NEW AND EMERGING CARDiac TECHNOLOGIES IN AUSTRALIAN AND NEW ZEALAND PUBLIC HEALTH SERVICES OVER THE NEXT DECADE

PREPARED FOR HEALTHPACT

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# TABLE OF CONTENTS

## BACKGROUND AND CONTEXT

- The burden of cardiovascular diseases ................................................................. 1
- CVD and service demand ...................................................................................... 1
- This review ............................................................................................................ 3
- Scope and limitations of the review ..................................................................... 3

## REVIEW METHODS

- Background analysis and literature review ......................................................... 4
- Consultation with expert informants .................................................................... 5
- Financial analysis .................................................................................................. 5
- Included technologies ........................................................................................... 6
- Device costs ........................................................................................................... 6

## PERCUTANEOUS VALVE REPLACEMENT AND REPAIR

- Technologies – mitral valve replacement ............................................................ 27
- Technologies – mitral valve repair ...................................................................... 25
- Background ........................................................................................................... 23
- Impacts on service delivery .................................................................................. 20
- Evidence of cost-effectiveness .............................................................................. 15
- Evidence of effectiveness ..................................................................................... 12

## TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

- Background ........................................................................................................... 9
- Technology ............................................................................................................. 11
- Evidence of effectiveness ..................................................................................... 12
- Evidence of cost-effectiveness .............................................................................. 15
- Impacts on service delivery .................................................................................. 20
- Evidence of cost-effectiveness .............................................................................. 15
- Evidence of effectiveness ..................................................................................... 12

## TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

- Background ........................................................................................................... 23
- Technologies – mitral valve repair ...................................................................... 25
- Technologies – mitral valve replacement ............................................................ 27
- Evidence of effectiveness ..................................................................................... 27
- Evidence of cost-effectiveness .............................................................................. 31
- Impacts on service delivery .................................................................................. 33

## LEFT ATRIAL APPENDAGE OCCLUSION DEVICES

- Background ........................................................................................................... 35
- Technology ............................................................................................................. 37
- Evidence of effectiveness ..................................................................................... 38
- Evidence of cost-effectiveness .............................................................................. 42
- Impacts on service delivery .................................................................................. 45

## PUMPS / ASSIST DEVICES AS A DESTINATION THERAPY FOR THE

## MANAGEMENT OF HEART FAILURE

- Background ........................................................................................................... 47
- Technology ............................................................................................................. 51
- Evidence of effectiveness ..................................................................................... 53
- Evidence of cost-effectiveness .............................................................................. 55
- Impacts on service delivery .................................................................................. 57

## NEXT GENERATION PACEMAKER AND IMPLANTABLE CARDIAC

## DEFIBRILLATOR DEVICES

- Background ........................................................................................................... 59
- Technology ............................................................................................................. 64
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

Evidence of effectiveness .......................................................................................................................... 67
Evidence of cost-effectiveness .................................................................................................................. 68
Impacts on service delivery .......................................................................................................................... 69

RENAL SYMPATHECTOMIC DENERVATION FOR THE TREATMENT OF RESISTANT HYPERTENSION .......................................................................................................................... 71
Background .................................................................................................................................................. 71
Technology .................................................................................................................................................. 73
Evidence of effectiveness .......................................................................................................................... 74
Evidence of cost-effectiveness .................................................................................................................. 76
Impacts on service delivery .......................................................................................................................... 79

GENETIC TESTING IN THE ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASES .......................................................................................................................... 81
Background .................................................................................................................................................. 81
Technology .................................................................................................................................................. 83
Evidence of effectiveness .......................................................................................................................... 88
Evidence of cost-effectiveness .................................................................................................................. 91
Impacts on service delivery .......................................................................................................................... 92

SUMMARY .................................................................................................................................................. 94

APPENDIX 1 – ‘BREAKTHROUGH TECHNOLOGIES’ .......................................................... 96

DIAGNOSTIC TECHNOLOGIES .................................................................................................................. 96
Cardiac monitoring .......................................................................................................................................... 96
  Wireless pulmonary artery haemodynamic monitor ................................................................................. 96
  Next generation remote cardiac arrhythmia monitoring .......................................................................... 96
  Smart T shirt ............................................................................................................................................. 97
Electrophysiology ........................................................................................................................................... 98
  Stretchable silicon electronics .................................................................................................................. 98
Imaging .......................................................................................................................................................... 98
  Combination intracardiac echocardiography and ultrasound system .................................................... 98
  High resolution miniature ultrasound probe .......................................................................................... 99
  Ultrafast single-photon emission computed tomography (SPECT) ....................................................... 99

TREATMENT TECHNOLOGIES .................................................................................................................. 101
Chamber ...................................................................................................................................................... 101
  C-Pulse cardiac assist device .................................................................................................................. 101
  Cardiac tissue engineering ...................................................................................................................... 101
Electrophysiology ........................................................................................................................................... 102
  Next generation balloon ablation technologies ....................................................................................... 102
  Epicardial ablation system ....................................................................................................................... 103
  Guided medical positioning system .......................................................................................................... 103
  Wireless cardiac stimulator ....................................................................................................................... 104
  Microelectronic pacemaker ....................................................................................................................... 105
  Wireless power for cardiac devices .......................................................................................................... 106
  Optogenetic cardiac pacemaker .................................................................................................................. 106
  Faraday sock .......................................................................................................................................... 108
Valvular ....................................................................................................................................................... 109
  Percutaneous pulmonary valve implantation ............................................................................................ 109
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

Sutureless aortic valve replacement
Vascular
Stents
Fractional flow reserve-guided stenting equipment
Extracorporeal shockwave myocardial revascularisation
Robotic system for percutaneous coronary interventions

APPENDIX 2 –DISEASE BURDEN AND PROCEDURAL DEMAND DATA

Total number of cardiovascular procedures (public and private) performed in Australian public hospitals, 2000/01-2009/10
Trends in cardiovascular procedures, Australia, 2000/01 to 2009/10
Total hospital separations for circulatory conditions, Australia, 1998/99 to 2009/10
Trends in cardiovascular procedures, New Zealand, 2003 to 2007
BACKGROUND AND CONTEXT

Cardiac disease is highly prevalent in populations within Australasia and internationally and is associated with substantial morbidity and mortality. It is therefore not surprising that development of cardiac technologies is an area of intensive scientific and clinical research activity.

The report, commissioned by the Health Policy Advisory Committee on Technology (HealthPACT), describes key new and emerging cardiac technologies, what they are used for and the extent to which they are likely to be available in the future. It is intended to identify the most promising emerging cardiac technologies and anticipate how they may influence the demand for and delivery of cardiovascular services in Australasia over the next ten years.

The burden of cardiovascular diseases

In 2007–08, it was estimated that 3.5 million Australians, or 17 % of the population, had a long-term cardiovascular disease (CVD) (including heart and arterial blood vessel diseases). Nearly 50,000 deaths are attributed to CVD in Australia each year.

An estimated one in twenty adults in New Zealand have been diagnosed with coronary heart disease (161,000 adults) including 118,500 with angina and 89,400 with myocardial infarction. CVD is the leading cause of death in New Zealand, accounting for 40% of deaths annually. New Zealand has a high incidence of ischaemic heart disease, and is above the 75th percentile for male and female deaths from ischaemic heart disease compared to other OECD countries.

CVD is not uniformly distributed among the Australian and New Zealand population:

- prevalence is lower in major city areas compared with more remote locations;
- prevalence is higher is Aboriginal and Torres Strait Islander, Māori and Pacific populations; and
- prevalence is highest in individuals in the lowest socioeconomic group.

CVD and service demand

CVD is a common reason for patients accessing health care services.

CVD is a frequent indication for hospitalisation in Australia, directly responsible for 475,000 a year and indirectly responsible for a further 797,000 hospitalisations each year. Of these hospitalisations, 34 % are for coronary heart disease, 10 % for heart failure and cardiomyopathy, stroke (7%),


peripheral vascular disease (5%), transient ischaemic attack (3%), hypertensive heart disease (2%) and rheumatic heart disease (1%)\(^4\).

In New Zealand, the aged-standardised publicly funded hospital discharge rates for selected diagnoses (2009/10) were ischaemic heart disease (383.9), other forms of heart disease (395.8), cerebrovascular disease (136.2), hypertensive disease (19.9) and chronic rheumatic heart disease (11.8) per 100,000 people. Rates for each diagnosis were higher in the Māori compared with the non-Māori population, including almost four times the non-Māori hospitalisation rate for chronic rheumatic heart disease, and twice the rate other forms of heart disease and hypertension\(^5\). Across privately funded hospital discharges, rates were ischaemic heart disease (9.5), other forms of heart disease (6.7), cerebrovascular disease (2.8), hypertensive disease (0.5) and chronic rheumatic heart disease (0.7) per 100,000 people.

In 2009-10, there were 578,119 cardiovascular procedures performed in Australian public hospitals. The majority of these procedures were conducted on the coronary arteries (182,654), of which 119,437 were coronary angiograms and 34,705 were coronary angioplasty with stenting. In addition, there were 57,985 procedures on the heart ‘other sites’ which included:

- 17,154 for the insertion of permanent transvenous electrode for cardiac pacemaker or defibrillator;
- 12,842 for the insertion of cardiac pacemaker generator or implantable cardioverter-defibrillator (ICD); and
- 8,554 for electrophysiological studies\(^6\).

In 2009-10 there were 60,227 procedures performed on the cardiovascular system in New Zealand. The age-standardised publicly funded hospital procedure rates for selected procedures were coronary angioplasties (85.5), coronary artery bypass grafts (57.0) per 100,000 people. In comparison, private hospital procedure rates were coronary angioplasties (2.9 and coronary artery bypass grafts (2.7) per 100,000 people. Publicly available data demonstrate increasing demand for cardiac surgery over time in New Zealand (Figure 1).

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\(^6\) Appendix 2 of this report
This review

Technologies that can be used in the treatment of cardiac disease are diverse and represent some of the most exciting opportunities to improve the quality of cardiac care. However, they may also be associated with substantial costs to the healthcare sector (public and private). It is therefore imperative that their effectiveness and cost-effectiveness are understood in the formulation of policies and funding models to support their appropriate introduction to clinical practice.

This report describes key new and emerging cardiac technologies, what they are used for and the extent to which they are likely to be available in the future. The most promising emerging cardiac technologies and their potential to influence the demand for and delivery of cardiovascular services in Australia over the next ten years are described in detail.

The potential of the technology to improve quality of care, including its effectiveness and efficiency, is considered for each technology described. The report also highlights organisational issues that will need to be addressed in order to introduce the technology in an equitable and systematic way.

This report does not make any specific recommendations on which technologies policymakers should or should not implement.

Scope and limitations of the review

The scope of new cardiac technologies currently under development is vast. Many of these technologies will not be introduced to the market; others will have limited impact on cardiac practice due either to the nature of the technology itself, or the limited patient group in whom the technology is indicated.

This review therefore includes technologies that have recently been introduced or are emerging that have the greatest potential to transform cardiac practice in the next ten years.

A number of technologies that have not yet reached the stage of market introduction, but which were identified by stakeholders as having the potential to be ‘breakthrough’ technologies over the next ten years, are summarised at Appendix 1.
A limited number of clinical experts were invited to provide advice regarding the completeness, accuracy and relevance of findings from the background analysis. Clinical experts were nominated by HealthPACT members according to their knowledge and experience in clinical practice relating to new and emerging cardiac technologies. Consultation with clinical experts was not exhaustive, a limitation of this report.

**REVIEW METHODS**

Successful identification, evaluation and implementation of new cardiac technologies as they emerge presents a challenge as the evidence regarding their effectiveness and cost-effectiveness has not, by definition, been extensively developed. This report is therefore based on a structured review and appraisal of the peer-reviewed and ‘grey’ literature combined with stakeholder consultation with experts in the field of cardiology and financial modelling using the best available data.

**Background analysis and literature review**

A systematic search of information sources was conducted in order to identify and classify new cardiac technologies. Information sources included the following:

- the US National Institutes of Health registry and results database of federally and privately supported clinical trials conducted in the US and internationally (www.clinicaltrials.gov);
- the peer-reviewed medical and technology literature;
- international networks (EuroScan, Health Technology Assessment International, International Network of Agencies for Health Technology Assessment);
- conference abstracts and public domain presentations since 2010 from conferences and scientific meetings specific to the field of emerging cardiac technology, including the world congress of cardiology scientific sessions; and
- grey literature (policies, position statements, technology publications, industry literature, health technology association / professional body websites) identified through Google® and Google Scholar® searches.

From this information technologies were grouped according to relevant clinical practice areas, namely:

- **Diagnostic technologies:**
  - cardiac monitoring;
  - electrophysiology;
  - imaging; and
  - pathology.
- **Treatment technologies:**
  - chamber:
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

- electrophysiology;
- valvular; and
- vascular.

A summary of the newly introduced and emerging technologies that were identified in the background analysis and through stakeholder consultation is provided at Appendix 1.

Consultation with expert informants

Clinical experts were consulted to provide advice regarding the completeness, accuracy and relevance of findings from the background analysis. Issues discussed with clinical experts included the following:

- new cardiac technologies that may be introduced into clinical practice in the near future;
- their stage of readiness for introduction into clinical practice;
- the patient groups in whom the technology is likely to be introduced;
- strengths and limitations associated with the new cardiac technology;
- their likely impact on quality and safety of care; and
- teaching and training implications associated with the new technology's introduction.

Financial analysis

This analysis makes use of cost data presented in the National Hospital Cost Data Collection. It is not the intention to necessarily match a new procedure with an existing DRG. It is acknowledged that analysis is currently being undertaken to determine how these new procedures will be coded within activity based funding under the National Health Reform Agreement. Currently, different coding outcomes are occurring in different jurisdictions.

Rather the purpose here is to identify a pattern of resource use as set out in the NHCDC for a particular DRG that reflects key aspects of the likely pattern of non-prosthesis costs for the new procedure. Some adjustments to the costs have been made, especially as they relate to length of stay, which impacts particularly ward medical and nursing costs. The prosthesis cost from the 2009/10 NHCDC are substituted with the new prosthesis costs to reflect the cost impact of the new technology.

Other costs including pre-admission investigation and management costs and post-discharge and follow-up costs are included where possible.

Where there is evidence as to costs avoided by the use of new technologies, this information was included in the analysis.

Estimates of the national caseload were made based on available administrative data collections, so an estimate of the total annual costs of the new technologies could be made where feasible. Administrative data upon which the financial analysis was based is provided at Appendix 2.
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

Included technologies

The following new and emerging treatment and diagnostic technologies were identified by selected stakeholders and the published literature as having the greatest potential to influence cardiac practice in public hospitals over the next ten years:

- Percutaneous valve replacement and repair;
- Left atrial appendage occlusion devices;
- Pumps / assist devices as a destination therapy for the management of heart failure;
- Next generation pacemaker and implantable cardiac defibrillator devices;
- Renal denervation systems; and
- Genetic testing in the assessment and management of cardiovascular diseases.

These are described in detail below

Device costs

Clearly an important consideration with the introduction of new procedures is the impact on the total cost of new devices. Cost of device data is on occasions provided in the literature and also reported in national health technology assessments. This data is summarised in Table 1.

Table 1: Approximate costs of cardiac devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Australia</th>
<th>North America</th>
<th>United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVI</td>
<td>AUD25,000-30,000 (jurisdictional advice)</td>
<td>CAND37,606 (CADTH, 2012)</td>
<td>GBP12,500 (UK DoH)</td>
</tr>
<tr>
<td>Mitraclip</td>
<td>AUD37,000-40,000 (jurisdictional advice)</td>
<td>-</td>
<td>GBP14,500 (UK DoH)</td>
</tr>
<tr>
<td>LAA occlusion device</td>
<td>AUD15,000 (jurisdictional advice)</td>
<td>-</td>
<td>GBP4,000 (UK DoH)</td>
</tr>
<tr>
<td>Ventricular assist device</td>
<td>AUD70,000-100,000+ (jurisdictional advice)</td>
<td>USD80,000 (3rd generation)</td>
<td>GBP40,000 (UK DoH)</td>
</tr>
<tr>
<td>Artificial heart</td>
<td>AUD125,000</td>
<td>USD125,000</td>
<td>-</td>
</tr>
<tr>
<td>Subcutaneous implantable</td>
<td>-</td>
<td>USD50,000</td>
<td>-</td>
</tr>
</tbody>
</table>

7 Canadian Agency for Drugs and Technology in Health, Draft Environmental Scan Transaortic Valve Replacement, 2011, at www.cadth.ca/media/pdf/es0274_keytavit_draft_e.pdf accessed 10 December 2012
8 UK Department of Health, A Review of emerging technologies and their potential impact on cardiac services over the next ten years, London, 2011
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost (jurisdictional advice)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cardioverter defibrillator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal denervation catheter</td>
<td>AUD7,000</td>
<td></td>
</tr>
</tbody>
</table>
PERCUTANEOUS VALVE REPLACEMENT AND REPAIR

The two most common forms of valvular heart disease are aortic stenosis and MR, accounting for over 70% of cases of acquired valvular disease\textsuperscript{11}. The number of procedures being performed on valves is increasing over time and is likely to continue to increase in Australia and New Zealand over the next ten years (Figure 2).

\textbf{Figure 2: Cardiac surgical discharges involving a valvular procedure, Australia and New Zealand 2002/03 to 2007/08}

Hospitalisations for aortic and mitral valve disease have increased in Australia and New Zealand over time, particularly for aortic valvular disease\textsuperscript{12,13}. In both countries, aortic valvular disorders are

\textsuperscript{12} AIHW. Hospitalisations data cubes. Accessed December 2012.
\textsuperscript{13} New Zealand Cardiology Clinical Network.
the main type of valve disorder occurring people dying with valvular heart disease, followed by mitral valve disorders\textsuperscript{14,15}.

Percutaneous treatment of valvular heart disease is now one of the fastest developing areas of cardiology. Aortic and mitral valve disease are the main clinical indications for percutaneous valve intervention. Transcatheter aortic and pulmonary valve replacement and percutaneous mitral valve repair have been performed in growing numbers of patients internationally\textsuperscript{16}.

Given the increasing prevalence of aortic stenosis with population ageing, and the significant association between aortic stenosis and patient morbidity and mortality, aortic valve implantation in particular is expected to become more common in Australia and New Zealand over the next ten years.

\section*{TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)}

\textbf{Background}

Aortic valve stenosis (AS) is the most commonly occurring acquired valvular disease, accounting for 43\% of all valvular heart disease\textsuperscript{17}. The three primary causes of valvular AS are congenital abnormalities with superimposed calcification (unileaflet or bileaflet), calcific disease of a trileaflet valve or rheumatic valve disease. These causes have clinically distinct underlying aetiologies.

Symptomatic AS is associated with sudden cardiac death, arrhythmias, endocarditis, cardiac failure, increased bleeding tendency and, infrequently, embolic events\textsuperscript{18}.

There are a number of procedures that may be performed for the management of AS: aortic valve repair, replacement of the aortic valve with either a mechanical valve or bio-prosthetic valve, including stented aortic valves, stentless aortic valves, aortic homografts, the Ross procedure and the use of biological aortic root prostheses.

Surgical aortic valve replacement is the well-established mainstay of treatment of symptomatic AS and offers substantial improvements in symptoms and life expectancy\textsuperscript{19}.

In Australia since 2000/01 the number of aortic valve replacement procedures performed annually has increased. Bio-prostheses are the commonest form of aortic valve replacement performed (Figure 3)\textsuperscript{20}.

\begin{thebibliography}{99}
\bibitem{14}ABS. Causes of Death, 2010.
\bibitem{15}National Health Committee. Briefing report on Transcatheter Aortic Valve Implantation. September 2012.
\bibitem{17}Lung B et al. A prospective survey of patients with valvular heart disease in Europe. European Heart Journal 2003; 24: 1231-43.
\bibitem{19}Kelly T et al. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. American Journal of Cardiology 1988;16:123-130
\end{thebibliography}
In 2009/10 the following aortic valve procedures were performed in New Zealand public and private hospitals (Table 2).

**Table 2: Aortic valve procedures, New Zealand, 2009/10**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Public hospital discharges</th>
<th>Private hospital discharges</th>
<th>Total hospital discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision procedures on aortic valve</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Repair of aortic valve</td>
<td>103</td>
<td>3</td>
<td>106</td>
</tr>
<tr>
<td>Replacement of aortic valve</td>
<td>752</td>
<td>48</td>
<td>800</td>
</tr>
<tr>
<td>Other procedures on aortic valve</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Aortic valve replacement is indicated in essentially all patients with symptomatic AS who are medically able to receive surgery. With some exceptions, valve replacement should not be performed for isolated severe AS in asymptomatic patients\(^2\). Aortic valve surgery entails substantial risks for some patients with severe comorbidities, and for some considered at “extreme” risk, surgery is not appropriate. In others, technical limitations, e.g. severe calcification of the aorta, may mean that surgery is not feasible. In these circumstances,\(^2\)

options include percutaneous aortic valvotomy, transcatheter aortic valve replacement or medical management.

In patients who are considered unsuitable for aortic valve surgery, transcatheter aortic valve implantation (TAVI) is a potential treatment option. In the absence of TAVI the standard of care is medical management. Percutaneous aortic valvotomy may be used as a palliative or a bridging procedure in some patient subgroups\(^{(22,23)}\).

TAVI has been approved for use in New Zealand public hospitals as an alternative to surgery, where clinically appropriate.

Percutaneous AVR started to be performed in New Zealand in 2008 (specifically TAVI, which was piloted at Waikato DHB from 2008 to 2010) and in 2011 started to diffuse to other New Zealand Cardiac centres. There have been over 100 TAVI procedures performed in New Zealand to date. Publicly funded annual TAVI reported volumes for 2008 to 2011 were 18, 18, 14 and 33 respectively, the majority being performed in Waikato DHB but with small numbers reported in 2011 in the Auckland, Canterbury and Southern DHBs.

There are currently four hospitals across three District Health Boards providing TAVI in New Zealand. These District Health Boards accept referrals and provide TAVIs to people from other District Health Boards.

**Technology**

A number of types of percutaneous transcatheter aortic valves are currently available:

- CoreValve® (Medtronic, Inc.; Minneapolis, Minn);
- Edwards SAPIEN® Transcatheter Heart Valve (Edwards Lifesciences LLC; Irvine, Calif);
- Edwards SAPIEN XT™ and SAPIEN 3 (Edwards Lifesciences LLC; Irvine, Calif);
- JenaValve (JenaValve Technology, Munich, Germany);
- Engager (Medtronic);
- Direct Flow Medical Aortic Valve (Direct Flow Medical);
- Sadra Medical Lotus (Boston Scientific);
- Portico THV (St Jude Medical);
- Vitality and Vanguard (ValveXchange);

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NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

- Heart Leaflet Technology valve (Bracco Diagnostic); and
- Acurate TA™ valve (Symetis, Ecublens, Switzerland).

TAVI is performed by deploying the stent valve by expansion of a balloon on a balloon-expandable stent or by withdrawal of a sheath that releases a self-expanding stent or by mechanical device expansion. The deployed stent valve must remain securely implanted with displacement of the diseased native valve so that the new tissue valve can begin to function immediately.

Careful patient screening for vascular access and accurate assessment of aortic annulus dimensions for correct valve sizing are very important.

The device can be deployed using a transaortic, transaxillary or subclavian approach. The choice of approach depends on operator experience and the individual case. The antegrade approach, requiring transseptal puncture and negotiation of the mitral valve, is no longer used. However, a number of studies of effectiveness assessed TAVI using this approach.

Evidence of effectiveness

TAVI has been the subject of HTA in both Australia and in New Zealand. The following section is not an exhaustive account of the literature regarding the effectiveness of TAVI. Rather, key studies that demonstrate outcomes associated with TAVI are highlighted. Readers are referred to the New Zealand and Australian HTAs for a comprehensive account of the literature regarding effectiveness of TAVI.

TAVI procedures have been performed in approximately 50,000 patients worldwide with the longest patient experience being nearly 7 years.24 Research experience is greatest with the Edwards Sapien valve. The PARTNER studies are the most comprehensive conducted to date.

The early Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) study assessed feasibility of the technique and anatomical and procedural success. Of 36 patients enrolled on compassionate grounds (all had been declined surgery), 35 were taken to the catheterisation laboratory (one died of sudden cardiac death awaiting the procedure). Of the remaining 35 patients, a valve implantation success rate of 86% was achieved using an antegrade transeptal approach in 26 patients and a retrograde approach in the other seven patients. The 30-day mortality experienced by these patients was 12%.25

The subsequent phase I trial (REVIVAL) demonstrated that the results of percutaneous therapy are comparable to conventional therapy. The study included 55 patients with aortic valve area greater

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than 0.7 cm², age older than 70 years, EuroSCORE higher than 20, Society of Thoracic Surgeons mortality risk score higher than 10, and New York Heart Association functional class III or IV.

The PARTNER Phase II study primary safety endpoints were 30 days and 6 months mortality. Primary efficacy endpoints were haemodynamic and functional improvement at 12 months. One hundred and thirty patients (69 transaortic and 61 transfemoral) aged 82.1 ± 5.5 years were included. Valve implantation was successful in 96.4% and 95.4% of patients respectively. Thirty days and 6 months survival were 81.2% and 58.0% (transaortic) and 91.8% and 90.2% (transfemoral). In both groups, mean aortic gradient decreased from 46.9 ± 18.1 to 10.9 ± 5.4 mmHg 6 months post-TAVI. In total, 78.1% (transaortic) and 84.8% (transfemoral) of patients experienced significant improvement in NYHA class.

At two year follow-up of the PARTNER participants, the rates of death at 2 years were 43.3% in the TAVI group and 68.0% in the standard (medical) therapy group (P<0.001), and the corresponding rates of cardiac death were 31.0% and 62.4% (P<0.001). The survival advantage associated with TAVI that was seen at 1 year remained significant among patients who survived beyond the first year (hazard ratio, 0.58; 95% CI 0.36 to 0.92). The rate of stroke was higher after TAVI than with standard therapy (13.8% vs. 5.5%, P=0.01). In the first 30 days there were more ischaemic strokes in the TAVI group (6.7% vs. 1.7%, P=0.02) and beyond 30 days there were more haemorrhagic strokes in the TAVI group (2.2% vs. 0.6%, P=0.16). At 2 years, the rate of re-hospitalisation was 35.0% in the TAVI group and 72.5% in the standard-therapy group (P<0.001). TAVI, as compared with standard therapy, was also associated with improved functional status (P<0.001).

Long-term outcome data were published by Unbehaun et al. describing outcomes from transapical aortic valve implantation in 300 high-risk patients. The 30-day mortality was 4.7% and cumulative survival was 83% at 1 year, 76% at 1.5 years, and 65% at 2 years and beyond.

A systematic review of the literature performed for development of the 2012 NICE guidance for TAVI cites the following studies:

- A European register study of 1,038 patients reported short-term procedural success of 94%, defined as deployment of the valve, retrieval of the delivery catheter, no conversion to conventional surgery and the patient leaving the intervention room alive.


A case series based on the UK TAVI register of 877 procedures (870 patients) reported procedural success in 97% of procedures. The 1-year survival rate was 79% and a 2-year survival rate was 74%. Survival at 1 year and 2 years was significantly better for those who had a transfemoral approach than for those who had a transapical approach (81% \[488/599\] versus 72% \[196/271\], \(p = 0.002\) and 77% \[464/599\] versus 65% \[177/271\], \(p < 0.001\) respectively)\(^{32}\).

RCT of 358 patients with severe aortic stenosis who were considered unsuitable for surgical aortic valve replacement (PARTNER trial cohort B). Patients were randomised to treatment either by TAVI (\(n = 179\)) or standard (non-surgical) therapy (\(n = 179\)). Death from cardiovascular causes occurred in 21% and 45% of patients respectively at 1-year follow-up (hazard ratio 0.39, 95% confidence interval 0.27 to 0.56). A total of 75% of participants randomised to treatment by TAVI were asymptomatic at one year or had only mild symptoms (NYHA I or II) compared with 42% randomised to treatment by standard therapy (\(p < 0.001\))\(^{33}\).

RCT of 699 patients well enough for surgical aortic valve replacement but at high risk compared 348 patients randomised to TAVI with 351 patients randomised to surgery (the PARTNER trial cohort A). Rate of death from any cause was 3.4% in the TAVI group and 6.5% in the surgical group at 30 days (\(p = 0.07\)) and 24.2% and 26.8% respectively at one year (\(p = 0.44\)). Patients in the transcatheter group had a significantly shorter length of stay in the intensive care unit (3 days, vs. 5 days in the surgical group) and a shorter index hospitalisation (8 vs. 12 days) (\(P < 0.001\) for both comparisons). At 1 year, patients in both groups had improvement in cardiac symptoms and 6-minute walk test distance, but no significant differences between groups were reported. Similar proportions of patients required readmission to hospital within 1 year after being randomised to TAVI or surgical aortic valve replacement (18% versus 16%, \(p = 0.38\))\(^{34}\).

Results from the prospective multicenter study of the French national transcatheter aortic-valve implantation registry (FRANCE 2) were published in 2012 after the inclusion period for the above systematic review. In FRANCE 2 a total of 3,195 patients with a mean age of 82.7±7.2 years, 49% of whom were women, had been enrolled. All patients were highly symptomatic and were at high surgical risk for aortic-valve replacement. Edwards SAPIEN and Medtronic CoreValve devices were implanted in 66.9% and 33.1% of patients, respectively. Approaches were either transarterial (transfemoral, 74.6%; subclavian, 5.8%; and other, 1.8%) or transapical (17.8%). The procedural success rate was 96.9%. Rates of death at 30 days and 1 year were 9.7% and 24.0%, respectively.


At 1 year, the incidence of stroke was 4.1%, and the incidence of periprosthetic aortic regurgitation was 64.5%\(^{35}\).

**Evidence of cost-effectiveness**

The key issues in determining the effect on cost of TAVI relate to:

- the number of patients who are likely to access the therapy;
- the index admission;
- outpatient expense post-discharge; and
- any subsequent in-patient admission.

A 2011 Belgian HTA conducted a cost-utility analysis on TAVI. Findings were adapted in a UK analysis. Results concluded that it was inappropriate to fund TAVI for high-risk operable patients given high rates of stroke compared with standard surgery and an average Incremental Cost-Effectiveness Ratio (ICER) over €750,000 per QALY\(^{36, 37, 38}\). In inoperable patients they found TAVI significantly reduces death rates compared with a non-surgical approach, with an average ICER of about €45,000 per QALY.

The May 2011, Review of emerging technologies and their potential impact on cardiac services over the next ten years undertaken by the UK Department of Health estimated that there was an immediate population need of 16 per million population, which in the Australian context represents a case volume of 350 per annum. As these are patients are typically too unwell to have an open operation, these would be new, not replacement procedures. Table 3 describes the key steps in the clinical pathway for TAVI and the costs associated with each pathway step.

**Table 3: Treatment and intervention matrix**

<table>
<thead>
<tr>
<th>Clinical pathway step</th>
<th>Medical management</th>
<th>TAVI planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admission</td>
<td>It is current practice that this cohort of patients will undergo a valvotomy.</td>
<td>New costs based on existing national benchmarks for the same diagnosis, with reference to inpatient length of stay and other costs. In addition, about 30% of patients also require the</td>
</tr>
</tbody>
</table>


## Index admission

Guidance about the current per episode cost of cardiac valve procedures is available from the National Hospital Cost Data Collection (NHCDC), with the latest available relating to the 2009/10 year (Round 14). There are four DRGs (F03A, F03B, F04A, F04B) that relate to cardiac valve replacement surgery, which are differentiated as to whether or not:

- a cardiopulmonary by-pass pump is used;
- invasive investigations are performed; and
- the patient suffers catastrophic complications.

In addition other patients with valvular disorders are managed with percutaneous interventions, which code to DRG F19Z.

The most up-to-date publicly available NHCDC cost of each DRG, the average length of stay and key cost components are set out in Table 4.

In the literature, patients in the transcatheter group had a significantly shorter length of stay in the intensive care unit (3 days, vs. 5 days in the surgical group) and a shorter index hospitalisation (8 versus 12 days) (P<0.001 for both comparisons)\(^3\). Other literature suggests that the average length

---

of stay for uncomplicated admissions is 11 days and 16 days when there are significant complications\textsuperscript{40}.

Table 4: Breakdown of NHCDC costs for cardiac valve procedures, 2009/10

<table>
<thead>
<tr>
<th>Cost component</th>
<th>F03A: Cardiac valve procedure + CBP pump + invasive investigation + catastrophic complication</th>
<th>F03B: Cardiac valve procedure + CBP pump + invasive investigation - catastrophic complication</th>
<th>F04A: Cardiac valve procedure + CBP pump - invasive investigation + catastrophic complication</th>
<th>F04B: Cardiac valve procedure + CBP pump - invasive investigation - catastrophic complication</th>
<th>F19Z: Trans-vascular percutaneous cardiac intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of stay (days)</td>
<td>22.34</td>
<td>11.15</td>
<td>13.06</td>
<td>7.93</td>
<td>3.43</td>
</tr>
<tr>
<td>Average cost</td>
<td>$61,400</td>
<td>$37,576</td>
<td>$46,260</td>
<td>$32,906</td>
<td>$12,048</td>
</tr>
<tr>
<td>Operating room (direct)</td>
<td>15%</td>
<td>18%</td>
<td>20%</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>Critical care (direct)</td>
<td>15%</td>
<td>10%</td>
<td>16%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Prosthesis</td>
<td>11%</td>
<td>18%</td>
<td>13%</td>
<td>15%</td>
<td>22%</td>
</tr>
<tr>
<td>Ward nursing (direct)</td>
<td>10%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Ward medical (direct)</td>
<td>11%</td>
<td>8%</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Special procedure suite (direct)</td>
<td>3%</td>
<td>6%</td>
<td>0%</td>
<td>0%</td>
<td>14%</td>
</tr>
<tr>
<td>All direct costs</td>
<td>84%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>86%</td>
</tr>
<tr>
<td>All overhead costs</td>
<td>16%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Based on these lengths of stay, it appears to be most similar to current DRG F03B, with variation in costs likely to relate to:

- the cost of the prosthesis, with the NHCDC cost for DRG F03B being $6,604 compared with the TAVI cost of about $30,000;
- lower operating theatre costs and higher special procedure room costs, depending on where the procedure is undertaken. The estimated theatre cost of $6,917 for DRG F03B,
is likely to be an overestimate for the TAVI procedure when compared for instance to the special procedure room cost of $1,655 for DRG F19Z (Transvascular Percutaneous Cardiac Intervention), so in the cost estimate this expense has been discounted by 50%;

- critical care costs, with potentially shorter length of stay with transcatheter replacements, though the estimated NHCDC cost of $3,382, is low for a multi-day ICU stay, as average costs typically exceed $2,000 per day;

- about 30% of patients who have the TAVI procedure also require the insertion of a pacemaker. DRG F17A identifies $4,692 of expense for prosthesis, operating room and special procedure room costs. These would be additional costs during the course of the index admission in 30% of cases. Informal clinical advice indicates that: i) a ‘cheap/simple’ pacemaker costing ~$3,000 is adequate for this cohort; and ii) not all patients would necessarily be implanted with a pacemaker in the TAVI episode, meaning additional costs for a subsequent admission (NB: no data re this rate).

Substitution of the cost of the TAVI for the standard cardiac valve and with all other cost parameters left unchanged provides an indicative cost of $58,890 with the valve representing about 51% of the cost compared with the 18% now. The NHCDC costs relate to the 2009/10 year, however, Victorian payments per WIES have increased by 15.7% in the three years to 2012/13, which if applied to the non-prosthesis NHCDC costs would increase the estimated cost of the TAVI procedure to $63,425 which includes the cost of the prosthesis.

The above analysis has been undertaken so that an estimate of likely costs of the procedure and related management can be made. However, the forward cost implications for jurisdictions and hospitals relate to the how this procedure will be coded and reimbursed in the future. A number of DRGs, which are set out in Table 5, have been identified as being potentially pertinent in this regard, though with no final determination yet made. Table 5 includes the cost weights determined by the Independent Health Pricing Authority for 2012/13 and the case payment based on the Victorian reimbursement amount of $4,164 for the same year. The estimated cost of the TAVI procedure of $63,425 far exceeds the current level of expected reimbursement based of any of these DRGs.

**Table 5: Reimbursements for possible DRG coding for TAVI**

<table>
<thead>
<tr>
<th>DRG</th>
<th>Description</th>
<th>2012/13 IHPA inlier bounds</th>
<th>2012/13 IHPA inlier weight</th>
<th>2012/13 Victorian casemix</th>
</tr>
</thead>
<tbody>
<tr>
<td>F19Z</td>
<td>Trans-vascular percutaneous cardiac intervention</td>
<td>1-10 days</td>
<td>2.5758</td>
<td>$10,726</td>
</tr>
<tr>
<td>F21A</td>
<td>Other circulatory system OR procedures with catastrophic complications</td>
<td>5-48 days</td>
<td>6.0095</td>
<td>$25,024</td>
</tr>
<tr>
<td>F21B</td>
<td>Other circulatory system OR procedures without catastrophic complications</td>
<td>1-16 days</td>
<td>1.7447</td>
<td>$7,265</td>
</tr>
<tr>
<td>F42A</td>
<td>Circulatory disorders without AMI, with invasive cardiac investigative procedure</td>
<td>2-22 days</td>
<td>2.6645</td>
<td>$11,095</td>
</tr>
</tbody>
</table>
Post-discharge care – two years

Table 6 sets out some indicative post-discharge costs. Variation between procedures is attributed in part to the different rates in mortality for the two groups of patients, so that on average the non-intervention group would access 32% of possible interventions compared with 57% for the TAVI group. These costs are likely to understate the true costs incurred in maintaining all patients in the community.

Table 6: Post-discharge interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Medical management</th>
<th>TAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Level C GP consult, item 36, $69/visit</td>
<td>0.32<em>24</em>$69=$530</td>
<td>0.57<em>24</em>$69=$944</td>
</tr>
<tr>
<td>Monthly routine bloods, item 66512, $17.80/visit</td>
<td>$137</td>
<td>$244</td>
</tr>
<tr>
<td>Monthly PBS scripts for ACE inhibitors, statins, diuretics, the cost to the Commonwealth of $58, $23, $9 respectively</td>
<td>$691</td>
<td>$1,231</td>
</tr>
<tr>
<td>Monthly specialist visit at public hospital cost of $256/visit</td>
<td>$1,966</td>
<td>$3,052</td>
</tr>
<tr>
<td>6 monthly echocardiograph, item 55113, $230.65</td>
<td>$295</td>
<td>$526</td>
</tr>
<tr>
<td>Total</td>
<td>$3,619</td>
<td>$5,997</td>
</tr>
</tbody>
</table>
New and Emerging Cardiac Technologies in Australia and New Zealand

Additional excess post-discharge costs for TAVI

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admission</td>
<td>$63,425 less the indexed cost of DRG 19Z ($13,940), so an additional $49,485</td>
</tr>
<tr>
<td>Post-discharge care</td>
<td>Additional $2,378</td>
</tr>
<tr>
<td>Re-hospitalisation</td>
<td>Saving $4,858</td>
</tr>
<tr>
<td>Cost per patient</td>
<td>Additional cost of $47,005 per patient</td>
</tr>
<tr>
<td>Cost annual caseload of 350 patients</td>
<td>$16,451,750</td>
</tr>
</tbody>
</table>

Re-hospitalisation costs – two years

The PARTNER study indicates the likelihood of another hospital admission in the following two years at 35% for the intervention group and 72.5% for the control group. For a diagnosis of F62A, heart failure with shock and complications, the cost attributed in 2009/10 was $11,196 for an average length of stay of 9.93 days, which would provide an average saving of $4,199 for TAVI patients, which with indexation brings the projected saving to $4,858.

The projected additional cost per patient is therefore estimated at $47,005 and the total cost for the annual caseload of patients receiving TAVI in Australia is estimated at $16,451,750 (Table 7).

Table 7: Summary of cost implications for TAVI

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost implication</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Cost annual caseload of 350 patients</td>
<td>$16,451,750</td>
</tr>
</tbody>
</table>

Impacts on service delivery

Most stakeholders consulted for the purposes of this report stated that for patients with aortic stenosis who are unsuitable for surgical aortic valve replacement, TAVI is likely to become a mainstream therapeutic option over the next ten years. The view of these stakeholders is that even though TAVI is not currently recommended in patients with aortic stenosis for whom surgical aortic valve replacement is considered suitable and not to pose a high risk, the procedure may become the preferred approach for valve replacement in this patient group in the near future.

The main reason cited include that the technology is improving rapidly and likely to become the aortic valve replacement treatment of choice for a broader group of patients in the future. Some stakeholders report that the next generation of TAVI devices are already more suitable for implantation in a broader range of patients. Advantages of the newer devices are primarily related to lower complication rates, the ability to re-position them and to retrieve them if required and greater ability to appose the patient’s anatomy reducing paravalvular leak.

However, other stakeholders expressed an alternative view. Head-to-head comparison to date has only two years of follow-up data therefore it is too soon to determine whether TAVI outcomes will be equivalent to surgical outcomes. Data demonstrating increased paravalvular leak and late mortality with TAVI suggest that surgery will continue to be the preferred treatment approach into
the future for patients who are suitable. Further, surgical technology is improving as well. For example, sutureless aortic valve replacement has recently been developed and may provide patient benefits compared with existing technology. Sutureless aortic valve replacement is summarised at Appendix 1.

The demand for TAVI is likely to increase with the aging of the population as a greater proportion of patients unsuitable for surgical aortic valve replacement are in the older age group. This will present the difficult ethical dilemma for clinicians about how widespread this well tolerated but costly therapy should become. Guidelines to inform use and the ongoing collection of outcomes data will be required to inform development of the appropriate clinical pathways for the judicious use of the technology.

The following issues remain to be resolved:\textsuperscript{41}:

- Complications such as device migration, compression of the left main artery, mitral valve laceration, paravalvular leak and thromboembolism;
- The need for pacemakers in a significant number of patients;
- Expanding indications, such as valve-in-valve procedures for previous TAVI recipients; and
- Technical issues persist relating to reduction of delivery system and prosthesis profiles, balloon-expandable stents, repositionable and retrievable devices and different sizes of devices.

In spite of these issues, overseas experience is that TAVI use is increasing and the patient groups in whom TAVI is being performed are becoming broader. In Germany, TAVI accounts for almost 25% of patients in the German aortic valve registry. Analysis of registry data demonstrates a clinical tendency emerging for applying TAVI for younger and lower-risk patients\textsuperscript{42}. However, German policy allows for TAVI use in all patient cohorts, not just for patients considered unsuitable for SVR.

According to NICE guidance\textsuperscript{43}:

- TAVI is a technically challenging procedure that should be performed only by clinicians and teams with special training and experience in complex endovascular cardiac interventions. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications; and
- Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist and an expert in

\textsuperscript{41} NICE. Transcatheter aortic valve implantation for aortic stenosis. IPG 421. March 2012.


\textsuperscript{43} NICE. Transcatheter aortic valve implantation for aortic stenosis. IPG 421. March 2012.
cardiac imaging. The multidisciplinary team should determine the risk level for each patient.

Stakeholder feedback reflects the NICE guidance. Stakeholders report that TAVI is a high-risk procedure and carries with it specific education and training needs for operators. In addition to training in the use of the device, cardiology providers may also require additional education and training in the use of imaging techniques relevant to implantation and in the management of complications should they occur.
TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

Background

Mitral regurgitation (MR) is a common valvular disorder that can arise from abnormalities of any part of the mitral valve apparatus. These include the valve leaflets, annulus, chordae tendineae, and papillary muscles. The prevalence of MR varies inversely with severity - in the Framingham Heart Study, a population-based cohort, MR of mild severity on colour Doppler echocardiography was present in 19% of men and women.

MR may be due to a primary abnormality of the valve apparatus or may be secondary to another cardiac disease. The causes of primary MR include mitral valve prolapse, infective endocarditis, trauma, rheumatic heart disease, certain medication use, congenital abnormalities and mitral annular calcification. Secondary causes include ischaemic heart disease, left ventricular systolic dysfunction and hypertrophic cardiomyopathy.

Surgery is indicated for severe, chronic MR. Two surgical procedures confined to the mitral valve itself are available for the treatment of chronic MR: valve repair and valve replacement.

In Australia since 2000/01 the number of mitral valve repairs and replacements has increased. The rate of increase in mitral valve repairs has been greater over this period (Figure 4).

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In New Zealand in 2009/10 the following numbers of mitral valve procedures were performed across public and private hospitals (Table 8).

Table 8: Mitral valve procedures, New Zealand, 2009/10

<table>
<thead>
<tr>
<th></th>
<th>Public hospital discharges</th>
<th>Private hospital discharges</th>
<th>Total hospital discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repair of mitral valve</td>
<td>99</td>
<td>6</td>
<td>105</td>
</tr>
<tr>
<td>Mitral valve annuloplasty</td>
<td>140</td>
<td>9</td>
<td>149</td>
</tr>
<tr>
<td>Replacement of mitral valve</td>
<td>229</td>
<td>14</td>
<td>243</td>
</tr>
<tr>
<td>Other procedures on mitral valve</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Mitral valve repair at experienced surgical centres is the preferred approach because of both functional and survival benefits compared to valve replacement.\(^{49}\)\(^{50}\)

When required, mitral valve replacement can be performed with a mechanical or bioprosthetic valve. The following recommendations for the selection of a bioprosthetic or mechanical mitral valve were made by the 2006 American College of Cardiology / American Heart Association guidelines.\(^{51}\)

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Bioprosthetic valves are recommended in patients who cannot or will not take warfarin or have a clear contraindication to warfarin therapy.

Among patients who can take warfarin, the weight of evidence supports the following approach:

- A mechanical valve in patients under age 65 who have long-standing AF.
- A bioprosthetic valve in patients ≥65 years of age.

The timing of surgery is determined by a number of factors, including the severity of the MR, the presence or absence of symptoms, the functional state of the left ventricle, the feasibility of valve repair, the presence of AF, the presence of pulmonary hypertension at rest or with exercise and the preference and expectations of the patient.

Technologies – mitral valve repair

Methods for percutaneous mitral valve repair to treat MR are under investigation. Techniques include edge-to-edge valve repair devices, indirect annuloplasty devices and mitral / ventricular remodelling approaches.

The following are potential elements of a percutaneous mitral valve repair.

Edge-to-edge repair

Edge-to-edge repair is a surgical strategy for treating MR caused by anterior leaflet prolapse. The technique opposes the central portions of the anterior and posterior mitral valve leaflets to create a double-orifice valve with reduced leaflet excursion and less regurgitation.

An analogous transcatheter-based technique has been developed. Two devices are now available that can be used for percutaneous mitral valve repair: the MitraClip (Evalve) and the Mobius II (Edwards Lifesciences).

Delivery requires a trans-septal puncture followed by deployment of a clip or suture to create a bridge between the anterior and posterior valve leaflets. The clip can be reopened and repositioned until the operator is satisfied with the position of the clip; only after the final position is confirmed is the delivery system detached. In some cases, deployment of two devices is required to achieve adequate reduction of MR.
The procedure is performed with general anesthesia under the guidance of fluoroscopy and TOE. By six months, the device is incorporated into the tissue bridge, mimicking the result of surgery\textsuperscript{55}.

*Annuloplasty*

Annuloplasty is an important component of most mitral valve surgery and can sometimes be used alone to treat MR. The goal of annuloplasty is to reduce annular dilation and to promote better valve leaflet coaptation\textsuperscript{56}.

Surgical edge-to-edge repair is usually accompanied by an annuloplasty\textsuperscript{57}. This is not currently the case in the corresponding catheter-based edge-to-edge procedure. However, newer annuloplasty devices are under development that may be used in conjunction with catheter-based edge-to-edge procedures\textsuperscript{58}.

Shortening or reshaping the annulus by inserting a device into the coronary sinus has the potential to mimic a surgical annuloplasty. This is referred to as an indirect annuloplasty. Experimental proof-of-concept and initial human feasibility studies have been conducted using a range of percutaneous devices. The Carillon mitral contour system (Cardiac Dimensions) is the only indirect annuloplasty system commercially available at the time of writing\textsuperscript{59}.

Direct annuloplasty techniques are independent from the coronary sinus and are directly applied to the mitral annulus. Approaches include retrograde insertion of sutures in the region of the mitral annulus, delivery of ultrasonic energy or implantation of a ring. Each available system has certain advantages compared with the indirect techniques (described in ‘evidence for effectiveness’ below). However, in general, their application is more complex. All systems currently used in humans have the disadvantage that treatment of the mitral valve comprises only the posterior annulus and not the entire annulus\textsuperscript{60}.

*Combined mitral valve and left ventricular remodelling*

Off-pump mitral valve and left ventricular remodelling can be achieved through placement of a tensioning cable directly through the left ventricular chamber (Coapsys, Myocor). In this technique,
anchoring pads on either side of the ventricle are used to allow the cable to apply tension across the chamber. This shortens the septal lateral dimension and remodels the left ventricular chamber.\footnote{Bouma W et al. Chronic ischaemic mitral regurgitation. Current treatment results and new mechanism-based surgical approaches. European Journal of Cardiothoracic Surgery 2010; 37: 170-85.}

**Technologies – mitral valve replacement**

Percutaneous mitral valve replacement was first performed in humans in June 2012.\footnote{http://www.crtonline.org/pr.aspx?PAGE_ID=10187}

- The EndoValve-Herrmann prosthesis (EndoValve) is implanted from the LA side via a right mini-thoracotomy on a beating heart. The device is a foldable nitinol structure that attaches to the native valve with specially designed grippers, is fully valve sparing, and repositionable before release. Animal models have been successful, and a true percutaneous version is planned.

- The Lutter prosthesis, a nitinol stent-valve, has been implanted transapically in porcine models.

- The CardiAQ (CardiAQ Valve Technologies) prosthesis has reached first-in-man testing. The device is delivered transseptally.

The ability to perform the procedure percutaneously is limited due to the asymmetric shape of the mitral annulus; concerns about cuff design or anchoring and accurate device sizing; mitral annular dilation; and a foreshortened and restrictive subvalvular apparatus in rheumatic mitral stenosis and mitral annular calcification.\footnote{Glower D. Surgical approaches to mitral regurgitation. Journal of the American College of Cardiology 2012; 60: 1315-22.}

**Evidence of effectiveness**

*Edge-to-edge systems*

To date, the largest clinical experience has been with the MitraClip.

In the Phase I Endovascular Valve Edge-to-Edge Repair Study (EVEREST) trial clips were implanted in 24 of 27 patients with moderate-to-severe MR due to degenerative disease and without annular dilatation. There were no procedural complications but four major adverse events (3 patients experienced partial clip detachment, subsequently requiring surgery, and 1 experienced a limited neurologic event). At six months 18 patients remained free from surgery and 13 had MR that was no worse than mild.\footnote{Feldman T et al. Edge-to-edge mitral valve repair using the Evolve MitraClip: One year results of the EVEREST phase I clinical trial. American Journal of Cardiology 2005; 96: 49H.}

In the Phase II trial (EVEREST II), 279 patients with moderately severe or severe MR were randomised to receive the device or usual surgery. At 12 months, the rates of the primary end point
for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group \((P=0.007)\). The respective rates of the components of the primary end point were as follows: death, 6% in each group; surgery for mitral-valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%. Major adverse events occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days \((P=0.001)\). At 12 months, both groups had improved left ventricular size, New York Heart Association functional class, and quality-of-life measures, as compared with baseline\(^{65} \).

**Indirect annuloplasty**

The Monarc system (Edwards Lifesciences) consists of three connected components, two self-expanding stents connected with a nitinol bridge. The Monarc device is implanted in the coronary sinus via the internal jugular vein. The EVOLUTION I (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of MR) trial implanted the device in 59 of 72 participants. Participants had functional MR \(\geq\) grade 2+. Overall, 85.7% of participants demonstrated some reduction of MR after implantation. After 12 months, 50% of participants with the device showed a reduction in MR by \(\geq\) 1 grade. The primary safety endpoints were freedom from death, tamponade or myocardial infarction after 30 days. These were achieved in 91% of patients after 30 days and in 82% after 1 year\(^{66} \).

The follow-up EVOLUTION II study was terminated by the sponsor in 2010 due to slow inclusion and the complexity of the trial. Production of this device has stopped.

The Viacor percutaneous transvenous mitral annuloplasty (PTMA) system (Viacor) is also implanted in the CS and comprises a polytetrafluoroethylene catheter with three lumens and round nitinol rods. The PTOLEMY (Percutaneous Reduction of Mitral Valve Regurgitation in Heart Failure Patients) safety and feasibility study of this device included 27 patients with functional MR grade 2+ through 4+. The device was implanted in nine of these patients. After 3 months, three-dimensional echocardiographic reconstruction indicated a reduction in the septolateral diameters of the mitral annulus by \(4 \pm 1.2 \text{ mm} \)\(^{67} \). The follow-up PTOLEMY II study included 37 patients with 27 implantations\(^{68} \). The company ended operations and the study was discontinued in 2011.

The Carillon mitral contour system (Cardiac Dimensions) comprises a self-expanding proximal and distal anchor, connected with a nitinol bridge. Via access through the jugular vein, the system is first attached with the distal anchor in the great cardiac vein. Manual pullback on the catheter exerts pressure on the mitral annulus, resulting in improved coaptation of the mitral leaflets. The AMADEUS (Carillon Mitral Annuloplasty Device European Union Study) trial included 48 patients, and the Carillon device was implanted in 30 of them. After 6 months, MR reduction on

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\(^{66}\) Harnek J et al. Transcatheter implantation of the MONARC coronary sinus device for mitral regurgitation. JACC Cardiovascular Interventions 2011; 4:115-122.


\(^{68}\) Sack S. Emerging experiences and insights with the Viacor PTMA system. Presented at: Transcatheter Cardiovascular Therapeutics 2010; September 21-25, 2010; Washington, DC.
echocardiography of 22% to 32% was observed and an increase in the 6-minute walking distance of 307 ± 87 m at baseline to 403 ± 137 m (P < .001) after 6 months69. The follow-up study, TITAN included 65 patients with a Carillon device implanted in 36 patients. Major adverse events occurred in 1.9% of participants after 1 month and 25% after 12 months. None of these were believed to be device related. After 12 months, a reduction in MR was found in 40% of the patients with the implant, as well as an improvement in clinical symptoms70. Two additional studies are underway; the INTEGRAL study, a single-center study in South America, the TITAN II study, a multicenter study in Europe, and the PRIME study of long-term safety and efficacy71.

The Mitral Cerclage Annuloplasty system (National Institutes of Health) is an experimental device designed to achieve a circumferential tension in the region of the mitral annulus. A CS guidewire traverses a short segment of the basal septal myocardium that has to be reentered in the right heart where it is exchanged for a suture. Subsequently, tension is applied interactively during imaging and secured with a locking device. Currently, only data from a pig model are available72.

Ventricular reshaping

Combined mitral and left ventricular remodeling has been used in numerous patients in a phase I clinical trial, with durable results lasting as long as 1 year, and has undergone phase II testing in the Randomised Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve (RESTOR-MV) trial. This trial tested the Coapsys device (Myocor), a ventricular shape change device placed without cardiopulmonary bypass to reduce functional MR. The device compresses the mitral annulus and reshapes the ventricle73. The study was terminated when the sponsor failed to secure ongoing funding; 165 patients were randomised to either control (indicated surgery) or treatment (coronary artery bypass graft with Coapsys ventricular reshaping). Standard indicated surgery was either coronary artery bypass graft alone or coronary artery bypass graft with mitral valve repair. In each stratum, randomisation was to either control and Coapsys both produced decreases in left ventricular (LV) end-diastolic dimension and MR at 2 years (p < 0.001); Coapsys provided a greater decrease in LV end-diastolic dimension (p = 0.021). Control had lower MR grades during follow-up (p = 0.01). Coapsys showed a survival advantage compared with control at 2 years (87% vs. 77%) (hazard ratio: 0.421; 95% confidence interval: 0.200 to 0.886; stratified log-rank test; p = 0.038). Complication-free survival (including death, stroke, myocardial infarction, and

70 Goldberg S. Emerging insights and experiences from the CDI Carillon. Presented at: Transcatheter Cardiovascular Therapeutics 2010; September 21-25, 2010; Washington, DC.
Direct annuloplasty

The Mitralign system (Mitralign) consists of a set of devices delivering two pairs of surgical implants on the posterior annulus via a retrograde transaortal approach. The implants of each pair are pulled together and locked from the ventricular site of the annulus with a small stainless steel lock, reducing the posterior annulus by approximately 15 mm. The results of first-in-man studies in 12 patients found that after 30 days, one device-related major adverse cardiac event was registered (pericardial effusion). A significant improvement in heart failure was observed (decrease in New York Heart Association classification from 2.8 at the beginning of the study to 1.9 after 30 days) (n = 10) (P = 0.02)\textsuperscript{75}.

With the GDS Accucinch system (Guided Delivery Systems), up to 12 anchors are positioned in the region of the mitral annulus via retrograde femoral artery access. The individual anchors are connected by a cord and shortening the cord brings the anchors closer together. In the first-in-man study, reduced papillary muscle displacement, reduced tenting height, and increased coaptation were directly observed during the procedure\textsuperscript{76}. Additional clinical trials data are unavailable. The CINCH 2 safety and feasibility study is underway in Germany and Canada.

The ReCor system (ReCor Medical) delivers ultrasonic energy by a balloon catheter in the region of the posterior mitral valve annulus. Heating of the collagen in the annulus causes shrinking and reduction of the annulus size. No implanted foreign objects remain in the body of the patient. Animal study data suggest an 11% reduction in the mitral annulus using this device\textsuperscript{77}. The SATURN I (Safety and Performance Assessment of Therapeutic Ultrasound for the Treatment of MR) first-in-man study was suspended in September 2011.

The QuantumCor system (QuantumCor) delivers radiofrequency energy at a subablative temperature to the mitral annulus. In a sheep model, an acute reduction of the mean anteroposterior annular distance by a mean value of 23.8% (anteroposterior diameter reduction 5.75 ± 0.86 mm; P < .001) was demonstrated\textsuperscript{78}. First-in-man studies have not been completed.

The Cardioband femoral system (Valtech Cardio) is a type of ribbon which is fixed with different anchors in the region of the mitral annulus and is inserted via transseptal access to enable direct

\textsuperscript{74} Grossi E et al. Outcomes of the RESTOR-MV trial. Journal of the American College of Cardiology 2010; 56: 1984-93.
\textsuperscript{75} Kuck K. An update on Mitralign first in man study. Presented at: Joint Interventional Meeting 2011; February 10-12, 2011; Rome, Italy.
\textsuperscript{78} Goel R et al. The QuantumCor device for treating mitral regurgitation. Catheterisation and Cardiovascular Interventions 2009; 74: 43-8.
annuloplasty of the mitral valve. This system has not been tested in humans\textsuperscript{79}. The enCorTC system (MiCardia Corporation) consists of a percutaneously implanted, adjustable annuloplasty ring and is a next generation of the enCor dynamic mitral valve repair system. This newer device is currently still in the developmental phase\textsuperscript{80}.

**Evidence of cost-effectiveness**

Costs are unable to be estimated for mitral valve replacement technologies at present as the role of the technology within clinical practice has not yet been clearly identified.

Costs can be estimated for percutaneous mitral valve repair, comparing edge-to-edge repair with surgical mitral valve repair. A limitation of this analysis is the inability to include annuloplasty and ventricular remodelling techniques into cost estimates, again due to a lack of certainty regarding the roles of these technologies within clinical practice and the ability to combine these technologies with percutaneous edge-to-edge repair when required.

A portion of patients receiving transcatheter mitral valve repair are very sick and would otherwise not receive surgery. Other patients receive transcatheter procedures as an alternative to surgical procedures. There are therefore two major comparisons for the purposes of analysis of costs:

- Transcatheter mitral valve repair versus mitral valve surgery; and
- Transcatheter mitral valve repair versus no intervention.

At 12 months in the Phase II trial (EVEREST II), the rates of the primary end point for efficacy were 55\% in the percutaneous-repair group and 73\% in the surgery group, with the main difference being the rate of surgery for mitral valve dysfunction, 20\% versus 2\%. A significant proportion of patients who had a percutaneous repair subsequently required surgery, which impacts the overall cost assessments (Table 9).

**Table 9: Treatment and intervention matrix**

<table>
<thead>
<tr>
<th>Clinical pathway step</th>
<th>Medical management</th>
<th>Surgical repair</th>
<th>Percutaneous repair in patients who otherwise would undergo open treatment</th>
</tr>
</thead>
</table>
| Index admission       | Not applicable     | Average NHCDC costs and LOS for mitral valve surgery:  
F03A: $61400; 22.3 day  
F03B: $37576; 11.2 day  
New costs based on existing national benchmarks for a similar procedure, with reference to type of anaesthetic, inpatient length of stay and other | |

\textsuperscript{79} Schofer J. The Valtech Cardioband. CSI Frankfurt, June 28-30 2012.

\textsuperscript{80} MiCardia Corporation. enCor technology for mitral valve. Available at: http://www.micardia.com/annuloplasty-rings-dynaplasty.php (accessed October 2012)
NEW AND EMERGING CARDIAC TECHNOLOGIES IN
AUSTRALIA AND NEW ZEALAND

<table>
<thead>
<tr>
<th>Post-discharge / ongoing medical management</th>
<th>F04A: $46260; 13.1 day costs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F04B: $32906; 7.9 day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subsequent MV surgery</th>
<th>Re-surgery rate of 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>New surgery rate of 20%*</td>
</tr>
</tbody>
</table>

An approximate existing benchmark DRG for transcatheter mitral valve repair is F19Z (transvascular percutaneous cardiac interventions), the 2009/10 average costs of which are set out in Table 10.

**Table 10: Cost metrics DRG F19Z, 2009/10**

<table>
<thead>
<tr>
<th>Metric</th>
<th>NHCDC result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of stay</td>
<td>3.43 days</td>
</tr>
<tr>
<td>Operating room cost</td>
<td>$1,195</td>
</tr>
<tr>
<td>Special procedure room cost</td>
<td>$1,655</td>
</tr>
<tr>
<td>Prosthesis cost</td>
<td>$2,624</td>
</tr>
<tr>
<td>Total direct cost</td>
<td>$10,046</td>
</tr>
<tr>
<td>Total cost (direct and overhead)</td>
<td>$12,048</td>
</tr>
<tr>
<td>Total cost excl prosthesis cost</td>
<td>$9,424</td>
</tr>
</tbody>
</table>

It is projected that transcatheter mitral valve repair procedures would incur similar non-prosthesis inpatient costs to mitral valve surgery, which when indexed to bring up to 2012/13 levels equates to $10,904. On advice, the MitraClip costs approximately $40,000, which would provide a total inpatient cost of about $51,000.

The 2009/10 NHCDC costs for the four valve surgery DRGs range from $32,906 to $61,400, with a simple average of $44,536, which when indexed amounts to $51,528.

However, as discussed in the previous section, whilst the cost of the MitraClip procedure and admission is estimated at $51,000, the practical implications for the jurisdictions and public hospitals is that the procedure may well map to a DRG, the current level of reimbursement of which

* This assumes that the patient will have a second MitraClip procedure, however the patient may be a suitable for a surgical procedure as an alternative.
is much less. As set out in Table 9, a number of surgical DRGs have been identified that are currently being used to code TAVI procedures. It is likely that TAVI reimbursement will be coded to a medical DRG in future. However, according to current DRGs and cost weights (F42A), TAVI is only likely to realise reimbursement of approximately $10,000 per case.

According to the results of the EVEREST II trial, in patients with severe MR without previous surgery mitral valve implantation was associated with a 45% reduction in hospital admissions in the first 12 months after implantation compared with no intervention. About two thirds of patients with severe MR can expect to be admitted to hospital in a given year for treatment of heart failure, so a 45% reduction would reduce this rate in the transcatheter mitral valve repair group to about 37%. A similar impact is assumed for the surgery group.

NHCDC costs for DRG F62A (Heart failure and shock with catastrophic complications) are $11,196 with an average length of stay of 9.93 days, when indexed the costs increase to $12,954. Total costs are therefore estimated at $54,803 for surgical repair and $63,454 for transcatheter repair (Table 11).

Table 11: Summary of cost impacts

<table>
<thead>
<tr>
<th>Cost impact</th>
<th>Medical management</th>
<th>Surgical repair</th>
<th>Percutaneous repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admission</td>
<td>n/a</td>
<td>$51,528</td>
<td>$50,904</td>
</tr>
<tr>
<td>Hospital admission – heart failure</td>
<td>$12,954*0.67 = $8,679</td>
<td>$12,954*0.37 = $4,793</td>
<td>12,954*0.37 = $4,793</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>Similar for each cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission/ readmission for surgery</td>
<td>$51,528*0.02= $1,031</td>
<td>$51,528*0.2= $10,306</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$8,679+</td>
<td>$57,352+</td>
<td>$66,003+</td>
</tr>
</tbody>
</table>

Impacts on service delivery

According to stakeholders, repair procedures are technically very demanding and highly complex. They are likely to be limited to specialist centres with experienced interventionalists and echocardiologists who work closely together.

New skills will be mandatory for interventionalists to become skilled in this field including transcatheter repair techniques themselves, the management of complications associated with device deployment and with device failure, interpretation of radiological investigations in the context of device use and in the identification and device-related management of various forms of valve pathology.

The learning curve for new providers is likely to be long according to stakeholders.

At present, industry facilitates access to some training and skills development for interventional cardiologists. Cardiologists who become proficient in procedures provide training to their colleagues. As these procedures become more established, stakeholders predict that education and
training will need to be integrated into existing continuing professional development and registrar training programs.
LEFT ATRIAL APPENDAGE OCCLUSION DEVICES

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It has an estimated prevalence of 1.2% in the Australian population and one in four Australians aged over 40 will develop AF at some stage during their lives. The prevalence of AF increases with increasing age in Australia, from 0.1% in persons younger than 55 years, to 3.8% in persons 60 years or older and 10% in persons 80 years or older.

The prevalence of AF in New Zealand is estimated at 2.0%. Age standardised data from 2001-02 suggested that Māori had almost twice the rate of AF as compared with the total New Zealand population (Figure 5). Additionally, AF affects Māori at a younger age, with prevalence in 40-60 year-olds 1.78 times the non-Māori population of the same age.

Figure 5: Prevalence of atrial fibrillation in New Zealand by age group and ethnicity, 2010/11

People with AF are at high risk of stroke, heart failure, overall mortality and reduced quality of life.


82 Abdel Latif A and Messinger-Rapport B. Should nursing home residents with atrial fibrillation be anticoagulated? Cleveland Clinic Journal of Medicine 2004;71:40-4

83 Due to limitations in international administration data sets in ascertaining the true prevalence of disorders, the prevalence rate was estimated by including any patient with a diagnosis of AF in the last 20 years and a current prescription for one of 13 relevant cardiac medications, and those with a diagnosis of AF in the last five years.


The estimated annual cost of AF in Australia is $1.25 billion with 64% of this due to major events such as cerebrovascular accident (stroke) and heart failure86. Cost estimates for New Zealand are not available87.

AF is responsible for 10% of all ischaemic strokes and 50% of all cardioembolic strokes88. In New Zealand in 2010-11, approximately 2.3% of those patients diagnosed with AF were admitted with a stroke in the following 12 months89. Stroke affects approximately 347,000 Australians and is the second leading underlying cause of death in the Australian population90 91. There are approximately 35,000 hospitalisations for stroke in Australia each year92 93.

Known risk factors for stroke in patients with AF include male sex, valvular heart disease (rheumatic valvular disease), heart failure, hypertension, diabetes, increasing age and previous stroke. AF increases the risk of stroke by four to five-fold in patients without rheumatic heart disease and up to 17-fold in patients with rheumatic valvular disease94.

The impact of AF as a risk factor for stroke increases with age; the annual incidence of stroke in patients with atrial fibrillation is 1.5% in patients aged 50–59 years but almost 25% in patients aged 80 to 89 years95. Given the ageing population, the total burden of disease from stroke that is associated with AF is likely to increase five-fold by 205096.

The cornerstones of atrial fibrillation management are rate control and anticoagulation, and rhythm control for those symptomatically limited by AF97. Anticoagulation with aspirin, warfarin or anti-

91 AIHW. Cardiovascular Health. Data from ABS 2007-08 National Health Survey.
95 Ibid
platelet agents is indicated depending on the patient’s risk of thromboembolism\textsuperscript{98}. Warfarin is the most effective anticoagulant but carries with it the highest risk of bleeding and is not tolerated by all patients. According to the 2011 update to American College of Cardiology/American Heart Association/HRS guidelines on atrial fibrillation, if warfarin is not used, adding clopidogrel to aspirin may be considered\textsuperscript{99}. Novel anticoagulants are the subject of widespread clinical trials and have been shown in randomised controlled trials to have favourable efficacy and safety compared with warfarin and are associated with reduced risk of bleeding.

An alternative to the use of anticoagulants may be the surgical or percutaneous occlusion of the left atrial appendage (LAA).

**Technology**

There are two types of LAA occlusion technologies – surgical devices and percutaneous devices.

Surgical excision of the LAA can be performed by removing the LAA or the LAA can be excluded by placing sutures or clips on either side of the endocardial or epicardial surface, isolating the LAA from the left atrium. The latter form of surgery is facilitated by the AtriClip surgical closure device\textsuperscript{100}.

Percutaneous procedures are performed under general anaesthesia or conscious sedation in a cardiac catheterisation laboratory, with fluoroscopic and transoesophageal echocardiography guidance. The size of the orifice of the LAA from the left atrium is evaluated by imaging and a suitable size implant selected. A catheter is introduced into the right atrium via the femoral vein and the LAA is accessed through the fossa ovalis by a septal puncture. The majority of percutaneous devices consist of an implant that is placed in the orifice of the LAA, thereby preventing the passage of thrombi into the arterial circulation\textsuperscript{101}.

The percutaneous device is designed to be permanently implanted at, or slightly distal to, the opening of the LAA to trap potential emboli. Patients are usually treated with warfarin initially then are maintained on antithrombotic therapy long-term, mainly aspirin with or without clopidogrel. The position and patency of the occlusion device is confirmed by echocardiographic imaging. After a period of weeks to months the device endothelialises\textsuperscript{102}.

\begin{footnotesize}
\textsuperscript{102} Ibid
\end{footnotesize}
Evidence of effectiveness

A HealthPACT prioritising summary was produced by ASERNIP-S for Watchman device in November 2010. The following section provides a brief summary of key studies for each device type.

Surgical devices

The AtriClip (Atricure) is a device for closure of the LAA. The LAA is inserted into the device, which then clips at the base, separating the appendage from the left atrium. The initial trial assessing the safety and efficacy of the device included 34 patients with AF who were undergoing elective cardiac surgery via a median sternotomy. Patients underwent computed tomography studies to assess the device location as well as looking for evidence of blood flow within the LAA. Operative mortality was 8.8%, however none of the deaths were attributable to the device. All patients had successful LAA closure at 3 months and there were no reports of stroke or transient ischaemic attacks at 3 months\(^{103}\). A nonrandomised, prospective multicenter trial of the device (the EXCLUDE trial) comprised 71 patients who were undergoing primary elective cardiac operations with a median sternotomy and had AF or an increased risk of stroke. LAA exclusion was successful in 96% of patients. By the 3-month follow-up, 98% of patients had successful exclusion of the LAA. There were no adverse advents attributable to the AtriClip procedure\(^{104}\).

Percutaneous devices

The percutaneous devices for closure of the LAA are the Amplatzer septal occlude, Amplatzer cardiac plug, PLAATO device, WATCHMAN device, Coherex Wave Crest and LARIAT device. Only the WATCHMAN device has been subjected to a randomised controlled trial against a warfarin control group; with remaining devices being assessed by registry data or prospective trials to assess safety and efficacy:

- The WATCHMAN device (Atritech) is a percutaneous LAA closure system delivered via a transseptal approach and implanted at or immediately distal to the ostium of the LAA. Warfarin is prescribed with a target International Normalised Ratio (INR) of 2.0 to 3.0 for a period of 45 days post-device implantation to allow endothelialisation of the device. This is discontinued if repeat transesophageal echocardiography demonstrates either complete closure of the LAA or minimal residual peri-device flow. Following cessation of warfarin treatment, antiplatelet therapy with clopidogrel and aspirin is prescribed for 6 months then aspirin alone lifelong thereafter\(^{105}\).

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Evaluation of the WATCHMAN device against a conventionally treated warfarin control population was performed in the PROTECT-AF RCT of anticoagulant versus device therapy. The study randomised 707 patients, aged 18 years or older with nonvalvular atrial fibrillation and a CHADS2 risk score of ≥1 and followed patients for 1,065 patient-years with mean follow up of 18 months per patient. Successful device implantation occurred in 408 of the 463 randomised to LAA closure. The primary efficacy event rate (strokes, cardiovascular or unexplained death or systemic embolism) was 3.0 per 100 patient-years (95% CI 1.9–4.5) in the intervention group compared with 4.9 per 100 patient-years (95% CI 2.8–7.1) in control patients receiving warfarin.

An excess of adverse outcomes occurred in the WATCHMAN device group compared with controls; there were 7.4 adverse events per 100 patient-years (95% CI 5.5–9.7) in the WATCHMAN group and 4.4 per 100 patient years in controls (95% CI 2.5–6.7). The most frequent adverse outcome was that of a significant pericardial effusion, requiring either percutaneous or surgical drainage, carrying a 4.8% procedural risk. Other adverse procedure related outcomes included major bleeding requiring a transfusion of ≥2 units of packed red cells or surgical intervention (3.5%), procedure related ischaemic stroke (1.1%), device embolisation (0.6%), haemorrhagic stroke (0.2%), oesophageal tear (0.2%) and procedure-related arrhythmia (0.2%).

Analysis of outcomes from the first and second half of the PROTECT-AF trial suggests that device implantation is associated with a learning phase for the device implanter and that the incidence of adverse safety outcomes have declines with increasing operator experience.

A subsequent randomised controlled trial (PREVAIL) will enrol up to 475 patients with non-valvular AF with a CHADS2 score of at least 2 AND who are eligible for warfarin. This is a higher risk group than used in the PROTECT-AF trial. The primary end-point is a composite of ischaemic/haemorrhagic stroke, systemic embolism and cardiovascular or unexplained death. The estimated study completion date is June 2017.

Data from the ASA Plavix (ASAP) registry suggest that in patients with contraindications to warfarin use, WATCHMAN implantation is possible with aspirin and clopidogrel for six months followed by life-long aspirin. The registry includes 82 patients in whom the device was successfully implanted and includes a median follow-up of 6 months. In this cohort two patients suffered an ischaemic stroke however no thrombus was identified on the surface of the device or in the left atrium on transesophageal echocardiography in either patient. Further device-related thrombus was found in an additional two patients on


107 Ibid

108 Ibid
routine follow-up transesophageal echocardiography. Further data is needed to assess the safety and feasibility of this approach in patients with contraindications to warfarin\textsuperscript{109}.

- The AMPLATZER Septal Occluder (St. Jude Medical) was initially designed for patent foramen ovale and atrial septal defect closure. However, the device has been trialled in 16 patients for LAA occlusion\textsuperscript{110}. Over a four month follow-up there were no adverse events attributable to the device implantation or thromboembolic events noted. No further clinical trials have been conducted using this system for LAA occlusion.

- The AMPLATZER cardiac plug (St. Jude Medical) consists of a lobe designed to sit within the LAA and an occlusive disc which fits over the LAA orifice. The lobe and disc are connected by a central waist, with the lobe containing hooks to ensure device position. Registry data have been published which demonstrate successful device implantation in 132 of the 141 patients\textsuperscript{111}. Serious adverse outcomes occurred in 10 (7.0\%) patients, including three ischaemic strokes, two device embolisations (both recaptured percutaneously) and five clinically significant pericardial effusions. Data from the AMPLATZER Cardiac Plug European post-market registry reveal similar procedural success and similar rates of procedure-related adverse events, occurring in eight of 145 registry patients (5.5\%) within 7 days of the procedure\textsuperscript{112}. The device is currently undergoing a phase I randomised controlled trial comparing the device with conventional warfarin therapy.

- The PLAATO system (eV3) consists of a percutaneously delivered self-expanding cage covered with an expanded polytetrafluoroethylene and 3 rows of anchors, delivered via a transseptal approach. Animal data demonstrated proof of concept with LAA occlusion being achieved in all cases\textsuperscript{113}. Human trials demonstrated successful implantation in 108 of the 111 patients enrolled\textsuperscript{114}. Patients were treated with anticoagulants and, in some participants, subacute endocarditis prophylaxis. During the initial one and six-month follow-up period there were two strokes in two patients and three transient ischaemic


\textsuperscript{110} Meier B et al. Transcatheter left atrial appendage occlusion with AMPLATZER devices to obviate anticoagulation in patients with atrial fibrillation. Catheterisation and Cardiovascular Interventions 2003; 60: 417–22.

\textsuperscript{111} Park J et al. Left atrial appendage closure with AMPLATZER cardiac plug in atrial fibrillation: initial European experience,” Catheterisation and Cardiovascular Interventions 2011; 77: 700–6.

\textsuperscript{112} Park J. AMPLATZER cardiac plug post-market registry interim results. CSI Frankfurt 2011; June 23-25.


\textsuperscript{114} Ostermayer S et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with nonrheumatic atrial fibrillation: results from the international multicenter feasibility trials. Journal of the American College of Cardiology 2005; 46: 9–14.
attacks (TIAs) in an additional two patients\textsuperscript{115}. At 5-year follow-up of 64 patients, there were seven deaths, five major strokes, three minor strokes, one cardiac tamponade requiring surgery, one death from probable cerebral haemorrhage and one myocardial infarction\textsuperscript{116}. The annualized stroke/ TIA rate was 3.8%; less than expected rate of 6.6%/year\textsuperscript{117}. The PLAATO device has been discontinued for commercial reasons.

- The Coherex Wave Crest LAA occlusion system is a percutaneous transeptally delivered LAA occluder. Initial pilot phase results in nine patients demonstrated two embolic events, prompting device modifications prior to further trials. The revised Coherex Wave Crest has been the subject of clinical trials in limited numbers of patients, demonstrating a 10% embolic event\textsuperscript{118}. A multicentre study is currently underway to evaluate the safety and efficacy of the device in 200 patients with non-valvular atrial fibrillation and an ongoing indication for anticoagulation\textsuperscript{119}.

- The LARIAT procedure (SentreHEART) for percutaneous LAA closure requires both endocardial and epicardial access. A preoperative CT is required to exclude large bilobar appendages and other anatomic variants. A magnet-tipped guide wire system is placed at the endocardial surface of the LAA apex, via femoral venous access and a transseptal puncture. A second magnet-tipped guide wire system is percutaneously introduced into the pericardium overlying the LAA apex. This requires an anterior approach to percutaneous pericardial access. The magnet-tipped wires align the endocardial and epicardial aspect of the LAA under fluoroscopy. The LARIAT Suture Delivery Device is guided over the LAA in an over-the-wire approach to slip a pre-tied suture loop over the appendage under transesophageal echocardiographic guidance to achieve appendage closure\textsuperscript{120}.

Early human experience demonstrated successful LAA ligation in 78 of 82 patients undergoing this procedure. The remaining four patients suffered from access-related complications. An additional 13 patients were assessed but were excluded from undergoing the procedure due to anatomical unsuitability and LAA thrombus on the pre-procedure transesophageal echocardiogram. Of the 70 patients undergoing successful

\textsuperscript{115} Block S et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (percutaneous left atrial appendage transcatheter occlusion) study,” JACC. Cardiovascular Interventions 2009; 2: 594–600.


\textsuperscript{117} Ibid

\textsuperscript{118} Muller D. Coherex WaveCrest: device design and human results. In: Proceedings of the Transcatheter Cardiovascular Therapeutics, 2011.


LAA ligation who had 1 month transesophageal echocardiographic follow-up, 96% had complete acute closure of the LAA. There were no device-related complications.\textsuperscript{121}

Overall, limitations of the LAA device trials to date include the following: \textsuperscript{122}

- the number of patients studied is substantially less than the anticoagulant trials;
- patients treated with the device still had to be on warfarin in the periprocedure period. This limits the procedure to patients who can tolerate warfarin at least transiently;
- few events in trials lead to wide confidence intervals.

**Evidence of cost-effectiveness**

A treatment and intervention matrix can be constructed for the pre-, admission and post-hospital phases of management comparing LAA occlusion costs with the costs of medical management (Table 12).

**Table 12: Treatment and intervention matrix**

<table>
<thead>
<tr>
<th>Clinical pathway step</th>
<th>Medical management</th>
<th>LAA occlusion device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-admission assessment and management</td>
<td>Anti-coagulation and anti-arrhythmic medication; routine maintenance investigations</td>
<td>Warfarin and anti-arrhythmic medication; routine maintenance investigations; routine pre-op assessment</td>
</tr>
<tr>
<td>Index admission</td>
<td>No costs incurred</td>
<td>New costs based on existing national benchmarks for similar procedure, with reference to inpatient length of stay and device and other costs.</td>
</tr>
<tr>
<td>Post-discharge management</td>
<td>Will incur usual pharmaceutical, investigation and management costs</td>
<td>Will incur usual pharmaceutical, investigation and management costs</td>
</tr>
<tr>
<td>Risk of stroke</td>
<td>Expected rate of stroke/TIA of 6.6% per year</td>
<td>Estimated rate of stroke/TIA of 3.8% per year</td>
</tr>
</tbody>
</table>

An approximate existing benchmark DRG for the application of left atrial appendage occlusion device is F09C (Other cardiovascular procedures without CPB pump and without catastrophic complications), the 2009/10 average costs of which are set out in Table 13. As stated in the introduction, these approximations are for the purposes of providing an estimate of resource use.

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\textsuperscript{122} Ibid
based on a similar length of stay, theatre and diagnostic use. Medical or surgical DRGs may be assigned to these procedures in the future.

**Table 13: Cost metrics DRG F09C, 2009/10**

<table>
<thead>
<tr>
<th>Metric</th>
<th>NHCDC result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of stay</td>
<td>3.47 days</td>
</tr>
<tr>
<td>Ward nursing</td>
<td>$1,099</td>
</tr>
<tr>
<td>Ward medical</td>
<td>$1,352</td>
</tr>
<tr>
<td>Hotel</td>
<td>$211</td>
</tr>
<tr>
<td>Prosthesis cost</td>
<td>$1,187</td>
</tr>
<tr>
<td>Total direct cost</td>
<td>$8,990</td>
</tr>
<tr>
<td>Total cost (direct and overhead)</td>
<td>$10,896</td>
</tr>
<tr>
<td>Total cost excl prosthesis cost</td>
<td>$9,709</td>
</tr>
</tbody>
</table>

Local advice indicates that actual length of stay for these patients is closer to 2 days, which would reduce ward nursing, ward medical and hotel costs by about 40%, which would bring the total cost excluding prosthesis costs to $8,644, with indexation this becomes $10,001. Patients also require an intraoperative transoesophageal echocardiograph, which in the private sector costs about $350. In Australia the cost of the prosthesis is $15,000, which brings the total cost to $25,354. Follow-up TOE, not being intraoperative, costs about $140.

The projected cost of more than $25,000 again, significantly exceeds the current rates of reimbursement for the likely DRGs to which the procedure will code, F19 of F42, which at most are funded at about $11,000 (Table 14).

**Table 14: Reimbursements for possible DRG coding for LAA occlusion**

<table>
<thead>
<tr>
<th>DRG</th>
<th>Description</th>
<th>2012/13 IHPA inlier bounds</th>
<th>2012/13 IHPA inlier weight</th>
<th>2012/13 Victorian casemix</th>
</tr>
</thead>
<tbody>
<tr>
<td>F19Z</td>
<td>Trans-vascular percutaneous cardiac intervention</td>
<td>1-10 days</td>
<td>2.5758</td>
<td>$10,726</td>
</tr>
<tr>
<td>F42A</td>
<td>Circulatory disorders without AMI, with invasive cardiac investigative procedure with catastrophic or severe complication</td>
<td>2-22 days</td>
<td>2.6645</td>
<td>$11,095</td>
</tr>
<tr>
<td>F42B</td>
<td>Circulatory disorders without AMI, with invasive cardiac investigative procedure without catastrophic or severe</td>
<td>1-9 days</td>
<td>1.3462</td>
<td>$5,606</td>
</tr>
</tbody>
</table>
The annualized rate of stroke or TIA in receiving LAA occlusion devices is approximately 3.8% compared with an expected rate of 6.6% in patients receiving medical management, which is an absolute reduction in risk of 2.8%. Table 15 describes the average length of stay and estimated costs for stroke and TIA separations in 2009/10. Overall, the weighted average cost associated with TIA and stroke DRGs is $7,252. When indexed this increases to $8,391.

**Table 15: TIA and stroke DRGs, NHCDC, 2009/10**

<table>
<thead>
<tr>
<th>DRG</th>
<th>Description</th>
<th>Average length of stay (days)</th>
<th>Average cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>B69A</td>
<td>TIA &amp; precerebral occlusion with complications</td>
<td>5.97</td>
<td>$6,823</td>
</tr>
<tr>
<td>B69B</td>
<td>TIA &amp; precerebral occlusion with complications</td>
<td>2.48</td>
<td>$3,128</td>
</tr>
<tr>
<td>B70A</td>
<td>Stroke and other cerebrovascular disorder with catastrophic complications</td>
<td>15.14</td>
<td>$17,662</td>
</tr>
<tr>
<td>B70B</td>
<td>Stroke and other cerebrovascular disorder with severe complications</td>
<td>8.44</td>
<td>$9,920</td>
</tr>
<tr>
<td>B70C</td>
<td>Stroke and other cerebrovascular disorder without severe or catastrophic complications</td>
<td>5.30</td>
<td>$6,496</td>
</tr>
<tr>
<td>B70D</td>
<td>Stroke and other cerebrovascular disorders, died or transferred less than 5 days</td>
<td>1.54</td>
<td>$2,595</td>
</tr>
<tr>
<td></td>
<td>Weighted average of all separations for the six DRGs</td>
<td>6.25</td>
<td>$7,532</td>
</tr>
</tbody>
</table>

The Australian Institute of Health and Welfare in *How we manage stroke in Australia* (2006), reported that 45% of patients with stroke have a period of inpatient rehabilitation. Based on an average length of stay of 16 days, a further $9,280 of costs is incurred in inpatient rehabilitation. Therefore, in Australia approximately $12,600 of direct inpatient hospital expense are generated for each stroke patient with additional community resources also being used to support the patient and family. Indirect costs associated with loss of productivity after stroke are not included in the estimates but may be substantial.

Overall, after accounting for savings generated through reduced numbers of strokes, (an overall annualised inpatient saving of a lower rate of stroke and TIA is estimated at $350 from the above calculations), the net cost of the procedure is estimated at $24,650.
Estimated annual caseload costs

Approximately 75% of patients with AF have an intermediate or high risk of stroke according to the CHADS2 score and should receive treatment with warfarin therapy\textsuperscript{123}. However, 20% of patients have a contraindication to warfarin therapy\textsuperscript{124,125}. These patients are considered a higher priority for LAA occlusion\textsuperscript{126}. Approximately 1.2% of Australians (260,000 persons) have AF, of whom 198,000 have a clinical indication for warfarin therapy. Of these, an estimated 40,000 have a contraindication to warfarin therapy and would be potential candidates to receive LAA occlusion devices. At a per-patient cost of $24,650, the total annual caseload cost in Australia is estimated at $986 million dollars.

A Canadian cost-utility analysis has been published that accounts for rates of non-compliance with medical management in estimating the cost per QALY associated with LAA occluders. In a reference case of 65 year old males with a stroke risk score of 2.5, the incremental cost per quality adjusted life year gained for LAA occlusion compared to no treatment was estimated to be $40,229. Though no strict willingness to pay threshold exists in Canada, an intervention with this cost per QALY would generally be considered reasonably cost-effective\textsuperscript{127}.

However, the cost-effectiveness results are highly dependent on the treatment effect assumed for LAA occlusion. If the comparator group in the analysis was assumed to be on aspirin treatment instead of no treatment, the relative risk of stroke for LAA occlusion would have been assumed to be around 0.60 instead of 0.36. Under this scenario, the cost per QALY of LAA occlusion would be estimated to be $107,239. An intervention with a cost per QALY of $107,239 may be perceived as being cost-ineffective\textsuperscript{128}.

Impacts on service delivery

This procedure can only be performed in specialist units where there are arrangements for cardiac surgery in the event of complications. The procedure is likely to be performed in a specialist unit, such as a cardiac catheterisation laboratory, and will require a 48 hour hospital stay.

Most stakeholders report that LAA occlusion devices are not yet suitable for widespread clinical use. Concerns raised include the following:

- there are many other potential trouble sources of emboli, including the atrial septum, left-sided valves, carotids, and aorta;

\textsuperscript{127} Canadian Agency for Drugs and Technology in Health. Left Atrial Appendage Occlusion. October 2010.
\textsuperscript{128} Ibid
most of the risk factors for stroke in patients with AF are systemic; e.g. age, hypertension, and diabetes. Since stroke risk in AF is a systemic not an anatomic problem, occlusion of the LAA is an incomplete strategy.

Rigorous education and training are essential for knowledge and skills transfer. The Watchman trial demonstrated that serious adverse events were twice as likely in the device arm and that adverse events are learning curve dependent.

Stakeholders reported that in light of the paucity of long-term follow-up data following LAA occlusion the place of LAA occlusion in the prevention of stroke in patients with AF is still unknown and further research is required to define long-term outcomes and need for ongoing anticoagulation following these approaches.
PUMPS / ASSIST DEVICES AS A DESTINATION THERAPY FOR THE MANAGEMENT OF HEART FAILURE

Background

Heart failure is a complex syndrome that can result from structural or functional cardiac impairment and reduces the heart’s ability to support the circulation of blood through the body.

The disease affects one in seven people aged 85 years and over compared with one in 35 people aged 65 to 74 years. The incidence of heart failure is thought to be increasing because the population is ageing and because survival after a myocardial infarction, the leading cause of heart muscle damage leading to heart failure, has improved over time.\textsuperscript{129,130}

It is projected that the proportion of the population over 65 years of age will increase from 12\% in 2001 to 18\% in 2021 in New Zealand. This will increase the number of people affected by heart failure by approximately 50\% over the next three decades in New Zealand.\textsuperscript{131}

The direct cost of heart failure to the Australian health system are approximately 10\% of the total health care costs attributable to CVD.\textsuperscript{132} Most of this cost is attributable directly to hospital inpatient care. The overall costs associated with heart failure account for 1.5\% to 2\% of the total New Zealand health budget.\textsuperscript{133}

From 2002 to 2006 there were between 7,000 and 8,000 hospital admissions for heart failure each year in New Zealand (Figure 6).\textsuperscript{134}


\textsuperscript{130} National Heart Foundation of New Zealand. New Zealand Guideline for the Management of Heart Failure, 2009 Update.

\textsuperscript{131} Ibid


\textsuperscript{133} National Heart Foundation of New Zealand. New Zealand Guideline for the Management of Heart Failure, 2009 Update.

\textsuperscript{134} Ibid
Hospitalisations have increased since 2006 in Australia (Figure 7)\textsuperscript{135}. There are currently approximately 45,000 hospitalisations for heart failure each year in Australia.

Heart failure is the leading cause of cardiac transplantation in adults\textsuperscript{136}. There are approximately 75 to 80 heart transplants performed in Australia and New Zealand each year; numbers have been relatively stable since 1998 (Figure 8)\textsuperscript{137}.

\textsuperscript{135} AIHW. Hospitalisations data cubes.

\textsuperscript{136} Australian and New Zealand Cardiothoracic Organ Transplant Registry. 16th Annual Report, 1984 to 2011.

\textsuperscript{137} Ibid
The two most common underlying causes of heart failure leading to transplantation are cardiomyopathy and ischaemic heart disease (Figure 9)\textsuperscript{138}.

Pre-transplant, a growing number of patients are supported by ventricular assist devices (VADs) (Figure 10)\textsuperscript{139}.

\begin{figure}[h]
\begin{center}
\includegraphics[width=\textwidth]{heart_transplants.png}
\end{center}
\caption{Heart transplants, Australia and New Zealand, 1990 to 2011}
\end{figure}

\begin{figure}[h]
\begin{center}
\includegraphics[width=\textwidth]{reason_for_transplant.png}
\end{center}
\caption{Reason for transplant, all hearts, 1984 to 2011}
\end{figure}

\textsuperscript{138} Australian and New Zealand Cardiothoracic Organ Transplant Registry. 16th Annual Report, 1984 to 2011.

\textsuperscript{139} Ibid
Between 10% and 15% of people on the waiting list for a heart transplant will die before receiving their transplant, mainly due to the lack of available donor organs\textsuperscript{140}.

Implantable mechanical pumps include total artificial hearts and VADs. VADs are usually designed to support one side of the heart (mainly the left) and have been widely used in patients awaiting transplant (a bridge to transplant), to support patients who are acutely unwell and who are awaiting recovery of the heart (a bridge to recovery) and have been trialled in patients with refractory heart failure who are not eligible for a heart transplant (destination therapy)\textsuperscript{141}. Total artificial hearts (TAHs) are designed to provide biventricular support and have been used as a bridge to transplant or as destination therapy\textsuperscript{142}.

Cardiac transplantation is the accepted treatment of choice for patients with end-stage heart failure\textsuperscript{143}. However, the availability of heart transplantation is limited by the shortage of suitable donor hearts. Further, patients undergoing transplantation are prone to rejection of the donor organ and are maintained on a range of immunosuppressive and prophylactic drugs for life\textsuperscript{144}.

\begin{flushright}
\textsuperscript{140} Australian and New Zealand Cardiothoracic Organ Transplant Registry. 16th Annual Report, 1984 to 2011.
\textsuperscript{141} Rector T et al. Use of Left VAD as destination therapy in end-stage congestive heart failure: a systematic review. Department of Veterans Affairs Evidence-Based Synthesis Program. May 2012.
\textsuperscript{142} http://www.fastcompany.com/most-innovative-companies/2011/profile/syncardia.php
\textsuperscript{143} National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.
\textsuperscript{144} Australian and New Zealand Cardiothoracic Organ Transplant Registry. 16th Annual Report, 1984 to 2011.
\end{flushright}
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

Technology

Total artificial heart

ASERNIP-S completed a TAH brief in November 2011. The following provides a brief overview of key developments in TAH technology.

The SynCardia total artificial heart consists of a portable driver attached to a total artificial heart pump device. Their use is currently temporary whilst awaiting cardiac transplant rather than as a destination therapy. Approximately 1,000 have been implanted worldwide as at February 2012.145 St Vincent’s Hospital Sydney has SynCardia certification for implantation of the device.

The BiVACOR total artificial heart is a rotary turbo pump that is used as a BiVAD (BV Assist) if a chance of heart recovery is anticipated, whilst patients identified as having no chance of heart recovery can have the device implanted as a total artificial heart (BV replace). The pump design improves durability and flow balancing issues associated with older generation technology, positioning this device as a next generation for bridge to transplantation or destination therapy. Use in paediatric and adult patients is anticipated. The device is designed to have a within-patient life in excess of ten years. The device has been built and tested both in-vitro and in-vivo. Nine short term pre-clinical studies have confirmed proof of concept. Animal studies have commenced. First-in-man studies are anticipated in the next 12 months.146

Cleveland Clinic also has a TAH in development – the Smartheart. Bioprosthetic myocardial material (e.g. bioengineered cell sheets) is used in this device.147 The device is still in the experimental stages of development.

Ventricular assist devices

VADs are implanted under general anaesthesia, usually through a chest incision. Surgery takes several hours. The inflow of the pump is inserted into the left side of the heart, usually the left ventricle, and the outflow is inserted into the arterial system, usually the aorta.148 However, newer generation devices may be used as biventricular pumps (dual pumps, left and right heart) or right-sided pumps.149

There are over 30 different types of VADs that are commercially available, including:

- Thoratec VADs (HeartMate II, HeartMate III and HeartMate X);
- HeartWare VADs (HVAD pump, MVAD pump);

145 www.syncardia.com
146 http://bivacor.com/?page_id=34
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

- Jarvik 2000 LVAD;
- MicroMed CardioVascular Heart Assist; and
- CircuLite Synergy MicroPump.

Berlin EXCOR is already established in clinical practice in Australia.

In Australia pumps are predominantly used as a bridge to transplant or bridge to recovery after surgery. Criteria for clinical indication of a device as destination therapy for heart failure are essentially the same for each device\(^{150}\):

- NYHA Class IV symptoms of heart failure that have not responded to optimal medical management for at least 45 of the last 60 days or have been balloon pump dependent for 7 day or IV inotrope dependent for 14 days;
- a left ventricular ejection fraction (LVEF) less than 25%;
- demonstrated functional limitation with a peak oxygen consumption of 14 ml/kg/min or less unless the patients is balloon pump or inotrope dependent or physically unable to perform an exercise test;
- not a candidate for heart transplantation; and
- appropriate body size for the device.

Current US criteria for use of a VAD as destination therapy also include an estimated 1-year survival without the device of less than 50% or an overall life expectancy without the device of less than 2 years\(^{151}\)\(^{152}\)\(^{153}\). A validated method for making these predictions has not been established, nor has a validated method been developed to determine which eligible patients have unacceptably high operative risk. Analysis of INTERMACS registry data indicated that the presence of cardiogenic

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150 Rector T et al. Use of Left VAD as destination therapy in end-stage congestive heart failure: a systematic review. Department of Veterans Affairs Evidence-Based Synthesis Program. May 2012.


shock, concomitant surgery and poorer renal function as indicated by higher blood urea nitrogen were associated with higher mortality within 30 days of the operation.154

The relationship between VADs and cardiac resynchronisation therapy (CRT) along the clinical pathway for management of severe heart failure is not incorporated into the above criteria even though CRT has become part of the standard of care when clinically indicated for patients with heart failure.155

The 2011 Australian National Heart Foundation Guidelines for the prevention, detection and management of chronic heart failure in Australia make reference to the use of left VADs as destination therapy for heart failure.156 The guidelines state the following:

“The prohibitive cost, large size, lack of total implantability and risk of complications limit the widespread use of currently available LVADs in patients with end-stage CHF. Compact continuous-flow LV assist systems are undergoing clinical trial with the promise of a more favourable serious adverse event profile. They may also suit smaller adults and children with CHF who currently have no available mechanical circulatory support option (Grade C recommendation)”.

However, guidelines issued by the Heart Failure Society of America in 2010 recommend that permanent mechanical assistance may be considered in highly selected patients with severe heart failure refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from inotropic support by an experienced heart failure centre.157

Further, the 2011 Canadian Cardiovascular Society Heart Failure Guidelines recommend that permanent mechanical circulatory support be considered for highly selected patients who are ineligible for heart transplantation.158

Evidence of effectiveness

The earliest generation of VADs (HeartMate I) was assessed in the REMATCH RCT. The use of this pulsatile flow VAD was associated with improved survival (48% reduction in risk of death from any cause compared with optimal medical management) and improved quality of life in patients with end-stage heart failure who were ineligible for cardiac transplantation. Actuarial survival was higher for patients with the HeartMate compared with optimal medical management at one year (52%...
versus 25%) and two years (23% versus 8%). There was, however, a greater than twofold increased risk of serious adverse events, including infection, bleeding, thromboembolism and device malfunction.

A randomised trial compared a continuous-flow VAD with a pulsatile-flow VAD in patients with advanced chronic heart failure in whom current therapy had failed and who were ineligible for heart transplantation. Almost 80% of the patients were receiving intravenous inotropes and 20% had intra-aortic balloon pumps at the time of enrolment. The continuous-flow VAD significantly improved the primary composite endpoint of survival free from disabling stroke and reoperation to repair or replace the device at 2 years (46% versus 11%, P < 0.001). Furthermore, actuarial survival at 2 years was improved (58% versus 24%, P = 0.008) and major adverse events and re-hospitalisations were less frequent.

A 2012 systematic review published by the US Department of Veterans Affairs assessed patient outcomes with VADs as destination therapy for heart failure. One high quality randomised clinical trial was identified that assessed the HeartMate II used as a VAD for destination therapy compared with the older pulsatile flow HeartMate XVE device. The 200 patients enrolled in this study were ineligible for a heart transplant, symptomatic at rest or with minimal exertion (NYHA class IV heart failure) despite optimisation of other therapies for heart failure and had a left ventricular ejection fraction less than 25%. After 24 months, the primary endpoint of survival free of disabling stroke or reoperation to remove the device was 46% versus 11% (p < 0.01). Survival in the HeartMate II group was significantly better (58% versus 24% after 2 years) and subjects spent a greater percentage of their follow-up time outside hospital (88% versus 74%) largely due to a lower readmission rate. During follow-up survivors with the HeartMate II also had fewer functional limitations due to heart failure as measured by the NYHA class, Minnesota Living with Heart Failure Questionnaire and clinical component of the Kansas City Cardiomyopathy Questionnaire. The incidences of several adverse events were lower as well including right heart failure, cardiac arrhythmias, device-related infections, sepsis, respiratory failure, renal failure, and device replacement.

Two reports of case series provided survival estimates for patients receiving the Heart Mate II as destination therapy. Although these reports provided lower quality evidence, survival at one year in


161 Rector T et al. Use of Left VAD as destination therapy in end-stage congestive heart failure: a systematic review. Department of Veterans Affairs Evidence-Based Synthesis Program. May 2012.


163 Park S et al. for the HeartMate II Clinical Investigators. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circulation: Heart Failure 2012 Jan 26;
these cases series was similar to the 68% 1-year survival in the HeartMate II group in the randomised clinical trial\textsuperscript{164, 165}.

More recent survival estimates without heart transplantation or heart recovery from the INTERMACS registry that are based on 740 cases were 74% and approximately 60% after 1 and 2 years, respectively\textsuperscript{166}.

The non-randomised HeartWare ADVANCE trial in 140 patients with NYHA IV heart failure awaiting transplant found 30 day mortality of 1.4%, 91% survival at 1 year and a similar adverse event profile to the HeartMate II device\textsuperscript{167}.

The CircuLite Synergy MicroPump is designed for long-term support and has been bench-top tested for >3.5 years of continuous use. Clinical experience in 44 patients demonstrated improved haemodynamics, functional status and quality of life. The longest patient support provided by the pump is 2.5 years.

Clinical trials of other newer generation continuous flow VADs and pumps for destination therapy in adults are commencing or are in early trial stages:

- HeartWare (ADVANCE bridge to transplant trial, ENDURANCE destination therapy trial, REVIVE-IT trial of the pump in NYHA Class III patients)\textsuperscript{168-170};
- Jarvik 2000 (first destination therapy prospective, randomised trial against other destination therapy VAD commenced in 2012);
- CircuLite Synergy MicroPump (pilot randomised controlled trial commencing 2012).

**Evidence of cost-effectiveness**

In Australia, the 2009/10 NHCDC identifies 38 separations for the insertion of a ventricular assist device (DRG A10Z) from eight reporting hospitals, with an average cost of $258,801 per separation (Table 16). This is the most expensive of all the DRGs reported. The reason for use of the VAD


\textsuperscript{165} Strüber M et al. HeartMate II left ventricular assist device; early European experience. European Journal of Cardiothoracic Surgery 2008; 34:289-94.

\textsuperscript{166} Kirklin J et al. Fourth INTERMACS annual report: 4,000 implants and counting. Journal of Heart and Lung Transplantation 2012; 31:117-26


\textsuperscript{170} ClinicalTrials.gov. A clinical trial to evaluate the HeartWare® ventricular assist system (ENDURANCE). NCT01166347. Available at http://clinicaltrials.gov/ct2/show/record/NCT01166347.
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

(bridge to transplant, bridge to recovery or destination therapy) is not explicitly available from the NHCDC.

The most significant contributors to total cost are the cost of the device, here reported as $100,000 and prolonged intensive care admissions. ICU contributes more than $90,000 to the hospital stay, which on average was nearly 50 days per separation.

Table 16: Cost metrics DRG A10Z, 2009/10

<table>
<thead>
<tr>
<th>Metric</th>
<th>NHCDC result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of stay</td>
<td>49.88 days</td>
</tr>
<tr>
<td>Cost of VAD</td>
<td>$100,000</td>
</tr>
<tr>
<td>Critical care cost</td>
<td>$91,604</td>
</tr>
<tr>
<td>Operating room cost</td>
<td>$15,014</td>
</tr>
<tr>
<td>Ward medical and nursing costs</td>
<td>$22,522</td>
</tr>
<tr>
<td>Pathology cost</td>
<td>$9,900</td>
</tr>
<tr>
<td>Pharmacy cost</td>
<td>$8,704</td>
</tr>
<tr>
<td>Direct cost</td>
<td>$247,744</td>
</tr>
<tr>
<td>Overhead cost</td>
<td>$38,934</td>
</tr>
<tr>
<td>Total cost</td>
<td>$286,678</td>
</tr>
</tbody>
</table>

The SynCardia total artificial heart is more expensive again, costing approximately $125,000 (USD)\(^1\).\(^{171}\)

The projected total caseload in Australia for use of VADs and pumps as destination therapy is difficult to estimate as some people who currently receive cardiac transplantation may instead be suited to VADs or pumps as destination therapy. However, for the purposes of analysis, it is assumed that patients currently receiving cardiac transplantation for destination therapy continue to do so.

There are approximately ten patients who die on the waiting list for cardiac transplantation each year in Australia. These patients may otherwise be suited to receiving a mechanical device. If patients who die on the waiting list are assumed the minimum caseload of patients who would receive a device as destination therapy, the estimated total annual caseload cost is between $2.8 million (for devices costing $100,000) and $3.3 million (for devices costing $125,000). In comparison, the cost for an adult cardiac transplantation is approximately $155,592 according NHCDC data. Costs are also incurred for the ongoing out patient management of patients, which includes specialist review,  

investigations and monitoring and immunosuppression therapy, which costs about $1,500 each month.

Some economic evaluation data are available from the industry-funded (Thoratec) economic evaluation reports. According to industry analysis, continuous-flow VADs have an estimated incremental cost effectiveness ratio (ICER) of $198,184 per quality-adjusted life year and $167,208 per overall life years not adjusted for in the patients’ quality of life172.

The ICER estimates used “base case” assumptions regarding: survival, costs related to the initial implantation of the ventricular assist device, costs of medical management, re-hospitalisation rates and costs, device replacement costs, outpatient care costs, end-of-life costs and estimates of quality of life (utility) for each of the four NYHA classes of limitations due to symptoms of heart failure that patients may fall in after implantation of the device. The quality of life assessment did not incorporate other medical conditions including the impact of device complications. Changes to base assumptions altered estimates of cost-effectiveness ranging from $150,000 to $300,000 per quality-adjusted life year.

Prior analyses that compared use of the older generation VADs have generated conflicting results. Analysis of the cost-utility of the older generation HeartMate VE demonstrated a cost-effectiveness ratio of $802,700 per quality-adjusted life year173. In contrast, a UK economic evaluation conducted of the earlier generation of VADs found that VADs for long-term chronic support in heart failure were cost-effective. They found that the baseline cost per QALY of the first-generation HeartMate LVAD was £170,616. The authors estimated that a 60% improvement in survival over first-generation devices was necessary before the incremental cost-effectiveness approached £40,000 per QALY174.

**Impacts on service delivery**

Stakeholders expressed some concern at the prospect of widespread use of pumps as destination therapy in patients with heart failure. Given their high cost and the prospect of a substantial increase in demand with an ageing population and increasing prevalence of heart failure, this therapy has the potential to consume substantial proportions of the health budget if not used judiciously. Stakeholders supported the development of guidelines to inform effective and cost-effective use, and systems for monitoring clinical practice in order to ensure guidelines are followed. The ongoing collection of detailed outcomes data will be required to ensure clinical pathways are appropriate for the efficient and effective use of the technology.

Stakeholders identified that ethical problems will arise with equitable and appropriate access to this technology that will need to be addressed by policymakers.

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According to US access provisions, destination therapy is reasonable and necessary only when the procedure is performed in a facility approved under the Disease-Specific Care Certification Program for Ventricular Assist Device developed by the Joint Commission on Accreditation of Healthcare Organizations\textsuperscript{175}. According to these criteria, facility staff must have implanted at least 10 VADs or total artificial hearts as a bridge to transplant or as destination therapy during the past 36 months with at least one procedure within the past 18 months. The facility also must have in place staff and processes that assure that prospective recipients receive all information necessary to assist them in giving informed consent for the procedure, and so that they and their families are fully aware of the aftercare requirements and potential limitations as well as benefits.

Stakeholders consulted for the purposes of this review agreed that these procedures should only be performed in highly specialised cardiac surgical units with the ability to provide specialist cardiac surgery in the event of complications. Some stakeholders felt that, given the very high device costs, strict patient selection was required in order to ensure devices were used efficiently. It was proposed by some stakeholders that the high costs of the devices may warrant consideration of development of Nationally Funded Centres.

Regardless of the site at which devices are implanted, cardiology professionals will require knowledge and skills development in the after-care of patients who receive VADs or pumps as destination therapy.

Given the paucity of long-term data regarding patient outcomes, particularly compared with cardiac transplantation, and the high costs associated with the use and maintenance of the devices, a device registry with collection of detailed patient outcomes data was proposed by stakeholders should increased use of devices for destination therapy be contemplated by policymakers.

NEXT GENERATION PACEMAKER AND IMPLANTABLE CARDIAC DEFIBRILLATOR DEVICES

Background
Pacemakers and implantable cardioverter-defibrillators (ICDs) are cardiac devices indicated in the management of specific cardiac arrhythmias.

Pacemakers
Permanent pacemakers are implantable devices that sense intrinsic cardiac electric potentials and, if these are too infrequent or absent, transmit electrical impulses to the heart to stimulate myocardial contraction. Absolute indications for pacemaker placement include the following:

- Sinus node dysfunction (sick sinus syndrome);
- Third-degree atrioventricular block (complete heart block);
- Symptomatic sinus bradycardia;
- Atrial fibrillation with sinus node dysfunction;
- Chronotropic incompetence (inability to increase the heart rate to match a level of exercise); and
- Long QT syndrome.

Relative indications for pacemaker placement include the following:

- Dilated cardiomyopathy; and
- Severe refractory neurocardiogenic syncope.

A specialized type of pacemaker therapy, cardiac resynchronization therapy (CRT) with biventricular pacing is an adjunctive therapy for some patients with heart failure.

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Guidelines developed by the National Heart Foundation, American College of Cardiology and the American Heart Association on the diagnosis and management of heart failure in adults recommend the indications below for CRT\textsuperscript{181, 182, 183}:

- CRT, with or without an ICD, is indicated for patients with an LVEF of 35% or lower, sinus rhythm, and New York Heart Association (NYHA) functional class II, III or IV heart failure symptoms who are on optimal medical therapy and have evidence of cardiac dyssynchrony (as demonstrated by a QRS duration of more than or equal to 150 ms);

- CRT, with or without an ICD, is reasonable for the treatment for NYHA functional class III or IV heart failure symptoms in patients on optimal medical therapy with chronic atrial fibrillation, an LVEF of 35% or lower, and a QRS duration of 120 ms or longer; and

- CRT, with or without an ICD, is reasonable for patients who have frequent dependence on right ventricular pacing, an LVEF of 35% or lower, and NYHA functional class III or IV symptoms on optimal medical therapy.

**Implantable cardiac defibrillators (ICDs)**

ICDs are the first-line treatment and prophylactic therapy for patients at risk of ventricular tachycardia (VT) or ventricular fibrillation (VF)\textsuperscript{184, 185}. There are two broad categories for use: primary and secondary prophylaxis. Primary prophylaxis is for patients who are at risk for, but who have not yet manifested, sustained ventricular arrhythmias. These account for most ICD implants. Secondary prophylaxis is for preventing sudden cardiac death in patients with a history of life-threatening VT or VF\textsuperscript{186}.

Current devices offer anti-tachycardia pacing schemes and low-energy and high-energy shocks in multiple tachycardia zones. Sophisticated discrimination algorithms minimise shocks for atrial fibrillation, sinus tachycardia, and other non–life-threatening supraventricular tachyarrhythmias\textsuperscript{187}.

\textsuperscript{181} National Heart Foundation. Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.


\textsuperscript{184} National Heart Foundation. Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.


\textsuperscript{186} Ibid

An ICD shock is generally painful and devices may deliver inappropriate shocks, particularly where atrial fibrillation, sinus tachycardia, and other types of supraventricular tachycardia are present. Inappropriate shocks may also result from sinus tachycardia, illicit drug use (as with cocaine and methamphetamine) and ventricular oversensing. Patient with inappropriate shocks have greater all-cause mortality\textsuperscript{188}.

ICD implantation may worsen quality of life, and the mortality benefit from ICD implantation needs to be balanced against the effects of living with a device that delivers painful shocks which are not controllable by the patient. The majority of patients will tolerate infrequent shocks in the knowledge that these are potentially lifesaving\textsuperscript{189}.

\textit{Trends in device use}

A comprehensive survey of the number of pacemakers and implantable cardioverter defibrillators was undertaken in Australia and New Zealand for the year 2005. Data were obtained via a survey of all companies that sold and registered pacemakers throughout Australia and via individual hospitals in New Zealand. During 2005 there were 123 Australian and seven New Zealand centres routinely performing the implantation of pacemaker devices. A total of 12,990 pacemakers were sold in Australia during 2005, of which 11,850 were new implants and 1,140 (8.8\%) were replacement devices. This figure represents a 17.7 \% increase in the number of devices implanted in the year 2001 (11,034) and equates to a rate of 590 implanted pacemakers per million of population (Figure 11). A small fraction of these devices were biventricular pacemakers (461, 3.5\%) used for cardiac resynchronisation therapy. No information was available as to the clinical indications for implantation in Australia\textsuperscript{190}.

In New Zealand for the same year, there were a total of 1,450 pacemakers implanted which was a significant increase (30.7\%) compared to the number implanted in 2001 (1,109). Of these, the majority were new implants (1,134) with 21.8 \% (316) being replacement pacemakers. This number equates to a rate of 275 implanted pacemakers per million of population (Figure 11). Only 16 biventricular pacemakers were implanted. Clinical indications were collected for New Zealand with 49 \% of pacemakers implanted for atrioventricular block, sinus node disease (28\%), atrial fibrillation (18\%), neurocardiogenic and carotid sinus syncope (2\%) and all forms of cardiomyopathy\textsuperscript{191}.

\textsuperscript{189} National Heart Foundation. Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.
\textsuperscript{191} Ibid
Figure 11: Trends in pacemaker and ICD device use, Australia and New Zealand, 1972 to 2005

In Australia, the number of separations where a pacemaker or an ICD has continued to increase since 2005. The total number of pacemaker insertions is substantially higher than insertions of ICDs (Figures 12 and 13)\(^1\). However, the rate of increase in insertions of ICDs over time has been greater than the rate of increase in insertions of pacemakers (Figure 13)\(^2\).

Figure 12: Number of public and private hospital separations with a pacemaker insertion procedure, Australia, 2000/01 to 2009/10


193 Ibid
In New Zealand, the following cardiac device procedures were performed in 2009/10, indicating increasing device demand since 2005 (Table 17).

Table 17: Cardiac device procedures, New Zealand, 2009/10

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Public hospital discharges</th>
<th>Private hospital discharges</th>
<th>Total hospital discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion of temporary transvenous electrode for cardiac pacemaker or defibrillator</td>
<td>157</td>
<td>1</td>
<td>158</td>
</tr>
<tr>
<td>Insertion of permanent transvenous electrode for cardiac pacemaker or defibrillator</td>
<td>1,672</td>
<td>8</td>
<td>1,680</td>
</tr>
<tr>
<td>Insertion of other electrode or patch for cardiac pacemaker or defibrillator</td>
<td>76</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td>Insertion of cardiac pacemaker generator</td>
<td>1,289</td>
<td>8</td>
<td>1,297</td>
</tr>
<tr>
<td>Insertion of cardiac defibrillator generator</td>
<td>341</td>
<td>3</td>
<td>344</td>
</tr>
<tr>
<td>Adjustment, replacement or removal of electrode for cardiac pacemaker or defibrillator</td>
<td>222</td>
<td>4</td>
<td>226</td>
</tr>
<tr>
<td>Adjustment, replacement or removal of cardiac pacemaker generator</td>
<td>499</td>
<td>3</td>
<td>502</td>
</tr>
<tr>
<td>Adjustment, replacement or removal of cardiac defibrillator generator</td>
<td>123</td>
<td>1</td>
<td>124</td>
</tr>
</tbody>
</table>

Design features of devices

Pacing systems and ICDs both consist of a pulse generator and pacing leads. The pulse generator contains a battery, as well as sensing, timing, and output circuits. The battery in a pacemaker (most
commonly lithium-iodide) typically has a lifespan of 5-10 years. In contrast, ICD batteries last approximately five to six years\textsuperscript{194,195}.

Pacemaker endocardial leads are inserted transvenously and advanced to the right ventricle, the right atrium, or both, where they are implanted into the myocardial tissue or, in the case of biventricular pacing, to the coronary sinus, from which point the lead is advanced to a terminal vein adjacent to the posterior surface of the left ventricle. The pulse generator is placed subcutaneously or submuscularly in the chest wall.

ICD endocardial leads are inserted transvenously and advanced to the right ventricle, where they are implanted into the myocardial tissue. The pulse generator is placed subcutaneously or submuscularly in the chest wall.

**Technology**

*Mechanical leadless pacemakers*

Pacing leads are associated with complications and lead extraction, when required, is a high-risk procedure. With new device systems that often require implantation of multiple leads and with patients living longer, the incidence of lead complications is becoming compounded over time\textsuperscript{196}. There is a strong demand to develop a pacing system that eliminates the pacing lead as a conduit for energy transfer. New technologies are also being developed for leadless pacemakers including mechanical devices and bio-artificial pacemakers (gene- and cell-based). Bio-artificial pacemakers have not progressed beyond proof-of-concept stage\textsuperscript{197}.

Leadless pacing can potentially remove the complications associated with lead placement, described above; can allow for pacing at more than two ventricular sites, left ventricular endocardial pacing, epicardial pacing and transapical pacing; and can address the barriers to left ventricular pacing using leads\textsuperscript{198}.

Up to 40% of patient receiving biventricular pacing for heart failure do not benefit. An important cause for lack of benefit is suboptimal left ventricular stimulation. Restrictions imposed by the difficulty of positioning and by the anatomy of the coronary sinus and its branches limit the ability to select a more optimal left ventricular site. Further, left ventricular stimulation is restricted to sites


\textsuperscript{197} Wilkoff B and Brachmann J. Leadless ICD and leadless pacemaker. Cardiostim 2012; June 15, 2012; Nice, France.

\textsuperscript{198} Ibid
on the epicardium, the coronary sinus courses on the epicardium and surgically implanted left ventricular leads are placed into the epicardium\(^{199}\).

Clinical trial data suggest that endocardial or subendocardial stimulation improve the efficacy of pacing\(^{200,201}\). This can theoretically be more easily achieved using leadless pacing\(^{202}\).

Mechanical technologies in development have been described as self-contained, small pellet-like pacing devices that can be installed under local anesthesia in the right ventricular apex, left atrium, an epicardial location, the coronary sinus or multiple sites. Multiple devices could be implanted to work in concert with each other "without the tethers" of current transvenous lead-bound technologies\(^{203}\).

Many concepts have been patented for the development of a leadless pacing system. The majority use ultrasound energy as a power source for the device. Ultrasound-mediated energy is used to drive a remotely positioned electrode for direct myocardial stimulation, using the mechanical-to-electrical properties of piezoelectric materials for transformation of energy\(^{204}\). The Wireless Cardiac Stimulation system (WiCS), the first leadless pacemaker to be successfully implanted in human clinical trials, uses this power system. The device consists of a leadless electrode to convert mechanical energy, wirelessly transmitted from an ultrasonic pulse generator, into electrical energy which is used to pace the heart\(^{205}\). Medtronic's leadless pacemaker is expected to be available in the market in 2014\(^{206}\).

The system includes an ultrasound generator implanted subcutaneously in the acoustic window of the chest wall and an endocardial receiver electrode. The receiver electrode is delivered by a steerable transvascular catheter to the target heart chamber, and can be detached and implanted onto the endocardium directly. The receiver and transmitter are programmed to operate at the same frequency of ultrasound pulses to avoid external interference. The ultrasound beam is optimised and focused onto the receiver electrode in order to improve the efficacy of energy transfer\(^{207}\).

Alternative energy sources are under development:

\(^{200}\) Rademakers L et al.  Electrical and hemodynamic benefits of endocardial CRT with chronic infarction and LBBB.  Presented at Heart Rhythm 2009, Boston, USA, 13–16 May 2009.
\(^{203}\) Ibid
\(^{204}\) Lee K.  Recent advances in pacing and defibrillation.  Asia-Pacific Cardiology 2011; 3: 74-6.
\(^{205}\) Cambridge Consultants.  Leadless pacemaker brings new hope to cardiac patients.  Press Release, November 2011.
\(^{207}\) Lee K et al.  Temporary leadless pacing in heart failure patients with ultrasound-mediated stimulation energy and effects on acoustic window, Heart Rhythm, 2009;6:742–8.
• An alternating magnetic energy source tested in a pig model for leadless cardiac stimulation consists of an external transmitter unit and a receiver unit in contact with the myocardium. The subcutaneous primary coil generates an alternating magnetic field, converted by the secondary coil inside the heart to a voltage pulse for pacing stimulation\(^{208}\).

• Sirius has developed a piezo-electric power generator that uses the motion of the heart to create enough electricity to power the device as a "self-perpetuating" battery\(^{209}\).

**Bio-artificial leadless pacemakers**

Various gene- and cell-based approaches have been pursued in the past decade to develop bio-artificial pacemakers, with a particular emphasis placed on the use of pluripotent stem cells and the hyperpolarisation-activated cyclic nucleotide-gated-encoded pacemaker gene family.

At the molecular and cellular levels, the process of pacemaking involves the complex interplay of a range of ionic channels and pumps, which in turn give pacemaker action potentials a unique signature waveform. Unlike rhythmically firing pacemaker cells, adult atrial and ventricular muscle cells are normally electrically silent unless they get stimulated by signals transmitted from neighbouring cells that originate from the sino-atrial node. This quiescent nature of cardiac muscle cardiomyocytes is due to the absence of \(I_f\) and the intense expression of \(IK_1\), encoded by the Kir2 gene family, which stabilises a negative resting membrane potential. Gene- and cell-based approaches aim to confer upon normally quiescent cardiac muscle cells the ability to intrinsically fire action potentials similar to genuine nodal pacemaker cells as potential biological alternatives or supplements to electronic devices\(^{210}\).

Proof-of-concept experiments have been performed in vitro and in swine\(^{211}\). Human studies have not been performed.

**Subcutaneous ICDs**

Lead dislodgment and, less commonly lead failure, are important complications associated with ICD leads\(^{212}\). The subcutaneous implantable cardioverter-defibrillator (S-ICD) is a new device that allows the lead to be placed under the skin rather than through a vein into the heart.

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The S-ICD System has been approved only for patients who do not also require a pacemaker or pacing therapy. Many patients who need ICDs also need antiarrhythmic pacing, which the subcutaneous device cannot deliver, limiting the patient population that can benefit from the S-ICD.

Evidence of effectiveness

Leadless pacemakers

The feasibility and safety of ultrasound-powered leadless pacing has been demonstrated in animals.213 Following animal experiments, human studies were performed demonstrating ultrasound-mediated pacing at a total of 80 pacing sites in the right atrium, right ventricle and left ventricle in 24 subjects. There were no adverse events.214

Unresolved challenges require ongoing research. The long-term safety of continuous ultrasound exposure is unknown. Tissue injury secondary to heating with continuous exposure is theoretically possible. The risks associated with environmental interference are incompletely understood.215

There have been no published results of randomised trials directly comparing the performance of a subcutaneous or leadless system and a system with a transvenous system.

S-ICD

Numerous studies have demonstrated the safety and efficacy of the S-ICD. Results from large-scale randomised trials comparing devices with conventional ICD patients are yet to be published. HealthPACT and the Australian Health Technology Association (AHTA) completed a detailed assessment of S-ICD in November 2010. The following section makes reference to key studies of S-ICD effectiveness.

A case-control study was conducted in 69 patients (50 male, mean age 45.7±15.7 years) who received a S-ICD and were compared with 69 sex and age matched conventional ICD patients. The mean follow-up was 217±138 days. The mean implantation time was 70.8±27.9 minutes (p=0.398). Conversion rates of induced ventricular fibrillation were 89.5% for 65 Joules (15J safety-margin) and 95.5% including reversed shock polarity (15J safety-margin) in the study group. Termination of induced ventricular fibrillation was successful in 90.8% (10J safety-margin device dependant) of the control patients (p=0.815). Procedural complications were similar between the two groups. During follow-up, three patients with S-ICD were appropriately treated for ventricular arrhythmias. Three inappropriate episodes occurred (5.2%) in three S-ICD patients due to T-wave oversensing, whereas


atrial fibrillation with rapid conduction was the predominant reason for inappropriate therapy in conventional devices \( p = 0.745 \)^{216}.

A Dutch cohort study followed 118 patients (75% males, mean age 50 years) who received a S-ICD. After 18 months of follow-up, 8 patients experienced 45 successful appropriate shocks (98% first shock conversion efficacy). No sudden deaths occurred. Fifteen patients (13%) received inappropriate shocks, mainly due to T-wave oversensing, which was mostly solved by a software upgrade and changing the sensing vector of the S-ICD. Sixteen patients (14%) experienced complications. Adverse events were more frequent in the first 15 implantations %re compared with subsequent implantations (inappropriate shocks 19% vs. 6.7%, \( p = 0.03 \); complications 17% vs. 10%, \( p = 0.10 \)^{217}. A Dutch prospective randomised controlled trial (PRAETORIAN) is underway to compare S-ICD with transvenous ICD to compare major ICD-related events^{218}.

The FDA required the manufacturer to conduct a post-marketing study in 1,616 patients to assess long-term safety and device efficacy. This study - EFFORTLESS - is an observational registry study involving 50 centres worldwide. Patients requiring an ICD for the treatment of ventricular tachyarrhythmias will be implanted with the S-ICD system and followed for up to 60 months. The patients' perception of their therapy will be evaluated using Quality of Life assessments and the Registry will include an exploratory analysis of resource utilisation and costs based on measures of clinical outcome such as complication rates, unscheduled hospitalisations and length of stay. The objective will be to enable comparison of costs of the S-ICD system versus a standard transvenous system. Estimated study completion is December 2016. There are no participating Australian centres however New Zealand has a trial centre (Auckland City Hospital)^{219}.

**Evidence of cost-effectiveness**

Device costs for the S-ICD are estimated at $50,000 USD; the EFFORTLESS study is powered to assess the cost effectiveness of the S-ICD. Results are not available until December 2016^{220}.

The NHCDC includes costs for seven DRGs that relate directly to ICDs and pacemakers. Table 18 sets out the average length of stay in 2009/10 in reporting public hospitals. The weighted average cost of the prosthesis and the separation have also been presented for each matched pair of DRGs.

**Table 18: NHCDC costs for ICD and pacemaker procedures, NHCDC, 2009/10**

<table>
<thead>
<tr>
<th>DRG</th>
<th>DRG description</th>
<th>Average length of</th>
<th>Weighted prosthetic</th>
<th>Weighted</th>
</tr>
</thead>
</table>


218 National Institutes of Health. Trial ID NCT01296022


220 Ibid
### NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Stay</th>
<th>Cost</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>F01A</td>
<td>Implantation/Replacement AICD, total system + catastrophic complications</td>
<td>11.73</td>
<td>$15,371</td>
<td>$27,884</td>
</tr>
<tr>
<td>F01B</td>
<td>Implantation/Replacement AICD, total system without catastrophic complications</td>
<td>3.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F02Z</td>
<td>Other AICD procedures, eg adjustment of transvenous catheter</td>
<td>4.47</td>
<td>$3,409</td>
<td>$12,404</td>
</tr>
<tr>
<td>F12A</td>
<td>Implantation/Replacement pacemaker, generator and electrodes + catastrophic complications</td>
<td>10.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F12B</td>
<td>Implantation/Replacement pacemaker, generator and electrodes without catastrophic complications</td>
<td>3.55</td>
<td>$3,838</td>
<td>$12,993</td>
</tr>
<tr>
<td>F17A</td>
<td>Insertion/replacement of pacemaker generator + severe or catastrophic complications</td>
<td>5.45</td>
<td></td>
<td>$2,806</td>
</tr>
<tr>
<td>F17B</td>
<td>Insertion/replacement of pacemaker generator without severe or catastrophic complications</td>
<td>1.42</td>
<td></td>
<td>$6,784</td>
</tr>
</tbody>
</table>

If the weighted non-prosthesis costs for DRGs F01A and B are indexed to 2012/12 levels and the new estimated prosthesis cost of $50,000 is factored in the projected cost becomes $64,478. With a projected annual caseload of 7,000, the total sector cost would be in the order of $450 million. Indexation of the NHCDC cost of implantation of pacemakers brings the average cost to $15,033, which with a current annual caseload of 32,000 brings the projected total expense to $481 million.

**Impacts on service delivery**

According to stakeholders, the demand for these devices will increase with the ageing of the population. Stakeholders reported that guidelines will need to provide clinicians with criteria that address issues of effectiveness, cost-effectiveness and ethics when device implantation is indicated. Increased pacemaker / ICD insertions are also likely to lead to increased demand for pacemaker / ICD lead removal.

The educational needs of medical practitioners, electrophysiologists, EP Fellows and EP laboratory staff, nurses, nurse practitioners and other allied health professionals involved in the management of patients with cardiac arrhythmias will include but not be limited to training in device implantation and after-care.

Education and training needs associated with the implantation of leadless pacemakers cannot be determined at this stage of product development. However, the devices are expected to simplify
implantation for the treating clinician. From the clinician’s perspective, leadless technology will benefit by:\(^{221}\):

- eliminating the need to traverse the venous system;
- minimising the use of fluoroscopy; and
- eliminating the need to manage complications that arise from current generation lead systems.

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RENAL SYMPATHETIC DENERVATION FOR THE TREATMENT OF RESISTANT HYPERTENSION

Background

Hypertension is defined as abnormally high arterial blood pressure (BP) indicated by an adult systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg. Hypertension is a major factor in the progression of cardiovascular disease and is a contributing factor in the rising morbidity and mortality rates associated with coronary heart disease, chronic kidney disease and stroke.\textsuperscript{222}

Approximately 9\% of Australians report that they have hypertension.\textsuperscript{223} The total number of Australian public hospital separations for hypertensive disease (ICD-10 codes I10-I15) has decreased over time (Figure 14).\textsuperscript{224}

\textbf{Figure 14: Public hospital separations for hypertension, Australia, 1998/99 to 2009/10}

In New Zealand approximately 37\% of Māori, 38\% of Pacific people and 22\% of others have raised blood pressure. Raised blood pressure is undetected in a significant proportion of these affected population groups, with 7\% of Māori, 6\% of Pacific people and 2\% of others having undetected high blood pressure.\textsuperscript{225}


\textsuperscript{223} ABS, National Health Survey. Summary of Results, 2007/08. Cat. No. 4364.0.


The mainstay of hypertension management is lifestyle modification and antihypertensive medications. According to current Australian guidelines immediate initiation of antihypertensive drug treatment is indicated in patients with:

- grade 3 hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg)
- isolated systolic hypertension and widened pulse pressure (SBP ≥ 160 mmHg and DBP ≤ 70 mmHg)
- one or more associated conditions or evidence of end-organ damage even if BP is within the high-normal range
- high absolute risk for cardiovascular disease assessed according to clinical indicators or the risk calculator

New Zealand guidelines state that everyone with a BP ≥170/100 mmHg should have drug treatment and specific lifestyle advice to lower risk factor levels. Most of the treatment benefit is achieved by reaching the following BP levels:

- <140/85 mmHg in people without clinical CVD;
- <130/80 in people with diabetes or CVD; and
- 125/75 mmHg in people with chronic kidney disease and significant albuminuria.

Renal sympathetic denervation (‘renal denervation’) has been proposed as an alternative therapy for the management of hypertension in patients with ‘resistant’ hypertension. Resistant hypertension is defined as persistent high blood pressure despite treatment with three antihypertensive agents of different classes. Approximately 13% of patients with treated hypertension correspond to the definition of resistant hypertension.

The kidney plays a vital role in the regulation of blood pressure (sodium filtration, blood volume etc.) and renal sympathetic nerve hyperactivity (both afferent and efferent) has been demonstrated to be a major factor in the pathophysiology of hypertension.

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Renal denervation is a procedure performed in a catheterisation laboratory using standard renal artery catheterisation techniques. The procedure is minimally-invasive and image-guided: access is achieved via a peripheral access to the vascular system and the displacement of the catheter is visualised using X-ray fluoroscopy. A special ablation catheter, connected to a specific generator, is delivered through a guiding catheter, along the femoral artery and advanced into the renal artery – under fluoroscopic control - to the desired point. The catheter is positioned in contact with the vessel wall and the generator is activated, thus delivering radiofrequency ablation. Ablation is carried out in many places along the vessel wall since many points of the tissue are innervated.

The procedure is usually performed in less than an hour with the patient under local anaesthesia using conscious sedation.

Anticoagulation is generally used during the procedure. After ablation, the device is withdrawn and the arterial access site may be closed as with standard percutaneous interventional techniques.

Renal denervation systems usually work in the monopolar mode, meaning that one electrode is located on the tip of a catheter positioned against the renal artery wall through standard catheterisation technique, while the other electrode is a ground pad placed on the patient thigh to collect all current flow back to the generator. Little power is needed to achieve the desired effect on renal nerves. Systems have a temperature control system on the tip of the catheter. This allows the system to interrupt current delivery when temperature of the tissue overcomes a given threshold (usually 70°C).

The following systems have been assessed with at least one clinical trial either completed or ongoing:

- **Medtronic Symplicity Renal Denervation System**;
- **Johnson & Johnson Thermocool Irrigated tip Catheter / Stockert 70 RF Generator and Cool Flow Pump**;
- **St. Jude Medical EnligHTN Renal Denervation System**.

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236 Renal sympathetic modification in patients with essential hypertension (NCT01417221)

237 Ablation-induced RSD trial (NCT01438229)
Other systems in pre-market or early market phases include:

- Kona Medical externally applied focussed ultrasound;
- CardioSonic TIVUS system;
- ReCor Medical Paradise system;
- Mercator MedSystems Bullfrog microinfusion catheter;
- Covidien Oneshot renal denervation system; and
- Vessix Vascular V2 radiofrequency balloon.

**Evidence of effectiveness**

The proof-of-concept study for renal denervation was conducted by Krum et al (2009) in three centres in Australia and two centres in Europe. Hypertensive patients (n=50) were enrolled who satisfied the selection criteria of an office-based systolic BP of \geq 160 \text{ mm Hg}, despite being treated with at least three anti-hypertensive medications, including one diuretic. The mean age of patients was 58 ± 9 years (range 37-76 years). Mean reduction in office-based systolic / diastolic BP was -27 / -17 mmHg at 12 months follow-up. Six patients were non-responders.

In a multi-centre study Esler et al. randomly allocated 106 patients with resistant hypertension to catheter-based renal denervation (Symplicity) (52 patients) or usual care (54 patients). Mean age of participants was 58 years, participants were receiving at least 5 anti-hypertensive medications in more than 50% of the cases; their average values were 178 (SD 18) for systolic blood pressure (SBP) and 97 (standard deviation [SD] 16) for diastolic blood pressure (DBP). Follow-up was 6 months. For 49 patients in the renal denervation group office-based BP was reduced by 32/12 mmHg (SD 23/11) whereas in the control group (51 patients analysed) office-based BP changed by +1/0 mmHg (SD 21/10).

The findings of both the Krum (2009) and Esler (2010) studies are based on low numbers of patients followed up.

The Symplicity HTN-1 investigators treated 153 patients with catheter-based renal sympathetic denervation at 19 centers in Australia, Europe, and the United States. Mean age was 57±11 years, 39% were women, 31% were diabetic, and 22% had coronary artery disease. Baseline values included mean office-based BP of 176/98±17/15 mm Hg and a mean of 5 antihypertensive

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medications. Post-procedure office-based BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively.241

Mahfoud et al. allocated 37 patients to renal denervation (Symplicity) and 13 patients to usual care. Participants in the renal denervation group were 58.7 (SD 1.6) years of age compared with 62.5 (SD 2.9) years in the control group. Mean values of systolic and diastolic blood pressure, in all patients, were 178 (±3) and 97 (±2) respectively. Participants in the two groups were receiving on average 5.6 (±0.2) anti-hypertensive medications. Follow-up was over a 3 month period. Office-based systolic / diastolic BP reduced by 32/12 mmHg (SD 4/2) in the denervation group and 5/3 mmHg (SD 5/3) in the control group.242

Medication management appears necessary after renal denervation. In the Esler study, 10 patients (20%) who underwent renal denervation had a reduction of drug usage compared to 3 patients (6%) in the control group (p=0.04). Mahfoud reported that, after the 3 month follow up visit, in 13 (35.1%) treated patients, antihypertensive medication had to be reduced owing to hypotension associated with symptoms.

Queensland and Victorian government field evaluations are underway, which will focus on outcome indicators including central aortic pressure, aortic stiffness, left ventricular mass, and quality of life, none of which have been reported in current literature. The study participants will also be monitored for long term health outcomes such as reductions in adverse cardiovascular outcomes and cardiac arrhythmic risk. This primary data will also be used to inform an analysis of RDN’s cost-effectiveness.243

Symplicity HTN -3 is currently underway in the US. This is multi-centre, prospective, single-blind, randomised, controlled study of the safety and effectiveness of renal denervation compared with antihypertensive medications alone in 530 subjects with uncontrolled hypertension. Bilateral renal denervation will be performed using the Symplicity Catheter.244

Studies are also exploring whether renal denervation has a role in the management of some forms of heart failure. Taborsky et al. conducted a randomised controlled trial in patients with heart failure to receive either renal denervation and standard therapy (n=26) or standard therapy alone (n=25). At 12 months, 8 patients in the denervation group were re-hospitalized for HF compared with 18 in the standard therapy group (P<0.001).245

Evidence of cost-effectiveness

The total number of Australians with resistant hypertension, estimated from the above analysis, is 1.2% (260,000 persons). There is therefore potentially a substantial caseload of patients in whom renal denervation may be indicated.

Table 19 describes the points along the clinical pathway for management of resistant hypertension at which costs are incurred for renal denervation and for medical management.

### Table 19: Treatment and intervention matrix

<table>
<thead>
<tr>
<th>Clinical pathway step</th>
<th>Medical management</th>
<th>Renal denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-admission therapy and investigations</td>
<td>Antihypertensive therapy (about $100 / month for five different medication (ACE Inhibitor, B blocker and diuretic) and routine investigations</td>
<td>Antihypertensive therapy and routine investigations, plus additional preoperative procedures</td>
</tr>
<tr>
<td>Index admission</td>
<td>No costs incurred</td>
<td>New costs based on existing national benchmarks for similar procedure, with reference to inpatient length of stay and other costs.</td>
</tr>
<tr>
<td>Post-discharge</td>
<td>Ongoing usual costs</td>
<td>Somewhat reduced antihypertensive medication costs</td>
</tr>
</tbody>
</table>

The National Casemix and Classification Centre has remapped this procedure, 39323-00, to DRG F21 (other circulatory system operating room procedures with or without catastrophic complications). The key metrics drawn from the NHCDC are set out in Table 20.

### Table 20: Cost metrics, DRG F21, 2009/10

<table>
<thead>
<tr>
<th>Metric</th>
<th>F21A</th>
<th>F21B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost weight</td>
<td>5.07</td>
<td>1.95</td>
</tr>
<tr>
<td>Average length of stay</td>
<td>16.24 days</td>
<td>5.07 days</td>
</tr>
<tr>
<td>Ward nursing</td>
<td>$6,917</td>
<td>$1,885</td>
</tr>
<tr>
<td>Ward medical</td>
<td>$3,786</td>
<td>$1,394</td>
</tr>
<tr>
<td>OT and procedure room</td>
<td>$2,500</td>
<td>$2,384</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$1,472</td>
<td>$371</td>
</tr>
<tr>
<td>Pathology</td>
<td>$1,099</td>
<td>$244</td>
</tr>
</tbody>
</table>
The structure of the costs and the extended length of stay for both DRGs is not expected to be typical for the renal denervation procedure, which would expect to have a short length of stay, (80% being same day and 20% overnight stays), low ward staffing costs, significant operating theatre / procedure room, imaging and prosthesis costs. This cost structure is in fact found in DRG F14C (vascular procedures except major reconstruction with CPB pump and without complications), though it is noted this is a surgical rather than procedural DRG.

Alternative advice indicates that the procedure may code to one of the following DRGs: F67B (hypertension without complications), F62B (heart failure and shock) or L60C (renal failure), the cost metrics of which are set out in Table 21.

Table 21: NHCDC cost metrics, DRG F14C, F62B, F67B and L60C, 2009/10

<table>
<thead>
<tr>
<th>Metric</th>
<th>F14C</th>
<th>F62B</th>
<th>F67B</th>
<th>L60C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of stay</td>
<td>1.96 days</td>
<td>4.69 days</td>
<td>2.31 days</td>
<td>2.69 days</td>
</tr>
<tr>
<td>Imaging costs</td>
<td>$1,388</td>
<td>$146</td>
<td>$2,542</td>
<td>$125</td>
</tr>
<tr>
<td>Operating theatre costs</td>
<td>$1,289</td>
<td>$11</td>
<td>$10</td>
<td>$31</td>
</tr>
<tr>
<td>Prosthesis costs</td>
<td>$604</td>
<td>$2</td>
<td>$4</td>
<td>$4</td>
</tr>
<tr>
<td>Ward nursing</td>
<td>$698</td>
<td>$1,259</td>
<td>$470</td>
<td>$806</td>
</tr>
<tr>
<td>Ward medical</td>
<td>$619</td>
<td>$657</td>
<td>$340</td>
<td>$405</td>
</tr>
<tr>
<td>Total cost (including 20% overhead)</td>
<td>$6,220</td>
<td>$5,241</td>
<td>$2,542</td>
<td>$3,391</td>
</tr>
</tbody>
</table>

If the amounts in F14C, excluding the prosthesis costs, are adjusted for a projected shorter length of stay and then indexed to 2012/13 levels the amount becomes $5,735 and with the cost of the new catheter of $5,300-$7,000 included the total estimated cost is $11,035 - $12,735. This is consistent with published literature, which suggests an indicative cost of renal denervation of approximately $12,500 per procedure.246

As previously identified earlier in this report, the estimate of the cost of the procedure is a separate consideration from the level of reimbursement which it is likely to attract. Renal denervation is likely at this stage to be coded as F67, which in Victoria has a case payment of $1,810 - $5,564 (Table 22) which is significantly less than the projected cost of $12,500.

Table 22: Reimbursements for possible DRGs for renal denervation

<table>
<thead>
<tr>
<th>DRG</th>
<th>Description</th>
<th>2012/13 IHPA inlier bounds</th>
<th>2012/13 IHPA inlier weight</th>
<th>2012/13 Victorian casemix</th>
</tr>
</thead>
<tbody>
<tr>
<td>F67A</td>
<td>Hypertension with catastrophic or severe complications</td>
<td>1-17 days</td>
<td>1.3362</td>
<td>$5,564</td>
</tr>
<tr>
<td>F67B</td>
<td>Hypertension without catastrophic or severe complications</td>
<td>1-7 days</td>
<td>0.4346</td>
<td>$1,810</td>
</tr>
</tbody>
</table>

The total cost of performing renal denervation on the approximately 260,000 Australians with resistant hypertension at $11,035 per procedure is therefore $2.9 billion without factoring in the costs of ongoing antihypertensive use by patients after the procedure. According to Krum et al., the total number of antihypertensive medications used may not decrease; however, BP control associated with medication management improves\(^\text{247}\). The total annual cost of medication management of patients (assuming five antihypertensives are used in combination) is approximately $312 million.

Assessment of costs associated with renal denervation have been estimated in an Italian study of resource consumption and costs associated with renal denervation. In this study the total cost of renal denervation, including pre-intervention, intervention and follow-up phases, was estimated to be €7,327. The composition of this estimation was: 84% (€6,189) for the cost of procedure and 13% for overhead costs. Remaining costs for pre-intervention and follow-up costs were marginal\(^\text{248}\).

Geisler et al., in an analysis of Symplicity study data, found that the discounted lifetime incremental cost-effectiveness ratio for renal denervation was $3,071 per quality-adjusted life-year. Findings were relatively insensitive to variations in input parameters except for systolic blood pressure reduction, baseline systolic blood pressure, and effect duration. The 95% credible interval for incremental cost-effectiveness ratio was cost-saving to $31,460 per quality-adjusted life-year\(^\text{249}\).

Other costs include the price of the catheter with electrode or probe, the associated costs of imaging procedures and a radiologist to guide the catheter in place and the cost of the radiofrequency generator. The Medtronic Symplicity radiofrequency generator costs $27,000.

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Impacts on service delivery

Stakeholders consulted believe that renal denervation will become a mainstream therapy for resistant hypertension in the next ten years. However, most report that trials with a higher number of patients and longer follow-up are needed to confirm the results of currently published trials before the therapy becomes widespread. Until then renal denervation should be reserved for selected patients with resistant hypertension and accessed through health care facilities that are collecting long-term outcome data using rigorous methods.

A 2012 French consensus statement proposed limiting renal denervation to patients with essential hypertension uncontrolled by four or more antihypertensive therapies and meeting the following criteria:\(^{250}\):

- treatment that includes at least a diuretic;
- past or present exposure to spironolactone (at a dose \(\geq 25 \text{ mg/d}\)); and
- office BP greater or equal to 160 mmHg and/or 100 mmHg for systolic and diastolic BP, respectively, confirmed by daytime ambulatory or home BP measurement, with systolic BP greater than 135 mmHg and diastolic BP greater than 85 mmHg.
- renal artery anatomy and kidney function should allow proper intervention (i.e. two functional kidneys, absence of previous renal angioplasty).

Patient selection should be carried out by a multidisciplinary team including a physician with expertise in hypertension and a specialist in endovascular interventions, giving consideration to the number of antihypertensive drugs that have failed to control the patient's blood pressure and the anatomical suitability of their renal arteries. Patient selection in public hospital settings can be facilitated with the use of a clinical pathway outlining the specialist management of patients with treatment resistant hypertension and clearly defining which patients should receive renal denervation\(^{251}\).

According to stakeholders, the procedure is technically straightforward for an interventional cardiologist to perform. Device manufacturers offer training in the procedure. However, renal denervation requires appropriate training, including in the management of associated arterial complications should they arise. The procedure should only be done by specialists who are experienced in endovascular interventions and with facilities for emergency stenting in case this is required\(^{252}\).

Post-procedure management should occur under close specialist supervision and antihypertensive treatment should not be interrupted immediately after the procedure as the BP-lowering effect is

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\(^{251}\) NICE. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. NICE interventional procedure guidance 418. January 2012.

\(^{252}\) Ibid
progressive over the 12 months after the procedure\textsuperscript{253}. Monitoring of BP, renal function and renal artery anatomy is required 12 months and 36 months after the procedure\textsuperscript{254}.


GENETIC TESTING IN THE ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASES

Background

CVD is a heritable condition with heritability estimates as high as 60% for coronary heart disease\(^\text{255}\). Both monogenic and polygenic variations in genes have been described that are associated with predisposition to various cardiac diseases\(^\text{256, 257}\).

\textit{Monogenic variation}

Sudden cardiac death (SCD) is death from a cardiac cause occurring soon after the onset of symptoms. The annual incidence of SCD is 1 in 1,000 per year in the general population, 5% per year in the patient with a previous coronary event, 15% in the patient with an ejection fraction <35%, and 20% in the cardiac arrest survivor\(^\text{258}\).

Identifying patients at risk of SCD is a diagnostic challenge for clinicians. People who experience SCD commonly have no significant abnormality on examination. Similarly, in the situation when the patient survived the episode, often the investigations do not reach a concluding reason for the event\(^\text{259}\).

Genetic testing can assist in identifying patients at risk of SCD. Monogenic variations are associated with long QT syndrome, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy\(^\text{260}\).

Clinical genetic testing can be used in the management of families with hereditary disease and assists in determining which individuals require lifelong clinical evaluation versus those who need no further evaluation beyond those recommended for the general population\(^\text{261}\).


\(^{258}\) Brugada R. Sudden death. Heart 2011; 97: 676-81.

\(^{259}\) Ibid


\(^{261}\) Ibid
Polygenic variation

The bulk of the cardiovascular disease burden is associated with polygenic variations rather than being caused by a single gene mutation\(^\text{262}\).

Coronary heart disease (CHD) is the leading cause of cardiovascular disease burden and familial clustering of premature disease is common. Individuals with a parent with CHD are at a twofold greater risk, which is even greater if siblings are affected. Although such families represent only 14\% of the general population, they account for 72\% of early CHD cases and 48\% of CHD at all ages, thus underscoring the social and economic importance of genetic predisposition to CHD\(^\text{263}\).

Genes associated with polygenic disease burden may require the presence of environmental factors (such as smoking and obesity) to trigger heart disease. Less commonly, specific monogenic variations can cause heart disease outright. Other variations may indicate how well patients respond to particular medications\(^\text{264}\).

Many of the versions of genes that cause or predispose to cardiovascular disease are still unknown. However, “polymorphisms” have been described that can theoretically be applied to the development of new technology to facilitate genetic testing for cardiovascular disease, risk or treatment\(^\text{265}\):

- Different gene versions are encoded by variants at the DNA level, in what are called "polymorphisms."
- Some polymorphisms lie within the actual genes and affect what the genes do.
- Most polymorphisms are found in the long stretches of DNA between genes, and do not directly affect gene activity. These polymorphisms tend to remain associated with the genes they border from generation to generation.
- The most common kind of polymorphisms are single nucleotide polymorphisms (SNPs).
- The phenotypes of CVD are due to the sum of multiple polymorphisms, each with relatively small effects on gene expression and disease\(^\text{266}\).

Genome-wide association studies conducted to assess the contributions of common polymorphisms have identified new loci related to myocardial infarction and other CVD phenotypes. Having one of


263 Ibid


these marker polymorphisms may increase the risk of getting the disease by one-and-a-half to two times, although this number can vary widely\textsuperscript{267}.

Population screening for polygenic conditions can be performed in patients with symptoms of cardiac disease or may be performed before symptoms develop i.e. pre-symptomatic testing (PST). Performance of a genetic test on an asymptomatic individual at risk of a condition aims to determine whether the person has inherited a disease-causing mutation. Genetic tests performed in patients with symptoms in order to determine the presence of a particular underlying disease state e.g. coronary artery disease with occlusion.

Despite advances in the science of sequencing, genomic information is not widely applied in clinical cardiology. Whereas, for example, gene expression profiling is actively used in the clinical practice of oncology to determine the cancer entity and to guide therapy, large-scale transcriptome assessment in CVD has not entered the clinical routine\textsuperscript{268}.

**Technology**

Sequencing technology has improved rapidly over the past five years. Traditional Sanger sequencing has high fidelity but is slow and expensive compared with next generation sequencing methods. Advances in sequencing-based technologies enable greatly increased parallel sequencing. Real-time sequencing replaces the use of natural nucleotides or reversible terminators via the detection of continuously added fluorescently labelled nucleotides to the growing DNA strand, thereby enhancing the speed of production and the output length of nucleotide sequence reads\textsuperscript{269}.

As technology improves, it is anticipated cardiac genomics will become more widely applied in clinical practice over the next ten years, particularly in\textsuperscript{270}:

- Testing for monogenic conditions;
- Population screening for polygenic conditions; and
- Pharmacogenomics to optimise drug therapy.

*Testing for monogenic conditions*

Genetic testing for cardiovascular disease is established for a range of conditions\textsuperscript{271}. Internationally, numerous professional society guidelines and position statements recommend genetic testing for a


variety of hereditary cardiovascular diseases including long QT syndrome, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC)\(^{272, 273, 274, 275, 276}\).

The number of genes associated with cardiac conditions continues to increase, and the number of clinically available genetic tests for cardiac conditions has expanded rapidly in recent years (Table 23).

**Table 23: Genes associated with hereditary cardiac conditions\(^{277}\)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of cases</th>
<th>Gene</th>
<th>% of cases</th>
<th>Gene</th>
<th>% of cases</th>
<th>Gene</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>12-20%</td>
<td>LMNA</td>
<td>4-6%</td>
<td>MYBPC3</td>
<td>10-30%</td>
<td>TNNI3</td>
<td>1-3%</td>
</tr>
<tr>
<td>MYH6</td>
<td>2-6%</td>
<td>MYBPC3</td>
<td>7-10%</td>
<td>TNNI3</td>
<td>1-3%</td>
<td>TNNI3</td>
<td>1-3%</td>
</tr>
<tr>
<td>TNNI3</td>
<td>1-3%</td>
<td>TNNI3</td>
<td>1-3%</td>
<td>DSP</td>
<td>6-16%</td>
<td>TNNT1</td>
<td>3-7%</td>
</tr>
<tr>
<td>TNNT1</td>
<td>3-7%</td>
<td>TNNT1</td>
<td>3-7%</td>
<td>EB1</td>
<td>6-16%</td>
<td>JUP</td>
<td>3-7%</td>
</tr>
<tr>
<td>TNNT1</td>
<td>3-7%</td>
<td>TNNT1</td>
<td>3-7%</td>
<td>SCNA</td>
<td>5-10%</td>
<td>CALM1</td>
<td>5-10%</td>
</tr>
<tr>
<td>SCNA</td>
<td>5-10%</td>
<td>SCNA</td>
<td>5-10%</td>
<td>CADM1</td>
<td>5-10%</td>
<td>CADM1</td>
<td>5-10%</td>
</tr>
<tr>
<td>TPMT</td>
<td>1-3%</td>
<td>TPMT</td>
<td>1-3%</td>
<td>CALM1</td>
<td>5-10%</td>
<td>CALM1</td>
<td>5-10%</td>
</tr>
<tr>
<td>CALM1</td>
<td>5-10%</td>
<td>CALM1</td>
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<tr>
<td>CALM2</td>
<td>5-10%</td>
<td>CALM2</td>
<td>5-10%</td>
<td>CALM2</td>
<td>5-10%</td>
<td>CALM2</td>
<td>5-10%</td>
</tr>
<tr>
<td>CALM3</td>
<td>5-10%</td>
<td>CALM3</td>
<td>5-10%</td>
<td>CALM3</td>
<td>5-10%</td>
<td>CALM3</td>
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<tr>
<td>CALM4</td>
<td>5-10%</td>
<td>CALM4</td>
<td>5-10%</td>
<td>CALM4</td>
<td>5-10%</td>
<td>CALM4</td>
<td>5-10%</td>
</tr>
</tbody>
</table>


Although genetic testing for hereditary disease is available in Australia and New Zealand, the range of genetic mutations able to be tested for continues to increase as new genetic associations continue to be identified.

**Testing for polygenic conditions**

Approaches to testing for polygenic conditions include genotype-based risk prediction and detection of biomarkers.

Genotype-based risk prediction has a number of advantages over conventional biomarkers as genotypes are: (1) fixed from birth, allowing early risk prediction; (2) less susceptible to biological variation over life, such as during intercurrent illness, etc; and (3) are easy to obtain with minimal measurement error.

Genotyping risk variants aims to capture the genetic burden of risk over an individual’s lifespan.

Some companies are marketing SNP chips that will identify the presence of common markers that have been found to be associated with cardiovascular disease. However, many challenges remain in the development of products for clinical pre-symptomatic testing. First, genome-wide association studies typically use only common SNPs. Rarer SNPs with stronger effects may not be identified. Second, a clear CVD phenotype is required. Clinically important variation in manifestation, therapeutic approach, and prognosis exists for phenotypes as left main disease, diffuse versus focal coronary artery disease, ectatic lesions, and the degree of coronary calcification that influence the predictive value of genetic tests.

**Products testing for alternations in gene expression**

Alterations in gene expression in peripheral blood cells is sensitive to the presence and extent of CHD. Gene expression tests can be used in the diagnosis of obstructive CHD.

Gene expression tests can be performed on a routinely collected blood sample. Test results are generally combined with other non-invasive assessments in order to assess the likelihood of the presence of disease.

Corus CHD is a gene expression test that is marketed for use in stable patients presenting with symptoms suggestive of obstructive coronary artery disease and who:

- are not diabetic;

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have not been diagnosed with prior myocardial infarction nor have had a previous revascularization procedure; and

- are not currently taking steroids, immunosuppressive agents or chemotherapeutic agents.

Results are used to assess the likelihood that the patients has obstructive coronary artery disease and can be used to guide decisions regarding whether coronary angiography should be performed.

**Pharmacogenomics**

Patients vary in their responses to drug therapy, and some of that variability is genetically determined\(^2\). Researchers over the past decade have identified genetic contributors to this variability.

New cardiac genetic technologies are being developed and introduced to the market that exploit this to facilitate personalised decision-making for a range of cardiovascular medicines, including HMGCoA reductase inhibitors (statins), antiarrhythmic medicines, warfarin and antiplatelet agents.

The following are examples of established gene-factor associations in cardiovascular disease:

- Reduced LDL-lowering effect of statins has been associated with variation in a number of genes e.g. pharmacodynamic candidate genes (\(HMGCR\) and \(LDLR\)) and \(CYP3A4\) (metabolises simvastatin, atorvastatin, and lovastatin).

- Statin-related myotoxicity is associated with variants in \(CYP3A5\) and \(SLCO1B1\), estimated to account for approximately 60% of risk\(^2\).

- A mis-sense SNP, Trp719Arg (rs20455), in KIF6 appears to be associated with increased risk of coronary artery disease and myocardial infarction\(^3\).

- QT interval prolongation and the polymorphic ventricular tachycardia, torsades de pointes, develops in 1% to 5% of patients exposed to QT-prolonging antiarrhythmic drugs (sotalol, dofetilide, quinidine); Small studies have estimated that 10% to 40% of subjects with drug-induced torsades de pointes have subclinical congenital long QT syndrome gene mutations\(^4\).

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Variability in PR and QRS durations have also been analysed in genomic studies. As with QT, the results point to previously implicated genes, as well as to loci previously not implicated in cardiac electrophysiology\(^{285}\).

Chromosome 4q25, has consistently been associated with risk of atrial fibrillation\(^{286}\). Preliminary data have linked 4q25 variants to outcome for ablation\(^{58}\) and of antiarrhythmic drug therapy for atrial fibrillation\(^{287}\).

Genetic determinants of blood pressure and long-term outcomes in hypertensive patients are being identified. Their role in choosing among therapies is undergoing active investigation\(^{288}\).

In heart failure, associations between ADRB1 SNPs and beta-blocker–mediated improvements in left ventricular ejection fraction and clinical outcomes have been described\(^{289}\).

Variants in CYP2C9 are associated with lower warfarin dose requirements and increased bleeding risk in Caucasian populations\(^{290}\).

Dual antiplatelet therapy with aspirin and clopidogrel is the standard of care for prevention of thromboembolic events in patients at high risk for myocardial infarction. There is marked interindividual variation in response to aspirin and clopidogrel\(^{291}\). \textit{CYP2C19}^*2 has been identified as a determinant of clopidogrel response in patients undergoing percutaneous coronary intervention for atherosclerotic heart disease\(^{292}\).


Evidence of effectiveness

Testing for monogenic conditions

Genetic testing assists in identifying patients at risk of SCD. Cardiological and genetic examination in surviving relatives of young (≤40 years of age) SUD victims identifies an underlying inherited disease and probable cause of death in up to 40% of families. Simple procedures (examining many relatives) and routine tests (resting/exercise ECG) produce the highest diagnostic yield, with supportive information provided by genetic testing.

A study using targeted next-generation sequencing to screen the 13 known congenital long QT syndrome disease genes and other arrhythmia susceptibility genes identified rare variants predicted to be deleterious to protein function in 20 of 31 patients (64.5%).

In long QT syndrome genetic testing has been shown to be useful to assist risk stratification and to guide clinical management of mutation carriers in 1 of the 3 most common genes: KCNQ1, KCNH2, and SCN5A. Each of these genetic variants has a distinguishing morphology of the ST-T–wave complex, a typical trigger for arrhythmic events and a variable response to [beta]-blockers.

In Brugada Syndrome ten different genes have been reported that are causally linked to the syndrome. Overall, no more than 30% of the genetic tests sent to genotyping facilities turn out positive for a disease-causing mutation. Genetic testing cannot currently guide therapeutic decisions.

Mutations in six genes have been identified that are associated with short QT syndrome but they account for only a few families each. The proportion of patients with short QT who are successfully genotyped is unknown, and no single gene accounts for >5% of cases. Therefore, the value of genetic testing in the syndrome is limited and does not bear prognostic implications.

297 Ackerman M et al. Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13:1077–1109.
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterised by a high incidence of cardiac events among untreated patients (79% in patients up to 40 years of age) and 30% incidence of sudden cardiac death. Approximately 60% of CPVT individuals carry an RyR2 mutation. Although no prognostic value is linked to specific RyR2 mutations, the value of genotyping resides in the importance of extending genetic screening to family members to identify and protect mutation carriers with antiadrenergic therapy because [beta]-blockers are effective.

Development of clinical pathways for screening for familial hypercholesterolaemia has also been undertaken including subsequent cascade screening, with WA piloting a statewide trial.

**Effectiveness of testing for polygenic conditions**

There is still insufficient evidence demonstrating the effectiveness of genotype-based risk prediction or biomarker detection in improving cardiovascular disease outcomes. No controlled clinical trials of currently available commercial products were identified in this review that assessed the impact of product usage on clinical outcomes for patients.

Further, evidence has not yet demonstrated that pre-symptomatic polymorphism testing for cardiovascular disease successfully predicts who will or will not get a disease, nor has SNP analysis been shown to be better in the prediction of heart disease than routine methods of pre-symptomatic evaluation.

A hypothetical model with 10 SNP was proposed by Talmud et al. to enhance the detection of increased cardiac disease risk. However, Paynter et al. examined a 12 SNP model of CHD variants and a larger 100 SNP model incorporating other metabolic variants in 19 000 women and found no significant association with incident events after adjustment for classic risk factors and also no improvement in the reclassification index. Another larger study found significant association between SNPs and cardiovascular events but did not demonstrate that genotype-based risk prediction added more information to that currently available. Successful models of genotype-based prediction will probably require even more variants given their small effect sizes.

Even where genetic markers of increased disease risk are identified, their impact on patient behaviours may be limited. For example, in a trial of genome-wide genetic profiling of employees...

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of health and technology companies employees did not change nutritional or exercise behaviours over a 6-month period\textsuperscript{306}. Products testing for alternations in gene expression have not been shown to successfully predict the presence of obstructive coronary disease compared with conventional detection methods\textsuperscript{307 308}.

A Centers for Disease Control and Prevention initiative, entitled the ‘Evaluation of Genomic Applications in Practice and Prevention Working Group’ recently examined the predictive value of genetic testing using three criteria: analytical validity, clinical validity and clinical utility. The group concluded that there are virtually no data to support the clinical utility of genomic applications, that there is ‘insufficient evidence to recommend testing... genes to assess risk for cardiovascular disease’ and that the ‘net health benefit from use of any of these tests alone or in combination is negligible’\textsuperscript{309}.

**Pharmacogenomics**

There is limited evidence assessing the efficacy of pharmacogenomic testing products in improving patients outcomes. However, recommendations to include their use in the delivery of clinical care are increasing\textsuperscript{310 311 312}.

Dosing algorithms have been developed that incorporate both clinical and genetic information to predict warfarin dose requirements. The International Warfarin Pharmacogenetics Consortium (IWPC) algorithm and an algorithm developed by Gage et al. use both clinical and genetic information for dose prediction with the addition of genetic data\textsuperscript{313 314}. It is currently unknown if pharmacogenetic-based dosing of warfarin will improve anticoagulation control and clinical

\begin{small}


\textsuperscript{309} Kraft P and Hunter D. Genetic risk prediction e are we there yet? New England Journal of Medicine 2009; 360:1701e3.


\textsuperscript{312} Dehghan A et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation 2011; 123:731– 8.


\textsuperscript{314} Gage B et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clinical Pharmacology and Therapeutics 2008; 84:326 –331.
\end{small}
outcomes. An RCT including 206 patients did not demonstrate an advantage of pharmacogenetic dosing on anticoagulation control, despite the dosing algorithm predicting the final stable dose better than a clinical-only algorithm. Another small study that used CYP2C9 only to determine dosing did show some benefit on anticoagulation control and minor bleeding, but it had a high dropout rate.

Point-of-care genetic testing to identify carriers of the CYP2C19*2 allele and to tailor a pharmacogenetic approach to dual antiplatelet treatment after percutaneous coronary intervention has been trialled in two hundred patients enrolled into the prospective, randomised RAPID GENE study. Patients undergoing PCI either electively or following an acute coronary syndrome were randomised to either point-of-care genotyping or to standard treatment. Carriers of the CYP2C19*2 allele were given 10 mg of prasugrel daily, whereas all other patients in the trial were give 75 mg of clopidogrel daily. The primary endpoint was the proportion of CYP2C19*2 carriers with high on-treatment platelet reactivity after 1 week of dual antiplatelet treatment. One hundred and eighty-seven patients completed follow-up. In each group 23 individuals carried at least one CYP2C19*2 allele. None of the 23 carriers in the rapid genotyping group had evidence of inadequate platelet inhibition after 7 days, compared with 7 (30%) who were given standard treatment (p=0.0092). The point-of-care genetic test had a sensitivity of 100% and a specificity of 99.3%.

Evidence of cost-effectiveness

Testing for monogenic conditions

Monogenic testing has been assessed in a number of economic evaluations.

An economic decision model comparing cascade screening by genetic, as opposed to clinical methods for hypertrophic cardiomyopathy demonstrated an incremental cost per life year saved was €14 397 for the cascade genetic compared with the cascade clinical approach. Genetic diagnostic strategies were more likely to be cost-effective than clinical tests alone. Ingles et al. conducted a cost-effectiveness study of genetic testing in families with HCM using a probabilistic Markov decision model to compare two strategies for family management, cascade and serial screening. The model was built to estimate the lifetime resource costs and health outcomes, and focuses specifically on how clinical surveillance is altered due to a predictive genetic test result and sudden cardiac death prevention in clinically affected HCM individuals. When considering genetic testing, the


incremental cost-effectiveness ratio (ICER) was $A785 (£510 or €587) per QALY gained, and $A12,720 (£8261 or €9,509) per additional life year gained. The addition of genetic testing to the management of HCM families is therefore highly cost effective when compared with conventional management.

**Commercial tests for polygenic conditions**

It is not possible to estimate the cost-effectiveness of the majority of gene-based diagnostic tests as the efficacy of these tests in altering cardiovascular disease trajectory has not been established. For reference, the following costs are provided:

- The costs of whole-genome sequencing are between $1,000 and $5,000 USD\textsuperscript{320,321}.
- Direct-to-Consumer genome-wide association analysis genotyping costs approximately $500 USD\textsuperscript{322}.
- The costs of products for testing for specific alterations in gene expression are approximately $150 USD\textsuperscript{323}.

Industry-funded economic evaluation of Corus CAD as a means of identifying patients who need no referral versus those who need referral to MPI or invasive coronary angiography demonstrated that the test costs $72,202 per quality adjusted life year\textsuperscript{324}.

**Impacts on service delivery**

In the next ten years, genetic information may be increasingly used in cardiology practice.

According to stakeholders, products are consistent with those used in other clinical areas (e.g. oncology) and are not expected to create additional burden for specialised education and training.

**Monogenic testing**

Heart Failure Society of America guidelines recommend that genetics evaluation for hereditary cardiovascular disease are best performed by providers with the skills, training and time that the level of complexity in these cases demands. Patients who receive evaluations in specialised cardiovascular genetics clinics that include genetic counselling have better psychological outcomes, including better adjustment to their disease and less worry\textsuperscript{325}. The managing cardiology team should

\textsuperscript{320} Roden D. Personalised medicine and the genotype-phenotype dilemma. Journal of Interventional Cardiology Electrophysiology 2011; 31: 17-23.


\textsuperscript{322} Roden D. Personalised medicine and the genotype-phenotype dilemma. Journal of Interventional Cardiology Electrophysiology 2011; 31: 17-23.

\textsuperscript{323} Phelps C et al. 34th Annual Meeting of the Society for Medical Decision Making. October 2012.

\textsuperscript{324} Ibid

consider consulting with a cardiovascular genetics group if they do not have a team member who can provide adequate genetic counselling, pedigree assessment, and interpretation of genetic test results. Such a consultation can supplement the patient’s ongoing care, without interfering with the relationship the patient has with their primary cardiologist\textsuperscript{326}.

Downstream impacts of genetic testing on cardiac pharmaceuticals and devices have the potential to significantly impact costs of delivering cardiac care. Long QT syndrome testing will be associated with increased procedural activity associated with insertion of pacemakers / ICDs and more widespread testing for familial hyperchoesterolaemia with use of HMG CoA reductase inhibitors. As there are cost benefits associated with the prevention of acute cardiac / coronary events with early detection and management of cardiac conditions, the net cost impacts of these ‘downstream’ costs associated with genetic testing are difficult to estimate reliably.

\textit{Polygenic testing}

Despite the limitations in genotype-based risk prediction and biomarker detection and the limited data demonstrating their clinical impact, biotechnology companies continue to explore the commercial application of genomics by offering direct-to-consumer genetic testing\textsuperscript{327}.


\textsuperscript{327} Patel R et al. Genetic determinants of coronary heart disease: new discoveries and insights from genome-wide association studies. Heart 2011; 97: 1463-73.
SUMMARY

CVD is responsible for a significant proportion of hospitalisations in Australia and New Zealand, the majority of which are for coronary heart disease. However, heart failure, hypertension and arrhythmias contribute to an increasing CVD and total disease burden in both countries.

Options for CVD management are increasingly procedural. The majority of CVD procedures are conducted on the coronary arteries, mainly coronary angiography and coronary angioplasty with stenting. However, defibrillator and pacemaker insertion procedures have increased over time.

The development of cardiac technologies is an area of intensive scientific and clinical research activity. Given the substantial disease burden, it is predicted that the most promising emerging cardiac technologies are likely to influence the delivery of health services in general, and cardiovascular services in particular, over the next ten years.

The technologies identified as having the greatest potential to influence cardiac practice over the next ten years were:

- Percutaneous valve replacement and repair;
- Left atrial appendage occlusion devices;
- Pumps / assist devices as a destination therapy for the management of heart failure;
- Next generation pacemaker and implantable cardiac defibrillator devices;
- Renal denervation systems; and
- Genetic testing in the assessment and management of cardiovascular diseases.

According to stakeholders and analysis of available data, these technologies collectively are likely to result in a net increase in the costs of delivering health services. CVD is already Australia’s most expensive disease group, costing in excess of $6 billion annually. Costs of treating CVD in the New Zealand population are also substantial. As demonstrated throughout this report, our current understanding of the effectiveness and cost-effectiveness of these technologies is incomplete.

Overall, stakeholders supported allowing clinical experience with new procedures to develop in a contained and evidence-based way building up high-level experience in selected centres first.

This report does not make any specific recommendations regarding whether policymakers should implement these technologies and, if so which patient groups they are indicated in. Rather, the report emphasises that the introduction of these cardiac technologies into services needs to be supported with clinical practice guidelines for their introduction, well-defined models of care that support the effective and efficient use of technologies, ongoing data collection to demonstrate their safety and effectiveness and development of the necessary skills within the health care workforce.

Given the limited evidence base for emerging technologies, post-market evaluation including the use of cardiac device registries is appropriate for collecting high quality cost and clinical effectiveness data.
data. Further, systems to support the early identification and remediation of safety concerns should be in place as emerging technologies have, by definition, been used to a very limited extent in clinical practice.
APPENDIX 1 – ‘BREAKTHROUGH TECHNOLOGIES’

DIAGNOSTIC TECHNOLOGIES

Cardiac monitoring

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wireless pulmonary artery haemodynamic monitor(^{328})</td>
<td>Implant that monitors fluid pressure in the pulmonary artery and transmits data to physician for medication adjustment</td>
</tr>
<tr>
<td>CardioMEMS, Oklahoma Heart Hospital</td>
<td></td>
</tr>
<tr>
<td>Clinical trials, no market introduction</td>
<td></td>
</tr>
<tr>
<td>Patients with Class III / Class IV cardiac failure</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

Next generation remote cardiac arrhythmia monitoring\(^{329\ 330}\)

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotronik Preventice (Mayo Clinic) (BodyGuardian)</td>
<td>Remote monitoring for patients with pacemaker, ICD and cardiac resynchronisation therapy. Monitors biometrics in patients with arrhythmias outside the clinical setting. Device collects ECG, heart rate, RR and activity level and transmits to physicians via wireless communication e.g. to a mobile phone. Supported by a cloud-based mHealth platform that collects data from devices and delivers information to medical monitoring professionals by clinician’s preferred means of communication.</td>
</tr>
</tbody>
</table>

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\(^{329}\) Rotariu C. Remote cardiac arrhythmia monitoring system using wireless sensor networks. 11th International Conference on Development and Application Systems, Romania, May 2012.

\(^{330}\) MTAA. Business case for public funding of remote monitoring of cardiac implantable electronic devices. December 2011.
### Patient groups
Rhythm disturbance requiring pacemaker / defibrillator

### Stage of development / introduction
FDA clearance of next generation devices for non-lethal arrhythmias

### Use in Australia
Remote cardiac monitoring occurs in Australia.
Next generation monitoring devices not widely available.

### Costs
The costs of remote monitoring include the cost of the patient monitor device and the cost of data monitoring by appropriate staff. There have been few economic studies of the cost-effectiveness of remote monitoring for cardiac devices. Results are dated and not generally applicable to Australia.331

### Technology
**Smart T shirt**332

### Manufacturers
University of Madrid
TESAN (Italy)

### Description
Replaces the hospital gown.
Patients wear the T shirt which automatically records the patient’s temperature, heart rate and acts as a GPS.

The system uses wearable heart, respiratory and activity monitoring sensors fitted to a light-weight T-shirt, alongside external devices such as a digital weight scale, glucometer, blood pressure monitor, spirometer and air quality sensor in the patient's home or room to measure vital, physical and environmental signs. These are connected to a mobile device such as a smartphone or PDA which in turn transmits the patient's data to their care provider where it is analysed with intelligent data processing software.

### Patient groups
All patients who require heart rate monitoring

### Stage of development / introduction
Product development

### Use in Australia
Not available

### Costs
Not available

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332 Chronious Project. European Commission. Project reference 216461
### Electrophysiology

<table>
<thead>
<tr>
<th>Technology</th>
<th>Stretchable silicon electronics&lt;sup&gt;333&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>University of Illinois</td>
</tr>
<tr>
<td>Description</td>
<td>Existing approaches use single-point electrical mapping catheters; newer systems exploit arrays of electrodes integrated on catheter-type delivery systems. Surgical tool covered in stretchable sensors that reduces time required to map electrical cardiac problems from over an hour to a few minutes.</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Treatment of atrial fibrillation.</td>
</tr>
<tr>
<td></td>
<td>Ablation in various forms of cardiac arrhythmias, including ventricular fibrillation and ventricular tachycardia.</td>
</tr>
<tr>
<td></td>
<td>Mapping of cardiac electrical activity for identifying sources of electrical dysfunction and to monitor local cardiac tissue behaviour during surgery.</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Product development</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>No</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

### Imaging

<table>
<thead>
<tr>
<th>Technology</th>
<th>Combination intracardiac echocardiography and ultrasound system&lt;sup&gt;334&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>St Jude</td>
</tr>
<tr>
<td>Description</td>
<td>Intracardiac echocardiography (ICE) uses a miniaturized transducer mounted on a wire, or catheter that is advanced inside the heart during a catheter ablation procedure. The combination system provides better visualisation of a patient’s cardiac anatomy and of the effects of ablation treatment in real-time.</td>
</tr>
</tbody>
</table>

<sup>333</sup> Kim D. Flexible and Stretchable Electronics for Biointegrated Devices. Annual Review of Biomedical Engineering 2012; Vol. 14: 113-128

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Multiple e.g. during ablation procedures, as an adjunct to TAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of development / introduction</td>
<td>The use of ICE during catheter ablation may improve safety and procedure results and allows rapid identification of potential complications. The system has Europe CE as an alternative to TEE for intra-procedural guidance during TAVI.</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Unknown</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology</th>
<th>High resolution miniature ultrasound probe³³⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>Description</td>
<td>Ultrasound device replacing the stethoscope for auscultating the heart</td>
</tr>
<tr>
<td>Patient groups</td>
<td>All patients</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Limited introduction to clinical practice</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Yes</td>
</tr>
<tr>
<td>Costs</td>
<td>$7,700 per device</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology</th>
<th>Ultrafast single-photon emission computed tomography (SPECT)³³⁶ ³³⁷</th>
</tr>
</thead>
</table>
| Manufacturers | Phillips  
Siemens  
GE Healthcare  
Digirad  
UltraSPECT |

³³⁵
NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

<table>
<thead>
<tr>
<th>Description</th>
<th>Newer designs for dedicated cardiac SPECT cameras that constrain the entire detector area to imaging only the heart. New software recovers image resolution and limits image noise. The advantages are better image quality, shortened study times and/or reduced radiation doses for patients. In contrast to traditional dual-headed, sodium iodide crystal and photomultiplier cameras with mechanical collimators, new SPECT camera designs utilize novel, collimators, and solid-state detectors that convert photons directly to electrical signals. These cameras simultaneously collect data from up to 76 small detectors narrowly focused on the heart. New noise regularization and resolution recovery/noise reduction reconstruction software interprets emitted counts more efficiently and thus more effectively discriminates between useful signals and noise. As a result, shorter acquisition times and/or lower tracer doses produce higher quality SPECT images than were possible before. New designs vary in the number and type of scanning or stationary detectors and in whether NaI, CsI, or cadmium-zinc-telluride (CZT) solid-state detectors are used. They all have in common the potential for a 5- to 10-fold increase in count sensitivity at no loss of, or even a gain in, resolution, resulting in the potential for acquiring a stress myocardial perfusion scan in 2 min or less if the patient is injected with a standard dose. In an ultrafast camera with a 10-fold increase in sensitivity using conventional radiopharmaceutical doses, the dose could be reduced by half and a 5-fold increase in sensitivity still be maintained.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient groups</td>
<td>Myocardial perfusion SPECT is often used in the noninvasive assessment of hemodynamically significant coronary artery disease.</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Extensively validated against invasive coronary angiography. Positive predictive value is high (91%) but negative predictive value is modest (63%).</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Cardiac SPECT available.</td>
</tr>
<tr>
<td>Costs</td>
<td>No economic evaluations of new generation SPECT identified.</td>
</tr>
</tbody>
</table>
### Chamber Technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>C-Pulse cardiac assist device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Sunshine Heart</td>
</tr>
<tr>
<td>Description</td>
<td>The pump wraps around the ascending aorta and increases the left ventricle output without directly coming in contact with the pumped blood. This approach theoretically reduces risks of intra-ventricular thrombosis. The extra-aortic counter-pulsation technology allows patients to temporarily turn off and disconnect the system from the power supply as needed for bathing and other tasks.</td>
</tr>
<tr>
<td>Patient groups</td>
<td>For use in patients with Class III and ambulatory Class IV heart failure</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>European CE approval  No FDA approval</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Not available</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology</th>
<th>Cardiac tissue engineering$^{338,339}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Miromatrix</td>
</tr>
<tr>
<td>Description</td>
<td>Decellularization of allogeneic or xenogeneic donor organs such as heart provides an acellular naturally occurring three-dimensional biologic scaffold material that subsequently can be seeded with either functional parenchymal cells or selected progenitor cell populations. Self-assembly of these seeded cells with the aid of a biofriendly three-dimensional matrix results in the formation of functional tissue in short-term preclinical animal models. This approach provides the opportunity for direct connection to the patient vasculature in either an orthotopic or heterotopic location. Numerous challenges for this three-dimensional organ-engineering approach remain including the determination of candidate species from which the donor organ can be harvested, optimal</td>
</tr>
</tbody>
</table>

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methods of donor organ decellularization, optimization of recellularization techniques and the most appropriate cell populations, endothelialization of the donor matrix vasculature, and determination of the appropriate use of ex-vivo bioreactors, among others.

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Patient requiring cardiac transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of development / introduction</td>
<td>Although significant advances have been made in the development of engineered tissues such as blood vessels, urinary bladder, and trachea, none of these tissues require an intact vascular network that can be connected to the host circulation at the time of implantation. Whole-organ constructs such as heart will require this type of immediate vascular supply. A successful regenerative medicine strategy for whole-organ replacement would represent a quantum leap forward in the treatment of patients with end-stage organ disease.</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Not available</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

### Electrophysiology

<table>
<thead>
<tr>
<th>Technology</th>
<th>Next generation balloon ablation technologies(^{340})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Medtronic</td>
</tr>
</tbody>
</table>
| Description | Contact-sensing feedback and multielectrode catheter systems, which can improve electrical mapping of complex arrhythmias and provide real-time force feedback during lesion formation.

Emerging balloon catheter–based systems rely on balloon substrates to conform to the anatomical structure of the PV ostium. These balloons inflate within the left atrium and create a continuous ring of conformal contact between the balloon and the tissue, followed by delivery of cryoenergy, high-intensity focused ultrasound (HIFU) – or laser-based ablation therapies.

Balloon ablation catheters do not provide sensory feedback about mechanical contact with soft tissue or information on the electrical state of intracardiac surfaces. |
| Patient groups | Ablation in various forms of cardiac arrhythmias, including ventricular fibrillation and ventricular tachycardia. |

---

### Epicardial Ablation System

<table>
<thead>
<tr>
<th>Technology</th>
<th>Epicardial ablation system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Estech</td>
</tr>
<tr>
<td>Description</td>
<td>System uses suction to tug on the target tissue and bring it into probe where radiofrequency energy ablates it, isolating the target section from the rest of the blood flowing through the heart.</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients requiring atrial wall transmural ablation for management of cardiac arrhythmia</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>FDA and European CE approval. Limited introduction into clinical practice</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Available in Australia</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

### Guided Medical Positioning System

<table>
<thead>
<tr>
<th>Technology</th>
<th>Guided medical positioning system&lt;sup&gt;341&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>MediGuide (St Jude Medical)</td>
</tr>
<tr>
<td>Description</td>
<td>A technology brief was completed by the HealthPACT in February 2012. The guided medical positioning system (gMPS) enables localisation, tracking and navigation of intra-cardiac devices. The system consists of three components: a transmitter to generate low-intensity alternating electromagnetic fields; a miniaturised passive single coil sensors implanted within the cardiac device, such as an electrophysiological (EP) catheter; and an electromagnetic field reference sensor attached to the patient’s sternum. The transmitter is mounted on the fluoroscopy detector of a conventional X-ray imaging system, aligning the fluoroscopy space with the 3D electromagnetic sensor field. The sensor detects the low-intensity</td>
</tr>
</tbody>
</table>

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magnetic field and generates an electrical signal, which allows the system to calculate the real-time position and orientation of the device. The location of the device is then displayed in real-time on fluoroscopic images, with images correlated with data obtained from a continuous ECG and the patient reference sensor to compensate for patient movement caused by heart motion and respiration, respectively. Continuous fluoroscopy is no longer required to ascertain the position of the device, therefore significantly decreasing the radiation exposure to both the physician and patient, especially during long interventions. An additional patient benefit is the reduced need for contrast agent.

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Patients requiring cardiac catheterisation and interventional cardiology procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of development / introduction</td>
<td>TGA approved 2011</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Nil</td>
</tr>
<tr>
<td>Costs</td>
<td>Nil available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology</th>
<th>Wireless cardiac stimulator[^342]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Vanderbilt University EBR Systems</td>
</tr>
<tr>
<td>Description</td>
<td>A pacemaker that regulates the heart by wirelessly ‘stimulating’ it with pulses of ultrasound. The device eliminates the need for pacing leads, a source of complications and reliability issues in cardiac stimulation technology.</td>
</tr>
</tbody>
</table>
| Patient groups | People with heart failure. This population is underpenetrated by Cardiac Resynchronization Therapy (CRT), despite numerous clinical trials illustrating these therapies benefits. Part of the reason for low penetration is the complexity of the procedure; the complications associated with coronary sinus leads used to pace the LV, and continued non-responder rates of approximately 30% despite advances in LV lead technology. The wireless cardiac stimulation technology is simpler, reduces implant times, reduces complications associated with leads (acute and chronic lead displacement, coronary sinus dissection, acute and chronic phrenic...

nerve stimulation, high pacing energy thresholds).

<table>
<thead>
<tr>
<th>Stage of development / introduction</th>
<th>Human trials in Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WiSE-CRT Study, a 100 patient feasibility, safety, and CE-Mark trial is underway in Europe assessing biventricular capture in heart failure patients. Patients successfully treated include those with acutely failed coronary sinus (CS) lead placement, chronically failed CS leads, patients “upgraded” from dual-chamber defibrillators and patients who have not yet responded to traditional cardiac resynchronization therapy (CRT).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use in Australia</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>CRT costs approximately $24,000 per initial implantation(^{343})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology</th>
<th>Microelectronic pacemaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Description</td>
<td>Pacemaker the size of a tic tac</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients requiring pacemaker insertion</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Product development phase</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>No</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

343 McAlister F. Cardiac resynchronisation therapy for patients with left ventricular systolic dysfunction. JAMA 2007; 297:2502.
### Wireless power for cardiac devices

**Manufacturers** Stanford University

**Description** Researchers at Stanford University have created an 0.8 mm diameter prototype wirelessly powered implanted cardiac device. The power source is radio waves transmitted from outside the body. This has the potential to lead to breakthrough as replacing the batteries in pacemakers and other implanted devices is a limitation to their use.

**Patient groups** People with implanted cardiac devices.

**Stage of development / introduction** Research

**Use in Australia** Not available

**Costs** Not available

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### Optogenetic cardiac pacemaker

**Manufacturers** SUNY Stony Brook

**Description** Technology that uses a combination of genetic manipulation of cardiac cells and applies pulses of light to stimulate the heart to beat. The therapy is intended to function by injecting the engineered light-sensitive cells into the heart and pacing them remotely with light, possibly from outside of the heart.

**Patient groups** Patients who require pacemakers

**Stage of development / introduction** Research only

**Use in Australia** Not available

**Costs** Not available

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<table>
<thead>
<tr>
<th>Technology</th>
<th>LifeVest wearable defibrillator&lt;sup&gt;346&lt;/sup&gt;&lt;sup&gt;347&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Zoll</td>
</tr>
<tr>
<td>Description</td>
<td>A non-invasive, wearable defibrillator (WCD) that is an alternative to an Implantable Cardioverter-Defibrillator (ICD).</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients in whom an ICD is indicated.</td>
</tr>
<tr>
<td></td>
<td>Bridge to ICD implantation.</td>
</tr>
<tr>
<td></td>
<td>Higher risk patients who are being considered for ICD implantation but who may not meet criteria yet for implantation e.g. patients who have recently had a myocardial infarction / new onset heart failure with severe impairment of LV function.</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Phase 3 clinical trial in 108 patients (age 58.5 +/- 13.2 years) who wore the WCD vest for a total of 6128 days (57.1 +/- 51.1 days) with a daily use of 20.5 +/- 3.8 h. 77% of patients wore the WCD on every day ordered. Observed outcomes include: 37% had improvements in LVEF, 37% received Internal Cardioverter-Defibrillator (ICD) implantation, 18% of patients discontinued the use of the WCD Vest early by choice (2 of whom a denial of coverage by insurance could be verified) and 8% refused ICD Therapy. One successful conversion of VF and one inappropriate shock due to user error occurred during use of the Zoll LifeVest&lt;sup&gt;348&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Unknown</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

<sup>346</sup> US National Institutes of Health. Evaluating the Effectiveness of the LifeVest Defibrillator and Improving Methods for Determining the Use of Implantable Cardioverter Defibrillators (VEST/PREDICTS). ClinicalTrials.gov Identifier: NCT00628966


## Faraday sock

<table>
<thead>
<tr>
<th>Technology</th>
<th>Faraday sock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Massachusetts Institute of Technology / Johns Hopkins University</td>
</tr>
<tr>
<td>Description</td>
<td>The prototype device is designed to sheathe the heart inside a Faraday cage to contain a shock that halts the arrhythmia without severe pain to the patient. Implantable Cardioverter-Defibrillators (ICD) are installed beneath the skin. A wire passes from the ICD into the heart through a vein and delivers shocks as needed. However, the shocks are painful, and patients often live in dread of them or choose to forgo treatment because of them. In practice, the sock would fit around the heart and serve as one electrode of the shock delivery circuit; when an attached sensor detected abnormal heart activity, an electrical coil implanted inside the heart would deliver the jolt.</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients in whom implantable cardioverter – defibrillators are indicated</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>The prototype has been tested in animals. The device resets the heartbeat using less energy than a standard ICD. The animal’s chest muscles contract less, reducing pain.</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Not available</td>
</tr>
<tr>
<td>Costs</td>
<td>Not available</td>
</tr>
</tbody>
</table>

349 [http://www.jhtonline.jhu.edu/TechnologyDetail.aspx?TechID=6BBDB902-7E3D-41D0-8F70-60CFF104EFAA](http://www.jhtonline.jhu.edu/TechnologyDetail.aspx?TechID=6BBDB902-7E3D-41D0-8F70-60CFF104EFAA)
### Valvular

<table>
<thead>
<tr>
<th>Technology</th>
<th><em>Percutaneous pulmonary valve implantation</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Description</td>
<td>HealthPACT assessment published February 2012</td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients with congenital heart defects involving malformation of the right ventricular outflow tract</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>Clinical trials, No TGA approval</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Yes</td>
</tr>
<tr>
<td>Costs</td>
<td>Studies of cost have been conducted. Procedural costs are approximately $50,000 per procedure. Over 5 years, surgical pulmonary valve replacement is approximately $20,000 (USD) cheaper than percutaneous pulmonary valve procedures.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Technology</th>
<th><em>Sutureless aortic valve replacement</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Medtronic, Sorin, Edwards Lifesciences</td>
</tr>
<tr>
<td>Description</td>
<td>A replacement valve that incorporate sutureless fixation which can be delivered using less invasive partial upper sternotomy.</td>
</tr>
<tr>
<td>Patient groups</td>
<td>For patients at high-risk from standard surgical AVR e.g. older people with severe comorbidities.</td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>European CE approval. No FDA approval</td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Yes</td>
</tr>
<tr>
<td>Costs</td>
<td>$15,000 (AUD) for the device</td>
</tr>
</tbody>
</table>

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# NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

## Vascular

<table>
<thead>
<tr>
<th>Technology</th>
<th>Stents</th>
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<tbody>
<tr>
<td></td>
<td>New drug-eluting</td>
</tr>
<tr>
<td></td>
<td>Bioresorbable</td>
</tr>
<tr>
<td></td>
<td>Self-apposing</td>
</tr>
<tr>
<td></td>
<td>Self-expanding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacturers</th>
<th>Multiple</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>Biolimus A9-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Element Platinum Chromium Stent</td>
</tr>
<tr>
<td></td>
<td>Self-expanding Nitinol Stent</td>
</tr>
<tr>
<td></td>
<td>Everolimus-eluting platinum chromium coronary stent</td>
</tr>
<tr>
<td></td>
<td>Novolimus-eluting stent</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel-eluting stent</td>
</tr>
<tr>
<td></td>
<td>Bioresorbable stents</td>
</tr>
<tr>
<td></td>
<td>Self-apposing stents (fits to contour of blood vessel; shape and diameter adapt as vessel dilates and initial clot dissolves during post-AMI phase)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Coronary occlusion</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Stage of development / introduction</th>
<th>Various clinical trials</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Use in Australia</th>
<th>Clinical trials</th>
</tr>
</thead>
</table>

| Costs | Vary. August 2012 analysis of costs and benefits of drug-eluting stents (DES) shows DES cost more than bare-metal stents (BMS) and necessitate prolonged dual antiplatelet therapy (DAPT), which increases costs, bleeding risk, and risk of complications if DAPT is prematurely discontinued. Authors analysed more than 1.5 million PCI procedures in the National Cardiovascular Data Registry - CathPCI registry from 2004-2010 and estimated 1-year target vessel revascularization (TVR) risk with BMS using a validated model and examined association between TVR risk and DES use and cost-effectiveness of lower DES use in low-TVR-risk patients (50% less DES use among patients with <10% TVR risk) compared with existing DES use. |

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There was marked variation in physicians’ use of DES (range 2%-100%). Use of DES was high across all predicted TVR risk categories (73.9% in TVR risk <10%; 78.0% in TVR risk 10%-20%; and 83.2% in TVR risk >20%), with a modest relationship between TVR risk and DES use (relative risk, 1.005 per 1% increase in TVR risk [95% CI, 1.005-1.006]). Reducing DES use by 50% in low-TVR-risk patients was projected to lower US health care costs by $205 million per year while increasing the overall TVR event rate by 0.5% (95% CI, 0.49%-0.51%) in absolute terms.

| Technology | Fractional flow reserve-guided stenting equipment[

| Manufacturers | St Jude |
| Description | Pressure wire FFR measurement technology. Measurements are taken by placing the Pressure Wire across the lesion of interest and inducing a state of maximum blood flow, thereby allowing the physician to determine if the narrowing is tight enough to cause ischemia. The system is referred to as ‘wireless’ FFR because the system does not require additional equipment or cabling in the cardiac catheterisation laboratory as the components are integrated into the catheter used to perform PCI. |
| Patient groups | The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. The results of FAME II suggest that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy appears superior to the best available medical therapy alone. However, comparisons with coronary angiography were not performed. |
| Stage of development / introduction | FAME II randomised trial conducted at 28 sites in Europe and North America showed that the use of PressureWire FFR measurement technology resulted in an 86% reduction in the relative risk for unplanned readmission to the hospital with urgent revascularization in patients with stable coronary artery disease. Previous generation FFR pressure wires are already introduced into clinical practice. |

<table>
<thead>
<tr>
<th>Technology</th>
<th>Extracorporeal shockwave myocardial revascularisation&lt;sup&gt;353&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Medispec</td>
</tr>
<tr>
<td>Description</td>
<td>The ESMR technology produces acoustic shock waves via a generator, supported against the patient’s chest by a water cushion. The generator produces an underwater spark at high voltage resulting in a high amplitude pulse delivered to the appropriate area of the heart, as determined by ultrasound imaging (echocardiography) which locates and defines the extent of ischaemia. Several treatment sessions are required to obtain optimal results.</td>
</tr>
</tbody>
</table>
| Patient groups | Patients with Canadian Cardiovascular Society (CCS) class III-IV angina despite medical therapy  
Patients with congestive cardiac failure of ischaemic origin  
Contribute to angiogenesis and improve symptoms of angina and left ventricular (LV) function |
| Stage of development / introduction | Human trials  
European CE Mark |
| Use in Australia | Unknown |
| Costs | Not available |

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<table>
<thead>
<tr>
<th>Technology</th>
<th>Robotic system for percutaneous coronary interventions&lt;sup&gt;354&lt;/sup&gt;</th>
<th>355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>Corindus Vascular Robotics</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Traditional guided angioplasties expose clinicians to radiation as they guide instruments through the patient’s vasculature. The robotic system (CorPath) allows physicians to work away from the patient, protected from exposure to radiation.</td>
<td></td>
</tr>
<tr>
<td>Patient groups</td>
<td>Patients requiring angioplasty.</td>
<td></td>
</tr>
<tr>
<td>Stage of development / introduction</td>
<td>FDA clearance. Clinical trials underway. Results to date show PCI successfully completed without having to convert to manual PCI in 98.8% of patients and without device-related complications. The overall procedure success rate is 97.6%. Radiation exposure reduced by 95%.</td>
<td></td>
</tr>
<tr>
<td>Use in Australia</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td>CorPath 200 system can be integrated with all major x-ray fluoroscopy systems, influencing the costs for introduction (the CorPath system alone or x-ray fluoroscopy as well if not already in place).</td>
<td></td>
</tr>
</tbody>
</table>

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## APPENDIX 2 – DISEASE BURDEN AND PROCEDURAL DEMAND DATA

Total number of cardiovascular procedures (public and private) performed in Australian public hospitals, 2000/01-2009/10

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery angiography</td>
<td>81,473</td>
<td>84,547</td>
<td>88,617</td>
<td>94,427</td>
<td>98,167</td>
<td>100,386</td>
<td>106,720</td>
<td>111,300</td>
<td>115,390</td>
<td>119,437</td>
</tr>
<tr>
<td>Valvular procedures</td>
<td>6,881</td>
<td>6,981</td>
<td>7,243</td>
<td>7,708</td>
<td>8,232</td>
<td>8,416</td>
<td>8,718</td>
<td>9,203</td>
<td>9,952</td>
<td>10,350</td>
</tr>
<tr>
<td>Veins (Harvested for CABG)</td>
<td>11,228</td>
<td>10,601</td>
<td>10,512</td>
<td>10,387</td>
<td>10,447</td>
<td>10,400</td>
<td>10,444</td>
<td>10,208</td>
<td>10,092</td>
<td>9,078</td>
</tr>
<tr>
<td>Pacemaker insertion</td>
<td>20,978</td>
<td>22,660</td>
<td>24,675</td>
<td>25,480</td>
<td>26,168</td>
<td>27,524</td>
<td>29,815</td>
<td>31,807</td>
<td>30,380</td>
<td>31,883</td>
</tr>
<tr>
<td>Defibrillator insertion</td>
<td>1,323</td>
<td>1,694</td>
<td>2,644</td>
<td>3,350</td>
<td>4,881</td>
<td>5,087</td>
<td>5,474</td>
<td>5,910</td>
<td>7,337</td>
<td>7,056</td>
</tr>
<tr>
<td>Electrophysiology studies</td>
<td>5,063</td>
<td>5,458</td>
<td>6,207</td>
<td>6,593</td>
<td>7,062</td>
<td>7,348</td>
<td>8,086</td>
<td>8,306</td>
<td>8,101</td>
<td>8,554</td>
</tr>
</tbody>
</table>
Trends in cardiovascular procedures, Australia, 2000/01 to 2009/10

- Coronary artery angiography (angiogram)
- Coronary artery angioplasty
- Veins (Harvested for Coronary arterial bypass)

- Pacemaker insertion
- Defibrillator insertion
- Electrophysiology studies
## Total hospital separations for circulatory conditions, Australia, 1998/99 to 2009/10

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic rheumatic heart diseases (I05–I09)</td>
<td>1,894</td>
<td>1,979</td>
<td>1,828</td>
<td>2,029</td>
<td>2,059</td>
<td>2,085</td>
<td>2,222</td>
<td>2,226</td>
<td>2,296</td>
<td>2,439</td>
<td>2,361</td>
<td>2,395</td>
<td>25,813</td>
</tr>
<tr>
<td>Hypertensive diseases (I10–I15)</td>
<td>7,969</td>
<td>7,807</td>
<td>7,507</td>
<td>7,421</td>
<td>7,484</td>
<td>7,598</td>
<td>7,218</td>
<td>7,222</td>
<td>7,524</td>
<td>7,434</td>
<td>7,030</td>
<td>7,314</td>
<td>89,528</td>
</tr>
<tr>
<td>Ischaemic heart diseases (I20–I25)</td>
<td>158,156</td>
<td>157,913</td>
<td>158,410</td>
<td>159,561</td>
<td>161,794</td>
<td>164,226</td>
<td>162,283</td>
<td>161,367</td>
<td>162,328</td>
<td>161,417</td>
<td>154,808</td>
<td>153,833</td>
<td>1,916,096</td>
</tr>
<tr>
<td>Pulmonary heart disease and diseases of pulmonary circulation (I26–I28)</td>
<td>7,769</td>
<td>8,526</td>
<td>8,443</td>
<td>8,477</td>
<td>8,495</td>
<td>8,572</td>
<td>8,659</td>
<td>8,940</td>
<td>9,780</td>
<td>10,565</td>
<td>11,076</td>
<td>11,382</td>
<td>110,684</td>
</tr>
<tr>
<td>Other forms of heart disease (I30–I52)</td>
<td>103,024</td>
<td>107,959</td>
<td>110,105</td>
<td>116,227</td>
<td>117,307</td>
<td>118,486</td>
<td>122,062</td>
<td>127,791</td>
<td>132,462</td>
<td>137,750</td>
<td>142,211</td>
<td>146,868</td>
<td>1,482,252</td>
</tr>
</tbody>
</table>
## NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

<table>
<thead>
<tr>
<th>I33 Acute and subacute endocarditis</th>
<th>1,059</th>
<th>1,164</th>
<th>1,147</th>
<th>1,259</th>
<th>1,204</th>
<th>1,129</th>
<th>1,098</th>
<th>1,221</th>
<th>1,348</th>
<th>1,273</th>
<th>1,430</th>
<th>1,490</th>
<th>14,822</th>
</tr>
</thead>
<tbody>
<tr>
<td>I34 Nonrheumatic mitral valve disorders</td>
<td>2,346</td>
<td>2,302</td>
<td>2,413</td>
<td>2,310</td>
<td>2,372</td>
<td>2,525</td>
<td>2,594</td>
<td>2,762</td>
<td>2,736</td>
<td>2,826</td>
<td>3,116</td>
<td>3,078</td>
<td>31,380</td>
</tr>
<tr>
<td>I35 Nonrheumatic aortic valve disorders</td>
<td>4,354</td>
<td>4,681</td>
<td>4,612</td>
<td>4,856</td>
<td>4,937</td>
<td>5,224</td>
<td>5,404</td>
<td>5,692</td>
<td>5,980</td>
<td>6,361</td>
<td>7,267</td>
<td>8,230</td>
<td>67,598</td>
</tr>
<tr>
<td>I36 Nonrheumatic tricuspid valve disorders</td>
<td>30</td>
<td>23</td>
<td>17</td>
<td>19</td>
<td>18</td>
<td>14</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>23</td>
<td>13</td>
<td>15</td>
<td>199</td>
</tr>
<tr>
<td>I37 Pulmonary valve disorders</td>
<td>28</td>
<td>46</td>
<td>47</td>
<td>57</td>
<td>79</td>
<td>66</td>
<td>64</td>
<td>56</td>
<td>82</td>
<td>92</td>
<td>90</td>
<td>130</td>
<td>837</td>
</tr>
<tr>
<td>I38 Endocarditis, valve unspecified</td>
<td>106</td>
<td>111</td>
<td>123</td>
<td>128</td>
<td>130</td>
<td>163</td>
<td>141</td>
<td>148</td>
<td>179</td>
<td>185</td>
<td>183</td>
<td>314</td>
<td>1,911</td>
</tr>
<tr>
<td>I44 Atrioventricular and left bundle—branch block</td>
<td>3,527</td>
<td>3,721</td>
<td>4,017</td>
<td>4,030</td>
<td>4,433</td>
<td>4,617</td>
<td>4,591</td>
<td>4,820</td>
<td>5,120</td>
<td>5,229</td>
<td>5,181</td>
<td>5,476</td>
<td>54,762</td>
</tr>
<tr>
<td>I45 Other conduction disorders</td>
<td>1,265</td>
<td>1,376</td>
<td>1,305</td>
<td>1,320</td>
<td>1,479</td>
<td>1,554</td>
<td>1,563</td>
<td>1,547</td>
<td>1,596</td>
<td>1,618</td>
<td>1,831</td>
<td>1,874</td>
<td>18,328</td>
</tr>
</tbody>
</table>
## NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIA AND NEW ZEALAND

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>I46</td>
<td>Cardiac arrest</td>
<td>1,745</td>
<td>1,743</td>
<td>1,787</td>
<td>1,839</td>
<td>1,915</td>
<td>1,788</td>
<td>1,409</td>
<td>1,435</td>
<td>1,545</td>
<td>1,475</td>
<td>1,284</td>
<td>19,780</td>
</tr>
<tr>
<td>I47</td>
<td>Paroxysmal tachycardia</td>
<td>5,958</td>
<td>8,114</td>
<td>8,464</td>
<td>9,469</td>
<td>9,691</td>
<td>10,466</td>
<td>10,852</td>
<td>9,776</td>
<td>10,811</td>
<td>11,325</td>
<td>11,654</td>
<td>116,342</td>
</tr>
<tr>
<td>I48</td>
<td>Atrial fibrillation and flutter</td>
<td>27,245</td>
<td>31,110</td>
<td>33,249</td>
<td>36,157</td>
<td>36,656</td>
<td>36,191</td>
<td>38,296</td>
<td>41,510</td>
<td>45,619</td>
<td>47,164</td>
<td>48,869</td>
<td>51,381</td>
</tr>
<tr>
<td>I49</td>
<td>Other cardiac arrhythmias</td>
<td>8,084</td>
<td>6,334</td>
<td>6,153</td>
<td>6,885</td>
<td>7,043</td>
<td>7,376</td>
<td>7,548</td>
<td>7,952</td>
<td>6,800</td>
<td>6,921</td>
<td>7,364</td>
<td>7,609</td>
</tr>
<tr>
<td>I50</td>
<td>Heart failure</td>
<td>41,894</td>
<td>41,703</td>
<td>41,108</td>
<td>41,884</td>
<td>41,050</td>
<td>41,425</td>
<td>41,322</td>
<td>42,071</td>
<td>43,681</td>
<td>45,212</td>
<td>45,197</td>
<td>45,004</td>
</tr>
<tr>
<td>I60</td>
<td>Cerebrovascular diseases (I60–I69)</td>
<td>40,286</td>
<td>40,673</td>
<td>40,641</td>
<td>40,243</td>
<td>40,249</td>
<td>40,791</td>
<td>40,723</td>
<td>41,454</td>
<td>41,483</td>
<td>41,716</td>
<td>41,773</td>
<td>41,977</td>
</tr>
</tbody>
</table>

**Total for IX. Diseases of the Circulatory System**

<table>
<thead>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>425,534</td>
<td>430,904</td>
<td>432,820</td>
<td>441,002</td>
<td>445,305</td>
<td>448,850</td>
<td>451,705</td>
<td>458,615</td>
<td>469,817</td>
<td>475,127</td>
<td>474,172</td>
<td>482,252</td>
</tr>
</tbody>
</table>

*Source: AIHW National Hospital Morbidity Database (public access)*

Source: AIHW National Hospital Morbidity Database (public access)
Trends in cardiovascular procedures, New Zealand, 2003 to 2007

Coronary angiography, 2006 to 2010

Coronary artery bypass grafts, 2002/03 to 2007/08

Cardiac and cardiology procedures, 2006 to 2010

Pacemaker insertion

Defibrillator insertion

Electrophysiology studies