundation, found TAVI had an incremental saving of $3,000 (£1,300) per patient compared with surgical AVR in high-risk patients.[186] TAVI and surgical AVR effectiveness was modelled from the two-year results of the PARTNER A trial and extrapolated out to ten years. Costs were based on national UK values, extrapolated from randomised and registry data. Consistent with our modelling, the additional device costs for TAVI appears to be outweighed by the greater length of stay cost (and intensive care stay) in the surgical AVR group. Cost data assumed a mix of both the Medtronic CoreValve and the Edwards-Sapien valve and the transfemoral and transapical approach approaches. The study reported a small incremental effect of 0.063 QALYs for TAVI; consequently, TAVI was the dominant intervention compared with surgery.

TAVI is expected to be discussed at the Australian Medical Services Advisory Committee in July 2015, including a discussion of the cost-effectiveness of TAVI in operable and inoperable patients.

7.1.29 The cost of aged care

Key points

- If costs unrelated to the medical condition or procedure, that are likely to afflict patients who live longer as a result of effective treatment are included in cost-utility analysis, then some effective treatments may not be funded. Hence MSAC, NICE and PHARMAC advise that non attributable ongoing costs should not be included in economic evaluations.
- We tracked the aged residential care costs of all patients who received TAVI between 2008 and 2014.
- Of 236 TAVI records, 16 patients (or 6.8%) received publicly subsidised aged residential care sometime in the five years post-intervention. The net cost to government for these patients was $520,000, about 4% of the index admission cost of 236 TAVI.
- TAVI may reduce the short-term probability of entering aged care as it improves health outcomes, but at the same time increase the lifetime probability of entering aged care.
- Though we consider aged care a non-attributable cost, inclusion in our cost-utility model reduces the cost-effectiveness of TAVI in technically inoperable patients from $40,000 to $43,500 per QALY.

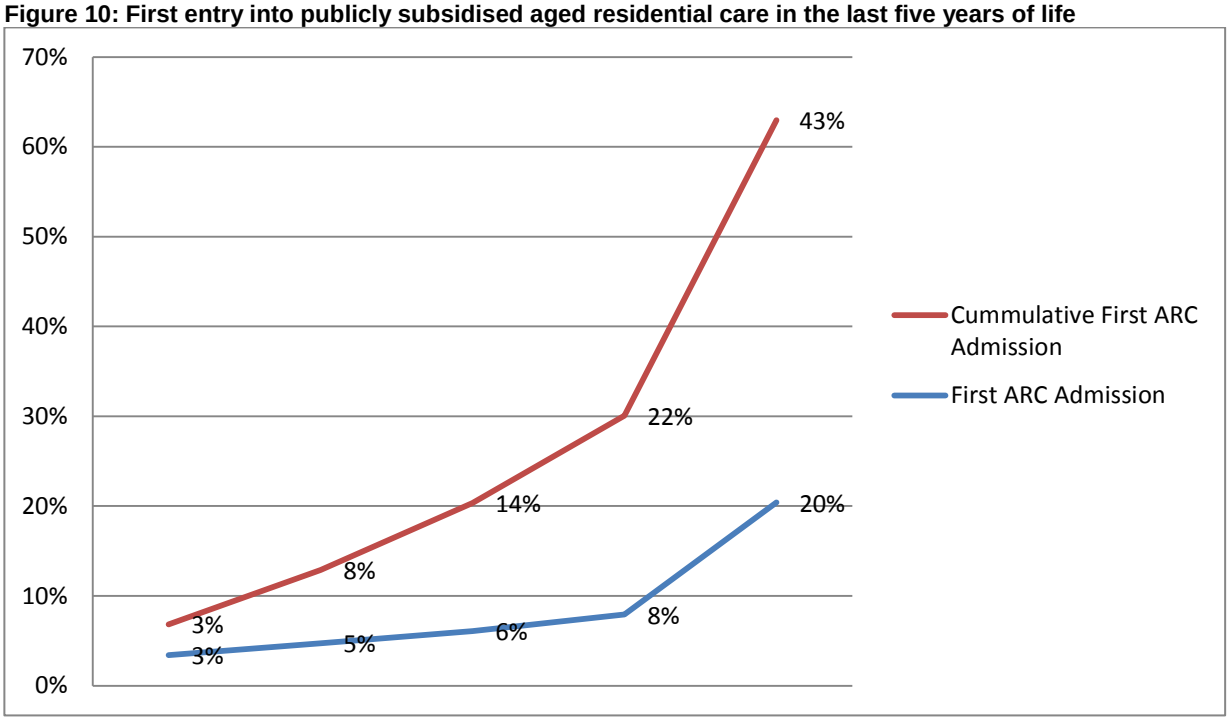
Through informal engagement with the sector, the NHC has been told that some DHBs were interested in the cost impact of aged residential care post TAVI.

Most older people will spend some time in aged residential care or receive home-based support services in their last years of life. A recent University of Auckland study found that about half of all older New Zealanders (65+) move into care at some stage of their lives.[200] In addition, data published by the Office of the Auditor-General suggests that about 12 percent of older people (65+) received home-based support services in 2012/13.[201] A study published by the Australian Institute of Health and Welfare found that three-quarters of older people (65+) who died in 2010/11 received residential care or community support in their last year of life.[202]

7.1.29.1 Entry into aged residential care prior to death

In 2013/14, 18,800 New Zealanders aged 75 years or older died. These mortality records were matched against aged residential care records in the Client Claims Processing System (CCPS). Of the 18,800 deceased, 9,600 (51%) had entered aged residential care at some point in their lives. Accounting for fully private payers, the lifetime uptake of aged residential care was about 56%, where uptake increased with proximity to death. As might be expected, the majority of aged care uptake occurs in the last five years of life. Of the 18,800 deceased, 43% entered aged residential care for the first time in the last five years of life. The rate of first aged residential care entry increased from 3% five years from death, to 20% in the year of death (Figure 10).

Figure 10: First entry into publicly subsidised aged residential care in the last five years of life



Source: NHC analysis using extract from the Client Claims Processing System (CCPS) for calculating inter-district flows

Increased rates of aged care admission prior to death have also been observed in Australia.[202] In 2010/11, permanent aged residential care uptake was 13.4% five years prior to death, increasing to 31.2% in the year of death, with a further 15.5% of older people receiving some combination of residential and community care. Interventions that extend life years in the elderly such as aortic valve repair are likely to delay entry into aged residential care. But with extended life, the cumulative probability of residential care may increase. The net effect may be a delayed but prolonged stay in residential care. For example, if a patient (not in residential care) has a life expectancy of 12 months without treatment, then that patient has a one in five chance of entering residential care. If the treatment is expected to increase that patient's life expectancy to five years, then their probability of entering aged residential care reduces to 3% in the immediate year, but their (remaining) lifetime expectancy of entering residential care increases to 43%. If the additional cost of residential care is attributed to the intervention, be it TAVI or any other intervention for the elderly, the intervention becomes relatively less cost-effective, and less attractive to fund.

The Medical Services Advisory Committee (MSAC) in Australia,[203] the National Institute for Health and Care Excellence (NICE),[204] and PHARMAC[192] advise that non-attributable ongoing costs should not be included in economic evaluations. If costs unrelated to the medical condition or procedure, that are likely to afflict patients who live longer as a result of effective treatment are included, then some effective treatments may not be funded. The key question is whether aged residential care is a cost that is attributable to TAVI, or simply a normal life-course cost. Given TAVI is associated with improved quality of life,[190] and a sustained reduction in the symptoms of heart failure,[108, 166] it is counter-intuitive that TAVI should directly increase residential care stay in the medium-term for most patients.

We tracked the aged residential care costs of all patients who received TAVI between 2008 and 2014. TAVI records were matched against aged residential care records in the Client Claims Processing System capturing all publicly subsidised patients. Of 236 TAVI records, 16 patients (or 6.8%) received

publicly subsidised aged residential care sometime in the five years post-intervention. The net cost to government for these patients was $520,000, about 4% of the index admission cost of 236 TAVI. The cumulative probability of being in aged residential care increased from 2% in the year following TAVI to 19% in the fifth year following the intervention (Table 35).

Table 35: Uptake of aged residential care for TAVI patients in New Zealand 2008-2014 in the five years post procedure

Year	1	2	3	4	5
Number of patients followed	204	138	78	44	31
Number of patients admitted to ARC	4	4	6	0	2
Admissions as % of followed patients	2%	3%	8%	0%	6%
Number of patients in ARC	4	8	8	6	6
Cumulative probability of being in ARC	2%	6%	10%	14%	19%

Source: NHC analysis using extract from the Client Claims Processing System (CCPS) for calculating inter-district flows

The average age of the 16 TAVI patients admitted to ARC was 88 years (81-100 years). The average age of TAVI patients at the time of intervention was 80 years. In 2013/14 the average ARC admission rate for an 80-84 year old was 7.3% nationally. The corresponding admission rates for the 85-90 year old and 90+ cohorts was 16.3%, and 36.4%, respectively. Though not a controlled comparison, it does not appear that TAVI patients have an elevated risk of aged residential care admission compared with the general public.

7.1.29.2 Evidence from Auckland DHB

As a check on our analysis, Auckland DHB undertook an analysis of 19 TAVI patients who received their intervention in 2012/13. As of September 2015, just one of these patients had been transferred to aged residential care.

7.1.29.3 International evidence

A Canadian cost-utility analysis, relying on clinical judgement, estimated that 5% of inoperable TAVI patients would require nursing home admission annually, and 30% in medically managed patients.[205] The same study reported an annual probability of home care of 13% for TAVI patients compared with 40% for medically managed patients.

A similar rate of nursing home admission has been observed in surgical AVR patients in France and Belgium. In a French study of 84 octogenarians, 91% were still living in their own homes nearly two years post-surgical AVR.[206] In a Belgium study of 220 octogenarians, 68% of survivors were living in their own home or with their families nearly five years after surgical AVR.[207]

A United States retrospective study tracked the resource use of 252 high-risk surgical AVR patients, compared with 1,223 non-high-risk patients, for five years from 2003 to 2008 using Medicare records.[82] It found that just under half of these patients had received skilled nursing facility care over the study period, compared with just over a third for non-high-risk patients, 49.6% vs 34.5%, respectively ($p<0.0001$). In addition, 9.9% of high-risk patients had had a long-term hospital admission compared with 4.7% for non-high-risk patients ($p=0.001$). The same study found 62% of high-risk patients had had home care during the study period, with 65% of non-high-risk patients receiving home care.

A UK cost-utility analysis reported annual probabilities of rest home admission of 10% and 67% for inoperable TAVI and medically managed patients, respectively.[208] These probabilities are reportedly based on unpublished research and the PARTNER B trial.

A Swiss study found six of 106 surviving high-risk TAVI patients, or 5.7%, had been admitted to a nursing home six months after their procedure.[209] The TVT Registry in the US (n=7,710) found 6% of high-risk and inoperable patients were discharged to a rest home.[18]

A Spanish cost-utility analysis, which risk matched surgical and TAVI patients, reported very low rates of rest home admission for intermediate risk TAVI and surgical AVR patients. One year post-intervention, the average days spent in rehabilitation or nursing home were 0 (n=48) and 1.56 (n=86) for the CoreValve and Edwards valves respectively, compared with 11.4 days for surgical AVR (n=52) ($p<0.05$).[181]

7.1.29.4 Home-based support services

Less has been published on the probability of receiving home-based support services. A Canadian cost-utility analysis, relying on clinical judgement, reported an annual probability of home care of 13% for TAVI patients compared with 40% for medically managed patients.[205] In Australia, about 30% of older people receive community support in the five years prior to death, with the probability of care remaining fairly constant over the five years.[202] Compared with residential care, which costs government about $31,000[7] per patient per year in New Zealand, home-based support services are relatively inexpensive, costing about $3,500 per patient year.[162, 201]

7.1.29.5 Impact on cost-effectiveness

Aged care, including residential care and home-based support services, are a normal life course cost. We do not see evidence for TAVI directly increasing aged residential care costs in the short to medium-term. TAVI may, as a consequence of its effectiveness, increase aged care costs in the longer term, but including such costs would bias against effective interventions for the elderly.

Nevertheless, we modelled the cost of aged care including home-based support services assuming:

- a cost to Government per patient year of $31,000 for aged residential care.
- a cost to Government per patient year of $3,500 for home-based support services.
- patients entering aged care stayed in aged care until death and are not in aged care when they received TAVI.
- a flat probability of receiving home-based services of 30% per annum.
- an increasing lifetime probability of receiving aged residential care the longer a patient lives post-TAVI (Table 36).

[7] Based on an average Government subsidy of $85 a day across all levels of aged residential care.

Table 36: Imputed probability of entering aged residential care prior to death

Years prior to death	% of deceased with first ARC entry	Imputed average days in ARC	Imputed probability of annual ARC stay	**Cumulative probability of entering aged residential care (ARC)**
1	20%	271	15%	**15%**
2	8%	640	7%	**22%**
3	6%	1002	6%	**28%**
4	5%	1369	4%	**32%**
5	3%	1734	3%	**35%**

Source: NHC analysis of CMS

Table 36 is derived from national records of all publicly funded aged residential care admissions. It suggests that an older person with five years of remaining life has a 3% chance of spending a year in aged residential care in their fifth year prior to death. If instead the older person had one year of life remaining, they would have a 15% chance of a first entry (and full year) in aged residential care. The probability of entering aged care is cumulative. A TAVI patient who lives for two years post-intervention is assumed to have a 7% chance of a first entry (and full year) in aged residential care two years prior to death; and a 15% chance in their final year of life. Their cumulative probability of spending two years in aged residential care is 22%.

In our Markov model, the cost of aged residential care and home-based support services were applied as a discounted payoff at death. While costs were increased for all interventions (TAVI, surgical AVR and medical management) cost-effectiveness was relatively insensitive to the inclusion of aged residential care costs. The cost effectiveness of TAVI in technically inoperable patients declined from $40,000 to $43,500 per QALY.

Although we have argued that aged care may not be an attributable cost, there are conceivable scenarios in which it could be. One such example would be systemic poor patient selection such that highly comorbid patients receive aortic valve replacement (TAVI or surgical AVR) with little ability to benefit. Such so-called futile intervention, discussed in the next section, might be expected to result in a more rapid transition from relative independence to dependence (or death), than has thus far been evidenced in New Zealand.

7.1.30 Palliative care

In New Zealand, palliative care has been defined as care for people of all ages with a life-limiting illness which aims to:

1. optimise an individual's quality of life until death by addressing the person's physical, psychosocial, spiritual and cultural needs.

2. support the individual's family, whanau, and other caregivers where needed, through the illness and after death.[(210)]

Palliative care is delivered in a variety of settings with palliative care generally available where the patient is – be that home, hospital, residential care or hospice.

We undertook a second assessment to assess the frequency of respite residential care for TAVI patients over the same 2008/09 to 2013/14 period, using general ledger code 6680. Two records were found for respite care.

Arguably our sample size and five-year time period may be insufficient to adequately reflect palliative care costs. We may not have enough patients sufficiently close to death to capture likely health system cost. The assessment may also not be relevant for inoperable patients currently not funded for TAVI who have a shorter life expectancy than the current cohort. To give some indication on the relative materiality of palliative care costs, however, work undertaken by the Ministry of Health indicates that the five- year average palliative care cost for a cancer patient in 2008/09 (understood to receive more palliative care than cardiac patients) was $923.[211]

Discussion

A number of assumptions and limitations have been outlined throughout this assessment. Possibly the most important limitation is the retrospective nature of our analysis, where in the absence of a prospective control we have had to retrospectively fit a medical management arm (for inoperable patients) and a surgical arm (for high risk patients). New Zealand costs and probabilities have been applied where they have been available, but we have also had to rely on international estimates of resource use for high risk and inoperable patients.

Despite the uncertainty around follow-up costs, our model showed cost-effectiveness was relatively insensitive to follow-up costs. The cost-effectiveness of TAVI in operable patients hinges on the relative cost of TAVI compared with surgical AVR. We found that TAVI was significantly less costly in a small population of high-risk patients (as classified by an STS score >8) comprising about 25 patients per annum. In a larger pool of moderate-risk patients (STS 4%≤ 8%) comprising at most an additional 77 patients per annum (511*15%); TAVI appears marginally more costly than surgical AVR. The relative efficacy of TAVI at the lower end of this risk threshold is only beginning to be tested. Hence it would be imprudent to advocate the expansion of TAVI further into the moderate-risk patient at this point in time. As this is a retrospective study, the quantity of cost savings should rightly be regarded with some scepticism. We believe, however, that there is a reasonable case that TAVI may be cost-saving to some degree in a small group of high-risk patients. This finding is support by recent economic evaluations.[186, 194]

A recent Spanish economic assessment observed that TAVI was likely to be more cost-effective in high-cost health systems where there is greater scope for cost savings.[181] The cost of medical management for severe aortic stenosis appears to be relatively low in New Zealand – reducing the scope for cost savings and increasing the incremental cost of TAVI. In the broad inoperable population, TAVI does not appear to be cost-effective. Expanding TAVI into this population would also be significantly cost-increasing, costing the health system in excess of $3 million per annum. TAVI may be significantly more cost-effective in the small subgroup of technically inoperable patients. There are nevertheless, significant shortcomings in the evidence for the relative efficacy of technically inoperable patients compared with medical management. Ideally we would have prospective pre-specified trial evidence with a matched control for technically inoperable patients. Unfortunately, the evidence we have presented for technically inoperable patients is neither pre-specified nor well matched (the control was 10 years older with more than twice the mean preoperative risk). The evidence for the efficacy of TAVI in technically inoperable patients is thus open to being a statistical aberration or a significant over-estimate.

8 Societal and ethical considerations

Key points

- The Midland region appears to have a higher TAVI intervention rate than other regions.
- Patients should be fully informed of the potential harms and benefits of TAVI: Right seven under the Code of Health and Disability Services Consumers' Rights.
- Futile intervention needs to be avoided. TAVI should not be undertaken if it is unlikely to increase survival with an acceptable quality of life.

What are the potential social and ethical implications that need to be considered?

HealthPACT, who undertake health technology horizon scanning assessments for Australia and New Zealand, reviewed TAVI in 2012 and identified 'no ethical, cultural or religious concerns' relating to the Sapien or Sapien XT device.[142] The Quebec Institute for Excellence in Health and Social Services undertook a health technology assessment of TAVI, published 2013, in which they identified four 'ethical considerations' relating to TAVI:

1. **Fairness of access.** The review recommended that patient selection criteria should be as objective as possible and thus reproducible across physicians and performing centres such that access to the procedure is fair and just. It noted that while it is reasonable to allow for some subjectivity of physician opinion regarding patient eligibility, selection criteria must be transparent and uniformly applied.
2. **Informed decision-making and consent.** The review recommended that patients be provided with clear information about the expected benefits and risks of the procedure. Specifically, patients should be made aware of the risk of death or serious complications such as stroke, and of the planned response of the procedure team regarding emergency open heart surgery in the event of a life-threatening problem during the TAVI procedure. Patient should also understand the uncertainty about the long-term durability of TAVI.
3. **Patient autonomy.** The review noted that 'what can be done' and 'what should be done' are not equivalent. Noting that "a patient's right to die with dignity must be respected".
4. **Benefit vs harm.** The review highlighted the need to consider the extent to which individual patient's quality of life can be expected to be improved. It noted that there were no globally-accepted easily applicable criteria to judge the appropriateness of TAVI, and that elderly patients may have significant comorbidities and be frail.[212]

Further context was not provided in the justification of the ethical considerations outlined; however, they are plainly issues that are not uncommon to many new and existing health technologies. With regards to the New Zealand context, we elaborate on each ethical consideration below.

Fairness of access

The Quebec guidance notes the need for consistency in the application of patient selection criteria for TAVI. At a population level, inequitable access can play out in regional or ethnic disparity in access to services.

8.1.1 Regional variation

Regional variation in access to services may arise when a new technology is not diffused at the same rate across regions. Diffusion rates can vary for a host of reasons including divergent clinical opinion about the value of the intervention; resource constraint (including scarce clinical expertise); and variation in underlying population need.

In New Zealand, TAVI is currently being performed in three district health boards (Waikato, Auckland and Canterbury) and one private hospital (Mercy Ascot). The first publicly funded TAVIs were performed in Waikato District Health Board (DHB) in 2008/09, with Auckland and Canterbury DHBs starting to offer the service from July 2011.

Table 37 shows regional variation by DHB domicile for TAVI and surgical AVR per 100,000 of population.[213] In 2012/13, just over half of all TAVI procedures were performed in Waikato DHB, hence the intervention rate in the Midland region is about twice the national average. The analysis was undertaken from the perspective of the patient's region of domicile. There is less variation in total AVR events (including TAVI, surgical AVR and sutureless AVR) across regions. There is some evidence of a substitution effect in the Midland region where a high TAVI intervention rate is offset by lower surgical AVR intervention rate – this is demonstrated through a total AVR intervention rate that is equivalent to the national average. The Northern region has a comparatively low overall AVR intervention rate compared with estimated population incidence of severe AS (43%). The mean clinical risk of patients undergoing TAVI in Waikato DHB is high (EuroSCORE 2 = 10.8):[27] therefore, it is possible that in other regions some such patients will be managed medically or managed with standard surgery.[39]

In technically inoperable patients, TAVI is a substitution for medical management rather than surgical AVR and thus raises issues of equity of access that would need to be worked through with the sector.

Table 37: Regional variation (DHB of domicile) in publicly funded TAVI and surgical AVR 2012/13

Region	Incidence per 100,000	TAVI per 100,000	All AVR per 100,000	AVR as proportion of incidence
Central	18	0.8	12	67%
Midland	22	2.9	11	51%
Northern	17	1.0	7	43%
Southern	22	1.6	14	66%
NZ	19	1.5	11	59%

Source: NHC analysis of national minimum dataset. AVR events are defined as events whose diagnosis included diagnostic codes I350,I352,I060,I062. Incidence was defined as a primary hospital diagnosis of AS during the year.

8.1.2 Ethnic variation

There is historic evidence of ethnic inequality in the provision of cardiovascular interventions in New Zealand.[214] Data from the mid-2000s show that while ischaemic heart disease mortality rates were more than two-times higher for Māori than non-Māori, cardiac revascularisation procedures were provided at similar rates for the two groups. It is important to ensure equality of access to health services, however, Māori have low incidence and prevalence of AS, and low associated mortality (Table 38).

Table 38 Māori/non-Māori prevalence, incidence and mortality 2011

	Age-standardised prevalence per 100,000	Age standardised incidence per 100,000	Mortality	Age standardised mortality per 100,000
Māori	49	7	4	1.3
Non-Māori	63	12	291	3.1
Total	62	12	295	3.0

Source: NHC analysis of NMDS and mortality records. Prevalence, incidence and mortality are age- standardised to the WHO population. Prevalence and incidence data is for 2012/13, whereas the latest mortality records at the time of analysis were for 2011.

The addition of TAVI to the care of patients with severe AS is unlikely to directly increase disparity between Māori and non-Māori, and the same may be said for Pacifica. However, if funding were prioritised for AS intervention over and above other treatments for conditions that are more prevalent in the Māori and Pacific population, then implementation of TAVI may have some indirect effect.

Informed consent

Informed consent is a right enshrined in the Code of Health and Disability Services Consumers' Rights (right seven). No health or disability service can be provided to a consumer without his or her informed consent.[215, 216] Corresponding rights include right five, the right to effective communication, and right six, the right to be fully informed – implying that patients should be fully informed of the potential harms and benefits of an intervention. Similarly, the National Institute for Health and Care Excellence (NICE) guidance on TAVI notes the need for informed consent, with patients required to be informed of the potential risks associated with the procedure.[145]

Patient autonomy and choice

The Quebec HTA advice, that patients have 'a right to die with dignity', might best be seen in light of recent end-of-life care legislation in the province allowing citizens to seek medical assistance in dying.[217] The ethical debate over the right to die with dignity is beyond the scope of this assessment. Suffice to say, the New Zealand Bill of Rights Act 1990, s11, grants everyone 'the right to refuse to undergo any medical treatment.'[218]

The flipside of respecting a patient's choice not to have an intervention is respecting a patient's choice to have an intervention. Here Botha et al (2013) comment that although the Health and Disability Commissioner Act (1994) provides a right to (health) services of an appropriate standard; rights do not extend to a right to any possible health care service.[219] Likewise, NICE's guidance on social value judgements in healthcare (developed with guidance from their Citizens Council[8]) acknowledges 'that respect for autonomy and individual choice are important for the NHS and its users.'[220] However, they note, "this should not mean that NHS users as a whole are disadvantaged by guidance recommending interventions that are not clinically and/or cost-effective." The French National Authority for Health's guidance on TAVI is less diplomatic: "Surgical aortic valve replacement is the standard of care for patients at low or moderate-risk surgical risk. If a patient in this category refuses surgical aortic valve replacement, this is a non-indication for TAVI."[7]

[8] The Citizens Council is an assembly of 30 members reflecting the age, gender, socioeconomic status and ethnicity of the people of England and Wales. Serving up to three years, council members are charged with providing NICE with a public perspective on overarching moral and ethical issues that NICE has to take account of when producing guidance.

Harm vs benefit – futility of intervention

At a basic level, any intervention ought to stand a fair chance of providing a patient more benefit than harm. If not, the intervention is futile. Elderly patients with cardiovascular disease are increasingly referred for complex and high-cost interventions. AVR, including TAVI, is a good example of such an intervention, as AS is a condition that predominantly affects those older than 70 years. While many elderly patients have good outcomes, and trials have demonstrated improvements in survival and symptoms after TAVI compared to medical management, a sizeable group of patients die or lack improvement soon after the procedure.[18] This raises important ethical questions about the need to identify and acknowledge futility in some patients considered for TAVI and aortic valve intervention in general.[190]

8.1.3 Medical futility

Fundamentally, there are two main considerations in determining if an intervention is medically futile. Namely, if it does not fulfil either of the following: increase survival with an acceptable quality of life, or if there is no survival benefit, improve a patient's quality of life. Researchers further characterise futility into so-called 'quantitative futility' and 'qualitative futility.' If an intervention is highly unlikely to produce a desired physiological effect, the intervention is said to be quantitatively futile.[221-223] If it is highly unlikely that the physiological effect will benefit the patient, the intervention is qualitative futility. Some authors further distinguish what's known as 'physiological futility'. Here there is certainty, or near certainty, that no physiological effect will be achieved from an intervention.[219]

Much of the futility literature is focused on physician, and in particular intensive care physician, responsibility when faced with situations of medical futility.[219, 221-225] In practice, the futility debate has played out in the setting of clinical criteria for futility, and the establishment of policies and ethics committees to guide decision-making regarding the sensitive issues surrounding end-of-life care.[222] In the United States, the US President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioural Research (1983) found medical futility sufficient grounds for physicians withholding or withdrawing life-prolonging therapy.[225] Today, the American Medical Association (AMA) policy on end-of-life care notes that 'Physicians are not ethically obligated to deliver care that, in their best professional judgment, will not have a reasonable chance of benefiting their patients'.[226] In New Zealand, policy on medical futility appears less explicit. Cole's Medical Practice in New Zealand, published by the Medical Council of New Zealand, notes that where possible, patient's wishes for cardiopulmonary resuscitation should be sought. It continues that "(i)f CPR is being withheld on the grounds of multiple comorbidities (so-called futility) the patient should be informed." Here, health professionals are advised to consult a proxy about the person's probable wishes, keeping in mind that under the law a Power of Attorney cannot withhold CPR; it can only give an indication as to what the patient would have wished.[227]

8.1.3.1 Medical futility and TAVI

There is very limited literature on futility relating to TAVI. The Joint American Heart Association/ American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease defines (surgical or transcatheter) intervention as futile if a patient with severe valvular heart disease has:

1. A life expectancy of less than one year, even with a successful procedure.
2. A chance of 'survival with benefit' of less than 25% at two years.

Survival with benefit is measured in terms of improvement by at least one New York Heart Association (NYHA) or Canadian Cardiovascular Society class in heart failure (HF) or angina symptoms, improvement in quality of life, or improvement in life expectancy. Patients with severe frailty may also fall into this category.[36] Likewise, European guidance notes that eligible patients should have a life expectancy of more than one year following the procedure and should also be likely to gain improvement in their quality of life, taking into account their comorbidities.[88]

Arnold et al (2013) define futility or a 'poor outcome after TAVI' as death, a poor quality of life (measured by the Kansas City Cardiomyopathy Questionnaire), or a substantial decline in quality of life six months post-intervention.[228, 229] By this measure, 35% of patients treated with TAVI had a poor outcome grouping PARTNER A and B arms.[228] In the extreme risk CoreValve study, the proportion of patients with a poor outcome at six months, equivalently defined, was 39%.[230] In a retrospective study of the Italian national registry of transapical TAVI, futility was defined as one year mortality in patients who did not experience 30 day all-cause mortality.[231] Of the 645 surviving patients at 30 days, 60 (10.8%) were dead within a year. The definition neglects a measure of poor quality of life and thus undercounts futile cases. It also excludes poor outcomes in the first 30 days. Whilst all procedural complications cannot be avoided, Arnold et al count poor outcomes (death or poor quality of life) even if due to a procedural complication, as from the patient's perspective, the outcome remains poor. If 30 day mortality were included, 20.7% of cases in the Italian registry would have been defined as futile.

8.1.3.2 Medical futility for TAVI in New Zealand

At the time of analysis there were 204 records of TAVI and 2,463 records of bioprosthetic AVR with a year of potential follow up data – records having been collected between 2008 and 2014 in the national minimum dataset. For these patients, we matched mortality records and primary hospital admissions for myocardial infarction (MI) or stroke that occurred within a year of intervention. Myocardial infarction and stroke are associated with significant morbidity and quality of life decrement.[232] In the absence of a quality of life record, stroke and MI are used as a limited proxy for poor outcomes other than death. We also recorded one-year primary diagnosis of cardiac arrest. Although excluded from Table 39, just one record was reported of cardiac arrest (for a patient who received a bioprosthetic AVR).

Table 39: Futility among TAVI and bioprosthetic AVR patients at 12 months post procedure

Intervention	Records	Deaths	MI	Stroke	Multiple events (stroke, MI)	Combined events
Bioprosthetic AVR	2463	7.8%	2.4 %	3.1%	0.1%	13.4%
TAVI	204	9.6%	4.8 %	4.5%	0.5%	19.1%

Source: NHC analysis of NMDS and mortality collections

While rates of death, MI and stroke look better for surgical AVR than TAVI, it should be noted that the populations are not equivalently risk stratified. The TAVI population pool is higher risk. We do no not have a good measure of patient quality of life, however, compared with the prior studies it appears there are lower rates of futility for New Zealand patients undergoing TAVI. If, following the Italian

analysis, futility is defined as one year mortality less 30 day mortality (30 day mortality was 3.8% in our assessment), then approximately 6% of TAVI performed might be classed as futile procedures. Accounting for quality of life, we would expect the measure to be somewhat higher than this. In the aforementioned PARTNER[228] and CoreValve extreme risk[230] analyses, mortality accounted for just over half the poor outcome measure (54%, and 56%, respectively) where poor quality of life accounted for the other half.

8.1.3.3 Prospective assessment of futility

The preceding estimates of futility are all retrospective, whereas clinical decision-making is prospective. Lindman et al (2014) propose a four-part framework to determine whether a patient is likely to meaningfully benefit from TAVI, including: 1) clinical risk stratification; 2) geriatric risk stratification; 3) anticipated clinical benefit; and 4) assessment of patient goals and preferences.[40] The detail of the framework goes beyond the scope of the societal and ethical assessment domain. Briefly, **clinical risk stratification** involves consideration of preoperative risk (patients with an STS >15% were shown to have no survival benefit compared with patients on medical therapy in PARTNER B[107]); assessment of left ventricular function impairment; and identification of significant severe comorbidities. **Geriatric risk stratification** goes beyond traditional clinical risk assessment focusing on factors such as frailty, disability, cognitive impairment, malnutrition, and social isolation. Frailty, in particular, has been associated with significant elevated 12-month mortality for TAVI. **Anticipated clinical benefit** includes assessment of likely survival benefit and quality of life gain (crossing over with clinical and geriatric stratification, where the prospective assessment of quality of life outcomes is less clear cut). **Assessment of patient goals and preferences** – as the assessment of futility is inherently values driven, patient preferences must be accounted for. Patient preferences and risk acceptability thresholds are unlikely to be homogenous – even faced with similar circumstances.[233] Patient preferences may also differ from those of clinicians. Gampel (2006) argues that patients, rather than doctors, are best placed to articulate their own preferences in the face of potential futility.[224] Accounting for patient preferences does not imply an unlimited right to healthcare, where physicians have a stewardship role in the allocation of finite medical resources,[222, 225] but it does require clear communication, shared decision-making, and informed consent.

9 Feasibility of adoption

This section attempts to answer the following research question:

What are the feasibility of adoption issues relating to TAVI in New Zealand when budget impact, workforce, policy congruence and regulatory issues are taken into account?

Key points

- New Zealand guidance for TAVI patient selection is dated and has not achieved its stated intention of containing TAVI to high-risk patients. The model of care for AS now requires revision.
- A number of elements should be included in the revised model including:
    - An evidence-based definition of 'high risk' – New Zealand and international research suggests that the STS-PROM should be used to define operative risk.
    - Other factors not considered in the STS such as frailty, 'hostile chest' and the presence of a porcelain aorta are also important considerations.
    - Data collected on patient quality of life to provide feedback to clinicians on the

value of intervention, and provide the evidence for any indication expansion.
    - A greater role for geriatricians in the heart team used to prioritise intervention.
- Neither the clinical nor the economic evidence reviewed in this report suggests significant expansion in TAVI is warranted. For patient safety, it is imperative that TAVI is undertaken in centres with sufficient volume and experience. As volumes are not expected to expand significantly in the foreseeable future, TAVI centres should be limited to the current three: Auckland, Waikato and Canterbury.
- Though there remain complex issues regarding workforce and capital planning, TAVI is not expected to significantly impact on either workforce or capital in the foreseeable future.
- Though TAVI appears to be undertaken in intermediate-risk patients, the current reimbursement regime, which reimburses TAVI at the same rate as conventional AVR, sets the right incentive for DHBs to fund the procedure when it makes sense – ie not in low-risk patients. No change to the reimbursement of TAVI is proposed.

What are the requirements for TAVI?

The 2014 American College of Cardiology/American Heart Association practice guideline for the management of patients with valvular heart disease makes a class I (level of evidence C) recommendation for heart team involvement for patients in whom TAVI or high-risk surgical AVR is being considered due to the complexity of the issues under consideration.[36]

Requirements for the use of TAVI include a sufficiently large facility to support the infrastructure and workforce described below, with a large referral base and high clinical case volumes such that the centre can undertake at least 20 procedures a year.[29] The volume requirement has important implications for the expansion of TAVI in New Zealand. Our analysis suggests that current volumes of TAVI are already in excess of the number of true high-risk patients. We do not see sufficient evidence from a clinical or a cost-effectiveness perspective for volumes to expand beyond 80 procedures per annum in the foreseeable future. That is assuming some growth from the current rate of about 66 procedures per annum. We therefore cannot support the addition of a new centre in the medium-term. This is subject to change with a maturing of the technology and the evidence base for its effectiveness and cost-effectiveness in lower-risk populations.

Facilities also need to be able to offer alternative treatment options for patients not referred for TAVI, including BAV (if appropriate), heart failure clinics and palliative care services. TAVI providers should also be proficient in the use of all available TAVI devices and should undergo some form of accreditation, audit and review. It has been suggested that not all cardiology units should provide TAVI services, and that the introduction of TAVI requires an academic environment, clinical research infrastructure, and experience with high volume cardiac services. European guidance notes that approximately 1-2% of TAVI patients require immediate cardiac surgery for life-threatening complications, hence it is recommended that TAVI should only be performed in hospitals with cardiac surgery on-site.[88] In Germany, where TAVI has been performed outside of cardiac surgery centres, the government has recently issued a directive to contain TAVI only to centres where cardiac surgery is performed.[234] Currently TAVI is only performed in cardiac surgical centres in New Zealand.

Infrastructure requirements include:

- cardiac imaging (including trans-thoracic and trans-oesophageal echocardiography and access to multi-detector CT scanning with experienced radiographers and a well-trained and experienced cardiac imaging team) – to support diagnosis, confirmation of intervention pathway and intervention approach;
- a catheterisation laboratory with adequate imaging quality and adequate size to accommodate sufficient staff (routinely 11+ staff in a teaching facility) to perform TAVI procedures;
- hybrid operating theatres (ideal comprise a purpose-built structural heart disease catheter laboratory with large floor size) to perform TAVI and open heart procedures if required;
- a high volume cardiothoracic surgery unit experienced in high-risk valve and coronary artery bypass surgery, rapid availability of surgeon and theatre, adaptable nursing staff and perfusionist – in case an open heart procedure is required;
- a dedicated coronary care unit with intensive care unit back-up; and
- a dedicated cardiac research unit with exposure to new technologies, data monitoring, contribution to the global pool of evidence and potential cost reduction by involvement in clinical trials.

The three centres that provide TAVI in New Zealand, Auckland, Waikato, and Christchurch, meet these infrastructure requirements.

Workforce requirements include (the minimum for a 'heart team'):

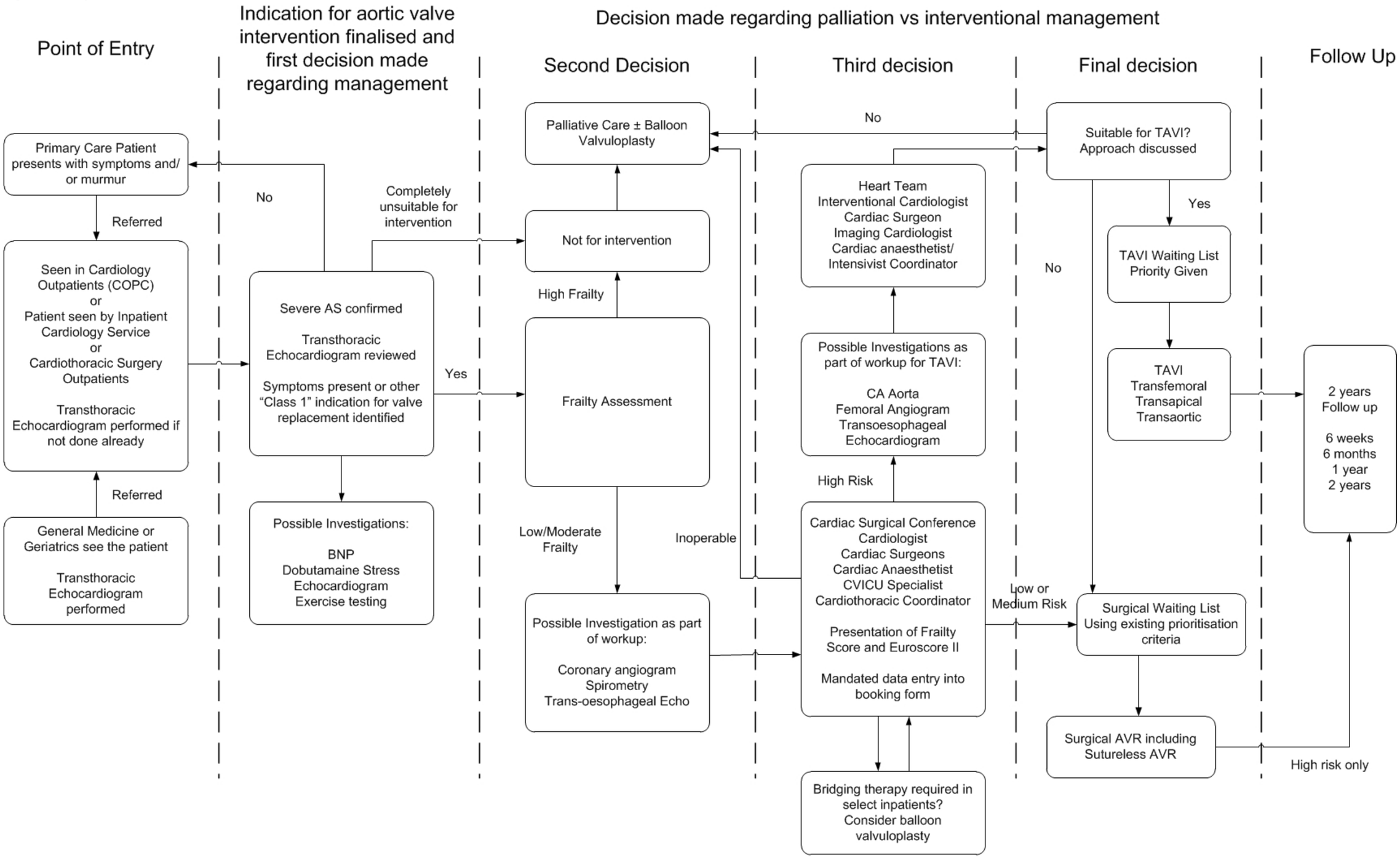
- interventional cardiologists
- imaging cardiologists
- cardiothoracic surgeons
- cardiac anaesthetists or intensivists
- coordinator, typically with a nursing background, for facilitating the throughput of TAVI patients
- geriatrician.[36, 88]

Current New Zealand guidelines require a heart team (TAVI selection group) approach, as discussed in section 5.2 of this report. In sector engagement workshops held between the NHC and key stakeholders, it emerged however, that one centre had replaced its multidisciplinary TAVI selection group with a 'high risk valve' clinic. Standardisation of a heart team approach is important to secure consistent and equitable access to TAVI across the country.

Model of care

During the course of 2014, the executive of the NHC engaged with stakeholders to better understand the model of care for severe aortic stenosis. This included two joint meetings. The NHC held its first stakeholder workshop on the 28 February 2014 and involved the following groups: the Cardiac Society of Australia and New Zealand (CSANZ), the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS), the New Zealand Cardiac Network, the College of Intensive Care Medicine of Australia and New Zealand (CICMANZ), Australian and New Zealand Society of Geriatric Medicine (ANZSGM). The second meeting, held on the 15 August 2014, also included representatives from DHB funding and planning, the national Health IT Cluster, and DHB clinical services directors. Out of these discussions a revised national clinical pathway of care for patients with AS, was developed (Figure 11).

Figure 11: Proposed model of care – aortic stenosis



There are multiple points of entry into this pathway, including referral from primary care and referral from general medicine or geriatrics electively or after an acute episode. A decision is then made around patient appropriateness for intervention – normally by a cardiologist, although other internal medicine specialists may screen out unsuitable candidates. The interventions in the model of care are surgical AVR, TAVI, sutureless AVR, balloon valvuloplasty, and medical management. After referral most patients are seen at their local DHB cardiology outpatient clinic or reviewed by cardiology services as an inpatient at their local DHB secondary care hospital. Diagnostic assessments, including echocardiogram, are undertaken to confirm diagnosis. Medical management is established for those patients unsuitable for intervention. A central part of any assessment for surgical or transcatheter intervention is an assessment of surgical risk – generally identified through a tool such as the EuroSCORE or the STS score. If a patient is a potential candidate for surgery or TAVI, their case will be presented at the regional cardiac surgical conference. The decision of the conference is the key determining factor around acceptance for surgery. All high-risk patients undergoing consideration for TAVI must then be presented at the multidisciplinary heart team meeting. The final decisions that are made at the cardiac surgical conference and the heart team meeting determine the care each patient receives. Patients deemed to be appropriate candidates for valve replacement undergo workup prior to surgery by their local cardiology service. If the regional cardiac surgical conference do not think the patient is an appropriate candidate for valve replacement, the patient cannot therefore proceed to surgical AVR or TAVI. These patients are provided medical management and/or palliative care. Interventional management for TAVI is provided by the regional cardiac centres at Auckland, Waikato, and Canterbury DHBs. After treatment and discharge from hospital TAVI patients are managed through established follow-up clinics.

The main points of difference from the current model of care that were discussed in the joint working groups were:

- Standardised patient selection criteria nationally for aortic stenosis interventions.
- Frailty and cognition testing as part of the clinical decision process.
- Mandatory inclusion of the specified multidisciplinary heart team.
- Mandatory entry of clinical and business data into a national surgical AVR/TAVI registry.

Standardised patient selection criteria nationally for aortic stenosis interventions

Current New Zealand patient selection guidelines are not consistent with the stated policy that TAVI be used for high-risk patients only (Figure 12).

As discussed, the logistic EuroSCORE overestimates risk and if used for prioritisation of high-risk patients is likely to lead to the inclusion of lower-risk patients. The STS-score, which provides a more accurate measure of preoperative surgical risk, should be used in preference to the logistic EuroSCORE. This is in line with the recommendations of recent New Zealand research and international guidelines. More concerning is the prima facie ability to define a patient as ‘high risk’ on the basis of single factors such as age, previous coronary artery bypass graft, or heavily calcified aorta. While this may not be true in practice, we are unaware of any evidence-based guidelines that allow ‘high risk’ to be so defined. The current criteria are consistent with the national TAVI intervention rate that is at least twice the size of the high-risk population.

It is also noteworthy that the STS-PROM already includes age and coronary artery bypass graft or percutaneous coronary intervention as part of its algorithm. The STS score also accounts for multiple comorbidities, though not all, seen to be associated with operative mortality; including: heart failure, renal failure, cardiac arrhythmia, diabetes, endocarditis, compromised immune system, chronic lung disease, cerebrovascular disease, peripheral arterial disease, and other valvular disease.

Figure 12: Identification of high-risk surgical cases

High-risk surgical cases are to be identified 'using one or more' of the following high-risk features:

- advanced years
- previous coronary artery bypass graft
- heavily calcified aorta
- high logistic EuroSCORE or STS score
- sum of comorbidities (such as renal, pulmonary, hepatic and cerebrovascular), severe pulmonary hypertension, previous chest radiation.

TAVI patients were/are expected to benefit from the procedure in terms of quality of life improvement, with an estimated life expectancy greater than two years.

Source: National Health Board Communication to Chief Executive Officers 7 October 2011

UK guidelines

UK commissioning guidelines stipulate that only high-risk or inoperable patients are eligible for publicly funded TAVI, where 'inoperability is primarily the result of anatomical limitations' (ie patients are technically inoperable); noting that it is generally agreed that patients with limited life expectancy due to concurrent conditions such as malignancy, dementia, primary liver disease, chronic obstructive pulmonary disease (COPD), among others, are not appropriate for AVR. They note the usual high-risk patient will have a logistic EuroSCORE of >20 or an STS score of >10. Patients need to be screened by a multidisciplinary team. They also note the importance of frailty and related conditions of debility and deconditioning as determinates in a patient's ability to benefit from AVR, even if they survive the procedure.[26]

European guidelines

European guidelines (as outlined in the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) 2012) again outline the importance of the multidisciplinary team, as previously specified. The guidelines support TAVI in high-risk or inoperable patients, but notes that TAVI "should not be performed in patients at intermediate risk for surgery and trials are required in this population." The heart team should consider the respective advantages/disadvantages of TAVI and surgery in high-risk patients. It is recommended that the team include cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if required, general practitioners, geriatricians, or intensive care specialists.

They note that the use of the STS scoring system >10% may result in a more realistic assessment of operative risk than the EuroSCORE, but note factors not considered within the STS, such as frailty and conditions such as porcelain aorta, history of chest radiation may make a patient high risk despite having an STS < 10%. Contraindications to TAVI include an estimated life expectancy of less than a year and no expected improvement in quality of life, so-called futile cases (Figure 13).[88]

Figure 13: Contraindications for TAVI

Absolute contraindications
Absence of a 'heart team' and no cardiac surgery on the site
Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical
Estimated life expectancy <1 year Improvement of quality of life by TAVI unlikely because of comorbidities Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical
Inadequate annulus size (<18 mm, >29 mm[a])
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF <20%
For transapical approach: severe pulmonary disease, LV apex not accessible

AVR = aortic valve replacement; LV = left ventricle; LVEF = left ventricular ejection fraction; TAVI = transcatheter aortic valve implantation.
[a]Contraindication when using the current devices.

Source:[88]

US guidelines

Consistent with the direction from Europe and the UK, United States guidelines (as outlined by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the management of Patients with Valvular Heart Disease 2014) also recommend a heart team approach to the decision to treat with TAVI. The highest recommendation, Grade I, is given for the employment of a heart valve team in the decision to treat high-risk patients in whom TAVI or surgical AVR are options. The heart valve team should optimise patient selection for available procedures through a comprehensive understanding of the risk:benefit ratio of different treatment strategies. The guidance recommends TAVI for inoperable patients with a predicted survival greater than 12 months (Grade I). TAVI is recommended as an 'alternative' option for surgical AVR in high-risk patients (Grade II). High risk is defined as an STS-PROM score of 8% to 15%, anatomic factors that increase surgical risk, or significant frailty. The guidance notes that surgical AVR should be considered over TAVI in patients who are at higher surgical risk but have severe multi-vessel coronary disease. As with the UK guidelines, TAVI is not recommended in patients in whom existing comorbidities would preclude any benefit from correction of AS. As with European guidelines, patients should have a reasonable expectation of benefiting from TAVI – defined in the US guidelines as a post-procedure life expectancy greater than one year; and at least a 75% chance of surviving two years with improvement in quality of life.[36]

Frailty and cognition testing as part of the clinical decision process

Historically, there has not been a robust scoring tool for clinical frailty to screen patients for cardiac surgery. Frailty has been shown to be a strong independent predictor of life expectancy and surgical outcomes in the literature.[235, 236] Patients with high frailty indices are unlikely to survive for reasons other than their primary cardiac condition and this can make invasive and expensive interventions like aortic valve replacement clinically futile and cost-ineffective.

There appears to be a developing acceptance that frailty needs to be assessed prior to assessment of operative risk. A formal scoring tool developed by the Ministry of Health, the Cardiac Surgical Appropriateness tool, is now under evaluation and includes measures of patient frailty, comorbidities, cognitive function, and surgical complexity. The NHC has also contributed to the evaluation of the scoring tool through the provision of Health Innovation Partnership funding for the 'Evaluation of Frailty and Comorbidity in Patients with Ischaemic Heart Disease' by Professor Ralph Stewart at Auckland DHB. The fields for this tool have been included in the national cardiology registry for the patients included in the trial.

Mandatory inclusion of the specified multidisciplinary heart team

A TAVI programme can only be offered by a hospital with a full cardiac surgery service. As mentioned above, it is not clear that all three TAVI centres in New Zealand are employing a comprehensive heart team approach. To the extent that this is the case, we recommend that practice is brought back into line with New Zealand, European and United States professional guidelines as outlined above.[36, 88]

With the acknowledged importance of cognitive and frailty testing prior to surgery, the role of the geriatrician in the heart team might be considered less optional in the multidisciplinary team due to their skills and experience in this field.

Cardiac surgery/cardiology conferences are long standing joint multidisciplinary decision-making bodies in New Zealand. For the centres providing TAVI, these are suitable decision-making mechanisms (ie multidisciplinary heart teams) for the final TAVI decision. However, for those cardiac centres referring potential TAVI patients to other cardiac centres, it would be appropriate for the referral to come through the existing cardiac surgery/cardiology conference or directly from the referring cardiologist. This is to ensure consistent, timely, cost-effective decision-making for patients and providers, and to enable alignment with professional guidelines and consistent patient selection and management for these patients.

Multidisciplinary heart teams ensure patients are clinically suitable for intervention. The heart teams have three options for patients: perform the TAVI; send the patient back to the regional cardiac surgical conference; or send the patient directly to medical management or palliative care. Ideally these decisions would be recorded in a national registry, discussed below. Without peer review, the risk of surgery could be overestimated by an interventional cardiologist, where today modern cardiac surgical practice allows for successful operations on high-risk patients. The requirement for two cardiac surgeons reviewing TAVI cases in the current model of care for TAVI is thus an important safeguard. In response to a massive increase in the supply of TAVI in Germany, the government recently reasserted the need for a heart team approach.[234]

It is recognised that the adoption of the multidisciplinary approach ie including a geriatrician, at each TAVI centre may impact on clinician time. It is our expectation, however, that the resource requirement is likely to pay off in terms of better outcomes for patients with severe aortic stenosis, including avoidance of unnecessary intervention and improved targeting of interventions to patients.

We are encouraged that multidisciplinary heart teams or clinical governance groups are in place or are being established by cardiac centres. This is still work in progress and not yet fully embedded within the system or model of care.

Mandatory data entry into a national TAVI registry

A registry, for the consistent collection of data, is a way of enabling access to TAVI, while collecting the information necessary to make informed decisions around its ongoing role in the model of care for AS.

Recently, the Ministry of Health has establishment two registries; one for cardiac surgery (National Cardiac Surgery Registry, Dendrite Clinical Systems) and the other for cardiology (Acute Predict, Enigma Solutions), which includes data on acute coronary syndromes and interventional cardiology procedures. Both registries are operational and neither registry is capturing any data on TAVI at the current time. DHBs are collecting information on TAVI in local databases.

The strength of the cardiac surgical registry is that all patients undergoing standard surgical AVR will be captured in the registry with a surgical risk assessment (currently EuroSCORE) and therefore, if a TAVI module was added then all national data around AS interventions could be captured in one place for easy access/comparison. However, one surgical centre has declined to use the Dendrite platform and this may cause some difficulty adding a TAVI module to the existing registry. Also, the surgical registry is only available at each of the surgical centres; whereas patients are worked up in all cardiology centres around the country and some of the data (eg frailty score) is intended to be captured prior to the patient being transferred for the intervention. The cardiac surgical registry is not currently configured to collect data on patients not referred for a procedure or intervention.

The cardiology registry has been designed to capture patient data in the long term through linkage to the Ministry of Health's national collections. Data entered into the cardiology registry can be transferred to the cardiac surgery registry for data analysis with surgical data. This registry is operational in all cardiology centres. Also there are currently staff funded in the coming two years to capture frailty data on this registry on all patients undergoing cardiac surgery as part of another research initiative, which is beneficial in the short term for the implementation of TAVI in the agreed model of care. The cardiology registry is endorsed and supported by the Regional Committee of the Cardiac Society of Australia and New Zealand.

The cardiology registry has been recently updated to include the fields for the Cardiac Surgical Appropriateness tool currently being evaluated. These fields are only available and used for those patients in the trial.

There are advantages and disadvantages of collecting AS model of care information in either registry. Either registry could be modified to include the national AS registry. The focus needs to be on the outcomes to be achieved and which registry is the most sustainable solution for the sector.

Neither registry includes an assessment of patient quality of life. World-leading registries, including the United States national Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC) TVT Registry and the German national GARY registry all include measurement of patient quality of life. In the GARY registry, patient quality of life is measured through a simple and well-established tool, known as the EQ5D. Quality of life is recorded at baseline and at one, three, and five years post-intervention for TAVI and surgical AVR patients.[9] In New Zealand, the

[9] https://clinicaltrials.gov/ct2/show/NCT01165827?term=GARY&rank=2

New Zealand Joint Registry also routinely collects quality of life data at baseline and five years using the Oxford 12 Questionnaire.

Quality of life data provides invaluable feedback to clinicians looking to avoid unnecessary and harmful intervention. It can also provide the health sector with the evidence required for cost-effective diffusion of emerging technologies. European and United States guidelines for valvular disease note the need for clinicians to consider the likely quality of life of patients post-intervention – where an anticipated life expectancy of one year or less, or no expectation of improved quality of life, are considered contraindications for aortic valve replacement.[88, 237]

Routine data is not currently being collected on the pathway of care for medically managed patients in either registry. We would encourage a multidisciplinary framework that involves medical specialists in the early decision-making process around severe AS to increase engagement in capturing clinical, frailty and cognition information for all patients with severe symptomatic AS. This information is important for the overall understanding of the AS model of care, particularly to inform how well the other AS interventions are delivering for patients compared with medical management. Ideally, all patients with AS would be included in one national registry.

The TAVI workshop held in Australia in February 2013 and the document prepared jointly by the ACCF/AATS/SCAI/STS, provide the following guidance around the establishment of a TAVI registry [16,89]:

- Data to be collected on all forms of aortic valve replacement to enable comparative assessments of effectiveness and safety of TAVI to be performed locally.
- Submission should be compulsory to facilitate completeness and minimise reporting bias.
- Industry may be a possible source of funds to pay for the development and maintenance of a registry.
- Standardised definitions for clinical events such as those described by the VARC-2 should be used and endpoints should be prospectively adjudicated using a blinded clinical event committee.
- Surgeon input into operability should be required to distinguish accurately between 'high risk' and 'inoperable patients'. This is cited as a limitation of current registries.

National governance of the registry is important for ongoing ownership and oversight. The NHC, if involved in funding the registry, would need to participate in the governance, in addition to cardiologists and cardiac surgeons from around New Zealand involved in the delivery of TAVI services.

Service delivery

It is expected that three centres nationally will continue to deliver TAVI services: Auckland will provide TAVI for the Auckland region and Northland, Waikato will serve the rest of the North Island and Christchurch will be the TAVI centre for the South Island. The centres already performing TAVI have the relevant infrastructure (catheterisation laboratory or hybrid theatre) to support the procedure, with the necessary cardiac surgery on site to back up. These centres also have non-invasive imaging particularly cardiac CT and MRI in addition to echocardiography to provide imaging support for valve sizing and procedural planning. International consensus statements exist for starting and maintaining a TAVI programme, including specific operator experience and institutional experience, facilities and core personnel.[16, 87] The existing centres comply with these requirements. The five existing cardiothoracic centres will continue to provide surgical AVR in the way they have been operating for many years.

9.1.1 Model of care implications

As identified previously, the revised model of care for AS includes a number of points of difference from the current model of care. The implications for service delivery of implementing these key elements is summarised below.

- Standardised patient selection criteria nationally for aortic stenosis interventions
    - The change management required to implement a nationally consistent process when services have developed in response to their own resources, staff, facilities and other constraints.
    - The move away from EuroSCORE to STS would require changes to registry databases and buy-in from surgeons and cardiologists, where the STS has more fields of entry than EuroSCORE.
    - Careful documentation of the patient-related factors in the national registry may place pressure on cardiology outpatient clinics where this information is collected.
- Frailty and cognition testing as part of the clinical decision process
    - The Cardiac Surgery Appropriateness tool is currently being resourced and evaluated. To meet the requirements of the revised model of care this, or another frailty tool, would need to be uniformly available across all sites in the AS model of care. The research is expected to be completed in April 2016, with the results likely to be shared with the sector some months later. If the outcome of the evaluation is positive, it will be expected to be implemented nationally with the associated cost. If the evaluation outcome is not positive, then another tool for assessing frailty may need to be identified or developed.
      The evaluation of the frailty tool is focused on patients with ischaemic heart disease considered for coronary angiography and those admitted with an acute coronary syndrome. Patients considered for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) are included.
- Mandatory inclusion of the multidisciplinary heart team
    - Multidisciplinary heart teams or clinical governance groups are being established by the cardiac centres, with the regional cardiac surgery/cardiology conferences well established in some centres. However, for some this is still work in progress and not fully embedded within the system or model of care.
    - To facilitate communication and timely intervention, a coordinator is required in each multidisciplinary team, as well as access to appropriate communications technology (including video or teleconferencing facilities). The adoption of the multidisciplinary heart team approach aligned with the international guidelines at each TAVI centre also impacts on clinician time. Therefore, resourcing the heart team would need careful discussion with DHBs to ensure that adequate FTE (ie including a geriatrician) and technological support was available for this meeting. Note this may be a marginal cost where the regional cardiac surgery conferences is utilised for TAVI decision-making.
- Mandatory data entry into a national TAVI registry
    - Ideally all patients who are diagnosed with severe AS will be included in the national registry, including those who go on to medical management or palliative care rather than a specific AS intervention. While desirable to collect data for all patients with severe symptomatic AS, we estimate about 860 patients per annum, so cost is an important factor. A large portion of these patients are inoperable, we estimate about 350 patients per annum. The prognosis of severe symptomatic AS patients who do not

receive intervention is well established. Patients have a mean survival time of 4.5 years after onset of chest pain, 2.6 years after the onset of fainting, and less than a year after the onset of left heart failure.[5] The subgroups of highest interest are the technically inoperable patients, comprising <20 patients per annum, high-risk patients, comprising <30 patients per annum, and moderate-risk patients, comprising <80 patients per annum. Surgical AVR remains the gold standard for low-risk patients and moderate-risk patients, but the clinical evidence frontier is now firmly focuses on the moderate-risk patient group, where we believe TAVI is already being undertaken in New Zealand. Hence, depending on the cost implication, the first areas for data collection ought to be the moderate to high-risk patient pool and possibly the technically inoperable pool.

- Lack of interoperability of registries for the treatment of aortic stenosis is a serious flaw in the current system. The establishment of two registries (cardiac surgery and cardiology) has potentially created a 'disconnect' in the model of care for AS. While cardiac interventions are currently included in the cardiac surgery register, the workup prior to surgery is managed through local cardiologists, who may not have access to the surgery registry. The New Zealand Cardiac Network and Cardiac Society have indicated a preference for the cardiology registry. The alignment of the entry of information into the registries with the AS model of care will need to be resolved as the TAVI module in the registry is established and embedded. This will be an additional cost to the sector.

9.1.2 Capital investment in facilities

There have been significant volume increases in cardiac procedures and interventional radiology of which the implementation of TAVI is only one intervention. In response to the increased demand, DHBs have made plans for additional capacity. A new hybrid catheterisation laboratory has recently been commissioned at Auckland DHB; a decision is to be made in the near future about the next catheterisation laboratory in the Northern region. Bay of Plenty DHB is making plans for a new hybrid laboratory (with no established on site cardiac surgical service) and two additional laboratories are planned for the Christchurch Hospital redevelopment. However, these capital planning decisions have been made in the absence of a current national plan for cardiovascular services.

There are also flow-on impacts to other facilities including intensive care, coronary care and ward facilities. These facilities also require significant capital investment, ongoing revenue streams, and efficient operating models to be sustainable. National planning should incorporate analysis to better understand when a step change in these facilities and other infrastructure may be required to respond to cardiac forecast demand or whether this can be managed by improving the utilisation of existing facilities. DHBs are making these expensive investment decisions based on continued introduction of high cost/high technology services without necessarily having an understanding of where expansion might end up or being able to trade off investment in cardiac service capacity with other investment demands.

There appears to be no national direction which brings together the medium to long-term direction for cardiology and cardiac surgery. The New Zealand Cardiac Network provides clear direction for improving current service delivery, particularly for cardiology services, but there appears to be no national planning which incorporates analysis to better understand when a step change in these facilities and other infrastructure may be required to respond to cardiovascular forecast demand or, for example, whether this can be managed by extending the hours of use of existing facilities.

We do not see TAVI significantly impacting on infrastructure for the foreseeable future, as the overall number of patients forecast to receive this treatment based on the status quo or even expansion into the technically inoperable patient population is less than 100 per year for the foreseeable future. There is insufficient evidence to justify material expansion, when very good outcomes can be achieved for most patients at lower cost using surgery. However, the forecast volume of TAVI patients does need to be considered in the overall planning suggested for cardiovascular services.

Workforce

DHBs suggest that there may be enough clinicians to respond to increasing demand for TAVI in the short to medium-term. However the skills required from these clinicians may not be aligned with forecast demand for new cardiovascular interventions. The sector still needs to maintain and support clinicians with a broad range of cardiothoracic surgical and cardiology skills to manage procedures such as complex multiple valve issues and paediatric cardiac surgery, as well as non-interventional cardiology services in local DHBs. There are other staff required to support the TAVI and the AS model of care, including perfusionists, geriatricians, technicians and specialist nurses/coordinators, where DHBs have reported there may be shortages in the medium-term.

There is also training required before a clinician is able to perform TAVI and achieve optimal outcomes. TAVI has a learning curve that is specific to the TAVI device and delivery system.

Health Workforce NZ has identified in its strategic intent and priorities to strengthen the health and disability workforce. This aligns with the requirements of the AS model of care as follows:

- Improve recruitment, retention and distribution of a sustainable, flexible and fit-for-purpose workforce.
- Professional staff required to support the TAVI (and AS) model of care.
- Align workforce development to meet service demand.
- Determine the optimal number and balance between cardiothoracic surgeons and cardiologists and the sub-specialty skill mix (including specialist cardiology imaging and interventional cardiology).
- The workforce required to support the multidisciplinary heart teams (specialist coordinator, clinicians etc).
- Workforce requirements at the regional cardiac centres as well as local district cardiology services.
- Strengthen health workforce intelligence to provide high quality support and advice.

Funding

As with all DHB provider arm services, including surgical procedures and medical treatment provided in hospital, elective surgery volumes are paid for through funding received by DHBs based on the national Population Based Funding Formula (PBFF). DHBs also receive centrally held ‘top slice’ funding specifically for elective surgery. This makes up around 30% of the total DHB spend on elective surgery. Of this funding, $20 million per year is ‘ring fenced’ for elective cardiac surgery. This means that patients having elective surgical AVR or TAVI could be funded through either DHB funding or electives funding. This does not vary depending on whether the patient is classified as ‘high-risk’ or ‘inoperable’.

Currently, provision of TAVI is restricted to ‘high-risk’ surgical patients as a substitute for surgical AVR. In this scenario, it has been argued that overall the same amount of time and labour is being

consumed in the hospital for TAVI as for surgical AVR. In contrast, 'inoperable' patients increase demand for theatre and labour time because previously they would have been treated via medical management. If TAVI were expanded to the broad inoperable patient, the cost impact would be material at about $3 to $4 million a year nationally. As many inoperable patients are unlikely to benefit from TAVI, we are not advocating expansion to the broad inoperable population. There is a 'technically inoperable' subgroup which appears to do as well as high-risk patients, though the evidence of efficacy is low quality. This population is small, comprising no more than 15 to 20 patients per year, with a cost impact of less than $1 million per annum. That is equivalent to roughly an additional patient every two months for each of the three centres, a volume increase we consider sustainable provided indication creep into other patient cohorts is avoided. The feasibility of such an expansion would hinge on tight agreed parameters, with prospective data collection, to ensure that TAVI did not expand into the broader inoperable population.

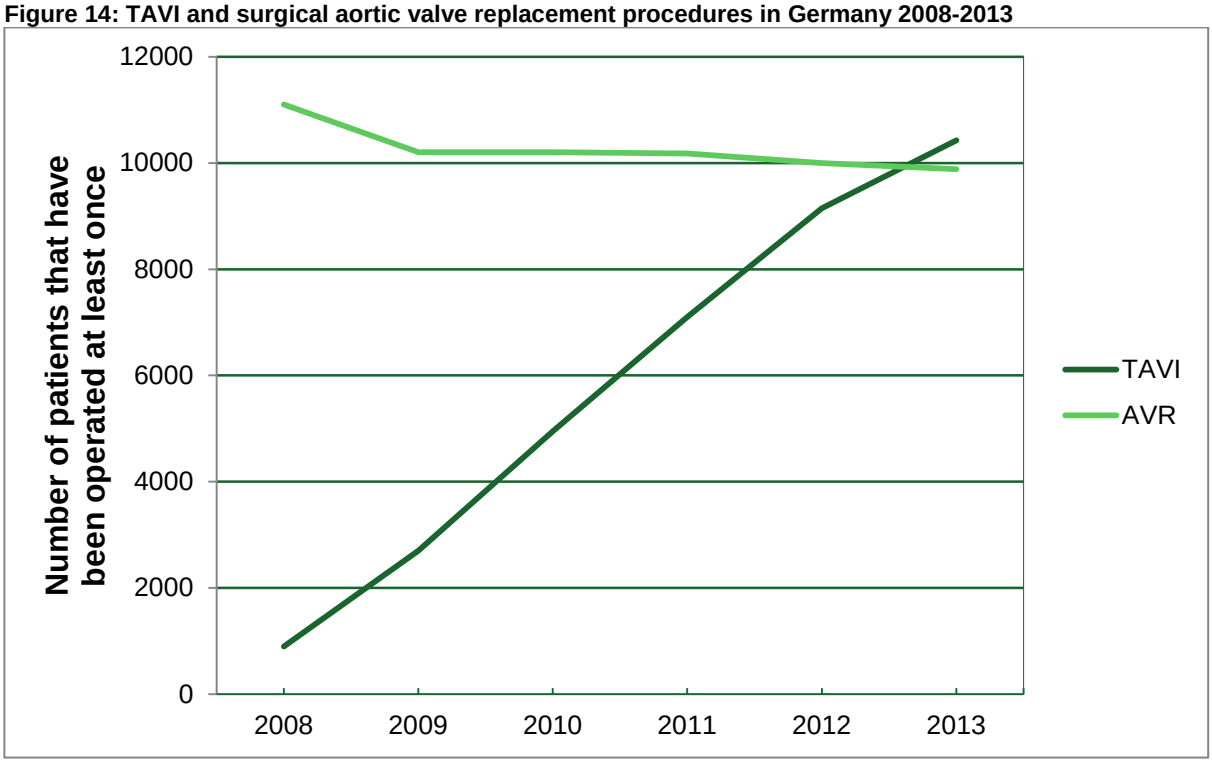
European experience is that higher TAVI intervention rates are observed in countries in which TAVI is completely reimbursed via a therapy-specific national diagnosis related group (DRG) tariff.[238] TAVI-specific national DRG-based reimbursement occurs in Germany, France, Switzerland, and Denmark. The United Kingdom, Spain, the Netherlands, Belgium, Portugal and Ireland do not have TAVI-specific reimbursement; rather the cost is incurred by a local healthcare trust or hospital. Likewise in New Zealand, the DRGs used for reimbursement are those used for surgical AVR. Funding for aortic valve replacement including TAVI is based on the diagnostic related group (DRG) the event appears in, predominantly F03A, F03B, F04A, and F04B.

TAVI-specific reimbursement may compensate for the full additional cost of the TAVI valve up-front, which in New Zealand is about $25,000, thereby making it more feasible for TAVI to be used in lower risk populations, where there is less opportunity to get compensatory savings in the form of reduced patient length of stay. Thus TAVI-specific reimbursement incentivises indication creep.

The German Federal Joint Committee[10] *Hospital Quality Report 2013* found 9,883 aortic valve replacements were undertaken using conventional AVR while 10,426 TAVI were undertaken in the same year.[239] Volumes have substantially increased since 2008 (Figure 14).

[10] The Committee is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. It decides which health services will be reimbursed for 70 million Germans, and specifies measures for quality assurance in inpatient and outpatient health care.

Figure 14: TAVI and surgical aortic valve replacement procedures in Germany 2008-2013



Source: [239]

In Germany it is acknowledged that TAVI has been used in young patients, low, and moderate-risk patients, and that this has come about in response to favourable reimbursement rate for TAVI.[22, 23] No health technology agency currently supports TAVI in low-risk patients. Data from the German Aortic Valve Registry suggests that about half of the TAVI procedures were undertaken on low to moderate-risk patients – logistic EuroSCORE < 20. [21] Economic evaluations do not currently support the cost-effectiveness of TAVI in low to moderate-risk patients – where surgical AVR remains the gold standard. At current costs, if New Zealand were to track a similar path to Germany and have half of all AVR undertaken using TAVI, the cost impact would be significant. On the assumption of no expansion into inoperable patients (which would be more cost increasing) the German intervention rate would imply about 150 low-risk patients receiving TAVI in New Zealand per year. At an incremental cost of $18,000, the net annual cost would be $2.8 million, for no proven benefit for patients relative to surgical AVR.

We have heard from some stakeholders that TAVI may be underfunded in New Zealand on a procedure basis. We have investigated this concern with the national Casemix Project Group within the National Cost Collection and Pricing Programme (NCCP). The team's role is to collect costs from DHBs annually to review the inter-district flow prices for DHB hospital services, including the cost weights used in the casemix funding that includes TAVIs and other high cost implants. The Casemix Project Group are aware of the need to ensure that implant costs are incorporated at the right level in the weighting model and continue to monitor the costs. Checks on the cost of surgical AVR and TAVI are made at DRG level rather than at the individual procedure/unit cost level. While individual line items may appear under or overvalued, it is the overall DRG view that is taken into account.

However, the NCCP does not always recognise the fully absorbed costs of running a service. These costs include the capital expenditure (facilities and equipment) and associated depreciation, workforce costs, consumables (pharmaceuticals, medical devices/implants, theatre linen,

disposable sterile packs, ward costs etc) and contribution to organisation overheads. There is an inherent tension between the national price paid by the funder for the episode of care (including procedure and inpatient stay) and the actual fully absorbed cost incurred by the provider who delivers the care. There is also a tension between the population funding provided to a DHB, the services to be delivered as part of the production plan by the DHB provider arm and those provided by other DHBs for that same population.

This is particularly relevant to TAVI as a shortfall is indicated in the 2013/14 data for TAVI events and for all events in the four DRGs identified (F03A, F03B, F04A, and F04B). This DRG will have been a loss-maker for the five cardiac centres, and more particularly the three that provide TAVI. Resolving this issue has been identified by the Casemix Project Group and steps are in place to address the issue, however this can take one to two years. There is also another revenue stream called the tertiary adjuster, which supplements base casemix funding for variations from the norm experienced by tertiary providers, and including allowance for new technology. This stream, too, should be taken into account when considering the revenue due for aortic valve replacement including TAVI.

We believe the current funding arrangement provides the correct incentive for DHBs to prioritise TAVI where it makes financial sense and where it is evidence based, ie in high-risk patients. This incentive is also enhanced through budget sharing, whereby TAVI and surgical AVR are provided from the same budget. TAVI is seen as a substitute for surgical AVR rather than an additional intervention. TAVI is likely to become a more routine intervention in New Zealand provided evidence is forthcoming for its use in lower risk groups, and provided the price of the valve becomes more competitive. We have witnessed a dramatic reduction in the cost of sutureless aortic valves in the past four years as a direct response to competition. In 2011, sutureless valves were about $10,000 more costly than a regular bioprosthetic valve; today they are almost price competitive. With more than a dozen companies competing for market share, we do not expect the current $25,000 premium for a TAVI valve to be sustained long -erm. As the technology evolves we may also see shorter patient length of stay and operating times, especially where patients do not require general anaesthetic. The current reimbursement system is expected to respond to this price signal with increased supply.

Cost-effectiveness and affordability

TAVI appears cost-effective in high-risk patients, but not in inoperable patients. This is fitting with the current Government policy that TAVI be funded in high-risk patients only. There is a small group of technically inoperable patients, probably no more than 15 to 20 patients annually that may benefit from TAVI. Though the evidence for the efficacy in this patient group is low quality, and there is a risk of indication creep without viable patient selection criteria. It is expected it would cost just under a million dollars a year to fund TAVI in this population. More significant, from a cost perspective, is the potential risk for indication creep into lower risk patients. Here the procedure is likely to be significantly cost increasing at no proven benefit to the patient.

Accountability and performance

Accountability and performance information is required to support the implementation of the revised model of care on a number of levels. Much of this information, including patient outcomes, process measures, clinical measures, cost data and volume data, is already collected through national systems, however there are some gaps.

Clinical and independence outcomes should be collected for high-risk patients who have had aortic valve replacement. This includes potential complications of the procedure such as stroke, vascular complications and death. There should also be periodic audit of all high-risk AS across New Zealand,

including clinical and cost parameters, to ensure TAVI continues to provide expected health and independence gains. There should also be collection and analysis of quality of life outcomes for these patients using a tool such as EQ5D.

To ensure appropriate targeting of TAVI, DHBs should be required to report on TAVI patient volumes by risk status based on the agreed national definition. DHBs have negotiated local targets for elective surgery, taking into consideration the health needs of their communities. Collectively these targets contribute to a national increase in elective surgery discharges. The current target is that the volume of elective surgery will be increased by at least 4000 discharges per year[11]. As TAVI patients are discharged from cardiology, they are not consistently included in the elective surgery target. However, as patients treated with TAVI is likely to be <100 patients per year in the foreseeable future (out of 153,000 surgical discharges) the impact is immaterial.

DHB performance monitoring of elective surgery performance indicators and targets, AVR intervention rates and production plans should be maintained to ensure TAVI patients are correctly accounted for each month.

[11] http://www.health.govt.nz/new-zealand-health-system/health-targets/about-health-targets/health-targets-improved-access-elective-surgery

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11 Appendix 1: Regulatory status of TAVI valves

Vendor	Product name	FDA approval	CE approved	Therapeutic Goods Administration approval	Date in WAND database
Advanced Bio Prosthetics	Perc Valve TM	No	No	No	N/A
Boston Scientific	LotusTM	No	28/10/2013	No	23/05/2014
Colibri Heart	Colibri	No	No	No	N/A
Direct Flow Medical	Direct Flow	IDE only 21/05/2014	1/01/2013	No	N/A
Edwards Lifesciences	SAPIEN XT Transcatheter Heart Valve - P130009	16/06/2014		No	13/07/2015
Edwards Lifesciences	SAPIEN XT Trans catheter Heart Valve - P100041	02/11/2011	5/02/2014	No	13/07/2015
Edwards Lifesciences	Sapien 3THV	02/11/2011	Yes	26/09/2013	27/10/2014
Edwards Lifesciences	Centera TM	No	No	No	N/A
EndoCor	TBD	No	No	No	
Hansen Medical	AorTXTM	No	No	No	N/A
Heart Leaflet Technologies	HLTTM	No	No	No	N/A
Medtronic	Medtronic CoreValve System - P130021/S010	30/3/2015	7/11/2011	6/05/2015	N/A
Medtronic	Medtronic CoreValve System - P130021/S002	12/6/2014	7/11/2011	6/05/2015	N/A
Jena Valve Technology	JenaValve™	No	1/09/2011	No	N/A

12 Appendix 2: International and Australasian TAVI registries

12.1.1 ADVANCE (Medtronic sponsored)

The ADVANCE study is a single arm study, carried out at 44 sites in 12 countries: Belgium, Colombia, Denmark, France, Germany, Greece, Israel, Italy, the Netherlands, Portugal, Switzerland and the United Kingdom. A total of 1015 patients were enrolled, from March 2010 to July 2011.[16] Patients with severe symptomatic aortic stenosis, who were considered inoperable or at high risk, but anatomically acceptable candidates for elective treatment, were considered for enrolment. A median logistic EuroSCORE of 16.0% and a median STS score of 5.3% were recorded.

Of the 996 patients that were implanted with the CoreValve system, 874 (87.8%) underwent implantation via the femoral artery, six patients (0.6%) via the iliac artery, 95 patients (9.5%) via the subclavian approach and 21 patients (2.1%) via the direct aortic approach.

12.1.2 SOURCE (Edwards Lifesciences sponsored)

The SOURCE registry consists of 1038 patients, from 32 centres who underwent TAVI between November 2007 and January 31, 2009.[62, 63] The 32 centres were located in Germany, The United Kingdom, France, Italy, Greece, Denmark, Spain, Sweden and Belgium.

Patients were eligible for TAVI if they were at high risk or non-operable patients. A mean logistic EuroSCORE of 27.6% was recorded. Of the 1038 patients, transplanted with the Edwards Sapien valve, 575 patients (55.4%) received the transapical delivery and 463 patients (44.6%) the transfemoral delivery. The transapical and transfemoral groups were significantly different in baseline characteristics, and therefore cannot be directly compared.

12.1.3 UK TAVI

The UK TAVI Registry has collected data on all TAVI procedures performed in the UK since the introduction of the technique in 2007.[67, 120] As such, there is likely to be some overlap with the preceding registries that have collected data from the UK. The registry is managed by the National Institute for Cardiovascular Outcomes Research (NICOR). Published records are for data collected between January 2007 and December 2009, including 870 patients from 25 centres throughout England and Wales. All patients were deemed to be at high risk for conventional surgery, based on clinical judgement. The median EuroSCORE was 18.5%. Follow-up data was available for 850 patients.

Of the 850 patients, 442 (52.5%) were implanted with the CoreValve while 401 (47.5%) were implanted with the Edwards Sapien valve. 581 patients (68.4%) received transfemoral delivery while 269 (31.6%) received non-transfemoral delivery. Results have been reported separately for the Medtronic CoreValve, the Edwards Sapien valve, and the transfemoral route was compared with non-transfemoral route.

12.1.4 GARY (Some investigators have financial conflict of interest with Medtronic and/or Edwards)

The German Aortic Valve Registry (GARY) is a joint registry of the German Cardiac Society and the German Society for Thoracic and Cardiovascular Surgery that aims to collect complete data on aortic valve interventions for aortic stenosis across Germany.[20, 21] The first year's findings reported on the records of 13,860 patients, who underwent AVR at 78 German centres in 2011. A total of 6523 patients underwent conventional AVR without coronary artery bypass grafting (CABG), 2462 patients underwent conventional AVR with CABG, 2694 patients underwent TAVI using the transvascular

approach and 1181 patients underwent TAVI using the transapical approach. Whether CoreValve or Edwards Sapien was inserted was not specified.

The mean logistic EuroSCORE was 8.8% in patients who underwent conventional AVR without CABG, 11.0% in patients who underwent conventional AVR with CABG, 25.9% in the transvascular TAVI group and 24.5% in the transapical TAVI patient group.

12.1.5 FRANCE 2 (Non-industry)

The French national transcatheter aortic valve implantation registry (FRANCE 2) enrolled 3,195 high risk patients between January 2010 and October 2011, at 34 centres[64]. Baseline characteristics of the overall patient group showed a mean logistic EuroSCORE of 21.9% and a mean STS score of 14.4%.

The Edwards Sapien (including SAPIEN XT) device was implanted in 66.9% of the patients (n=2,107) and the Medtronic CoreValve device in 33.1% of the patients (n=1,043). The transfemoral approach was used in 2,361 patients, 567 patients underwent transapical TAVI, and 184 patients underwent the subclavian approach. Results were individually reported for the two valves and the approaches (transfemoral, transapical or subclavian).

12.1.6 The Spanish National Registry

Ā total of 1,416 patients were included in the Spanish registry from January 2010 to December 2011. The Edwards Sapien device was implanted in 806 patients (56.9%) and 610 patients (43.1%) received the CoreValve device. A logistic EuroSCORE of 17.0% was noted in the baseline characteristics. Risk status was defined as a EuroSCORE > 15 (55% of the patient group). The study reported results for the CoreValve and the Edwards Sapien valve (transapical or tranfemoral).

12.1.7 TCVT-EU (Some investigators have financial conflict of interest with Medtronic and/or Edwards)

The Transcatheter Valve Treatment Sentinel Pilot Registry collected data between January 2011 and May 2012 from 2,571 patients undergoing TAVI in 137 centres of 10 European countries.[66] The 137 centres were located in the following countries: Czech Republic, France, Spain, Switzerland, the United Kingdom, Italy, Poland, Belgium, Germany and Israel. A logistic EuroSCORE of 20.2% was reported.

The two valves used in this study were the Edwards Sapien XT and the Medtronic CoreValve. The study reported on outcomes for the two valves as well as the access sites (transfemoral or transapical). In-hospital complications were assessed by valve type and access site.

12.1.8 TVT-US

The US transcatheter valve therapy (TVT) registry is a collaboration between the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), to monitor the safety and effectiveness of transcatheter valve replacement and repair technology including TAVI. The intention is for all TAVI undertaken to be recorded in the national database. Initial in-hospital and 30-day outcomes have been reported, from 7710 patients undergoing TAVI between November 2011 and May 2013.[18] The overall median STS PROM score was 7%. Patients were classified as either high risk (n=6151, 80%) or inoperable (n=1559, 20%).

Patients were compared based on the risk level (high-risk or inoperable) as well as the access sites (transfemoral or non transfemoral. Further results were reported at one year following-up.[19]

Outcomes were reported for 12,182 US patients undergoing TAVI between November 2011 and 30 June 2013. The median STS PROM score for the study cohort was 7.1%.

12.1.9 ANZ CoreValve (Medtronic funded study)

The ANZ CoreValve study is a single arm industry sponsored registry. Ten centres across Australia and New Zealand enrolled 540 patients between August 2008 and July 2013. New Zealand data came from Waikato Hospital and Mercy Hospital in Auckland.[17] Patients had a mean logistic EuroSCORE of 17.3% and an STS score of 5.7%, representing moderate preoperative risk. Patients were evaluated by a multidisciplinary heart team to establish eligibility.

12.1.10 SOURCE-ANZ (Edwards Lifesciences funded study)

The SOURCE-ANZ registry is a single arm industry sponsored registry assessing the outcomes of the Edwards Sapien valve.[118] A total of 132 high-risk patients were enrolled between December 2008 and December 2010 from eight centres in Australia and New Zealand. Sixty-three patients were treated transfemorally, 56 treated transapically, and two patients were withdrawn from the study. The study included 17 patients from Waikato Hospital. A mean logistic EuroSCORE was recorded of 26.8% in transfemoral patients and 28.8% in transapical patients.

12.1.11 Multicentre Canadian Experience study (Some investigators have financial conflict of interest with Edwards)

The Multicentre Canadian Experience study enrolled 339 high-risk patients who underwent TAVI with the Edwards Sapien valve between June 2005 and June 2009 in six Canadian centres.[114] An STS-PROM score of 9.8% was recorded for the patient cohort. The study recorded outcomes for the Edwards Sapien valve using the transfemoral access site (n=162, 47.8%) and the transapical access site (n=177, 52.2%).

12.1.12 NRCA registry (Various authors had financial conflict of interest with Edwards)

Data from 1,023 high-risk TAVI patients, implanted with the Edwards Sapien valve, were recorded in the US Non-randomised Continued Access (NRCA) Registry.[116] A total of 27 eligible sites enrolled patients between September 2009 and January 2012. The study employed a second generation Edwards delivery system, the RetroFlex 3 delivery system, using the transfemoral approach. The NRCA registry included patients who were either inoperable or high-risk. The logistic EuroSCORE and the STS score were 24.25% and 10.86%, respectively.

12.1.13 Italian multicentre registry

An Italian multicentre registry, a single arm study, consisting of 663 patients, collected data from 14 centres between June 2007 and December 2009.[115] Patients with symptomatic severe aortic stenosis received the third generation 18-Fr CoreValve valve. The logistic EuroSCORE for the overall population was 23.0%.

12.1.14 CoreValve extreme risk study

The CoreValve extreme risk study is a non-randomised single arm observational study of the CoreValve deliver system, using the iliofemoral approach, in 489 patients with severe aortic stenosis.[111] Mean STS was 10.3% ±5.5, greater than that in the CoreValve high risk RCT, and a little less than the PARTNER A and B trials (discussed above). Anatomical features making surgery difficult were reported including: porcelain aorta in 4.9% of patients; chest-wall deformity in 5.5% of patients; and a hostile mediastinum in11.9% of patients (not mutually independent classes). Amongst

TAVI patients, PARTNER B had higher rates of porcelain aorta (11.2%) and chest-wall deformation (8.4%) with 8.9% of patients having previous radiation to the chest, all considered anatomical issues for surgery.

13 Appendix 3: Ongoing and planned TAVI RCTs

Table 40: Current and planned TAVI RCTs

Study	Primary end point	Comparator	N	Primary completion date	Phase	Sponsor	Valve	Patient Risk	Clinical trial ID
PARTNER II Trial	All-cause mortality and stroke. Plus repeat hospitalisation (inoperable) [Timeframe: 2 years for high risk; 1 year other]	Surgical AVR	6650	1/07/2020	3	Edwards Lifesciences	SAPIEN XT™, SAPIEN 3™	High, Intermediate, Inoperable	NCT01314313
SURTAVI	All-cause mortality or disabling stroke [Timeframe: 24 months]	Surgical AVR	2500	1/08/2016	NA	Medtronic Cardiovascular	CoreValve and Evolut R System	Intermediate	NCT01586910
PORTICO-IDE	All-cause mortality and stroke at one year. [Timeframe: one year]	Portico TAVI system vs Other TAVI	1610	1/08/2019	NA	St. Jude Medical	Portico TAVI	High	NCT02000115
HighRisk CoreValve and Extreme Risk CoreValve (Non-randomised) Studies	Extreme Risk: All-cause Death or Major Stroke; High Risk Surgical: All-cause Mortality [Timeframe: 1 year]	Surgical AVR	1451	1/08/2020	NA	Medtronic Cardiovascular	CoreValve®	High	NCT01240902
REPRISE III	All-cause mortality stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications.	Lotus Valve vs CoreValve	1032	1/01/2021	NA	Boston Scientific Corporation	Lotus Valve vs CoreValve	High, and Intermediate	NCT02202434
BRAVO-2/3	Major Bleeding [Timeframe: 48 hours post-procedure or discharge]	TAVI + Bivalirudin vs TAVI + Unfractionated heparin (during procedure)	870	1/08/2015	3	The Medicines Company	TAVI	Inoperable, High	NCT01651780

Study	Primary end point	Comparator	N	Primary completion date	Phase	Sponsor	Valve	Patient Risk	Clinical trial ID
Protection by Remote Ischemic Preconditioning During Transcatheter Aortic Valve Implantation Trial	Extent of peri-interventional myocardial injury using troponin I serum concentrations [Timeframe: 72 post TAVI]	Remote ischemic preconditioning Before TAVI vs TAVI without RIPC-protocol	378	1/02/2017	2	University Hospital, Essen	Procedure: Remote ischemic preconditioning (RIPC) vs Pacebo in TAVI context	Inoperable, High	NCT02080299
Cerebral Protection in Transcatheter Aortic Valve Replacement Trial	Reduction in median total new lesion volume as assessed by DW-MRI at Day 4-7 post-procedure.	TAVI + Cerebral Protection System vs TAVI	359	1/05/2015	NA	Claret Medical Edwards Lifesciences	Edwards SAPIEN THV or Edwards SAPIEN XT. And Cerebral Protection System-The SENTINEL System	High	NCT02214277
NOTION	All-cause mortality + myocardial infarction + stroke [Timeframe: 1 year]	Surgical AVR	280	1/04/2018	2	Rigshospitalet, Denmark	TAVI, surgical AVR	Inoperable	NCT01057173
CHOICE Trial	Device success - VARC-2 defined [Timeframe: Immediately after the procedure]	Edwards Sapien XT vs Medtronic CoreValve	240	1/12/2018	3	Herz-Kreislauf-Zentrum Segeberger Kliniken GmbH	Edwards Sapien XT, Medtronic CoreValve	High	NCT01645202
REDUCE-AKI	Reduction of acute kidney injury using VARC 2 definition at 48-72 hours	Renal Guard vs Conventional Treatment	220	1/12/2016	4	Tel-Aviv Sourasky Medical Center	Renal guard forced diuresis with matched hydration versus conventional treatment for TAVI		NCT01866800
ARTE Trial	Incidence of death, MI, ischemic stroke/Transient ischemic attack (TIA) or life threatening/major bleeding [Timeframe: 12-month follow-up]	Aspirin + clopidogrel vs aspirin alone post TAVI	200	1/07/2016	4	Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Quebec	Edwards SAPIEN XT		NCT01559298
DIRECT	Device success Timeframe 30 days and as designated by the VARC-2	TAVI without balloon aortic valvuloplasty (BAV) vs TAVI with	170	1/05/2018	3	University of Athens	CoreValve	Intermediate	NCT02448927

Study	Primary end point	Comparator	N	Primary completion date	Phase	Sponsor	Valve	Patient Risk	Clinical trial ID
	criteria	BAV							
Use of Standardized Diagnostic Imaging Data for Image Fusion in the Hybrid Operating Room	Radiation Dose (mSv) administered to each patient [Timeframe: Day of intervention (day 1)]	Procedures (TAVI, MitraClip, Left Atrial Appendage Closure and Catheter Ablation) with and without a multimodal image fusion software support	140	1/01/2014	NA	University of Zurich	TAVI, MitraClip, Left Atrial Appendage Closure and catheter Ablation with or without HeartNavigator EchoNav		NCT01821651
CARE-TAVI	Post-procedural myocardial injury, measured with cardiac troponine T [Timeframe: 72 hours after intervention]	TAVI with or without RIPC (remote ischemic preconditioning)	120	1/04/2016	NA	Institut für Pharmakologie und Präventive Medizin			NCT02283398
SIMPLIFY TAVI	All-cause mortality, stroke, non-fatal MI, acute kidney injury, or pacemaker implantation at 30 days	TAVI without BAV vs TAVI with BAV	110	1/12/2014	NA	University Hospital, Bonn	CoreValve	High	NCT01539746
ELECT Trial	Paravalvular aortic regurgitation [Timeframe: Within 5 days after TAVI]	Edwards SAPIEN vs CoreValve®	108	1/11/2014	NA	UMC Utrecht	Medtronic CoreValve. Edwards SAPIEN	Inoperable, High	NCT01982032
EPICURE	Rate of red blood cell transfusion [Timeframe: 30 days]	TAVI + Erythropoietin vs TAVI + Placebo	100	1/06/2016	3	Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Quebec	TAVI erythropoetin vs placebo		NCT02390102
CLEAN-TAVI	Rate and the size of cerebral embolism (MRI 3 days after intervention).	TAVI + Cerebral protection Filter vs TAVI without	100	1/06/2015	NA	University of Leipzig	Claret MontageTM Dual Filter System with a Medtronic CoreValve®.		NCT01833052
DEFLECT III	All-cause mortality, all stroke, major bleeding, Acute kidney	TAVI with the TriGuard HDH embolic deflection	86	1/04/2015		Keystone Heart	TriGuard™ HDH Embolic Deflection Device.		NCT02070731

Study	Primary end point	Comparator	N	Primary completion date	Phase	Sponsor	Valve	Patient Risk	Clinical trial ID
	injury, major vascular complications [Timeframe: Up to 7 days]	device vs TAVI without					TAVI unspecified		
REAC-TAVI	Suppression of residual platelet reactivity by Verify-Now P2Y12 assay. [Timeframe: Three months following TAVI]	(Ticagrelor vs Aspirin + Clopidogrel vs standard therapy) after TAVI	60	1/08/2016	4	Andres Iñiguez Romo, MD, PhD	Unspecified		NCT02224066
Assessment and Cardiovascular Rehabilitation in Patients With Severe Aortic Stenosis Study	Functional Capacity by the Six-Minute Walk Test [Timeframe: Change from Baseline at 3, 6 and 12 months]	Surgical AVR	60	1/06/2017	1 and 2	Irmandade Santa Casa de Misericórdia de Porto Alegre	Unspecified		NCT02468219
TAo-EmbolX	New brain injury post TAVI [Timeframe: Postoperative day 1-3]	Transaortic TAVI with EmbolX vs TAVI without	50	1/10/2013	NA	University Hospital, Essen	Edwards Embol-X: embolic protection management system and Edwards SAPIEN Valve		NCT01735513
Oxygenation of the Cerebrum and Cooling During Transcatheter Aortic Valve Implantation (TAVI) Procedures - Part II	Change in cerebral oxygen saturation during periods of rapid ventricular pacing and valve implantation	Cooling of the brain to 33°C during TAVI vs no cooling	30	1/12/2014	NA	Hasselt University	TAVI, targeted brain cooling (33°C) by RhinoChill device versus Placebo		NCT01822964

Source: NHC

14 Appendix 4: Cost of TAVI and AVR

Bioprosthetic AVR were identified with the International Classification of Disease procedure code, ICD-10.v6 “3848801”. At the time of analysis there was no specific code (Diagnostic Related Group code or ICD-10 procedure code) to identify TAVI in the national minimum dataset. To identify TAVI, we searched the free text field within the national minimum dataset. DHBs were then contacted to confirm or amend our records. Sixty-six records of TAVI were confirmed for the 2012/13 financial year, the latest year for which cost data was available in the NCCP dataset. Event IDs for these records were then used to interrogate the NCCP dataset to estimate the cost of TAVI. The cost includes all procedure costs associated with the inpatient event. All data was anonymised. A breakdown of the component cost of TAVI and Bioprosthetic AVR is contained in Table 41 below.

Table 41: Cost of TAVI and Bioprosthetic AVR 2012/13

Average cost	Average patient cost of TAVI (Waikato only n=35)	Average component cost (Waikato only)	Number of records	Average patient cost of bioprosthetic AVR (n=331)	Average component cost (NZ)	Number of records
Total costs	$55,000		35	$46,000		331
Implants and single use expensive items	$34,100	$34,100	35	$4,000	$5,100	284
Theatre/Procedure Rooms	$5,900	$5,900	35	$10,600	$11,500	306
Critical care	$4,200	$4,200	35	$9,300	$10,000	309
Blood bank	$3,400	$3,400	35	$1,200	$1,700	243
Medical	$2,500	$2,500	35	$8,000	$8,700	314
Anaesthetists	$1,600	$1,600	35	$2,700	$3,200	276
Clinical support staff	$1,100	$1,100	35	$500	$500	326
Wards	$800	$1,100	25	$6,000	$6,100	309
Laboratory	$600	$600	35	$1,200	$1,300	307
Radiology	$400	$500	25	$600	$700	307
Outpatient utilisation	$300	$400	28	$50	$100	192
Other treatments	$0	$0	0	$1,700	$7,000	80
DHB emergency department	$0	$0	0	$50	$400	39
Pharmacy	$0	$0	0	$100	$100	223
Length of stay (days)	7		35	12		331

Source: NHC analysis of NCCP data, using cost schedule seven, from Waikato DHB confirmed cases of TAVI and all Bioprosthetic AVR cases in 2012/13.

The above analysis was conducted using the cost schedule seven. Definitions are contained in Table 42 below.

Table 42: CS7 Definitions

Code	Name	Definition
A010	Wards	The costs of providing the inpatient and day patient care within a ward setting.
A020	Outpatient utilisation	The cost of providing the outpatient clinic facility. This includes facilities providing pre-admission and post-discharge assessments, secondary obstetric clinics, orthopaedic fracture, pregnancy and parenting education, sexual health, specialist nursing clinics, and procedure units eg endoscopy.
A030	Medical	The cost of providing the medical staffing care to inpatients, day patients, outpatients and theatre or procedure room activities
A036	Anaesthetists	The cost of providing specialist medical officer anaesthetist care to inpatients, day patients and outpatients in any location.
A040	Laboratory	Costs including all staff types of maintaining laboratory services.
A050	Blood Bank	Costs of providing blood and blood products to patients, including all NZ Blood Service costs.
A060	Radiology	Costs including all staff types of maintaining radiology imaging services.
A070	Clinical support staff	The cost of providing health professional support services and supplies to patients in any setting.
A080	Theatre/ Procedure Rooms	Facility and staff costs for operating theatre and recovery rooms. Includes specific procedure rooms where anaesthesia may not always be required and maternity unit Caesarean theatres.
A090	Pharmacy	Costs of maintaining pharmacy services for individually prescribed drugs. The pharmacy staff cost of filling and maintaining imprest drug stores, where the individual patient receiving the drug is not electronically recorded, should be allocated to those drug store areas. Examples are emergency department, wards, and community nursing.
A100	Critical care	The cost of providing the inpatient and day patient care within an intensive care unit, neonatal ICU, coronary care unit or other high-dependency specialist unit.
A110	DHB emergency department	The cost of providing the emergency department service. This includes costs of acute assessment units managed within the same clinical directorate as the emergency department, but not assessment/short stay wards which are outside of the ED director's management scope.
A120	Implants and single use expensive items	Costs of implants and high-cost disposable items used in theatre and procedure rooms. Implants include all costs in code range 4500 to 4599 of the Common Chart of Accounts.
A140	Sterile supplies	The cost of providing sterile supplies intermediate products. Note: If these costs are not tracked to individually identified patient events, but instead are charged out to appropriate patient care areas, they should be included in the separate CS2 cost pool and included as a component of theatre, inpatient ward, and outpatient CS7 intermediate products. These costs should not be recorded as overheads in any area.
A145	Other patient support costs	The cost of providing other patients support costs to patients in any setting. Note: If these costs are not tracked to individually identified patient events, but instead are charged out to appropriate patient care areas, they should be included in the separate CS2 cost pool and included as a component of theatre, inpatient ward, and outpatient CS7 intermediate products. These costs should not be recorded as overheads in any area.
A150	Pharmaceutical cancer treatment	Costs of maintaining services for individually prescribed pharmaceutical cancer treatment drugs as specified in the PHARMAC schedule. The pharmacy staff cost of filling and maintaining imprest drug stores, where the individual patient receiving the drug is not electronically recorded, should be allocated to those drug store areas. Examples are emergency department, wards and community nursing.

Table 43: Cost of isolated surgical AVR and TAVI at Auckland Hospital 2012/13

	TAVI	Isolated surgical AVR
ALOS	8.79	10.04
Events	19	69
Total costs	$ 55,999	$ 42,145
Blood	$ 424	$ 424
Allied health	$ 847	$ 428
Anaesthetists	$ 535	$ 2,303
Other treatments	$ 3,573	$ 4,557
Wards	$ 1,850	$ 3,910
Radiology	$ 326	$ 295
Medical	$ 3,753	$ 6,362
Pharmacy	$ 77	$ 49
Laboratory	$ 802	$ 1,015
ED	$ -	$ 40
Implants	$ 30,000	$ 4,520
ICU	$ 9,595	$ 9,598
Theatre	$ 4,218	$ 8,643

Source: Auckland DHB Analysis of NCCP

Compared with Waikato DHB cost data, Auckland has much lower blood costs. The blood costs in the Waikato TAVI data are high owing to an individual patient who had very high use, where the patient later died.

15 Appendix 5: Cost-utility analyses and cost analyses for TAVI

Table 44: Cost-utility analyses and cost analyses for TAVI

Author/Date	Comparator	Health system	Time horizon (years)	Approach	Valve	Origin of data	Incremental values		ICER (cost per QALY)
							Cost	Benefit	
Reynolds et al (2012)[147]	surgical AVR	US	1	TF/TA	SAPIEN	PARTNER A	US$2,070	0.027	US$76,800
							TF: -US$1,250	0.068	TAVI dominant
							TA: US$ 9,906	-0.07	TAVI dominated
Reynolds et al (2012)[187]	MM	US	1	TF	SAPIEN	PARTNER B	US$ 79,800	1.29	US$61,900
Gada et al (2012)[240]	surgical AVR	US	Life expectancy	TF/TA	SAPIEN	Literature/registry	US$3,164	0.06	US$52,700
Gada et al (2012)[196]	surgical AVR	US	Life expectancy	TA	SAPIEN	Literature/registry	$100	-0.04	TAVI dominated
Fairbairn et al (2013)[186]	surgical AVR	UK	10	TF/TA	SAPIEN/CORE	PARTNER A Trial/literature	-£1,300	0.063	TAVI dominant
Neyt et al (2012)[198, 241]	surgical AVR	Belgium	1	TF/TA	SAPIEN	PARTNER Trial/literature	€20,397	0.027	€750,000
							TF: € 17,708	0.03	€546,384
							TA: € 26,685	0.01	€1,810,667
	MM			As above			€33,200	0.74	€44,900
Doble et al (2013)[197]	surgical AVR	Canada	20	TF/TA	SAPIEN	PARTNER Trial/literature	C$11,153	-0.102	TAVI dominated
	MM			As above			C$31,000	0.60	C$51,300
Orlando et al (2013)[193]	surgical AVR	UK	25	NR	NR	PARTNER Trial/literature	£7,983	-0.60	TAVI dominated
	MM			As above			£24,147	1.87	£12,900
Sehatzadeh et al (2013)[194]	surgical AVR	Canada	20	TF	SAPIEN	PARTNER Trial/literature	-C$4,642	-0.069	
	MM			As above			C$15,230	0.628	C$24,250
Scottish Health Technology Group (2010)[199]	surgical AVR	Scotland	Life expectancy	NR	NR	Literature/registry	£4,859	0.06	£87,293
	MM			As above			£14,680	0.65	£22,600
Osnabrugge et al (2012)[24][12]	surgical AVR	The Netherlands	1	TF	CORE	Directly assessed	€10,700	0.068	€150,000
Simons et al (2013)[195]	MM	US	Life expectancy	TF	SAPIEN	PARTNER B Trial/literature	US$83,800	0.7	US$ 119,300
Watt et al (2012)[242]	MM	UK	10	TF	SAPIEN	PARTNER B Trial/literature	£25,200	1.56	£16,200
Hancock-Howard et al (2013)	MM	Canada	3	TF	SAPIEN	PARTNER B Trial/literature	C$15,700	0.48	C$32,200
Queiroga et al (2013)[243]	MM	Brazil	5	TF	SAPIEN	PARTNER B Trial/literature	R$87,200	0.97 (per life year)	$R90,100 (per life year)
Murphy (2013)[208]	MM	UK	Life expectancy	TF	SAPIEN	PARTNER B Trial/literature	£15,800	0.44	£35,900
Studies published post systematic review									
Medtronic (2014)[244]	surgical AVR	US	Life expectancy	NR	CORE	CoreValve US High Risk Study	$13,700	0.20	$67,000
Ribera et al. (2014) [25][13]	surgical AVR	Spain	6 months	TF	SAPIEN	Appears to be direct assessment	€7,202	0.045	€161,086
					CORE		€7,476	0.003	€2,451,568
Kumar et al (2014)[245]	MM	Mexico	10	NR	NR	Literature	MXP $777,414	1.61 Life years	MXP $483,022
Brecker et al (2014)[246]	MM	UK	5	NR	CORE	PARTNER B and ADVANCE study	£22 009	1.24	£17,718
Chu et al (2014)[247]	MM	US	2	NR	SAPIEN	PARTNER B	US$65,813	0.5	US $132,155

[12] This study was for moderate-risk patients

[13] This study was for moderate-risk patients

Cost analyses						
Author/Date	Comparator	Health System	Time Horizon	Origin of data	Incremental Cost	Benefit
Bhattacharyya et al 2014[27]	TAVI vs surgical AVR in moderate to high risk patients	NZ	Index admission	District Health Boards – retrospective data	$NZ13,000 cost saving per procedure	Average length of stay in TAVI patients was half that of surgical AVR patients. ICU cost in surgical AVR patients was $10,000 higher than in the TAVI patients. On average, TAVI required 10% of the blood product costs associated with surgical AVR.
Rankin et al (2013)[165]	TAVI v.s High Risk surgical AVR in patients with severe aortic stenosis and age ≥80 years or logistic Euroscore ≥20% treated with TAVI or surgical AVR between the 2008–2011 Euroscore≥20%	Western Australia	1 year	Linking the cardiothoracic surgery, perfusion and echocardiography databases of the three adult acute tertiary hospitals with Hospital Morbidity Data from the WA Data Linkage System and cost data from hospitals.	AU$ $16,000 cost saving (30 days)	Thirty-day and 12-month mortality was 6.2% and 12.3% for TAVI and 0% and 10.8% for surgical AVR, (p = 0.79, 12-month) Lengths of hospitalisation were significantly shorter with TAVI (mean 8.2 days vs 20.1 days, p < 0.0001).
Toth et al (2014)[248]	TAVI v.s surgical AVR Patients not matched by preoperative risk	Belgium	5 years (appears to be index admission cost)	Appears to be single centre	(€28,436 [27,108; 32,677] vs. €14,170 [12,840; 18,060], for TAVI and surgical AVR respectively; p<0.001).	No difference in post-procedural hospital stay
Sinclair et al (2013) [249]	TAVI v.s surgical AVR Unclear if patients matched by preoperative risk	Canada	1 year	Single centre	TAVI had an incremental cost $NZ13,000. Procedure cost for TAVI versus surgical AVR were estimated to be C$29,755 versus C$17,395 respectively	

TF: transfemoral approach; TA: transapical approach; MM: medical management

Source: Cost-effectiveness summary adapted and updated from [250]

16 Methods

Most methods have been described up-front in the main body of the text. Additional detail is described below.

Literature search

The NHC previously undertook a systematic literature review of TAVI in 2012 (unpublished). A systematic review was not undertaken for this updated assessment due to the large volume of systematic reviews that already exist. The recent acceleration in trial evidence also made a systematic review impractical.

Mid-term mortality of TAVI patients in New Zealand

Two hundred and thirty-six records of Transcatheter Aortic Valve Implantation (TAVI) were identified in the National Minimum Dataset (NMDS) and confirmed with DHBs. The procedures, performed between 2008 and 2014, were matched to mortality records using encrypted national health index numbers.

Cost distribution isolated bioprosthetic TAVI (NZ) compared with TAVI (Waikato) 2013

TAVI events carried out at Waikato DHB were identified using the information recorded in the free text field of the NMDS. The records were sent to Waikato DHB for confirmation; the confirmed records were used in the analysis to ensure its accuracy.

Isolated bioprosethetic valve events were found by identifying records in the NMDS where the implantation of a bioprosethetic valve was an element of the care provided without any other form of AVR being provided in that episode of care.

Cost data from the National Cost Collection Project (NCCP) was used to estimate the cost of the TAVI and isolated bioprosethetic valve events.

Data collected in the NCCP project is sourced from the costing systems employed by DHBs to allocate the cost of care across events occurring in their hospitals. Costs are allocated on the basis of the length of stay in hospital and the procedures included in the care of the patient.

Costs for the TAVI and isolated bioprosethetic valve events were identified by linking the unique patient identification code recorded in the verified NMDS data and the NCCP data.

Regional variation in publicly funded TAVI and surgical AVR 2012/13

Publicly surgical AVR funded events for the 2013 financial year were sourced from the NMDS and the New Zealand Health Tracker where the primary diagnosis code was one of the following:

I350 Aortic (valve) stenosis

I352 Aortic (valve) stenosis with insufficiency

I060 Rheumatic aortic stenosis

I062 Rheumatic aortic stenosis with insufficiency.

The data was aggregated in to the following regions:

Northern: Northern, Waitemata, Auckland, Counties-Manukau District Health Boards (DHBs)

Midland: Waikato, Bay of Plenty, Tairawhiti, Taranaki, Lakes DHBs

Central: MidCentral, Hawkes Bay, Whanganui, Wairarapa, Hutt Valley, Capital Coast DHBs

Southern: Nelson Marlborough, West Coast, Canterbury, South Canterbury, Southern DHBs.

Publicly funded TAVI events were identified using the information recorded in the free text field of the NMDS. The records were sent to the DHBs which performed the procedures for confirmation. The confirmed records were used in the analysis to ensure its accuracy.

Rates per 100,000 were estimated using Statistics New Zealand population data aggregated into the regions described above as the denominator, the numerator was the events extracted from the NMDS and the New Zealand Health Tracker.

Māori/non-Māori prevalence, incidence and mortality for aortic stenosis – 2011

Mortality data for the 2012 calendar year was sourced from mortality statistic datasets maintained by the Ministry of Health. Mortality events were selected where the cause of death was coded as one of the following:

I350 Aortic (valve) stenosis

I352 Aortic (valve) stenosis with insufficiency

I060 Rheumatic aortic stenosis

I062 Rheumatic aortic stenosis with insufficiency.

The data was aggregated into the following:

a) Ethnicity
b) Age group
c) Aortic stenosis
d) Rheumatic aortic stenosis.

Age group population data was obtained from the World Health Organisation (WHO) website, aggregated and proportions calculated. Statistics New Zealand population estimates for the 2012 calendar were aggregated using:

a) Ethnicity Māori and non-Māori;
b) Age group.

The age adjusted rate was found by dividing the aggregated mortality data by the Statistics New Zealand population estimates, which were then weighted by the proportions derived from the WHO population statistics.

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