NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of personalised external aortic root support (PEARS) using mesh to prevent aortic root expansion and aortic dissection in people with Marfan syndrome

Marfan syndrome is a genetic disorder in which the large artery from the left side of the heart (the aorta) can expand to the point where the inner lining can tear, risking a fatal rupture. In this procedure, which is done under general anaesthesia, the chest is opened through the breastbone. A mesh is then wrapped around the outside of the aorta at the part closest to the heart (the aortic root). The aim is to support the aorta to stop it from expanding and reduce the risk of rupture.

Contents

Abbreviations

Word or phrase	Abbreviation
cardiovascular magnetic resonance	CMR
confidence interval	CI
New York Heart Association	NYHA
Personalised external aortic root support	PEARS
standard deviation	SD

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2021 and updated in February 2022.

Procedure name

- Personalised external aortic root support using mesh to prevent aortic root expansion and aortic dissection in people with Marfan syndrome

Professional societies

- Society for Cardiothoracic Surgery in Great Britain & Ireland
- British Cardiovascular Society.

Description of the procedure

Indications and current treatment

Marfan syndrome is a genetic disorder of the connective tissues. One effect of this is that the wall of the aorta can weaken and progressively widen. This may lead to tears in the wall of the aorta (dissection) and possible rupture, which is often fatal. The strongest predictors of dissection are the aortic root size and the rate of change in size over time.

The conventional treatment involves pre-emptive surgery to replace the ascending aorta with an artificial fabric graft. Some clinicians recommend this when the aortic diameter is 45 mm or more. The aortic valve is also usually replaced but may be conserved. Patients can experience considerable anxiety waiting for their aorta to reach the size threshold recommended for surgery.

If the patient has a mechanical valve implanted, they need lifelong anticoagulation. If a bioprosthetic valve is used, it is likely to eventually fail and the patient will need another operation. Valve-sparing root replacement surgery, in which the aorta is replaced with a tube graft and the native aortic valve is conserved, is also suitable for some patients with normal valve function. This is technically more challenging, and patients may need further surgery to replace the aortic valve at a later date.

What the procedure involves

The aim of personalised external aortic root support (PEARS) using mesh in people with Marfan syndrome is to reinforce the aortic root and ascending aorta to prevent enlargement and subsequent dissection or rupture. The native aortic valve is left intact so there is no need for lifelong anticoagulation after the procedure. This is a particular advantage for young women considering future conception. Cardiopulmonary bypass is usually not needed, and the operative time is shorter than traditional aortic root replacement.

The first step of the procedure is to do imaging studies of the patient's ascending aorta and aortic root. Computer-aided design is used to create a 3-dimensional model of the aorta, which is then used to make a bespoke external polymer mesh support. The mesh is soft, flexible and porous. Openings for the coronary arteries are fashioned into the mesh support.

Under general anaesthesia, a median sternotomy is done and the aorta is dissected away from adjacent structures and proximal to the coronary arteries. The mesh support is passed behind the aorta, sutured up the front and secured

to the aortoventricular junction. It fully encircles the aortic root and extends from the region of the valve annulus to the origin of the brachiocephalic artery.

Efficacy summary

Survival

In a cohort study of 200 patients (147 with Marfan syndrome), the estimated survival at 1, 2 and 3 years after PEARS was 98.3%, 97.6% and 97.6% respectively (Van Hoof 2021).

In a cohort study of 117 patients who were followed up for at least a year (range 2 to 12 years), 94% (110/117) of patients were alive with PEARS only, 2% (2/117) of patients were alive after revision surgery for progression of aortic regurgitation (at 93 and 105 months) and 2% (2/117) of patients had died (1 at day 5, described further in the safety section, and the other at 4.5 years after the procedure, which was related to an arrhythmia). In the 2 patients who had revision surgery, the right and non-coronary sinuses were not completely covered by the mesh because of deviations from the protocol for intraoperative reasons (Pepper 2020).

A total of 3 deaths were reported in a case series of 317 patients who had a personalised external aortic root support procedure (57% of whom had Marfan syndrome). In addition to the 2 deaths described above and in the safety section, 1 patient died 6.5 months after the procedure from chronic heart failure (Nemec 2020).

In a cohort study of the first 30 patients to have the procedure, cumulative survival at 7 years was 100% (Treasure 2014).

Ascending aortic dissection

In the cohort study of 200 patients, no ascending aortic dissections were observed at median follow up of 21.2 months (Van Hoof 2021).

Aortic regurgitation

In the case series of 24 patients, there was no increase in the percentage of patients with mild aortic regurgitation (33% [8/24] at baseline), and no patient had an increase in the severity of aortic regurgitation at follow up (Izgi 2018).

Aorta diameter

In a case series of 24 patients, there was no increase in the aortic root and ascending aorta diameters at mean follow up of 6.3 years. In the same period, the mean descending aorta diameter increased from 22.6 mm to 23.9 mm (change 1.25 mm, 95% CI 0.65 to 1.85 mm; p<0.001; Izgi 2018).

Histological appearance

In a case report of a patient who died 4.5 years after having an external aortic root support procedure, the aortic arch and descending aorta appeared normal. The external aortic mesh was fully incorporated in the adventitia and could not be separated from it. The supported aortic root had the histological appearance of a normal aorta. The histological appearance suggested the possibility that the incorporated support of the aortic root allowed recovery of the microstructure of the media. The cause of death was dilated cardiomyopathy, presumed to be related to Marfan syndrome (Pepper 2015).

Safety summary

Perioperative mortality

Perioperative mortality was reported in 1 patient with Marfan syndrome in a case series of 317 patients who had a procedure to insert a personalised external aortic root support. The patient had severe pectus excavatum and died 5 days after surgery because of an injury to the left coronary artery. The support was not placed during the surgery (Nemec 2020). This patient was also described in the cohort studies of 30 and 200 patients (Treasure 2014, Van Hoof 2021).

Vascular injury

Injury to the left coronary artery was reported in 1 patient in the case series of 317 patients. This was successfully resolved with coronary artery bypass grafting (Nemec 2020). Coronary injury was reported in 3.0% (6/200) of patients in the cohort of 200 patients (Van Hoof 2021).

Intraoperative aortic dissection was reported in 1 patient in the cohort study of 200 patients; this was treated conservatively (Van Hoof 2021).

Ischaemic events

Intraoperative ischaemic events and perioperative transient ischaemic attack related to atrial fibrillation were each reported in 2% (2/117) of patients in the cohort study of 117 patients (Pepper 2020).

Cerebrovascular event with hemiparesis was reported in 1.0% (2/200) of patients in the cohort study of 200 patients; both patients recovered completely (Van Hoof 2021).

Myocardial infarction

Myocardial infarction was reported in 2.5% (5/200) of patients in the cohort study of 200 patients (Van Hoof 2021).

Reoperation

Reoperation because of hypotension while in the intensive care unit was reported in 1 patient in the case series of 317 patients who had a procedure to insert a personalised external aortic root support. The axial suture line of the mesh implant was partially released. After 6 years, aortic valve regurgitation developed, and the patient had surgery to correct dilation of the non-coronary sinus. The mesh-reinforced aortic wall was identified and could be cut and sewn safely. A second patient had a reoperation because of acute heart failure immediately after the procedure caused by occlusion of his circumflex coronary artery. The support was adjusted, and a stent was implanted in the artery (Nemec 2020).

Blood transfusion

Transfusion of red cells was needed in 5% (1/20) of patients who had external aortic root support and 50% (9/18) of patients who had aortic root replacement ($p=0.002$) in a non-randomised comparative study of 40 patients. None of the patients who had external aortic root support needed platelet or fresh frozen plasma transfusion compared with 50% (9/18) and 67% (12/18) of patients, respectively, who had aortic root replacement ($p<0.001$ for both) (Treasure 2012).

Inflammatory characteristics

The peak level of C-reactive protein after the procedure was 264.5 mg/L in patients who had personalised external aortic root support and 184.6 mg/L in patients who had standard prophylactic aortic root surgery ($p=0.034$) in a non-randomised comparative study of 27 patients. ST elevation (the ST segment represents the interval between depolarisation and repolarisation of the

ventricles) after the procedure was reported in 85% (11/13) of patients who had personalised external aortic root support compared with 43% (6/14) of patients who had standard prophylactic surgery (p=0.024). The proportion of patients who had fever or pericarditis needing hospital readmission was also statistically significantly higher in patients who had external aortic root surgery compared with standard prophylactic surgery (Kockova 2019).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: short-lived postoperative pyrexia and seroma around the aorta, which resolves without intervention. They noted that if the sleeve does not cover the entire aortic root as far proximally as the aortic annulus, root dilatation will occur.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to PEARS using mesh for people with Marfan syndrome. The following databases were searched, covering the period from their start to 7 December 2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with Marfan syndrome.
Intervention/test	PEARS using mesh to prevent aortic root expansion and aortic dissection
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 180 patients with Marfan syndrome who had PEARS using mesh to prevent aortic root expansion and aortic dissection from 3 cohort studies, 2 non-randomised comparative studies, 2 case series and 1 case report (Van Hoof 2021; Pepper 2020; Treasure 2014; Izgi 2018; Treasure 2012; Pepper 2015; Kockova 2019; Nemec 2020).

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on PEARS using mesh to prevent aortic root expansion and aortic dissection in people with Marfan syndrome

Study 1 Van Hoof L (2021)

Study details

Study type	Cohort study
Country	Not reported (data were from 23 centres, including the UK)
Recruitment period	2004 to 2019
Study population and number	n=200 (147 with Marfan syndrome) Patients who had surgery with intent to use PEARS for primary aortic root dilatation.
Age and sex	Median 33 years (range 3 to 75 years); 69% (138/200) male
Patient selection criteria	Not reported
Technique	Prophylactic treatment with PEARS (ExoVasc personalised mesh support, Exstent Ltd.). 28 patients had concomitant procedures, including mitral valve repair (n=20) and off pump coronary artery bypass grafting (n=3). For 166 isolated aortic PEARS cases, cardiopulmonary bypass was used in 21.1%.
Follow-up	Median 21.2 months (range 0 to 190.5 months); clinical follow-up beyond 12 months was available for 72.1% (142/197) of patients.
Conflict of interest/source of funding	One author is the inventor of the ExoVasc device. He was the first patient to have PEARS surgery in 2004 and is a shareholder in Exstent Ltd.

Analysis

Follow-up issues: Of the 200 patients, 3 (1.5%) were lost to follow up.

Study design issues: Multicentre cohort study evaluating all consecutive patients who had surgery with an intention to perform PEARS for aortic root dilatation. Perioperative outcomes were collected prospectively and clinical follow-up was retrieved retrospectively. Surgeons were asked to provide detailed demographics, in-hospital outcomes and clinical follow-up data via anonymised spreadsheets.

Study population issues: Most patients (73.5%) had Marfan syndrome. Other indications were bicuspid aortic valve (8.5%), Loeys-Dietz syndrome (7.5%), ACTA2 mutation (1%) and idiopathic or other (9.5%). The preoperative aortic regurgitation grade was 0 or 0.5 (none or trivial) in 74.2% (147/198) of patients and 1 or 2

(mild or moderate) in 25.8% (51/198) of patients. The overall median root diameter was 47 mm (range 28 to 60 mm). For the 147 patients with Marfan syndrome, the median root diameter was 47 mm.

Key efficacy findings

Number of patients analysed: 200

Technical success

- PEARS completed=97.0% (194/200)
- Intraoperative conversion to total root replacement or valve-sparing root replacement=2.5% (5/200)
- Procedure abandoned=0.5% (1/200)

Aortic events

- No ascending aortic dissections were observed.
- A new type B dissection was identified on imaging at 3-year follow-up in 1 asymptomatic patient.

Survival

- Late deaths=2.0% (4/200); 1 patient died of heart failure unrelated to PEARS at 7 months postoperatively, 1 patient died from an unknown cause at 14 months, 1 patient died from COVID-19 at 3 years, and the other died in his sleep 4.5 years after the PEARS procedure.
- Kaplan-Meier estimates of survival at 1, 2 and 3 years=98.3%, 97.6% and 97.6%

Successful pregnancy

- 9 patients had 1 or more successful pregnancies without cardiovascular complications after the procedure.

Reoperation

- Late reoperation for failure to achieve complete coverage by the implant=1.5% (3/200)

Key safety findings

Perioperative adverse events

- Mortality=0.5% (1/200); the patient had Marfan syndrome and a severe pectus deformity. The procedure was abandoned after the left main stem was injured.
- Intervention for ischaemia or coronary injury=5.5% (11/200); coronary impingement was caused by the implant in 2 patients and coronary injury happened in 6 patients. In 3 patients, the adverse event was not caused by the implant.
- Myocardial infarction=2.5% (5/200)
- Intraoperative aortic dissection=0.5% (1/200) (treated conservatively)
- Cerebrovascular event with hemiparesis=1.0% (2/200) (attributed to atrial fibrillation after off-pump PEARS; both patients recovered completely)

Study 2 Pepper J (2020)

Study details

Study type	Cohort study
Country	Not reported (data were from 14 surgical teams, including the UK)
Recruitment period	2004 to 2017
Study population and number	n=117 Patients with life threatening aortic root aneurysm
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: aortic root/sinus of Valsalva and ascending aorta asymptomatic dilation of 40 to 50 mm in diameter in patients aged 16 and over. Patients with more than mild aortic regurgitation were excluded.
Technique	Prophylactic treatment with PEARS (ExoVasc personalised mesh support, Exstent Ltd.). 73% of procedures were done without cardiopulmonary bypass. An undersized mesh (95%) was used in some patients to correct aortic regurgitation. Of the 117 patients, 97 (83%) had personalised aortic root support alone, 12 patients also had mitral valve repair and 3 patients also had coronary artery bypass graft surgery. The operation was converted to a different procedure in 4 patients and was aborted in 1 patient.
Follow-up	At least 1 year (range 2 to 12 years)
Conflict of interest/source of funding	One of the authors is the inventor of the device. He was the first patient to have the procedure in 2004, and is a shareholder in Exstent Ltd.

Analysis

Follow-up issues: The follow up interval was from the date of surgery to the date on which the patient was last clinically assessed or had cardiac investigations. Relatively few patients had long term follow up because most patients were recruited in more recent years. There were no losses to follow up.

Study design issues: Retrospective analysis of prospectively collected multicentre data. The Kaplan-Meier method was used to estimate survival and reoperation rates. Follow up included annual MRI scans.

Study population issues: Of the 177 patients, 94 (80%) had Marfan syndrome. Other aetiologies included Loeys Dietz (n=5), bicuspid aortic valve (n=8), non-syndromic (n=9) and post-mechanical aortic valve replacement (n=1). About 25% of patients had some aortic regurgitation before the procedure.

Key efficacy findings

Number of patients analysed: 117

IP overview: Personalised external aortic root support (PEARS) using mesh to prevent aortic root expansion and aortic dissection in people with Marfan syndrome

Survival

At the time of reporting, 94.0% (110/117) of patients were alive with PEARS only, 1.7% (2/117) of patients were alive after revision surgery for progression of aortic regurgitation (at 93 and 105 months) and 1.7% (2/117) of patients had died (1 at day 5, which is described in the safety section below, and the other at 4.5 years after the procedure, which was related to arrhythmia).

In the 2 patients who had progression of aortic regurgitation and needed revision surgery, the right and non-coronary sinuses were not completely covered by the mesh because of deviations from the protocol for intraoperative reasons.

Key safety findings

Perioperative adverse events

- Repositioning of external support, n=1
- Release of sleeve, n=1
- Coronary injury, n=1
- Perioperative transient ischaemic attack related to atrial fibrillation, n=2
- Intraoperative ischaemic events, n=2 (resulting in 19- and 25-day hospital stays)
- Death, n=1 (at day 5, caused by damage to the left main stem at operation; also described above)

Apart from the patient who died, all 7 patients who had perioperative complications made a complete recovery.

There were no major bleeding events and only 1 superficial wound infection.

Study 3 Treasure T (2014)

Study details

Study type	Cohort study (and comparison with published meta-analysis)
Country	UK and Belgium
Recruitment period	2004 to 2011
Study population and number	n=30 Patients with Marfan syndrome
Age and sex	Mean 32 years; 67% (20/30) male
Patient selection criteria	Inclusion criteria were that patients should have little or no aortic regurgitation, and an ascending aortic root diameter of 40 to 45 mm. All patients had at least 1 year of follow up.
Technique	PEARS procedure. One patient had corrective surgery of a pectus excavatum at the time of the aortic root surgery.
Follow-up	Mean 4.4 years (range 1.4 to 8.8 years)
Conflict of interest/source of funding	One author is a shareholder and director of Exstent Ltd, which holds the Intellectual Property in the Personalised External Aortic Root Support project, the originator of the concept and the first recipient of the treatment. One author, as PhD student, worked on software development for CAD modelling (computer aided design), and continues to do this work for Exstent Ltd who manufacture the personalised supports. The project has been funded, to date, by Exstent Limited, a private limited liability company registered in the UK in July 2002.

Analysis

Follow-up issues: There were no losses to follow up.

Study design issues: Results from the first 30 patients to have a PEARS procedure were compared with a published meta-analysis of 1,385 patients who had aortic root replacement (Benedetto et al., 2011). Survival and the incidence of aortic valve-related events were compared between the 2 studies. Kaplan-Meier analysis was used for overall non-parametric survival estimates. Linearised occurrence rates were calculated by dividing the number of events by accumulated patient years and expressed as % per patient year.

Study population issues: Of the 30 patients, 29 were in NYHA class 1, and were either working or pursuing full-time study. One patient was in NYHA class 3 and unfit for work because of comorbidity predating surgery and unrelated to his aortic root disease. 87% (26/30) of patients were on medication, mostly protective treatment for their Marfan aortic disease: 19 patients were on beta blocker medication, 3 patients had ACE inhibitor or angiotensin II antagonist medication, 2 patients combined beta blocker medication with an ACE inhibitor or angiotensin II antagonist. One patient was on antidepressants and 1 was on warfarin, diuretics and beta blocker therapy. Mild aortic regurgitation was reported in 27% (8/30) patients before the procedure, 70%

(21/30) had no aortic regurgitation and data was missing for 1 patient. The mean preoperative aortic root diameter was 46.2 mm (range 40 to 54 mm).

Other issues: The authors noted that patients with severe aortic regurgitation are more likely to have total root replacement and are not candidates for external support of the aortic root using mesh, so cannot be directly compared. The external support is used at smaller aortic root size, and therefore, earlier in progression of the aortopathy than standard treatments.

Key efficacy findings

Number of patients analysed: 30

Procedural characteristics

Outcome	Result
Procedural duration, mean (range)	160 minutes (85 to 414 minutes)
Cardiopulmonary bypass, n (%); minutes	1 (3%); 20 minutes
Blood loss (n=27), mean (range)	287 ml (50 to 950 ml)
Blood products, n (%)	Blood 1 (3%); fresh frozen plasma 1 (3%); other 2 (6%)
Intensive care unit stay, mean (range)	25 hours (0 to 71 hours)
Postoperative hospital stay, mean (range)	6.6 days (4 to 16 days)
Total hospital stay, mean (range)	9.0 days (5 to 33 days)

- Cumulative survival at 7 years=100%
- During follow up, there were no cerebrovascular, aortic or valve-related events.
- There was 1 late death after completion of the analysis. A patient operated on in December 2008 at the age of 26 with an aortic diameter of 42 mm was found dead in bed in May 2013. The aorta and valve were intact and the external support was closely applied and firmly adherent to the aorta. There was no evidence of dissection. The coronaries were free of disease and without evidence of thrombosis or any other abnormality. The forensic pathologist found no cause of death but presumed this was a sudden cardiac death in the context of Marfan syndrome.

Comparison of PEARS with published results for total root replacement and valve-sparing root replacement

Outcome	PEARS (n=30)	Total root replacement (n=972)	Valve-sparing root replacement (n=413)
Mean patient age, years (SD)	31 (12)	35 (0.5)	33 (0.64)
Mean preoperative aortic root diameter, mm (SD)	46.2 (3.4)	61 (0.7)	52 (0.3)
Proportion of patients with dissection	0	0.30 (0.01)	0.18 (0.02)
Early mortality, % (95% CI)	0	4.1% (1.9 to 7.7)	3.2% (0.5 to 17.9)
Reintervention on aortic valve, % per year (95% CI)	0	0.3% per year (0.1 to 0.5)	1.3% per year (0.3 to 2.2)
Thromboembolic event, % per year (95% CI)	0	0.7% per year (0.5 to 0.9)	0.3% per year (0.1 to 0.6)
Endocarditis, % per year (95% CI)	0	0.3% per year (0.2 to 0.5)	0.2% per year (0 to 0.3)
Composite valve-related event, % per year (95% CI)	0	1.3% per year (0.6 to 2.0)	1.9% per year (0.8 to 2.9)

Key safety findings

Perioperative serious adverse events

1 patient had recurrent ischaemia on several attempts to close the suture line in the external support. It was known that there was a small non-dominant right coronary artery, which raised the suspicion of short left main coronary anatomy. The chest was closed and the patient recovered. Coronary angiography confirmed the suspicion, and with the imaging available, the support was safely positioned a few days later.

1 patient had a ventricular fibrillation arrest in the intensive care unit. The emergency team released the closing suture, and the heart rhythm became stable with restoration of a normal ECG. Subsequent imaging showed the aortic dimensions to be stable.

Although there were no perioperative deaths in the first 30 patients included in the planned analysis, there was a subsequent postoperative death of the intended 34th patient, 5 days after surgery. The left main coronary artery was tortuous with an upward loop and was injured during the surgical dissection. Access was limited because of severe pectus excavatum. The situation was rapidly retrieved with a suture but transoesophageal echocardiography showed turbulent flow and loss of myocardial contractility. Cardiopulmonary bypass was instated, and an internal mammary artery graft placed. The aorta was opened, and the coronary orifice inspected. Excellent flow was confirmed in the native vessel and in the graft, but myocardial contractility did not recover as expected, and myocardial stunning was thought to be a factor. The external support was not positioned. Biventricular support was instituted, and after 3 to 4 days, there was good myocardial recovery, but 5 days after surgery, there was acute onset fixed dilation of the pupils caused by an intracerebral bleed.

Serious adverse events

1 patient had exercise-induced constricting chest pain 6.7 years after the procedure (linearised occurrence rate 0.75% per patient year). It was found to be unrelated to the aortic root pathology or surgery. Coronary angiography showed an atherosclerotic left anterior descending coronary artery stenosis which was successfully stented. Aortography and coronary angiography done at that time showed widely patent coronary orifices with no sign of impingement of the external support on the smooth lumen of his coronary arteries.

Study 4 Izgi C (2018)

Study details

Study type	Case series
Country	UK
Recruitment period	2004 to 2012
Study population and number	n=24 Patients with Marfan syndrome
Age and sex	Mean 33 years (range 16 to 58 years); 67% (16/24) male
Patient selection criteria	Eligibility criteria were an aortic root size of 40 to 55 mm and no or only mild aortic regurgitation.
Technique	Device: (ExoVasc Personalized External Aortic Root Support, Exstent Limited, UK)
Follow-up	Mean 6.3 ± 2.6 years (79% [19/24] of patients had at least 5 years of follow up)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Three additional patients were treated during the study period but were excluded from the analysis. In 2 of these patients, the baseline and follow up imaging was by CT (1 patient had metallic spinal roads that caused significant artefacts and 1 patient had severe claustrophobia that precluded imaging by CMR). The third patient was living abroad and follow up imaging studies were not available.

Study design issues: Prospective single centre case series. The main aim of the study was to test stability of the aortic root size after the procedure, based on measurements by CMR. Patients had CMR before the operation, at 6 and 12 months after the operation and annually thereafter. A batch of 120 anonymised CMR studies was formed, including the baseline and the latest CMR studies of all the 24 patients as well as randomly selected studies of the patients acquired at any time during their follow up to try and minimise any possible measurement bias. A single operator measured the aorta size on these individual anonymised studies following a stringent, pre-defined protocol.

Study population issues: The mean of the largest aortic root diameter was 44.9 mm (range 41 to 52 mm).

Other issues: The authors noted that the cut-off size of 40 mm is lower than the recommended cut-off size for aortic root replacement, because the procedure was developed as a prophylactic surgery to prevent dilatation of the aortic root at an early point in the natural history of Marfan syndrome.

Key efficacy findings

Number of patients analysed: 24

Technical failure=8.3% (2/24); the mesh support did not fully cover the aortic root because of identifiable technical failures. These 2 patients were taken as outliers. In 1 patient, ischaemia with compromise of right coronary flow was suspected after the procedure. The chest was urgently reopened, and the seam of the mesh support was opened to release any possible impingement on the coronary arteries. The aortic root dilated in the uncovered area at follow up. In the second patient, there was localised dilation of the right coronary cusp of the aortic root where the opening for the coronary ostia was inadvertently cut large, leaving this region not adequately supported.

Comparison of preoperative and follow up aorta measurements, mean (SD) – all patients (n=24)

Measurement	Preoperative	Follow up	Change	95% CI	p value
Annulus diameter, mm	28.9 (2.2)	28.4 (2.3)	-0.42	-1.03 to 0.19	0.17
Sinus of Valsalva maximum diameter, mm	44.9 (2.8)	45.4 (4.0)	0.50	-0.97 to 1.97	0.49
Sinus of Valsalva mean diameter, mm	43.6 (2.3)	43.9 (3.8)	0.36	-0.92 to 1.64	0.57
Sinus of Valsalva area, cm^2	16.3 (1.9)	16.5 (2.9)	0.11	-0.85 to 1.06	0.82
Ascending aorta diameter, mm	32.4 (3.5)	32.4 (3.5)	0.00	-0.78 to 0.78	1.00
Ascending aorta area, cm^2	8.2 (1.7)	8.5 (1.8)	0.23	-0.14 to 0.60	0.21
Arch diameter, mm	24.2 (2.0)	24.6 (2.7)	0.38	-0.54 to 1.29	0.40
Descending aorta diameter, mm	22.6 (2.5)	23.9 (3.1)	1.25	0.65 to 1.85	<0.001
Descending aorta area, cm^2	4.0 (0.9)	4.4 (1.0)	0.35	0.13 to 0.57	0.003

Comparison of preoperative and follow up aorta measurements, mean (SD) – excluding outliers (n=22)

Measurement	Preoperative	Follow up	Change	95% CI	p value
Annulus diameter, mm	28.9 (2.3)	28.5 (2.4)	-0.39	-1.05 to 0.27	0.24
Sinus of Valsalva maximum diameter, mm	44.9 (2.9)	44.5 (3.0)	-0.37	-1.23 to 0.51	0.40
Sinus of Valsalva mean diameter, mm	43.5 (2.4)	43.2 (3.0)	-0.38	-1.16 to 0.40	0.33
Sinus of Valsalva area, cm^2	16.3 (2.0)	15.9 (2.4)	-0.42	-1.05 to 0.21	0.18
Ascending aorta diameter, mm	32.4 (3.6)	32.3 (3.7)	-0.10	-0.92 to 0.74	0.82
Ascending aorta area, cm^2	8.2 (1.7)	8.4 (1.8)	0.19	-0.20 to 0.59	0.33
Arch diameter, mm	24.1 (2.0)	24.5 (2.8)	0.41	-0.56 to 1.37	0.39
Descending aorta diameter, mm	22.9 (2.4)	24.2 (3.0)	1.32	0.70 to 1.94	<0.001
Descending aorta area, cm^2	4.1 (0.9)	4.4 (1.0)	0.35	0.12 to 0.58	0.004

There was no increase in the percentage of patients with mild aortic regurgitation (33% [8/24] at baseline), and no patient had an increase in the severity of aortic regurgitation at follow up.

2 female patients each had an uneventful pregnancy after the procedure without any significant changes in their aorta sizes.

Key safety findings

1 patient, whose procedure was described as a technical failure, had intractable hypotension in the recovery ward after the operation and noted to have ST-segment changes in the inferior electrocardiogram leads along with hypokinesia of the right ventricle on the echocardiogram. The chest was urgently reopened, and the seam of the mesh support was opened to release any possible impingement on the coronary arteries. The electrocardiogram changes immediately resolved with haemodynamic stability postoperatively.

Study 5 Treasure T (2012)

Study details

Study type	Non-randomised comparative study
Country	UK
Recruitment period	2004 to 2009
Study population and number	n=40 (20 PEARS, 20 aortic root replacement) Patients with Marfan syndrome
Age and sex	• PEARS: mean 33 years (range 16 to 58); 70% (14/20) male • Aortic root replacement: mean 37 years (range 18 to 63); 40% (8/20) male
Patient selection criteria	All patients in the study would have been candidates for either external support or root replacement. The external root support patients, by protocol, had aortic root diameters of 4 to 5.5 cm and no more than grade 1 (trivial) aortic regurgitation.
Technique	• PEARS • Elective aortic root replacement (4 composite valved graft aortic root replacement and 16 valve-sparing operations)
Follow-up	To hospital discharge
Conflict of interest/source of funding	Development costs were met by Exstent who manufacture the custom-made devices for each patient. Costs per device were partly recovered from NHS purchasing. One author is a shareholder and director of Exstent, which holds the intellectual property rights in the external aortic root support project. He was the originator of the concept and the first recipient of the device. No other author has any pecuniary interests or any other conflict of interests.

Analysis

Study design issues: Non-randomised retrospective comparative study. The comparison group were selected from patients who were operated on during the same time frame, in other hospitals where external aortic root support was not available. A matched comparison group, of similar age, aortic size and aortic valve function to those having external aortic root support, was constructed by minimisation. The main outcomes were hospital stay, blood loss and blood product usage.

Study population issues: The study includes the first 20 patients to have the PEARS procedure. There was a poor match for sex between the groups. The mean aortic diameter at baseline was 46 mm in the external aortic root support group (range 40 to 54 mm) and 48 mm in the control group (range 38 to 58 mm).

Key efficacy findings

Number of patients analysed: 40 (20 PEARS, 20 aortic root replacement)

Operative characteristics, median (range)

Outcome	PEARS	n	Aortic root replacement	n	p
Operation time (min)	148 (125 to 415)	20	240 (150 to 414)	19	Not reported
Bypass time (min)	0 (0 to 20)	20	134 (52 to 316)	20	Not reported
Ischaemic time (min)	0 (0 to 0)	20	114 (41 to 250)	20	Not reported
Postoperative days in hospital	6 (4 to 16)	20	7 (4 to 17)	20	Not significant
Chest tube drainage up to 4 hours after surgery (ml)	50 (25 to 400)	20	230 (85 to 735)	18	<0.02
Chest tube drainage up to 12 hours after surgery (ml)	120 (25 to 925)	20	385 (200 to 1010)	18	<0.02

Key safety findings

Red cell, platelet or fresh frozen plasma transfusion, number of patients

Transfusion product	PEARS, n=20	Aortic root replacement, n=18	p
Red cell	1 (single unit)	9 (mean 2.0 units per transfused patient)	0.002
Platelet	0	9 (mean 1.6 units per transfused patient)	<0.001
Fresh frozen plasma	0	12 (mean 4.8 units per transfused patient)	<0.001

Study 6 Pepper J (2015)

Study details

Study type	Case report
Country	UK
Recruitment period	2008
Study population and number	n=1 Patient with Marfan syndrome
Age and sex	26-year-old male
Patient selection criteria	Not applicable
Technique	PEARS with a macroporous mesh.
Follow-up	4.5 years
Conflict of interest/source of funding	None declared.

Key efficacy findings

The patient died 4.5 years after having a PEARS procedure. He was the first patient to die with an implant. At autopsy, there were expected pericardial adhesions but no blood in the pericardium or mediastinum. The aortic arch and descending aorta appeared normal. The external aortic mesh was fully incorporated in the adventitia and could not be separated from it. There was no aortic dissection. There was no impingement on the coronary arteries or their orifices by the external support. The examining pathologist found no reason to suspect that the mesh support had contributed to death. The mesh position was stable and it was fully incorporated by collagen. Examination of the heart confirmed a dilated cardiomyopathy presumed to be related to Marfan syndrome, as was the cause of death in his mother.

The supported aortic root had the histological appearance of a normal aorta. The histological appearance suggested the possibility that the incorporated support of the aortic root allowed recovery of the microstructure of the media.

Study 7 Kockova R (2019) - conference abstract

Study details

Study type	Non-randomised comparative study
Country	Czech Republic
Recruitment period	1998 to 2017
Study population and number	n=27 (13 PEARS, 14 standard prophylactic aortic root surgery) Patients with Marfan syndrome or non-Marfan genetic aortopathy
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	• PEARS • standard prophylactic aortic root surgery
Follow-up	Not reported
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Retrospective, single centre, non-randomised comparative study. The main aim was to compare the severity of inflammatory response of PEARS against standard prophylactic aortic root surgery.

Study population issues: Patient baseline characteristics were similar in the 2 groups, except aortic root was statistically significantly larger in the standard surgery group than in the PEARS group (60±12 mm compared with 48±5 mm; p=0.003). Most patients in both groups had Marfan syndrome (62% in the PEARS group compared with 79% in the standard surgery group).

Other issues: Study was published as a conference abstract, so there is limited information.

Key safety findings

Postprocedural inflammatory characteristics or adverse events	PEARS, n=13	Standard prophylactic aortic root surgery, n=14	p value
Peak level of C-reactive protein (mg/L)	264.5±84.4	184.6±89.6	0.034
Peak white blood cell count (10^9/L)	15.2±3.8	11.9±3.3	0.029
ST elevation, n (%)	11 (85)	6 (43)	0.024
Early fever needing hospital readmission, n (%)	10 (77)	5 (36)	0.032
Recurrent fever needing hospital readmission, n (%)	6 (46)	1 (7)	0.020
Early pericarditis needing hospital readmission, n (%)	4 (31)	0 (0)	0.024
Recurrent pericarditis needing hospital readmission, n (%)	4 (31)	0 (0)	0.024

All surgical procedures were successful and without major complications.

Study 8 Nemec P (2020)

Study details

Study type	Case series
Country	9 countries, including UK
Recruitment period	2004 to 2020
Study population and number	n=317 Patients who had PEARS
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	PEARS (ExoVasc Ltd.)
Follow-up	871 patient years
Conflict of interest/source of funding	None declared.

Analysis

Study design issues: The main aim of the study was to summarise aspects of the procedure including indications, surgical technique and safety. It includes a brief summary of data held by the manufacturer of the external aortic root support in a prospective database.

Study population issues: The most common indication was Marfan syndrome (57%).

Key efficacy and safety findings

Number of patients analysed: 317

The long-term experience comprises 871 patient/years with 1 patient living for 15 years and 19 patients living for more than 10 years.

Adverse events

- Perioperative mortality=0.3% (1/317); the patient had severe pectus excavatum and died 5 days after surgery because of an injury to the left coronary artery. The support was not placed during the surgery.
- Injury to the right coronary artery, n=1; successfully resolved with coronary artery bypass grafting.
- Reoperation because of hypotension while in the intensive care unit, n=1. The axial suture line of the mesh implant was partially released. After 6 years, aortic valve regurgitation developed, and the patient had surgery to correct dilation of the non-coronary sinus. The mesh-reinforced aortic wall was identified and could be cut and sewn safely.

- One patient died 4.5 years after the procedure from an unrelated cause: the reason was probably malignant arrhythmia (this is the same patient who is described in the earlier case report by Pepper et al., 2015). A second patient died 6.5 months after the procedure from chronic heart failure. He had a history of alcoholic cardiomyopathy. Immediately after the external aortic root support procedure, he had acute heart failure because of occlusion of his circumflex artery. It was managed successfully by a reoperation, adjustment of the support and implantation of a stent in the circumflex artery.

Validity and generalisability of the studies

- There are no randomised controlled trials.
- The studies include data from the UK.
- The studies include the first patients to have the procedure.
- There is significant patient overlap between the studies.
- Some studies include patients with indications other than Marfan syndrome.
- Follow up ranged from 0 to 190.5 months in the largest cohort study of 200 patients; 72% of patients were followed up beyond 12 months (Van Hoof 2021).
- A non-randomised comparative study that has only been published as an abstract has been included because it reports safety data that have not been reported elsewhere (Kockova 2019).

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Medical Technologies

- E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta. NICE Medical technologies guidance 16 (published in 2013; updated in 2018). Available from http://www.nice.org.uk/guidance/mtg16

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Professional expert questionnaire for PEARS using mesh for people with Marfan syndrome was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 13 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

None.

References

1. Van Hoof L, Rega F, Golesworthy T et al. (2021) Personalised external aortic root support for elective treatment of aortic root dilation in 200 patients. Heart doi: 10.1136/heartjnl-2021-319300
2. Pepper J, Golesworthy TJ, Izgi C et al. (2020) Personalised external aortic root support (PEARS) to stabilise an aortic root aneurysm. British Journal of Cardiology 27: 87–92
3. Treasure T, Takkenberg JJM, Golesworthy T et al. (2014) Personalised external aortic root support (PEARS) in Marfan syndrome: analysis of 1-9 year outcomes by intention-to-treat in a cohort of the first 30 consecutive patients to receive a novel tissue and valve-conserving procedure, compared with the published results of aortic root replacement. Heart (British Cardiac Society) 100: 969–75
4. Izgi C, Newsome S, Alpendurada F et al. (2018) External aortic root support to prevent aortic dilatation in patients with Marfan syndrome. Journal of the American College of Cardiology 72: 1095–105
5. Treasure T, Crowe S, John Chan KM et al. (2012) A method for early evaluation of a recently introduced technology by deriving a comparative group from existing clinical data: A case study in external support of the Marfan aortic root. BMJ Open 2: a1
6. Pepper J, Goddard M, Mohiaddin R et al. (2015) Histology of a Marfan aorta 4.5 years after personalized external aortic root support. European Journal of Cardio-thoracic Surgery 48: 502–5
7. Kockova R, Maly J, Krebsova A et al. (2019) Inflammatory response after ExoVasc personalized external aortic root support (PEARS) procedure in patients with Marfan syndrome or non-Marfan genetic aortopathy. European Heart Journal 40 (no. supplement1): 3482
8. Nemec P, Fila P, Pepper J (2020) Personalized external aortic root support. Interactive Cardiovascular and Thoracic Surgery 31: 342–5
9. Benedetto U, Melina G, Takkenberg JJ, et al. (2011) Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. Heart 97:955–8

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	07/12/2021	Issue 12 of 12, December 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	07/12/2021	Issue 12 of 12, December 2021
International HTA database (INAHTA)	07/12/2021	-
MEDLINE (Ovid)	07/12/2021	1946 to December 06, 2021
MEDLINE In-Process (Ovid)	07/12/2021	1946 to December 06, 2021
MEDLINE Epubs ahead of print (Ovid)	07/12/2021	December 06, 2021
EMBASE (Ovid)	07/12/2021	1974 to 2021 December 06
EMBASE Conference (Ovid)	07/12/2021	1974 to 2021 December 06

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Number	Search term
1	Marfan Syndrome/
2	(Marfan* adj4 syndrom*).tw.
3	MFS.tw.
4	Connective Tissue Diseases/
5	(connect* tissue* adj4 (disease* or disord*)).tw.
6	Aneurysm, Dissecting/
7	Aortic Aneurysm/
8	((aortic* or aorta*) adj4 (dissect* or dilat* or ascend* or aneurysm* or aneurism* or tear* or expand* or enlarge* or rupture* or regurgitat* or cut*or wide*)).tw.
9	or/1-8
10	PEARS.tw.

11	personalise* external* aortic* root support*.tw.
12	((bespoke* or custom* or tailor* or personal* or exact* or individual* or modif* or adapt*) adj4 (support* or graft*)).tw.
13	(aort* adj4 (support* or polymer* or mesh*)).tw.
14	Computer-Aided Design/
15	(comput* adj4 (assist* or aid*)).tw.
16	(digital* adj4 imag*).tw.
17	(rapid adj4 prototyp*).tw.
18	or/10-17
19	9 and 18
20	exovasc*.tw.
21	exostent.tw.
22	20 or 21
23	19 or 21
24	animals/ not humans/
25	23 not 24

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Austin C, Fittipaldi M, Thompson P et al. (2021) The consequences of incomplete covering of the critical part of the aortic root in Personalized External Aortic Root Support. European Journal of Cardio-thoracic Surgery 59: 1095	Case report n=1	In 2015, a patient had surgery in which the external aortic root support was incorrectly fitted. The surgeon cut-off and discarded the portion of the mesh, custom manufactured to fit the aortic sinuses and tethered the cut end of the remaining implant to the adventitia above the coronary arteries. The aortic diameter at the level of leaflet closure increased from 49 to 62 mm over 18 months with worsening aortic regurgitation. At reoperation, a further personalised mesh was fitted. Size reduction was achieved down to 46 mm on the postoperative measurement. The patient made a good recovery and remains well but with mild residual aortic valve regurgitation.	Case report in which the protocol for inserting the support was not followed, and the aortic root continued to expand.
Benedetto U, Jin XY, Hill E et al. (2016) An option for concomitant	Case report n=2	Two patients had mitral valve repair for severe regurgitation in the	Case report of concomitant external aortic

management of moderate Marfan root aneurysm at the time of mitral valve repair: a role for personalized external aortic root support. The Annals of Thoracic Surgery 102: e499–501		presence of a Marfan aortic root aneurysm. Concomitant PEARS was used at the same operation to halt aneurysm progression and to correct mild aortic regurgitation.	root support and mitral valve repair.
DiMario C, Pepper J, Golesworthy T et al. (2012) External aortic root support for the Marfan aorta: anatomically normal coronary orifices imaged seven years after surgery. Interactive Cardiovascular and Thoracic Surgery 15: 528–30	Case report n=1 FU=7 years	The patient presented with angina 7 years after having the procedure. The cause of angina was an atherosclerotic left anterior descending coronary artery stenosis, which was successfully stented. Aortography and coronary angiography showed widely patent coronary orifices with no sign of impingement of the external support on the smooth lumen of his coronary arteries.	Case report – already described within a larger study.
Izgi C, Nyktari E, Alpendurada F et al. (2015) Effect of personalized external aortic root support on aortic root motion and distension in Marfan syndrome patients. International Journal of Cardiology 197: 154–60	Case series n=24 FU=median 50.5 months	The procedure decreases systolic downward aortic root motion which is an important determinant of longitudinal aortic wall stress. Aortic wall distension and Windkessel function are not significantly impaired in the follow-up after implantation of the mesh which is also supported by the lack of deterioration of left ventricle volumes or mass.	A more recent study from the same author is included.
Pepper J, Chan KMJ, Gavino J et al. (2010) External aortic root support for Marfan syndrome: early clinical results in the first 20	Case series n=20 FU=median 20 months	Median change in aortic root diameter during follow-up (assessed by MRI scans) (n=16) = −1 mm (range −6 to +3).	Larger and more recent studies are included, with the same patients.

recipients with a bespoke implant. Journal of the Royal Society of Medicine 103: 370–5		One patient had a post-operative cardiac arrest with ventricular fibrillation. The circulation was restored after removing the anterior closing suture on the aortic root support. Another patient had anatomical anomalies in the coronary arteries, so further imaging was needed before the procedure could be completed a week later.	
Pepper J, Golesworthy T, Utley M et al. (2010) Manufacturing and placing a bespoke support for the Marfan aortic root: description of the method and technical results and status at one year for the first ten patients. Interactive Cardiovascular and Thoracic Surgery 10: 360–5	Case series n=10 FU=at least 12 months	For 8 of the 10 patients, the largest observed difference between the diameter of the aortic root before and at least 1 year after surgery was a marked reduction in diameter. There were no deaths, late events or detected changes in aortic valve function. Arrhythmia (transient atrial fibrillation) = 20% (2/10)	Larger and more recent studies are included, with the same patients.
Singh SD, Xu XY, Wood NB et al. (2016) Aortic flow patterns before and after personalised external aortic root support implantation in Marfan patients. Journal of Biomechanics 49: 100–11	Case series n=3	The qualitative patterns of the haemodynamics were similar before and after the procedure. The post-procedure aortas had slightly less disturbed flow at the sinuses, because of reduced diameters in the aortic roots. All values of helicity flow index were within the range reported for normal aortas.	Small study focusing on haemodynamics.
Treasure T, King A, Hidalgo Lemp L et al. (2018) Developing a shared decision support framework for aortic root surgery in Marfan	Survey n=142	46% of respondents had previous aortic root surgery. Overall, active lifestyle was more important to males (p=0.03). Patients placed	Study focusing on development of a decision support framework for aortic surgery in

syndrome. Heart (British Cardiac Society) 104: 480–6		more importance than doctors on not deferring surgery (p=0.04) and on avoidance of anticoagulation in the interests of childbearing (p=0.009). Qualitative analysis showed differing but cogently reasoned values that were sometimes polarised, and mainly driven by the wish to maintain a good quality of life and active lifestyle.	Marfan syndrome.
Treasure T, Petrou M, Rosendahl U et al. (2016) Personalized external aortic root support: a review of the current status. European Journal of Cardio-thoracic Surgery 50: 400–4	Review	More than 60 patients have had this surgery in a 12-year period. Operations have been done in 6 centres and follow up is more than 260 patient-years. It is possible that the procedure may prove to be a definitive means to hold the sinuses at a size and shape that allow the aortic valve to remain competent. In the 2 cases where the aorta has been examined years after the mesh has become incorporated, the macroscopic and histological appearances make acute aortic dissection originating in the root seem much less likely than it would otherwise have been.	Review
Treasure T, Takkenberg JJM, Pepper J (2016) Surgical management of aortic root disease in Marfan syndrome and other congenital disorders associated	Review	Three forms of surgery are now available: total root replacement with a valved conduit, valve sparing root replacement and PEARS with a macroporous mesh	Review

with aortic root aneurysms. Postgraduate Medical Journal 92: 112–7		sleeve. In evaluation of these 3 forms of surgery, the number needed to treat to prevent dissection and the balance of net benefit and harm in future patients must be considered.	
Treasure T, Takkenberg JJM, Pepper J (2014) Surgical management of aortic root disease in Marfan syndrome and other congenital disorders associated with aortic root aneurysms. Heart (British Cardiac Society) 100: 1571–6	Review	The recommended size criteria for intervention on the aortic root to avert dissection are based on the risk of further waiting balanced against the procedural risk of the surgery. Better data are needed to know the number needed to treat and to have comparative effectiveness and cost effectiveness data for the 3 surgical approaches.	Review
Treasure T, Golesworthy T, Pepper J et al. (2011) Prophylactic surgery of the aortic root in Marfan Syndrome: Reconsideration of the decision making process in the era of customised external aortic root support. Italian Journal of Vascular and Endovascular Surgery 18: 215–23	Review	At the time of the review, 25 patients had been treated. All were alive and well at median follow up of 44 months. In making the decision about the choice of surgery there is a complex trade off of the ongoing risk of dissection if surgery is deferred versus the risk of the operation itself and of the ensuing lifetime consequences.	Studies with more detailed outcomes from the same patients are included.