



# Valve-sparing versus valve-replacing aortic root operations in patients with Marfan syndrome

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**Abstract:** Aortic root dissection and rupture is the leading cause of death in patients with Marfan syndrome, a heritable connective tissue disorder that affects 1 in 10,000 individuals. Approximately 80% of those with Marfan syndrome experience annuloaortic ectasia, a distinctive form of aortic root dilation that often leads to aortic or mitral valve regurgitation, congestive heart failure, or aortic dissection or rupture. The cornerstone of care for preventing and managing such complications is replacement of the aortic root. Surgical procedures have evolved since Bentall and De Bono's first aortic root replacement (ARR) in 1968, largely in response to late complications. Today, ARR is low-risk, systematic, and easily reproducible and has all but normalized life expectancy in Marfan syndrome. Nevertheless, long-term effects and durability remain important concerns. ARR surgical approaches include valve-replacement surgery (VRARR) with either a mechanical or tissue prosthetic aortic valve, and valve-sparing surgery (VSARR). VRARR with a mechanical valve is considered a permanent method of repair but requires lifelong anticoagulation, and the durability of bioprosthetic (tissue) valves is unclear. VSARR carries risk for adverse outcomes as well, including a higher likelihood of aortic valve regurgitation and the need for late reoperation; the method also typically involves repair of the valve leaflet, which requires advanced surgical skills and experience. The choice between VSARR and VRARR is often made intraoperatively; whether VSARR is feasible and durable is ultimately determined on the basis of the native aortic valve's performance. For patients with leaflet fenestration, excessive tissue, annular dilation, or free margin elongation, VSARR is rarely applicable. Nonetheless, VSARR has been shown to be superior in terms of hemorrhage, thromboembolism, endocarditis, and re-exploration. Today, valve-sparing procedures are more commonly used than valve-replacement approaches in patients with Marfan syndrome.

**Keywords:** Marfan syndrome; aortic aneurysm; heart defects, congenital; sinus of Valsalva; heart valve prosthesis implantation; cardiac surgical procedures

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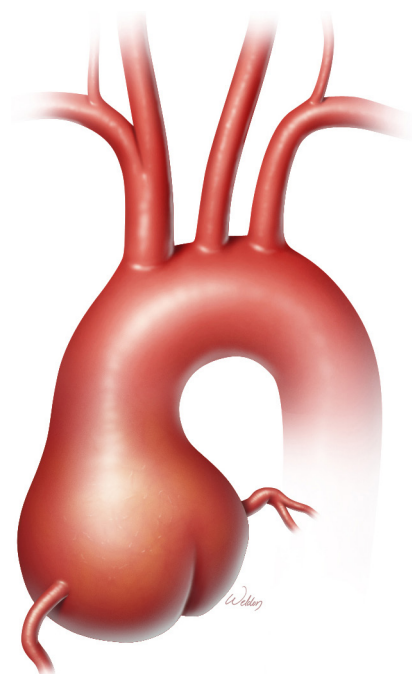
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## Introduction

Aortic root dissection and rupture are the leading causes of death in patients with Marfan syndrome (1,2). Marfan syndrome is a heritable connective tissue disorder with

autosomal dominant inheritance; it is caused by an *FBNI* gene mutation that results in irregular development and cellular handling of the fibrillin-1 protein, a crucial component of the extracellular aortic matrix. The syndrome



**Figure 1** Annuloaortic ectasia, a distinctive dilation of the aortic root in Marfan syndrome. Used with permission from Baylor College of Medicine.

affects approximately 1 in 10,000 individuals (3). The disease is detected using the revised Ghent-2 guidelines, which base the diagnosis on clinical symptoms, family history, and genetic testing (2).

Approximately 80% of patients with Marfan syndrome have annuloaortic ectasia (*Figure 1*), a distinctive form of aortic root dilation that often leads to aortic or mitral valve regurgitation, congestive heart failure, or aortic dissection or rupture (2-4). Any of these factors can shorten life expectancy in these patients (5,6). Before surgical intervention became common, median survival in Marfan syndrome was approximately 48 years, and most premature deaths were due to aortic pathology (6). With the availability of appropriate cardiovascular surgery to minimize the risk for aortic complications, life expectancy for Marfan patients is now similar to that of the general population.

### Evolution of aortic root surgery

The cornerstone of care for preventing and managing aortic complications related to Marfan syndrome is the surgical treatment of the aorta. The procedures undertaken

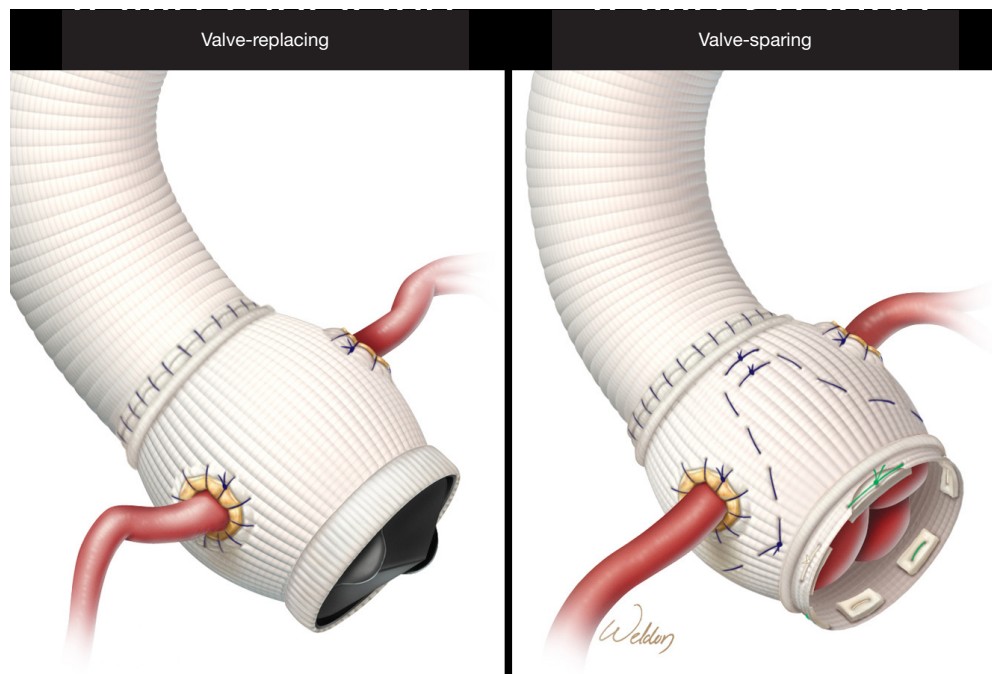
to address the risk for aortic dissection have evolved gradually since 1968, when Bentall and De Bono recorded their first aortic root replacement (ARR) at Hammersmith Hospital (7). This initial ARR, performed in a 33-year-old man with suspected Marfan syndrome, involved the insertion of a mechanical Starr-Edwards valve hand-sewn into a Teflon tube graft, in which the coronary orifices were sutured directly into the graft without separation from the aortic wall, and the native aorta was then wrapped around the root replacement. Two decades later, Kouchoukos *et al.* (8) modified this approach by mobilizing the coronary arteries on tissue buttons, thereby obviating the need for the inclusion technique and reducing the risk for late pseudoaneurysm.

ARR methods have undergone numerous adaptations over time, largely in response to late complications. Now that ARR-related perioperative risk is low and long-term survival is expected, long-term effects and surgical durability have emerged as important considerations. Although excellent results were obtained with ARR using a mechanical valve-replacement procedure, it committed younger patients to a lifetime risk for valve-related thromboembolism and an associated fear of bleeding from the anticoagulation needed to reduce that risk. This limitation engendered interest in developing an alternative approach, leading Yacoub *et al.* (9) and David *et al.* (10) to pioneer native aortic valve preservation during ARR.

### Indications for aortic root surgery in Marfan syndrome

For more than 40 years, patients with Marfan syndrome have undergone elective replacement of the aortic root (11). For those aged 20 to 50 years, elective ARR is usually performed on the basis of patient-specific factors, as stated in current guidelines. Guidelines for asymptomatic patients with Marfan syndrome recommend elective ARR for patients with any of the following: aortic root aneurysm  $\geq 50$  mm in diameter, aortic root aneurysm  $\geq 45$  mm and a family history of aortic dissection, rapid aneurysm expansion ( $>3$  mm per year), extreme aortic or mitral valve regurgitation, or pregnancy plans (12).

In contemporary practice, there are two competing ARR approaches in patients with Marfan syndrome: valve replacement surgery (VRARR) with either a mechanical or tissue prosthetic aortic valve, and valve-sparing surgery (VSARR) (*Figure 2*). VRARR with a mechanical valve requires lifelong anticoagulation; the durability of



**Figure 2** Two types of ARR surgery. (A) Valve replacement surgery with either a mechanical or tissue prosthetic aortic valve; (B) valve-sparing surgery. Used with permission from Baylor College of Medicine. ARR, aortic root replacement.

bioprosthetic (tissue) valves is unclear. VSARR methods include the scalloped remodeling approach developed by Yacoub and colleagues (9), multiple variations of the reimplantation and other techniques introduced by David and colleagues (10), and most recently the Florida sleeve (13), which failed to pass the long-term durability check (14). Notably, the Yacoub remodeling method tended to leave the annulus unsupported and prone to dilatation over time, frequently resulting in late regurgitation of the aortic valve and eventual need for reoperation (15); this has generally limited the use of the Yacoub approach to VSARR, although it may be considered in older patients.

Today, reimplantation approaches, as led by David, are the widely preferred VSARR method; notably, these techniques vary considerably among experienced centers (11,16).

### **The what, who, when, where, why, and how of ARR in Marfan syndrome**

The question for people with Marfan syndrome, their families, and their surgeons is whether to choose VSARR or VRARR, a decision that must take into account these techniques' competing risks; the evidence provided advises the choice but does not promote it.

Because patients with Marfan syndrome can expect an almost normal life span nowadays, the risk for thromboembolic and bleeding events resulting from lifelong oral anticoagulation after mechanical ARR is increasingly a concern, and VSARR appears to be an attractive option for minimizing these risks. Nonetheless, VSARR carries some risk for adverse outcomes. In a study of 1385 patients with Marfan syndrome who underwent ARR, Benedetto *et al.* (17) calculated a 0.7% per year thromboembolic hazard estimate associated with a mechanical valve, compared with a 1.3% per year risk for native valve failure requiring reoperation.

Accurately assessing an individual patient's risk for stroke versus the likelihood of reoperation can be difficult. The choice between VSARR and VRARR is often made intraoperatively; whether VSARR is feasible and durable is ultimately determined on the basis of the native aortic valve's performance. For patients with substantial leaflet fenestration, excessive tissue, annular dilation, or free margin elongation, VSARR is a poor choice in the hands of most surgeons (18).

In 1999, Gott *et al.* (19) published a landmark multicenter report showing that ARR can prolong life in patients with Marfan syndrome. Ten surgical centers, including our own, contributed data for this study. The

benefit of ARR in Marfan syndrome patients was clear: with low risk for surgical death (3.3%), prophylactic repair dramatically changed these patients' prognosis from a terminal sentence to a survivable condition. The vast majority of this experience was VRARR; however, a small cohort of VSARR was included. There were few differences in early results between the VRARR and VSARR cohorts, who had similarly low rates of operational death. The article described VRARR as a permanent method of repair and the treatment of choice for most surgeons, noting that "the role of valve-sparing procedures in Marfan syndrome patients remains unclear".

The AVOMP (Aortic Valve Operative Outcomes in Marfan Patients) prospective, international registry study examined early and mid-term VRARR and VSARR outcomes in Marfan syndrome patients (20). The overall impression from this study, given a significantly longer period of cardiopulmonary bypass, aortic cross-clamp, and surgery in the VSARR cohort, was that the form of ARR had no effect on early results. More specifically, results showed that VSARR does not have to be limited to technically gifted surgeons, but is a reproducible strategy.

In a subsequent study of 1-year results from the same registry, the survival rates for VRARR and VSARR groups were comparable, and the type of procedure was not significantly associated with any valve-related events (21). Although functional mortality rates were comparable (one in each group), 7% of VSARR patients had more than mild aortic valve regurgitation at 1 year, validating previous durability concerns.

A study from Hamburg (22) on ARR outcomes in patients with Marfan syndrome over a short observation period found two deaths from heart failure and arrhythmia during the observation period among 58 patients who underwent the David procedure. Freedom from aortic regurgitation rated as moderate or greater was 80% at 10 years, and only two patients (3.4%) had repeated aortic root surgery.

Benedetto *et al.* (17) published a systematic review and meta-analysis of 11 articles culled from an initial assessment of 530 studies identified via PubMed, Embase, and the Cochrane library. In this analysis of long-term results of 1,385 Marfan syndrome patients (Bentall procedure: 972 patients; VSARR: 413 patients), no differences were found in valve-related complication or endocarditis rates; however, the thromboembolism rate was higher in VRARR, and the aortic valve reintervention rate was higher in VSARR.

In a 2014 systematic review of six clinical trials, Hu

*et al.* (23) analyzed data from 539 patients with Marfan syndrome; the risk ratios for complications (re-exploration for hemorrhage, early mortality, thromboembolism, endocarditis, repeat surgery on the aortic root, late mortality) were calculated for VSARR versus the Bentall procedure, along with the incidence of moderate or severe regurgitation in various procedure types. The results confirmed VSARR's superiority in terms of hemorrhage, thromboembolism, endocarditis, re-exploration, and long-term survival. Moderate or severe regurgitation occurred in 2–5% of patients undergoing the David procedure, approximately 20% of patients undergoing the Yacoub procedure, and 0–8% of patients with a Valsalva graft; those undergoing the Yacoub procedure, which tends to leave the annulus unsupported, had a higher incidence of regurgitation than did the other VSARR patients.

A recent systematic review and meta-analysis reported by Flynn *et al.* (24) evaluated 23 studies reporting the outcomes of aortic root surgery in 2,976 Marfan patients. Of these, 1,624 patients were treated with VRARR and 1,352 patients were treated with VSARR. Compared with VRARR, VSARR was associated with reduced risk for thromboembolism, late hemorrhagic complications, and endocarditis. No significant difference was found in reintervention rates between VSARR and VRARR. This study showed that an increasing body of evidence indicates that VSARR can be reliably performed in patients with Marfan syndrome.

## Conclusions

Over time, prophylactic repair at lower aortic diameters in patients with Marfan syndrome has been made possible by advances ensuring that ARR could be repeated safely at multiple sites, could be accomplished with a low early mortality rate, and could extend life. Although unanswered questions remain about the optimal ARR approach for patients with Marfan syndrome, as evident in various contemporary publications (14,21–24), valve-sparing procedures are now more commonly used than valve-replacement approaches in these patients. Nevertheless, VSARR approaches were developed by master surgeons, and it should be borne in mind that this method often includes painstaking repair of the valve leaflet, which requires advanced surgical skills. In the end, the choice between VRARR and VSARR is complex and requires input from the patient as well as guidance from an experienced surgeon.

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## Footnote

*Conflicts of Interest:* Dr. Coselli consults for and participates in clinical trials with Medtronic and W.L. Gore; and consults for, participates in clinical trials with, and receives royalties and grant support from Terumo Aortic. Dr. Cekmecelioglu has no conflicts of interest to declare.

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