EuroScan International Network

Sutureless aortic valve replacement in patients with severe aortic valve stenosis

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Technology, Company and Licensing

Technology name	ATS 3f Enable® , Perceval S™ , INTUITY Valve System™, Arbor Trilogy™ Aortic Valve System
Technology - Description	Aortic stenosis is the narrowing of the aortic valve within the left ventricle. Blood flow through the aortic valve is obstructed, creating high blood pressure within the left ventricle, which leads to concentric ventricular hypertrophy and heart failure. Although usually asymptomatic for a period, during which associated morbidity and mortality are low, once a patient becomes symptomatic the average length of survival is two to three years with a high risk of sudden death. The symptoms of aortic stenosis include angina, syncope and heart failure. The 2006 American College of Cardiology and American Heart Association (ACC/AHA) clinical practice guidelines provide criteria for grading of aortic stenosis severity (see Table 1 in the report on the weblink). In adults, the most common cause of aortic stenosis is acquired degenerative calcification of a normal valve, or a congenital bicuspid valve.2 As calcification progresses, the degree of cusp opening during systole becomes increasingly limited. Risk factors for degenerative calcific aortic stenosis include hypertension, hypercholesterolemia, diabetes mellitus, and smoking. The Euro Heart Survey on valvular heart disease (VHD), conducted from April to July 2001 in 92 centres from 25 countries, included 5001 prospectively enrolled adults with moderate to severe native VHD.3 The aetiology of aortic stenosis was degenerative-calcific in the majority of patients (82%), rheumatic in 11 per cent, congenital in 6 per cent and post-endocarditis in the remaining 1 per cent. Once symptomatic, patients without serious comorbid conditions are considered to be candidates for surgical AVR, the definitive treatment. AVR is traditionally an open procedure performed via sternotomy and requiring CPB. The valve prosthesis may be mechanical or biological and is implanted following resection of the native valve and annulus calcifications. In patients considered high risk for open surgery, transcatheter aortic valve implantation (TAVI) provides a minimally-invasive alternative that does not require resection of the diseased valve.4 Evidence suggests that TAVI is associated with more vascular complications and a higher incidence of stroke as compared to AVR, whilst AVR is associated with more major bleeding and new-onset atrial fibrillation as compared to TAVI. Sutureless implantable valves are an alternative to traditional AVR and TAVI. These bioprostheses are mounted on self-expandable nitinol frames (Perceval and 3F Enable) or on expandable, cloth-covered stent frame (Intuity), which are implanted following resection of the diseased tissue. The procedure is similar to open AVR as sternotomy and CPB are still required; however, the sternotomy may be partial or full and CPB and aortic cross-clamp time may be reduced. Limited exposure of the operative field (partial sternotomy or minithoracotomy) usually makes more challenging the surgical procedure, including suturing and knotting the valve. This potential disadvantage is reflected in longer operative and cross clamp time compared to full sternotomy. Sutureless devices eliminate the need for many sutures as the valve is maintained in situ by the outward radial force of the frame or by the self-anchoring shape, which potentially makes valve deployment easier and faster.4

Company or developer	see Table 2 in the report (available on the weblink) for details
Reason for database entry	Innovative technology
Technology - stage in early warning process	Assessment complete
Technology - stage of development	Other
Licensing, reimbursement and other approval	The devices summarised in Table 2 in the report (available on the weblink) are sutureless aortic valves with a CE Mark of approval, or that have recently been used in clinical trials. No TGA approval for sutureless AVR yet.
Type(s)	Device
Use(s)	Therapeutic

Patient Indication and Setting

Patient indications	Patients with severe degenerative aortic valve stenosis or insufficiency who require aortic valve replacement
Disease description and associated mortality and morbidity	Aortic stenosis is the most common type of heart valve disease. In Western populations, approximately three per cent of people over 75 have severe aortic stenosis and 25 per cent over 65 have aortic sclerosis. In 2007-2008, 8,073 AVR or replacement procedures were performed on hospitalised patients in Australia, with an age-standardised rate of 47 per 100,000 for males and 27 per 100,000 for females.9 In 2009-2010, there were 7,439 principle diagnoses of aortic stenosis within Australian public hospitals.10 Table 3 summarises claims for Medicare Benefits Schedule (MBS) items related to AVR; 71 per cent of claims were for patients aged 65 and older. In New Zealand, the prevalence of aortic stenosis is approximately 1-2 per cent in people aged 65 and over and 4 per cent in those over 85. From 2008-2011, 3,042 AVR procedures were performed in New Zealand.11 Population projections in 2011 estimated the number of New Zealanders with aortic stenosis to be 10,000, of whom 5,000 were expected to be AVR candidates.11
Number of patients	
Technology - specialties	Cardiovascular disease & vascular surgery
Technology - Setting(s)	Specialist hospital
Setting - further information	

Impact

Alternative and/or complementary technology	
Current technology	Comparators to sutureless AVR include open AVR and percutaneous replacement procedures (for inoperable or very high risk patients), as well as balloon valvuloplasty (see Table 4 in the report on the weblink). Open surgical AVR is the current treatment standard and the most effective surgical treatment option for patients with symptomatic aortic stenosis.13
Health impact	
Diffusion	There is no published evidence to suggest that sutureless AVR surgery is being performed in Australia.

Cost, infrastructure and economic consequences	In New Zealand, a National Health Committee technology note reported that the price of one device was approximately NZD $16,000 in 2008.11 Pricing information has been requested from the manufacturers of both the Perceval S™ (Sorin Group, Italy) and 3f Enable® (Medtronic, USA) devices; however, no response has been received. During the 2010-2011 fiscal year, the average cost of heart valve replacement surgery in Australia was $47,012, including both hospital and medical service related charges.19 TAVI procedures have been reported to cost €43,600 (approximately $56,200 Australian dollars, 2012).20 Table 8 in the report (available on the weblink) provides claims data for MBS 38488 (heart valve replacement).
Ethical, social, legal political and cultural impact	No ethical, cultural or religious considerations were identified.

Evidence and Policy

Clinical evidence and safety	Martens et al (2011)4 Study description This prospective, multi-centre case series aimed to assess the safety and effectiveness of the ATS 3f Enable® sutureless bioprosthesis in patients undergoing AVR with or without concomitant procedures. A total of 140 patients across 10 sites were enrolled between March 2007 and December 2009 (prior to CE approval in 2010). Indications for surgery included degenerative native aortic valve disease (n=113; 81%), rheumatic heart disease (n=24; 17%), abnormality related to prior endocarditis (n=1; 1%) and other aortic valve pathology (n=2; 1%). There were a number of exclusion criteria such as active endocarditis or other systemic infections and life expectancy ≤ 24 months. Mid-term results are reported, with a total accumulated follow-up of 122 patient-years. Almost two thirds of patients were female (n=87; 62%), mean age was 76.1 ± standard deviation of 5.7 years. A complete physical examination, routine chemistry panel and transthoracic echocardiogram (TTE) were performed at the time of hospital discharge, 3-6 months post implantation, 11-14 months post implantation, and annually thereafter. No pre-operative values relating to mean and peak gradient and left ventricular cardiac output were provided. Pre-operative comorbidities were common, the most prevalent being systemic hypertension (n=120; 86%), coronary artery disease (n=77; 55%), hyperlipidemia (n=64; 46%) and diabetes mellitus (n=43; 31%). Safety Adverse events were divided into 'early' (less than 30 days postoperatively) and 'late' (more than 30 days postoperatively). Late adverse events were expressed as the number of events according to the total length of follow-up in patient-years. Five of 140 patients (4%) died within 30 days of surgery; two were classified as valve-related. One of these patients died of multi-organ failure and one of biventricular heart failure. Early non-fatal adverse events consisted of a single case of cerebrovascular accident (1%), major paravalvular leak (PVL) prompting valve explantation in three patients (2%), and minor PVL not requiring surgical intervention in a further three patients (2%). In the late postoperative period there were thirteen deaths, two of which were valve-related (2% per patient-year) and resulted in sudden cardiac death. The causes of the remaining eleven deaths were not reported. Late adverse events consisted of major PVL in one patient (1% per patient-year) prompting valve explantation, and endocarditis in three patients (3% per patient-year). Effectiveness Valve implantation was achieved using one suture in 119/140 (86%) patients, whereas three patients (2%) required two or more. Seventeen patients (12%) did not require sutures. No valve migration or tilting was noted post-implantation. Concomitant procedures were performed in 42 patients (30%), and consisted primarily of coronary artery bypass grafting (n=26; 19%), subvalvular myectomy (n=6; 4%) and left atrial appendage closure (n=5; 4%). Complete median sternotomy was required in 112 patients (80%), with the less invasive partial upper sternotomy performed on 28 patients (20%). Mean aortic cross-clamp and CPB times were approximately 60 and 85 minutes, respectively (two centres reported mean cross-clamp and CPB times as low as 37 and 55 minutes for their stand-alone procedures (n = 34)). Cumulative freedom from valve-related mortality and total mortality at one year, were 97 per cent and 85 per cent, respectively. The value of all haemodynamic parameters gradually decreased over time following hospital discharge (see Table 5 in the report on the weblink). The severity of cardiac disease was assessed both before and after surgery using the New York Heart Association (NYHA) functional capacity scale. Results demonstrate significant improvement post-surgery compared to baseline ($p<0.0001$). Prior to surgery, 62 per cent of patients were NYHA class III or IV, dropping to 1 per cent at 11-14 months after surgery. Subsequently, the proportion of patients classified as NYHA class I or II increased from 33 per cent pre-operatively to 99 per cent at 11-14 months postoperatively ($p<0.001$). The authors commented that early haemodynamic data were comparable to those obtained with conventional stented valves.

Folliguet et al (2012)18
Study description
This case series was a prospective, multi-centre study assessing the safety and effectiveness of the Perceval S™ sutureless bioprosthesis in patients undergoing AVR. A total of 211 patients aged > 65 years were enrolled between January 2007 and September 2011. Three patients were excluded from the analysis after receiving a larger annulus (>25 mm) during the procedure, resulting in a final cohort of 208 patients. The indication for surgery was degenerative native aortic valve disease in all cases.
Mean patient age was 79 ± 5.3 years, and 141 of included patients (68%) were female. In contrast to Martens et al (2011)4, patients were only eligible for inclusion if they were of NYHA class III (90%) or IV (10%).
In this mid-term analysis, mean follow-up was 10 ± 20 months, producing a cumulative total of 156 patient-years. Haemodynamic parameters were assessed using echocardiography before surgery, at discharge and during follow-up.
Safety
Adverse events were stratified as either early (less than 30 days postoperatively) or late (more than 30 days postoperatively). For the late postoperative period, adverse events were calculated as the number of events per 100 patient-years of patient exposure.
There were no intra-procedural deaths. Five patients (2%) died during the hospital stay; however, none were considered to be valve-related. Twenty patients died during follow-up but it was not specified how many deaths were valve-related.
Nine patients (4%) experienced peri-operative PVL, seven of which were subsequently treated with a Perceval S™ bioprosthesis and two with a stented bioprosthesis. A further nine patients (4%) experienced postoperative PVL which required reoperation; seven occurred between postoperative days 2-13, one occurred on day 163 and one on day 576. Minor PVL was observed in five patients (2%), the incidence of which was not separated into early and late cases.
There were nine early (4%) and four late (2%) instances of bleeding, all of which required transfusions. During follow-up, 10 cases of thromboembolism occurred, consisting of strokes (n=2; 1%), transient ischemic attack (n=1; 0.5%), limb embolism (n=3; 1%), pulmonary embolism (n=2; 1%) and retinal embolism (n=1; 0.5%).
Pericardial effusion requiring drainage occurred in four patients (n=2%), sepsis requiring antibiotics in 18 patients (8%), and heart failure requiring inotropic drugs in five patients (2%). Endocarditis was diagnosed in three patients (1%), two of whom required surgery. Pacemaker insertion for atrioventricular block was necessary in 16 patients (7%). There was no valve tipping or migrating, structural prosthetic deterioration, valve thrombosis, or significant transvalvular aortic regurgitation during the study period.
Effectiveness
Implantation was successful in 199 of 208 (96%) patients. Forty-four patients (21%) received concomitant coronary revascularisation, while 48 patients (23%) received concomitant coronary artery bypass graft (CABG) surgery. The majority of patients (163/208; 78%) required median sternotomy with the remainder (45/208; 22%) undergoing less invasive mini-sternotomy. Mean cross-clamp and CPB times were 33.5 ± 13.8 minutes and 54.5 ± 24.2 minutes, respectively.
Cumulative freedom from valve-related mortality was 87 per cent at 1 year, 82 per cent at 2 years, 82 per cent at 3 years, and 70 per cent at 4 years.
A decrease in aortic pressure gradient and increase in orifice area were observed via TTE at all follow-up time points (see Table 6 in the report on the weblink).
Prior to implantation, all patients were NYHA class III or IV. In contrast, only 18 per cent were NYHA class III or IV at the 1-year and 2-year follow-up visits ($p<0.0001$).
Breitenbach et al (2010)8
Study description
This multi-centre pilot study assessed the safety and effectiveness of AVR using the Trilogy™ system. Thirty-two patients were enrolled between November

	2006 and November 2008. Mean patient age was 71.7 ± 6.5 years, and 18 of the 32 patients were female (56%). All patients were followed up at 4-6 months, 11-14 months, and annually thereafter. Sixteen of 32 patients (50%) were NYHA class III or IV prior to surgery. No information was provided regarding surgical indication, baseline disease severity or baseline echocardiography. Safety There were no intraoperative deaths. One patient died of lung cancer during the follow-up period and there was an additional death unrelated to the AVR (cause of death not provided). A second patient developed endocarditis 22 months postoperatively due to a 1.5 cm vegetation at the non-coronary cusp with an abscess below the SecuRing component of the Trilogy™ system. Reoperation was performed using an aortic homograft and the patient had an uneventful postoperative course. Effectiveness Mean CPB and cross-clamp times were 111 ± 42 minutes and 70 ± 23 minutes, respectively. Valve implantation was successful in 30 out of 32 patients (94%); however, explantation of the valve was required in two patients (6%) due to the inability of the SecuRing to effectively seal the valve crown. This resulted in severe leakage between the gasket and crown in one of the two patients (3%), and device failure in the other patient (3%); both patients were converted to conventional AVR. Concomitant CABG surgery was performed in six patients (19%). Reductions in mean and peak gradient, and left ventricular outflow diameter, were observed during follow-up (see Table 7 in the report on the weblink). During this same period, effective orifice area increased; however, no measure of statistical significance was provided. At baseline, 16 out of 32 (50%) patients were NYHA class III or IV; whereas, at discharge, only 3 out of 29 (10%) patients were NYHA class III. At 11-14 months, only one of 27 patients (4%) was NYHA class III, with the majority (22/27; 82%) being NYHA class I.
Economic evaluation	
Ongoing research	Several clinical trials have been identified involving sutureless AVR devices, namely the 3f Enable®, Perceval S™ and Edwards INTUITY™ (details see Table 9 in the report available on the weblink); however, study completion dates, where reported, are two years or greater. On 1 May 2012, the Montreal Heart Institute (MHI) performed minimally-invasive sutureless AVR (5 cm incisions) on two patients using the Perceval S™ device and both surgeries were successful. As a result, the MHI is planning on performing 30 similar procedures in the coming year on elderly patients at high surgical risk.23 Several procedures using sutureless AVR devices have been performed in New Zealand.11
Ongoing or planned HTA	Although there are no comparative data, and completion dates for ongoing studies are distant, the diffusion of this technology may progress in the near future. As such, HealthPACT recommended that the technology be monitored for 24 months.
Web link	http://www.health.qld.gov.au/healthpact/

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Notes	In 2008, Medtronic and Arbor Surgical Technologies Inc. signed an exclusive global licencing agreement under which the Trilogy™ sutureless AVR device would be manufactured, marketed and distributed by Medtronic.21 Subsequent to this statement, Medtronic signed an agreement to acquire ATS Medical (29 April 2010), thereby inheriting the 3f Enable® platform.22 No evidence is available to suggest that the Trilogy™ sutureless AVR device is being manufactured or used at this time.