Register ID WP136
Name of Technology ExoVasc® External aortic root support
Purpose and target group The treatment of aortic distension in patients with Marfan syndrome
Speciality Cardiovascular disease and vascular surgery
Technology type Device
Setting Specialist hospital

Stage of development in Australia
- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Investigational
- Should be taken out of use
- Nearly established

Australian Therapeutic Goods Administration approval
- Yes
- No
- Not applicable

International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
<tr>
<td>Belgium</td>
<td>✔️</td>
</tr>
<tr>
<td>UK</td>
<td>✔️</td>
</tr>
</tbody>
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Impact summary
The external aortic root support device, ExoVasc®, has been developed by Exstent Limited for the treatment of aortic distension in patients with Marfan syndrome. The device is tailored to the anatomy of the patient’s aorta, and provides support to the distended vessel to reduce the risk of aneurysm formation, dissection and rupture. The procedure is an alternative to radical aortic replacement surgeries.

Evidence is limited to three low-level included studies which are based on a single cohort of twenty patients. The results of the studies are limited by a small number of patients and short-term follow-up (to a median of 20 months). There are occasional
adverse events: two patients required additional surgery as a result of ill-fitting devices. There were no deaths and no devices required removal. The device appeared to maintain aortic diameter, and may provide a less invasive option to Marfan patients who risk aortic distension and rupture.

Background
Marfan syndrome is an autosomal dominant disorder of the connective tissues. The syndrome is typically caused by mutations in gene FBN1, which encodes the connective tissue protein fibrillin-1. The disease is highly variable in its presentation between patients; clinical features commonly appear with age, primarily involving the cardiovascular, skeletal and ocular systems. The cardiovascular features of the syndrome range from mild to severe. Common symptoms may include fatigue, dyspnoea, palpitation, tachycardia, arrhythmia and angina. Progression of the syndrome results in mitral and aortic regurgitation, degeneration and prolapse of valves. The clinical features of the advanced disease are aortic dilatation and aneurism leading to aortic dissection and rupture.

Aortic dissection in Marfan syndrome has a high risk of mortality (reported at 50–70% survival at 10 years). It occurs due to tears in the inner wall of the aorta caused by the inability to make normal fibrillin. Over time the tears expand causing bleeding into and along the aorta wall and leading to further aortic dilatation, aneurism and aortic rupture. Rupture of the aorta is the most common cause of death (approximately 70%) among patients with Marfan syndrome.

Pathological dilatation of the aorta and dissection are commonly managed by prophylactic ascending aorta replacement. Total aortic root replacement (TARR) is considered the ‘gold standard surgery’, although the procedure carries a risk of death of 1–2 per cent. During the procedure, the aortic valve is also removed and the root replaced with a composite mechanical valve conduit graft. Coronary arteries are reimplanted if total aortic root replacement is performed. Cardiopulmonary bypass with full heparanisation is required.

The timing of the surgery is predicted based on history of the disease. The size of the aorta and its rate of dilation is monitored from an early stage using echocardiography until the aortic root diameter reaches 5 cm, or 4.5 cm in the presence of other risk factors (such as family history or rapid aortic growth). If the diameter of the aorta remains constant, the risk for aortic dissection or rupture is likely to be reduced.

External aortic root support (EARS) is a new device for the treatment of aortic dilatation. High quality digital magnetic resonance images of each patient’s aortic root are used to manufacture a former, shaped to the individual’s anatomy, using a dedicated computer-aided design (CAD) routine. This is used as the basis to make a
bespoke mesh external support which exactly fits the patient’s aorta (Figure 1). The external support has a vertical seam and is manufactured from a medical-grade polymer mesh. During the procedure the EARS is used to wrap the root of the aorta, from the aortoventricular junction to beyond the brachiocephalic artery. The device may obviate or at least postpone the need for aortic replacement surgery.

The procedure of insertion of the device to the ascending aorta is a less invasive surgery compared to conventional TARR. The mesh support is sutured into place around the ascending aorta via a median sternotomy. During the procedure the aorta and coronary arteries are left intact; therefore, patients have a minimum risk of thromboembolism and stroke. The procedure is likely to require less blood and fewer blood product transfusions compared to TARR. In addition, cardiopulmonary bypass or suppression of coronary circulation is not necessary to perform EARS surgery.

In terms of total procedure time, conventional TARR takes about five to seven hours, whereas EARS takes approximately two hours. Following implantation of EARS, ongoing medication, including anticoagulation therapy, is not required. As a result, EARS may allow young women to become pregnant and undergo C-section.

EARS was introduced and manufactured by Exstent Limited. The initial trial began in 2004 and was completed in June 2009, based at the Royal Brompton Hospital, London, United Kingdom (UK). The current prototype of EARS device is marketed as ExoVasc®.

Clinical need and burden of disease
Marfan syndrome is the most common inherited connective tissue disorder and has a world-wide prevalence of 1 in 5,000 live births. Data from the Australian Institute of Health and Welfare (AIHW) shows that for the primary diagnosis of
Marfan syndrome (ICD-10-AM code Q87.4) there were 15 separations in 2009–10, and 15 separations in 2008-09.11

**Diffusion of the technology in Australia**

Diffusion of the device is self-limiting, as the device is custom-made according to each patient’s aortic measurements. It is not entitled to the CE mark.9 The device ExoVasc® is not registered with the Federal Drug Administration (United States of America), the European Medicine Agency (European Union) or the Therapeutic Goods Administration (Australia). The procedure has been the subject of a National Institute for Health and Clinical Excellence (NICE) interventional procedures overview (IP 885)12 and interventional procedure guidance (394, issue date May 2011)13 which indicate that the procedure should only be undertaken with special arrangements for clinical governance, consent and audit or research.

A focused search on the use of the device in Australia did not identify any published local use. The procedure appears not to be undertaken in Australia, and no local trials are underway (Professor J Smith, personal communication).

**Comparators**

There are two main comparators to EARS: TARR and valve-sparing aortic root replacement (VART).

Defined by the first operation performed by Bentall at Hammersmith Hospital in the 1960s, TARR is currently the gold standard surgery to prevent and treat dissection of the ascending aorta.14 During the surgery, the ascending aorta and aortic valve are removed and replaced with an artificial Dacron graft incorporating a mechanical or bioprosthetic aortic valve. The operation is named after Bentall. To prevent blood clots forming on the graft or valve the patient has to take ongoing anticoagulant therapy. The implication for an active lifestyle and childbearing versus the risk of thromboembolism from the mechanical valve is an important consideration.

In VART surgery the aortic root is replaced without a prosthetic aortic valve, and is possible in patients who have isolated root pathology with functionally normal valve leaflets.15 The technique preserves native valves, so bears less risk for thromboembolism; however, this procedure may be prone to valve failure and re-intervention as a result of Marfan progression.16 17

Clinical expert input indicates that both TARR and VART are available in Australia for the treatment of aortic root dilatation in Marfan syndrome. TARR is the most common approach, due to the concern regarding progressive aortic valve degeneration. The final decision would be based on patient presentation.
According to the AIHW there were 126 procedures in 2009–10 for the replacement of the ascending thoracic aorta with aortic valve replacement (ICD procedure code 38553-03). It is unclear how many of these replacements would have been undertaken in Marfan patients. There are a number of MBS items for aorta replacement and repair procedures (Table 1). TARR is commonly utilised via MBS item 38556 in the current context; in the presence of aortic dissection or rupture MBS item 38572 would be used. In 2011–12 there were 286 services for repair or replacement of the ascending thoracic aorta, with aortic valve replacement or repair (MBS item 38556). During the same year 57 items were used for management of acute rupture or dissection (MBS item 38572). However, it is unclear how many of these services would have been provided to Marfan patients.

Table 1  Aorta repair procedures currently on the MBS list

<table>
<thead>
<tr>
<th>Item number</th>
<th>Description</th>
<th>Full fee</th>
<th>75%</th>
<th>Total services (2011–12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38550</td>
<td>ASCENDING THORACIC AORTA, repair or replacement of, not involving valve replacement or repair or coronary artery implantation</td>
<td>$2,106.15</td>
<td>$1,579.65</td>
<td>64</td>
</tr>
<tr>
<td>38553</td>
<td>ASCENDING THORACIC AORTA, repair or replacement of, with aortic valve replacement or repair, without implantation of coronary arteries</td>
<td>$2,669.05</td>
<td>$2,001.80</td>
<td>407</td>
</tr>
<tr>
<td>38556</td>
<td>ASCENDING THORACIC AORTA, repair or replacement of, with aortic valve replacement or repair, and implantation of coronary arteries</td>
<td>$3,046.80</td>
<td>$2,285.10</td>
<td>286</td>
</tr>
<tr>
<td>38572</td>
<td>OPERATIVE MANAGEMENT OF ACUTE RUPTURE OR DISSECTION, in conjunction with procedures on the thoracic aorta</td>
<td>$1,950.00</td>
<td>$1,462.50</td>
<td>57</td>
</tr>
</tbody>
</table>

Notes:  
* Total services reflects the number of procedures performed privately, as procedures performed in public hospitals do not require the use of an MBS item number. Consequently, there may be more activity than reflected in the MBS statistics. MBS: Medicare Benefits Schedule.

Safety and effectiveness

Three studies were included, one comparative study (NHMRC level III-3) and two case series (NHMRC level of evidence IV) that assessed the safety and efficacy of EARS. All the studies were based on the same trial, which took place at the Royal Brompton Hospital in the UK.

There was patient overlap between the studies, as they were all based on the same cohort of twenty patients. Pepper et al 2010a provided initial results of the first ten patients. Pepper et al 2010b provided results of the entire cohort of twenty patients who received treatment from 2004 to 2009. The retrospective case control study, Treasure et al compared results of the same trial with a matched group of patients who received total aortic root replacement during the same time period.
Pepper et al 2010b

Study description

The UK-based prospective case series was conducted over 2004 – 2009 to assess safety and efficacy of EARS patients in twenty patients with Marfan syndrome. Patient inclusion criteria were aortic root diameter of 40 – 55 mm without clinically important aortic regurgitation. No patient was excluded for any other technical reason. Study outcomes were not predefined. Out of the 20 patients who received the device, 13 were male. The patients were 16 – 58 years old (median 33 years). Each patient had a device custom-made from magnetic resonance imaging (MRI) images of their aorta taken pre-operatively. Patients were followed for a median of 20 months (range 0 – 67 months). The authors compared the EARS treatment with 28 consecutive patients who underwent total aortic replacement of the ascending aorta. This comparison was not formally planned within the study design. Seven of this cohort had Marfan syndrome and 21 had other pathologies. Of the patients with Marfan syndrome, two received TARR and the remaining five received valve-sparing operations.

Safety

No deaths following the procedure were recorded at the time of last follow-up. In no patient was there a need to convert to root replacement or other form of surgery.

Two patients experienced technical problems. One patient experienced postoperative cardiac arrest with ventricular fibrillation. The circulation was restored after additional surgery to remove the anterior closing suture on the EARS device to prevent complications. Misinterpretation of MRI images of coronary artery origins appeared to have led to this difficulty. The patient recovered and was discharged eight days after surgery. The second patient experienced a technical problem due to an anatomical anomaly of the coronary arteries which was identified during the initial operation. Additional imaging was undertaken to clarify the anatomy, and the EARS was completed as planned in the following week.

Cardiopulmonary bypass was used for 20 minutes in the first patient only. The reasons for this requirement are not reported.

Effectiveness

In terms of procedural effectiveness, patients who received EARS did so comparatively within a shorter operation time. Median operation time to perform EARS was 148 minutes (range 125 – 415 min) compared to the patients treated by aortic root replacement (median 374 min, range 240 – 493 min, n=7). Only the first patients who received EARS required cardiopulmonary bypass, which was required
for 20 minutes. In contrast, patients who received aortic root replacement required 139–323 minutes of bypass and 100–243 minutes of cross-clamp. EARS patients were discharged sooner compared to the comparator group. Median length of stay for EARS patients was 6 days (range 3–16), while aortic root replacement patients were hospitalised a median of 8 days (range 4–119 days). The anticoagulant warfarin was administered to three non-EARS patients for the potential risk of thromboembolism. None of the EARS patients required warfarin.

Postoperative follow-up at a median of 20 months on 16 EARS patients showed a median aortic root reduction of 1 mm (inter quartile range -2 to +1 mm).

Pepper et al 2010a

Study description
This study reports data of the initial 10 patients as reported in Pepper et al 2010b who received EARS in the Royal Brompton Hospital between May 2004 and March 2007.6

Prospective technical data was reported. The ascending aorta at the level of closure of the aortic valve cusps was measured using MRI preoperatively and at one-year follow-up. Images were also taken from 37 randomly-selected Marfan patients in order to provide an indication of measurement error and were examined by a blinded, experienced radiologist. The largest difference in aortic root diameter was calculated.

Safety
No deaths, late events or detected changes in aortic valve function were reported. Arrhythmia (transient atrial fibrillation) was recorded in two patients.

Effectiveness
Eight of the ten EARS patients showed a reduction in the diameter of the aortic root of up to 1.2 cm. Statistical analysis was not undertaken.

Treasure et al19
This retrospective case control study by Treasure et al19 compared the first 20 patients who received EARS at Royal Brompton Hospital (London, UK) with matched patients of similar age, aortic diameter and aortic valve function, who received conventional aortic replacement surgery during the same time period (between May 2004 and December 2009). Patients in the EARS group were aged 16–58 years while those in the comparison group were 18–63 years old. Aortic root diameters were 40–54 mm in the EARS group and 38–58 mm in the aortic root replacement group. Patients in the aortic root replacement group were excluded if they had repeat
cardiac surgery, aortic root diameter beyond the range 4–5.5 cm, or aortic regurgitation. Sixteen patients had valve-sparing surgery and four received TARR with composite valved grafts.

**Safety**

There were no deaths, late events or detected changes in aortic valve function in either patient population.

**Effectiveness**

Details of the reported procedural outcomes are provided in Table 2. All procedural outcomes were improved in favour of the EARS patients. Statistical analysis was not reported.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effectiveness outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>EARS</strong></td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass</td>
<td>0 (0-20) min</td>
</tr>
<tr>
<td>Myocardial ischaemic time</td>
<td>0 (0-0) min</td>
</tr>
<tr>
<td>4h blood loss</td>
<td>50 (25-400) ml</td>
</tr>
<tr>
<td>Patients required blood transfusion</td>
<td>1/20</td>
</tr>
<tr>
<td>Patients required platelet transfusion</td>
<td>0/20</td>
</tr>
<tr>
<td>Patients required frozen plasma transfusion</td>
<td>0/20</td>
</tr>
</tbody>
</table>

EARS: External aortic root support; TRR: Total root replacement.

**Cost impact**

No studies assessing the cost-effectiveness of external aortic root support in the treatment of aortic dissection in patients with Marfan syndrome were identified.

The manufacturer, Extent Limited, confirmed that:

for each patient, costs incurred in preparing an ExoVasc include the preparation from the CT image data of a CAD model the patient’s aorta and the production of a rigid former of the aorta on which is formed the porous, textile implant.

To allow for loss or damage to one implant in the operating room, the manufacturer supplies two sterile implants for each patient. Preparation and supply of a pair of ExoVasc implants personalised for a single patient is charged at £6,500 (approximately A$10,110 (at an exchange rate of A$1=£0.643)). The costs of surgical implantation are unclear.

For the comparator procedures, the 100 per cent MBS service fee for repair or replacement of the ascending thoracic aorta with aortic valve replacement or repair
is A$3,046.80 (Table 1). This fee does not include associated hospital costs or the costs of the prosthesis. The total cost for coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass in a tertiary cardiothoracic centre in the United Kingdom has recently been estimated at $7,431 \textsuperscript{21} (approximately A$11,559). However, it must be noted that aortic replacement surgery is more complex, takes longer and has greater risks than CABG, therefore is likely to cost more.

**Ethical, cultural or religious considerations**

No ethical, cultural or religious concerns were identified relating to the use of the external aortic root supports. Due to the relatively rare nature of Marfan syndrome, high quality trials or EARS with large numbers of participants may not be possible.

**Other issues**

Change in the diameter of the aorta is the most important variable determining the likelihood of dissection in Marfan syndrome. Studies with long-term follow-up are necessary to inform on the stability of aortic root diameter in EARS patients.\textsuperscript{12}

Clinical trial databases - clinicaltrials.gov, Current Controlled Trials (www.controlled-trials.com), WHO International Clinical Trials Search Portal (www.apps.who.int/trialsearch/) and Australian New Zealand Clinical Trials Registry (www.anzctr.org.au) were searched using the terms EARS or ExoVasc to identify trails currently in progress. No trials were identified as of 24 September 2012.

One of the authors, Tal Golesworthy, is a shareholder and director of Exstent limited, which holds intellectual property in the EARS project. He is also the first recipient of EARS.\textsuperscript{20} Professor John Pepper, a consultant surgeon of Royal Brompton Hospital and Harefield NHS Trust, and Professor Tom Treasure are clinical advisors to the Exstent Limited and also authors of the included studies.

Current guidelines of NICE (UK) indicate that the procedure should be only used with special arrangements for clinical governance, consent and audit or research.\textsuperscript{13} In the UK, the procedure appears to be undertaken under local health board approval and is subject to formal progress and adverse events reporting.

**Summary of findings**

The evidence included in this technology brief is limited by a single patient cohort of twenty patients. Based on this cohort, no deaths, late events or detected changes in aortic valve function were reported following placement of the device. However, two adverse events were reported: a postoperative cardiac arrest that was resolved after removing the anterior closing suture on the device, and one technical problem of an ill-fitting device that necessitated a second procedure for successful implantation.
The studies did not provide a long-term comparison of change of ascending aorta diameter, which is likely to be the primary outcome of interest. Median 20 month follow-up on 16 patients showed a median aortic root reduction of 1 mm;\(^6\) therefore, aorta diameter can be maintained. Comparison with a matched cohort who underwent aortic root replacement surgery showed that the EARS procedure is much less invasive than aorta replacement surgery, including avoidance of cardiopulmonary bypass and a reduced risk for myocardial ischemia.

**HealthPACT assessment**

Based on the evidence from low-level studies which were based on a single cohort of 20 patients, and given the potential uptake of the device is very low, it is recommended that the technology brief be archived.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT web site.

Total number of studies: 3
Total number of level III-3 studies: 1
Total number of level IV studies: 2

**References**


effectiveness and quality-adjusted life years in a randomized controlled trial'.
*Artif Organs*, 32 (11), 891–7.

**Search criteria to be used (MeSH terms)**
Marfan Syndrome (MeSH); Aorta, Thoracic (MeSH); Aortic Aneurysm, Thoracic (MeSH); Aneurysm, Dissection (MeSH).