NHS England

Evidence Review:

Personalised External Aortic Root Support (PEARS) for surgical management of enlarged aortic root (adults)

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Contents

1. Introduction

The aim of personalised external aortic root support (PEARS) is to prevent enlargement and subsequent dissection and rupture of the aorta. PEARS is suitable for enlarged aortic roots measuring 40-55mm in diameter, and growing by >5mm per year, as measured by echocardiography.

Aortic roots become enlarged predominantly as a result of genetic diseases such as Marfan syndrome. Many of these patients have weak aortas that can become enlarged and progressively widen, which may lead to tears in the wall of the aorta (dissection) and possibly rupture, which is frequently fatal. Other causes of enlarged aortic roots are bicuspid aortic valve (BAV) disease and previous cardiac correction surgieries (for example, surgery in infancy and the Ross procedure).

With the PEARS procedure, a bespoke external support for the ascending aorta and aortic root is made using computer-aided design. During surgery, the support is wrapped around the aorta, which remains intact. The aortic valve must be functional.

2. Summary of results

Annuloaortic ectasia is a cardiac anomaly which exists in about 75-85% of Marfan syndrome (MFS) patients. This includes dilatation of the aortic sinuses and annulus in addition to the ascending aorta, leading to aortic valve insufficiency. If left untreated there is a high risk of death due to dissection or rupture of the aorta or heart failure resulting from severe aortic regurgitation.

Currently there are three types of surgical methods to correct this anomaly including Total aortic root replacement (TRR), Valve-sparing aortic root surgery (VSARR) which includes two techniques reimplantation also called the David procedure and the remodelling as also called the Yacoub procedure. The other one is called the Personalised External Aortic Root Support (PEARS) developed by Treasure et al.
Total aortic root replacement (TRR) using a composite mechanical valve conduit by Bentall has long been considered the ‘gold-standard’ treatment in this setting, with good early and late postoperative outcomes. However, one of the limitation of this treatment is patients require long-term anticoagulation and experience complications related to anticoagulation. VSARR has emerged as an alternative to composite valve-graft aortic root replacement, particularly in patients with MFS who have isolated root pathology with functionally normal valve leaflets. This technique preserves native valves, thus avoiding the disadvantages of a mechanical prosthesis and the complication of lifelong anticoagulation. PEARS involves fitting a bespoke computer designed external support made of a fabric mesh manufactured from a macroporous textile from a medical grade polymer yarn.

Research questions:
• Is the proposed new procedure as effective as the existing procedure?
• Is the procedure better than the existing one in terms of improved outcomes for patients and for the clinical management of patients?

There are no studies reporting head-to head comparison of PEARS vs other two surgical techniques in patients with Marfan syndrome. The evidence for PEARS in Marfan syndrome mainly comes from studies published by Treasure et al and NICE Intervention Procedure Guidance 2011 https://www.nice.org.uk/guidance/ipg394/chapter/2-The-procedure authored by Treasure et al. The evidence for TRR and VSARR in Marfan syndrome is available from a systematic review by Benedetto et al 2011 and from a prospective multicentre study by Coselli et al 2014.

There are number of other studies (Liu et al 2011, Shrestha et al 2012, Hu et al 2014, Arabkhani et al 2015) comparing either TRR vs VSARR or comparing remodelling VSARR vs reimplantation VSARR which have a proportion of patients who are Marfan syndrome. As none of the studies report outcome on Marfan syndrome and are excluded from the evidence review

Short term outcomes: In a latest study by Treasure et al 2014 based on prospective case series of 30 Marfan patients undergoing PEARS had better outcomes compared to patients undergoing TRR or VSARR on number short term and long term clinical parameters as reported in studies for TRR and VSARR.The short-term 30 days peri-operative measures were better in PEARS (Treasure et al 2014) compared to TRR or VSARR (Coselli et al 2014). These included mortality, operation time, cardio pulmonary bypass time, myocardial ischemia time, blood transfusion, coagulation aid, ICU stay (hrs), major valve related and cardiac complications. However the baseline

characters of patients in these two studies are different in that patients in study by Coselli had higher proportion of patients with aortic regurgitation (30% PEARS vs 78% TRR and 54% VSARR) and non-elective operations (0% PEARS vs 23% TRR and 4% VSARR). Also for number of other baseline characteristics it appears that patients who had TRR or VSARR had poorer measurements than PEARS but cannot be verified due to lack of comparative data in two papers. This difference in baseline could be because PEARS group included patients who did not have higher level of severity and did not meet European (ESC/EATS) guidelines for TRR or VSARR.

Long term outcome measures: Long term outcome measures of aortic surgery in Marfan syndrome patients are available from a systematic review by Benedetto et al (2011), Coselli et al 2014 and Treasure et al 2014 and 2015. The main long term outcome measures were re-intervention on aortic valve, thromboembolic events, endocarditis, valve related events, survival and valve related death. For all the long-term outcome measures PEARS group had better results in that this group has had no events (0%) recorded for the above indicators (pls see worksheet labelled Table -long-term outcome measure). However compared to patients in TRR and AVSRR patient groups patients in the PEARS group were on average operated upon at a younger age with smaller aortic root diameter and with no or trivial aortic regurgitation. None in the PEARS group had dissection at the time of surgery or prior to it compared to 23% in TRR and 6% in VSARR group in Coselli et al 2014 and 0.3% TRR and 0.18 VSARR in Benedetto et al 2011.

In summary it can be concluded that PEARS is a safe and effective elective intervention in carefully selected patients with Marfan syndrome who are at lower risk (smaller aortic root diameters, no aortic regurgitation, and younger age patients). However it is difficult to compare outcomes for PEARS with other intervention such as TRR or AVSRR, because of the differences in baseline characters patients undergoing TRR and AVSRR. Generally patients in TRR and AVSRR are older and are high risk in terms greater aortic root diameter, persistence of aortic dissection and aortic regurgitation which are all known risk factors that influence outcome of surgery. There are no published studies evaluating PEARS in high risk Marfan syndrome or TRR/AVSRR in low risk patients similar to patient group in Treasure et al. Also as noted in NICE IPG 2011 long term safety and effectiveness are yet to be established.

A prospective cohort study comparing PEARS alongside TRR and AVSRR as proposed by Treasure et al should be considered for further evidence generation. Also as the low complication rate in PEARS group could be due to low risk profile of patients, watchful waiting' as a comparator group need to be considered. This could provide answer to question if patients receiving PEARS have had unnecessary intervention and exposed to the risks of complication from the intervention.

Research question:
• Is the treatment more cost effective than using the existing procedure?

There are no published literature comparing the cost effectiveness of PEARS to TRR or VSARR. Treasure et al suggest that there are likely to be cost savings due to lesser complications, reduced procedural costs and avoidance of anticoagulation. However intervening early a can lead to increased number of cases treated and therefore increased costs.

Research question:
• Are any subgroups identifiable from the evidence?

There are no sub-group analysis available from Treasure et al 2014 and 2015. A subgroup analysis by aortic dimensions, aortic aneurysm, previous cardiovascular operation, and other cardiac risk factors could add to the evidence of effectiveness. However based on the reported outcome both short and long term measures in Treasure et al it appears that the current inclusions criteria appears to be safe and effective as the results for valve related deaths, survival and complication rates are at their lowest rates and for some none.

3. Research questions

• Is the proposed new procedure as effective as the existing procedure?
• Is the procedure better than the existing one in terms of improved outcomes for patients and for the clinical management of patients?
• Is the treatment more cost effective than using the existing procedure?
• Are any subgroups identifiable from the evidence?

• [If beneficial, does the new treatment need to be restricted to centres with the right degree of expertise and facilities, such as MRI scanning and CT scanning, and likely to be able to maintain that expertise by carrying out a minimal number of procedures per year? Are there defined training requirements for centres that might be designated as expert centres?]

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Case series	30	PEARS	Clinical effectiveness of the intervention	Early mortality, reintervention. Thromboembolic phenomena, endocarditis, composite valve related event	Average patient follow-up was 4.4 years, ranging from 1.4 to 8.8 years and 100% of patients followed up until February 2013. Study reports no deaths and cumulative survival of100% at 7 years. no medical or surgical events related to the aorta or aortic valve or neurological have been reported. At 7 years postoperative only five of the original 30 patients were still at risk. Compared to this meta-analysis of published results for root replacement show the composite risk of a valve-related event (thromboembolism, re-intervention, endocarditis) among 972 patients who had TRR was 1.3% (95% CI 0.6 to 2.0), and for 413 who had VSRR it was 1.9 (95% CI 0.8 to 2.9).8 VSRR had highest re-intervention rate of 1.3% per year compared to 0% in PEARS and 0.3%/year with TRR	none mentioned	-	Treasure, Tom; Takkenberg, Johanna J. M.; Golesworthy, Tal; Rega, Filip; Petrou, Mario; Rosendahl, Ulrich; Mohiaddin, Raad; Rubens, Michael; Thornton, Warren; Lees, Belinda; Pepper, John. 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 2014;100(12):969-975.	-	As in primary outcome results	A retrospective case series reporting on the outcomes in 30 patients with Marfans undergoing PEARS. Authors report nil outcomes in terms of mortality, reintervention and 0% composite valve events. Authors compare to two other gold standard treatment of TRR and VSRR which have higher rate than PEARS. However as reported by the authors the patients group in PEARS is younger and lower mean op pre-op aortic root size and no more than grade 1 (trivial) aortic regurgitation which significant prognostic factors. So comparability of the results of PEARS with TRR and VSRR are limited by small sample size and baseline difference in mean aortic root size. and level of AR.
3	Cohort	20 EARS and 20 comparator group consisting if 16 valve sparing and 4 composite valved grafts	external aortic root support (EARS	Clinical effectiveness of the intervention	Operation time, ischaemic time, bypasstime, chest tube drainage and post operative days in hospital	Median Operation time (min) EARS =148 vs Comparison =240 Median bypass time (min) EARS =0, Comparison=134, Ischaemic time (min) EARS=0 vs Comparison=114. Medican Postoperative days in hospital EARS= 6 Comparison= 7, Median Chest tube drainage up to 4 h after surgery (ml) EARS=50 vs Comparison= 230 Medican Chest tube drainage up to 12 h after surgery (ml) EARS=120 vs Comparison= 385	none	-	Treasure, Tom; Crowe, Sonya; Chan, K. M. John; Ranasinghe, Aaron; Attia, Rizwan; Lees, Belinda; Utley, Martin; Golesworthy, Tal; Pepper, John. 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 2012;2(2):e000725.	-	-	This retrospective case series comparing 20 marfan patients with EARS compared with 20 cases of comparator surgeries matched for baseline factors selected from case series from other hospital. The results show that EARS had lower bypass, operation, ischaemic time but this did not translate into number of post operative hospital days . Also as identified by the authors the true measure is the time to aortic dissection which is not reported in the article. This article establishes EARS clinical benefits in short time and for the lack of patient outcome measures it is not possible to conclude on the wider impact on patient mortality and morbidity

3	Systematic	20 patients	PEARS	Clinical effectiveness of the intervention	Mean bypass time, mean operation time, cardiac complications	Included results of follow-up of 20 patients with a median follow-up of 20 months and following benefits were noted: 100% survival at 20 months and post-operative decrease in aortic root diameter (assessed by MRI) were ranging from a decrease of 6 mm to an increase of 3 mm, with the median change being a decrease in diameter of 1 mm. Reduced cardiopulmonary bypass during operation, reduced mean operation time(148 minutes vs 374 minutes), reduced bleeding compared to aortic root replacement. In the case series of 20 patients, 1 had a post-operative cardiac arrest with ventricular fibrillation and 2 had transient atrial fibrillation after the procedure. The NICE note that while PEARS may prevent future rupture or dissection of ascending aortic, and prevention of ascending aortic enlargement, there is uncertainty about whether the procedure will prevent aortic dissection in the long term, and whether it will prevent deterioration of the aortic valve.	none	-	Treasure, Tom; Pepper, John; Golesworthy, Tal; Mohiaddin, Raad; Anderson, Robert H.. External aortic root support: NICE guidance. Heart 2012;98(1):65-68.	-	as in primary outcome measure	This is NICE IPG guidance based on a report on small number of cases with a short follow-up period. The NICE note that while PEARS may prevent future rupture or dissection of ascending aortic, and prevention of ascending aortic enlargement, there is uncertainty about whether the procedure will prevent aortic dissection in the long term, and whether it will prevent deterioration of the aortic valve. The generalisability of results are limited due to small sample size, short follow-up period, lack of randomisation and lack of comparator included as part of he same study.
3	Case series	102	Wrapping of the ascending aorta with a fine Dacron mesh from the ventricular-aortic junction to the origin of the innominate artery	Clinical effectiveness of the intervention	Two sets of end points mentioned in the article-1.mortality, aortic diameter growth, dissection or rupture, or both 2.. early and late mortality, freedom from reoperation, and late valve function	The mean follow-up period was 5.7 years (median, 4.77 years; range, 9 days to 21 years). 1.Among the 81 patients (79%) who could be followed up 7 (7%) late deaths had occurred at 0.5, 1, 3, and 9 years after operation but were unrelated to aortic pathology. 2. In 2 patients, aneurysmal dilatation of the sinuses developed below the wrap and reoperation was required. 3. The mean (SD) preoperative diameter of the ascending aorta was 49.2 ±7.8 mm (range, 35 to 87 mm), the post wrap intraoperative diameter was 32.9 ±3.4 mm (range, 20 to 40 mm), and the follow-up postoperative aortic diameter was 35.6 ± 12.7 mm (range, 27 to 52 mm). The mean average change in the aortic diameter during the follow-up period was 2.6 ±14.8 mm (range, -7 to 22 mm), a mean of 8% and this was similar in both the sub-groups of <50mm AAD and >50mm AAD patients. 5. No infection, invasion, erosion of synthetic mesh through the aortic wall.	none	-	Cohen, Oved; Odim, Jonah; De la Zerda, David; Ukatu, Chidi; Vyas, Raj; Vyas, Neil; Palatnik, Kathy; Laks, Hillel. Long-term experience of girdling the ascending aorta with Dacron mesh as definitive treatment for aneurysmal dilation. Ann. Thorac. Surg. 2007;83(2):S780-784; discussion S785-790.	as in primary outcome measures	as in primary outcome measure	This is a long term retrospective review of patients treated with Dacron mesh wrapping for ascending aorta aneurysmal dilation. Of the 102 patients, five had Marfan syndrome and the mean age was 54 years. Concomitant surgeries were required in 97 patients (95%).The mean follow-up period was 5.7 years and among the 81 patients (79%) who could be followed up 7 (7%) late deaths occurred but were unrelated to aortic pathology. Two patients developed aneurysmal dilatation of the sinuses below the wrap and reoperation was required, The mean (SD) preoperative diameter of the ascending aorta was 49.2 ±7.8 mm (range, 35 to 87 mm) and mean average change in the aortic diameter during the follow-up period was 2.6 ±14.8 mm (range, -7 to 22 mm), a mean of 8% and this was similar in both the sub-groups of <50mm AAD and >50mm AAD patients. No infection, invasion, erosion of synthetic mesh through the aortic wall. Due to lack of comparator group, patient selections methods and small number of Marfan syndrome patients measure reporting the generalisability of results to the Marfan syndrome patients are limited .

1-	Systematic	672 participants, range 17 to 220).	reimplantation aortic root surgery	Clinical effectiveness of the intervention	Primary outcomes were early (30-day) and late mortality, reoperation related to moderate or severe aortic insufficiency, cardiopulmonary bypass and aortic clamping time.	Cardiopulmonary bypass time increased significantly in the reimplantation group versus the remodelling group (WMD 14.05 minutes, 95% CI 6.14 to 21.95, I2=29%; three studies). Aortic clamping time increased significantly in the reimplantation group versus the remodelling group (WMD 15.69 minutes, 95% CI 9.66 to 21.72, I2=51%; three studies). There was no significant difference in 30-day mortality between reimplantation and remodelling (five studies, only three of which contributed to the analysis, I2=0%) or late death (four studies, two contributed to the analysis, I2=0%). There was a significantly lower reoperation rate related to moderate or severe aortic insufficiency for reimplantation versus remodelling (RR 0.46, 95% CI 0.23 to 0.92, I2=40%; seven studies).	None	-	Liu, Lei; Wang, Wei; Wang, Xin; Tian, Chuan; Meng, Yan-Hai; Chang, Qian. Reimplantation versus remodeling: a meta-analysis. J Card Surg 2011;26(1):82-87.	As in primary outcome measure	As in primary outcome measure	This is a systematic review to compare the efficacy and safety of reimplantation with remodelling for valve-sparing aortic root surgery using PubMed for studies published between 2002 and 2010. Eligible aortic pathologies included aortic root aneurism and dissection (chronic or acute) with or without Marfan syndrome (emergent or elective). Primary outcomes were early (30-day) and late mortality, reoperation related to moderate or severe aortic insufficiency, cardiopulmonary bypass and aortic clamping time. Most studies were of both aneurism and dissection patients; one study was of aneurism patients only and one study of dissection patients only. Almost three-quarters of the studies included Marfan syndrome patients; one study focused on Marfan syndrome patients alone. Studies were assessed for random allocation sequence, allocation concealment, blinding, incomplete outcome data; selective reporting, and freedom from other biases and numbers of events for each outcome were extracted in order to calculate risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, mean differences were calculated with 95% CIs. Methods of synthesis Risk ratios and mean differences were pooled using a fixed-effect model to give weighted risk ratios and weighted mean differences (WMDs) with 95% CIs. Between-study heterogeneity was assessed using the X2 statistic (where significant heterogeneity was indicated, p<0.1) and the I2 statistic (where there was a high level of heterogeneity, I2 >50%). Publication bias was assessed visually using funnel plots. It was not possible to perform separate analyses for different aetiological groups due to the limited number of studies identified. Sensitivity analyses were not performed due to the low quality of the studies. The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. However has number of limitations including only one database was searched, all of the included studies were observational with limited details of study design. By the nature of studies, there was no allocation blinding, and there was also incomplete outcome data and selective reporting and therefore cannot rule out bias and confounding in the results. Also the review does not include sub-group analysis by different aetiological groups including Marfan syndrome. Overall due to limitations to the search evidence presented and lack of outcome analysis by Marfan syndrome the generalisability of the results is limited.

2++	Systematic	(1,385 participants) were included. Sample sizes ranged between 43 and 625. Mean follow-up time ranged between 1.58 and 9.5 years	Surgical techniques for Marfan syndrome evaluated including composite valve graft, composite valve graft or homograft, remodelling and reimplantation or remodelling	Clinical effectiveness of the intervention	Outcome measures were re-intervention on the aortic valve, thromboembolic event and endocarditis.	The re-intervention rate was lower in total root replacement compared to valve-sparing root replacement (0.3% per year, 95% CI 0.1 to 0.5 versus 1.3% per year, 95% CI 0.3 to 2.2; p=0.02). There was evidence of statistical heterogeneity for this analysis (total root replacement I^2=24%, valve-sparing root replacement I^2=71%). Thromboembolic events rate was higher in total root replacement compared to valve-sparing root replacement (0.7% per year, 95% CI 0.5 to 0.9 versus 0.3% per year, 95% CI 0.1 to 0.6; p=0.01). There was no evidence of statistical heterogeneity (I^2=0% for both groups). Compared to remodelling, reimplantation was associated with reduced rates of reimplantation among patients who underwent valve-sparing root replacement (0.7% per year versus 2.4% per year; p=0.02). There were no significant differences between total root replacement and valve-sparing root replacement for endocarditis rate or composite valve related events. There was some evidence of statistical heterogeneity for these comparisons except for the analysis of valve-sparing root replacement for endocarditis rate. Meta-regression analysis of differences in follow-up durations among studies for re-intervention rates after valve-sparing root replacement found that the highest rates were recorded in the studies with small sample size and short-follow-up. There was no association between mean age and urgent indication on valve-related complication rates. There was evidence for publication bias for re-intervention and endocarditis outcomes.	none	-	Benedetto, Umberto; Melina, Giovanni; Takkenberg, Johanna J. M.; Roscitano, Antonino; Angeloni, Emiliano; Sinatra, Riccardo. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. Heart 2011;97(12):955-958.	-	As in primary outcome measure	The objective of the review to compare results of total root replacement versus valve-sparing aortic root replacement in Marfan syndrome patients. The review question was broadly stated. It appeared that only studies published in English were included and this may mean that some relevant studies were missed. Study selection was conducted in duplicate, which minimised potential for reviewer error and bias. Quality of the included studies was unclear as there was no validity assessment. Appropriate methods were used to explore heterogeneity and combine study results. Most studies enrolled few patients. Authors report Valve-sparing root replacement may represent a valuable option for patients with Marfan syndrome with aortic aneurysm. The technique should be used with caution in patients with valve characteristics at risk for decreased durability. However generalisability of the results are limited due to review weaknesses that included potential publication bias, and unclear quality of included studies and small study sample sizes.

-	Systematic	-	-	-	-	-	-	-	Arabkhani, Bardia; Mookhoek, Aart; Di Centa, Isabelle; Lansac, Emmanuel; Bekkers, Jos A.; De Lind Van Wijngaarden, Rob; Bogers, Ad J. J. C.; Takkenberg, Johanna J. M.. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis. Ann. Thorac. Surg. 2015;100(3):1126-1131.	-	-	The objective of the study was study the efficacy and safety of reimplantation with remodelling for valve-sparing aortic root surgery (VSARR). Databases included Embase, MEDLINE, Cochrane, Web of Science for studies published between 2000 and 2014. Search terms are reported and the bibliography of each retrieved article was hand searched. Study selection - Studies that reported on reimplantation or remodelling for valve-sparing aortic surgery were eligible for inclusion if they had at least thirty patients with a mean age of 18 years or older, and analysis on mortality and morbidity after VSARR. Studies reporting solely on aortic artery dissection and >50% children in sample size were excluded. Two independent reviewers performed the selection. Assessment of study quality - There is no information on the criteria used to assess the studies which generally would include an assessment of random allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and freedom from other biases. Data extraction - Data extraction was performed in duplicate by two of the authors (B.A. and A.M.). Outcome events in individual studies were registered according to the 2008 American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery guidelines for reporting mortality and morbidity after cardiac valve interventions Methods of synthesis - Variables are reported as mean +/- standard deviation for continuous variables and percentages for discrete variables with 95% CIs. Linearized occurrence rates of valve-related adverse events were calculated as number of events divided by number of patient-years for each study and pooled on a logarithmic scale with the use of the inverse variance method in a random-effect model, to minimize the variance of the weighted average. Each random variable is weighted in inverse proportion to its variance. Subgroup analyses of outcome were performed for surgical technique (reimplantation vs remodelling), preoperative aortic regurgitation (AR) severity, bicuspid valve disease, connective tissue disease, and cusp repair. Heterogeneity between the studies was assessed with the use of the I2 test in Excel. Funnel plots were used to study publication bias The conclusion from the study was that there is low early and late mortality from VSARR, along with low incidence of thromboembolism, endocarditis, and haemorrhagic events. However there was linear trend higher reoperation hazard with preoperative severe aortic regurgitation. Comparing outcomes for the two VSARR techniques (remodelling and reimplantation technique) there was no difference in the groups in terms of survival or reoperation rates. The study has addressed a well-defined question in terms of participants, study design, and relevant outcomes using searched using multiple databases. Author do not report on quality of studies which are all observation studies and no study details are reported. Authors report there was publication bias with small number of studies reporting on the late outcomes. Statistical heterogeneity was assessed and observed lack of standard reporting of outcome. Most importantly there is subgroup analysis by cause of disease including Marfan syndrome and therefore the review has limited generalisability for this group.
2+	Systematic	539	valve-sparing (VS) surgery in the aortic root reconstruction of Marfan syndrome (MS) patients.	Clinical effectiveness of the intervention	Not available form the abstract but following can be deducted- Reexploration, thromboembolic phenomena, reoperation, endocarditis	Compared to CVG, VS surgery was associated with a lower risk for re-exploration (RR 0.48, 95% CI 0.24-0.97; p = 0.04), thromboembolic events (RR 0.17, 95% CI 0.05-0.57; p = 0.004) and endocarditis (RR 0.31, 95% CI 0.11-0.94; p = 0.04). No statistical differences were found between groups with regards to reoperation (RR 1.07, 95% CI 0.35-3.27; p = 0.91)	-	-	Hu, Rui; Wang, Zhiwei; Hu, Xiaoping; Wu, Hongbing; Wu, Zhiyong; Zhou, Zhen. Surgical reconstruction of aortic root in Marfan syndrome patients: a systematic review. J. Heart Valve Dis. 2014;23(4):473-483.	-	As in primary outcome measures results	A systematic review using PubMed, Embase and Cochrane to review evidence comparing the outcomes of VS and CVG surgery in MFS patients. Authors report using the Newcastle-Ottawa Scale evaluation scheme and Revman 5.0, supplied by Cochrane collaboration for data extraction and analysis. Results show that root reconstruction with VS surgery can effectively improve the prognosis of MFS patients and provide a promising alternative for surgical treatment. Full text is not available from PubMed so difficult to analyse the quality of the review. However due to the retrospective nature of the included studies generalisability of the results are limited due to chance and bias contributing to the observed results.

2+	Case series	316 AVS=239, AVR=77	Aortic Valve sparing surgery	Clinical effectiveness of the intervention	30 day post operative and 1 yr. follow up major adverse valve-related events (MAVRE), Valve-related complications including structural valvular deterioration (SVD), non-structural valve dysfunction (NSVD), valve thrombosis, embolism, and bleeding	Early 30-day outcomes- Overall early overall mortality rate of 0.6%. The incidence of valve-related complications and MAVRE was 5% in and7% in AVS group respectively and 5% and8% in AVR group respectively. Overall, both cardiac (P <.01) and pulmonary (P = .01) complications were more common in the AVR group. The total number of ICU days for AVR was 46 hrs, significantly different than AVS group (26 hrs). One year outcome: Major endpoints—including overall survival (P = .6), freedom from MAVRE (P = .6), and valve-related morbidity (P =.7)—were similar between the groups. Freedom from combined NSVD/SVD was greater in the AVR group (99%) than in the AVS group (90%; P = .04). The freedom from bleeding rate was 93% in the AVR group versus 99% in the AVS group (P = .01). The AVR patients had more combined MAVRE and cardiac complications (57% vs 70%, P= .006) than the AVS patients. The AVR group also had more cardiac and pulmonary complications. Regression analysis did not identify procedure type as a risk factor for any of the 1-year adverse endpoints. Preoperative AR ≥2+ was significantly associated with valve-related complications (P = .04), and intraoperative post procedural AR was significantly associated with MAVRE (P = .03).	None reported	-	Joseph S. Coselli, MD,a Irina V. Volguina, PhD,a Scott A. LeMaire, MD,a Thoralf M. Sundt, MD,b Heidi M. Connolly, MD,c Elizabeth H. Stephens, MD, PhD,d Hartzell V. Schaff, MD,e Dianna M. Milewicz, MD, PhD,f Luca A. Vricella, MD,g Harry C. Dietz, MD,h Charles G. Minard, PhD,i and D. Craig Miller, MD,d on behalf of the Aortic Valve Operative Outcomes in Marfan Patients Study Group (. Early and 1-year outcomes of aortic root surgery in patients with Marfan syndrome: A prospective, multicenter, comparative study. J Thorac CardiovascSurg 2014;;147:1758-67.	As in primary outcome measure	As in primary outcome measure	A prospective multinational registry based study of Marfan syndrome patients undergoing aortic surgery. The study had a defines objective, patient section criteria and data collection based on international guidelines. The results show that a low early and 1 yr. mortality which are similar in AVR and AVS groups. AVR had significantly higher rate of pulmonary and cardiac complications. At 1 year follow up major endpoints—including overall survival (P = .6), freedom from MAVRE (P = .6), and valve-related morbidity (P =.7)—were similar between the groups. Freedom from combined NSVD/SVD was greater in the AVR group (99%) than in the AVS group (90%; P = .04). Overall the AVS patients required more surgical reintervention and the AVR patients had a greater incidence of thromboembolic complications. However these two complications cancelled out each others effect when combined in the composite outcome variable. This is a well designed prospective study however due to lack of randomisation, short follow up of 1 year , lack of standardised surgical techniques and inconsistency between the centres on quality of digital images bias and confounding cannnot be ruled out.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	aortic OR aortics OR aorta OR aortas AND marfan OR marfan's OR root OR roots OR enlarg* OR dilat* OR ascend* OR expansion* OR expand* OR wide*
Updated search terms - Intervention	external AND support
Updated search terms - Comparator	bentall OR root replacement OR TRR OR valve-sparing OR valve sparing OR VSRR

Updated search terms - Outcome	n/a
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	The NICE IPG overview contains good background information and a rapid literature review. This review may need updating with new publications and any systematic reviews.
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	n/a