The freestyle valve as a right ventricle to pulmonary artery conduit.  
A systematic review and meta-analysis

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ABSTRACT

Introduction: Reconstruction of the right ventricular outflow tract is the most commonly performed valve repair/replacement procedure in congenital cardiac surgery. There is an ongoing shortage of homografts, and existing bioprosthetic options suffer from substantial rates of structural valve deterioration over time. The Medtronic Freestyle valve is used extensively in the aortic position, but little data is available on its performance in the pulmonary position.

Methods: A systematic review and meta-analysis of primary studies reporting echocardiographic and clinical outcomes, including reintervention and functional status, associated with the Freestyle valve in the pulmonary position for both Ross and congenital surgery.

Results: 13 observational studies including 334 patients with a mean follow-up of 34 months (range 10-98 months) fulfilled the eligibility criteria and were included in the review. Structural valve deterioration occurred in 4.8% (95% confidence interval 0.8-10.6%) of patients. Reintervention was required in 1.1% (95% confidence interval 0.0-3.3%). Freedom from symptoms of heart failure occurred in 97.7% (94.6-99.7%). The results did not change substantially when analysed according to Ross or congenital surgery.

Conclusions: The Freestyle valve performs well at short-term follow-up and provides a viable alternative when homografts are unavailable. Further long-term studies are required to better assess its role in right ventricular outflow tract reconstruction.

Keywords: pulmonary valve replacement, right ventricular outflow tract reconstruction, freestyle valve, tetralogy of Fallot, Ross procedure.

INTRODUCTION

Pulmonary valve replacement (PVR) or right ventricular outflow tract reconstruction (RVOTR) is the most common valve replacement/repair procedure performed in the Society of Thoracic Surgeons (STS) Congenital database, comprising 16% of procedures performed in the adult congenital population.

There is a growing population of children surviving well into adulthood with repaired congenital heart disease and the number of PVR/RVOTR procedures required will grow with this population.

Since Ross performed the first RVOTR using an aortic homograft in 1966 (1), the search for the optimal conduit choice has been the subject of much debate. Whilst a cryopreserved homograft is the gold standard, calcification and homograft failure remain an issue, with only 40-75% of homografts remaining free from structural valve deterioration (SVD) at 10 years in the congenital population (2, 3). Alternative bio-
prostheses face similar longevity problems (4, 5). An alternative is the Medtronic Freestyle valve, derived from a porcine aortic root, decellularised using glutaraldehyde and treated with alpha-amino oleic acid to minimize xenograft calcification. Potential benefits include its stentless design, the possibility to achieve a greater effective orifice area, the availability in a range of sizes (19-29 mm), and the lack of requirement for lifelong anticoagulation. Comparative outcomes however, remain uncertain.

The aim of this study, therefore, was to systematically review all of the primary publications describing the outcomes associated with using the Freestyle valve for RVOTR in both the Ross procedure and in congenital heart disease, primarily to determine short-term rates of structural valve dysfunction and reintervention, and functional status. These outcomes were compared to those outcomes with homografts and alternative bioprostheses.

**METHODS**

A review of available literature was undertaken via online searches of the major clinical databases: Medline, Pubmed, Cochrane database and Google Scholar. The search terms used were - “Freestyle” OR “Xenograft” OR “Stentless”, AND “Pulmonary Valve Replacement” OR “Right Ventricular Outflow Tract”. The search years included ranged from January 1980 to October 2014. Bibliographies, from included papers, were assessed for suitable references in an attempt to avoid missing potentially useful material.

Publications were eligible for inclusion if they presented original data on Freestyle valves in the pulmonary position. Review articles and opinion pieces, isolated case reports and animal studies were excluded because they lacked any outcomes of interest. All publications deemed suitable for inclusion on the above criteria were reviewed separately by two authors (BD and DA) to ensure suitability and disagreements resolved by consensus. Level of evidence for each study was recorded.

Data was extracted from the included studies into a prespecified case report form. The primary outcome of interest was rates of structural valve deterioration as defined by Akins et al. (6) in their joint STS/AATS/EACTS report. Secondary outcomes of interest included reintervention (defined as percutaneous balloon valvuloplasty, percutaneous PVR or surgical revision) and functional status (defined according to New York Heart Association class or modified Ross score).

Meta-analysis was undertaken where sufficient data existed to pool studies, using a fixed effects or random effects model depending on study heterogeneity. We defined a priori two subgroups: one group that underwent RVOTR as part of a Ross procedure and another group that underwent RVOTR as surgical management of congenital heart disease.

Two statistical models, namely, fixed effects and random effects models, were used depending on study heterogeneity. Fixed effects models were used if the between study variance was less than 0, whilst a random effects model was used, where the between study variance was larger than 0.

A search for comparative series of alternative bioprostheses and homografts was also performed to allow for comparison with the results of our meta-analysis.

**RESULTS**

A total of 435 papers were initially retrieved with the search strategy described above, of which 13 retrospective case series fulfilled the eligibility criteria and were included in the systematic review. No randomized
trials or prospective series were identified (Figure 1).
One study presented their data only as a Kaplan Meier curve and so could not be analysed with the other 12 studies but was reviewed separately. The twelve papers included in the meta-analysis yielded data on 311 patients with a mean follow-up of 33.6 months. Of the 12 studies, 2 reported on solely paediatric patients, 3 reported solely on adult patients and 7 reported data on both paediatric and adult patients. Seven of the papers solely reviewed cohorts of patients that RVOTR were performed on as part of a Ross procedure, while the other 5 papers were from series of predominantly congenital cases (Table 1).

**Structural valve deterioration.** Twelve studies (n = 311) reported echocardiographic data on SVD at 34 months follow-up (range 10-98 months). The mean rate of SVD was 4.8% (95% confidence interval (CI) 0.8-10.6%). Analyzing Ross recipients separately (7 studies, n = 137), the pooled rate of SVD was 7.1% (95% CI 0.2-19.3%) at 45 months follow-up. For congenital recipients (5 studies, n = 174 patients) the pooled rate of SVD was 3.5% (95% CI 0.9-7.3%) at 18 months.

Heterogeneity between studies was high, so random effects modeling was used for this analysis.

**Reintervention data.** Reintervention was reported in twelve studies (n = 311) with a
Table 1 - Characteristics of the included studies.

| Author            | Year | Study Design            | Level of Evidence | n  | Mean follow-up (months) | Ross/Congenital | Clinical follow-up |
|-------------------|------|-------------------------|-------------------|----|------------------------|-----------------|-------------------|
| Miskovic et al. (9) | 2012 | Retrospective case series | Level 4           | 73 | 36                     | Ross N          |                   |
| Novick et al. (10) | 2004 | Retrospective case series | Level 4           | 10 | 35                     | Ross N          |                   |
| Bilal et al. (11)  | 2006 | Retrospective case series | Level 4           | 14 | 51                     | Ross Y          |                   |
| Tsukube et al. (12)| 2002 | Retrospective case series | Level 4           | 4  | 24                     | Ross Y          |                   |
| Dohmen et al. (7)  | 2001 | Retrospective case series | Level 4           | 9  | 60                     | Ross Y          |                   |
| Konertz et al. (13)| 1996 | Retrospective case series | Level 4           | 9  | 12                     | Ross Y          |                   |
| Hechadi et al. (8) | 2013 | Retrospective case series | Level 4           | 18 | 98                     | Ross Y          |                   |
| Kanter et al. (14)| 2003 | Retrospective case series | Level 4           | 56 | 30                     | Congenital Y    |                   |
| Chard et al. (15)  | 2001 | Retrospective case series | Level 4           | 13 | 10                     | Congenital N    |                   |
| Hartz et al. (16)  | 2003 | Retrospective case series | Level 4           | 47 | 14                     | Congenital Y    |                   |
| Erez et al. (17)   | 2006 | Retrospective case series | Level 4           | 47 | 13                     | Congenital Y    |                   |
| Erek et al. (18)   | 2003 | Retrospective case series | Level 4           | 27 | 20.9                   | Congenital Y    |                   |
| Total              |      |                         |                   | 311| 33.6                   |                 |                   |

Table 2 - Pooled outcome data for Freestyle Valves.

|                  | Total  | Ross          | Congenital     |
|------------------|--------|---------------|----------------|
| n                | 311    | 137           | 174            |
| Overall follow-up (months) | 34     | 45            | 18             |
| SVD              | 4.8% (0.8-10.6%) | 7.1% (0.2-19.3%) | 3.5% (0.9-7.3%) |
| Reintervention   | 1.1% (0.0-3.3%) | 2.1% (0.0-6.4%) | 1.0% (0.1-3.7%) |
| Asymptomatic     | 97.7% (94.6-99.7%) | 91.7% (81.2-98.9%) | 97.6% (94.2-99.7%) |

SVD = Structural Valve Deterioration.
SVD, but did describe that three cases were due to conduit compression by the overlying sternum.

**Functional status.** Eight of the twelve studies (n=214) provided data on the functional status of their patients with a mean follow-up of 36 months. Freedom from the symptoms of heart failure was 97.7% (95% CI 94.6-99.7%). In the Ross population (n=53), it was 91.7% (95% CI 81.2-98.9%). In the congenital population (n=161), it was 97.6% (95% CI 94.2-99.7%). Heterogeneity between studies was low, so fixed effects modeling was used for this analysis (Table 2).

**RESULTS**

**Alternatives.** There are a number of alternative bioprostheses available for RVOTR. A review of all available prosthetic options was also performed to allow for comparison between the many available alternatives (see table 3). There is a shortage of truly long-term data available, however 5-year results are available for most bioprostheses. Across all bioprostheses a 5-year failure rate of 10-40% exists, with failure rates at 10 years climbing to 25-60% (Table 3).

**DISCUSSION**

To our knowledge, this is the first systematic review and meta-analysis of the performance of the Medtronic Freestyle valve in the pulmonary position. Several important findings bear further consideration. First, our results suggest that the Freestyle valve has a low incidence of SVD, reintervention and symptoms of heart failure, and compares well with alternative bioprostheses at similar relatively short duration of follow-up. Proximal suture line pannus was noted in a small minority of cases. This is an atypical failure mode for RV-PA conduits and it may relate to the stiffness of the Freestyle root wall in comparison to the mobility of the muscular RVOT leading to anastomotic site tension.

Second, long-term follow-up data for the Freestyle valve in the pulmonary position is limited. Only 3 studies (5, 7, 8) have truly long-term data on the performance of the Freestyle valve and display markedly different results. Dohmen (7) and Hechadi (8) had no SVD or Reintervention at 60 and 98 months follow-up respectively, while Lee (5) describes a 69% rate of Reintervention at 90 months. Further studies are required to truly determine the long-term outcomes of this valve in the pulmonary position.

Third, the promising findings potentially increasing options for RVOTR may stimulate competition within the industry and provide the impetus to reduce the cost of these bioprostheses; a cost-effectiveness analysis may provide further useful data to guide clinicians.

**Table 3 - Alternative bioprostheses.**

| Bioprosthesis            | SVD at 3 years | SVD at 5 years | SVD at 10 years |
|--------------------------|----------------|----------------|-----------------|
| Homografts               | 12% (19)       | 40% (2)        | 25-60% (2, 3)   |
| Bovine pericardial       | 11% (20)       | 22% (4)        |                 |
| Contegra                 | 20-27% (21, 22)|               |                 |
| Edwards Prima            | 20% (23)       | 7% (24)        |                 |
| Edwards porcine conduit  | 0% (25)        |               |                 |
| Hancock II               | 4.17% (26, 27) | 50% (5)        |                 |
| Melody                   | 2-10% (28-30)  |               |                 |
| Perimount                | 11-26% (27, 31)| 20% (5)        |                 |
| Toronto SPV              | 10.5% (32)     |               |                 |

SVD = Structural Valve Deterioration.
Finally, this study has a number of limitations. The meta-analysis did not include any randomized controlled trials of the Freestyle valve, the patient numbers were low and the duration of follow-up relatively short, precluding definitive conclusions in comparing valve outcomes. Nevertheless, early results with the Freestyle valve compare favourably with available alternatives. The included studies were also heterogeneous in nature with a mixture of pediatric and adult patients, and no data on valve sizes used was available. We did however identify a priori subgroups for analysis and did not find substantial differences upon analysis according to Ross or congenital procedure, although mean length of follow-up differed between these two groups.

**CONCLUSION**

Pulmonary valve replacement or right ventricular outflow tract reconstruction using the Freestyle valve is associated with satisfactory short-term echocardiographic and clinical outcomes, including functional status and freedom from reintervention at over 2 years. Freestyle valves may be a reasonable alternative to homografts or other bioprostheses, particularly when homografts are not readily available.

Determination of the optimal valve, however, is currently limited by lack of long-term comparative data and this review has identified a significant need for long-term data on the Freestyle valve in the pulmonary position.

**REFERENCES**

1. Ross D, Somerville J. Correction of pulmonary atresia with a homograft aortic valve. The Lancet. 1966; 288: 1446-7.
2. SelametTierney ES, Gersony WM, Altman K, Solowiczynk DE, Bevilacqua LM, Khan C, et al. Pulmonary position cryopreserved homografts: durability in pediatric Ross and non-Ross patients. The Journal of thoracic and cardiovascular surgery. 2005; 130: 282-6.
3. Meyns B, Jashari R, Gewillig M, Mertens L, Komarek A, Lesaffre E, et al. Factors influencing the survival of cryopreserved homografts. The second homograft performs as well as the first. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery. 2005; 28: 211-6.
4. Zaharia R, Malik S, Jaquiss RD, Imamura M, Gossett J, Morrow WR. Risk factors for prosthesis failure in pulmonary valve replacement. The Annals of thoracic surgery. 2011; 91: 561-5.
5. Lee C, Park CS, Lee CH, Kwak JG, Kim SJ, Shim WS, et al. Durability of bioprosthetic valves in the pulmonary position: long-term follow-up of 181 implants in patients with congenital heart disease. The Journal of thoracic and cardiovascular surgery. 2011; 142: 351-8.
6. Akins CW, Miller DC, Turina MJ, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. European Journal of Cardio-Thoracic Surgery. 2008; 33: 523-8.
7. Dohmen P, Hotz H, Lembcke A, Kivelitz D, Hamm B, Konertz W. Magnetic resonance imaging of stentless xenografts for reconstruction of right ventricular outflow tract. Seminars in thoracic and cardiovascular surgery. 2001.
8. Hechadi J, Gerber BL, Coche E, Melchior J, Jashari R, Glineur D, et al. Stentless xenografts as an alternative to pulmonary homografts in the Ross operation. Eur J Cardiothorac Surg. 2013; 44: 32-9.
9. Miskovic A, Monsef N, Doss M, Özaskan F, Karimian A, Möritz A. Comparison between homografts and Freestyle® bioprosthesis for right ventricular outflow tract replacement in Ross procedures. Eur J Cardiothorac Surg. 2012; 42: 927-33.
10. Novick WM, Anic D, Lora Solf A, Arboleda Torres M, Niño De Guzmán León I, Reid RW, et al. Medtronic freestyle valve for right ventricular reconstruction in pediatric Ross operations. The Annals of thoracic surgery. 2004; 77: 1711-6.
11. Bilal MS, Aydemir NA, Cine N, Turan T, Yildiz Y, Yalcin Y, et al. Intermediate-term results of Medtronic freestyle valve for right ventricular outflow tract reconstruction in the Ross procedure. The Journal of heart valve disease. 2006; 15: 696-701.
12. Tsuchibe T, Kawanishi Y, Murakami H, Hino Y, Matsukawa K, Ozaki N, et al. Reconstruction of right ventricular outflow tract with stentless xenografts in Ross procedure. Artifitial organs. 2002; 26: 1055-9.
13. Konertz W, Sidiropoulos A, Hotz H, Borges A, Baumann G. Ross operation and right ventricular outflow tract reconstruction with stentless xenografts. The Journal of heart valve disease. 1996; 5: 418-20.
14. Kanter KR, Fyfe DA. Mahle WT, Forbess JM, Kirshbom PM. Results with the freestyle porcine aortic root for right ventricular outflow tract reconstruction in children. The Annals of thoracic surgery. 2003; 76: 1889-95.
15. Chard RB, Kang N, Andrews DR, Nunn GR. Use of the Medtronic Freestyle valve as a right ventricular to pulmonary artery conduit. The Annals of thoracic surgery. 2001; 71: 361-4.
16. Hartz RS, Deleon SY, Lane J, Dorotan J, Joyce J, Urbina E, et al. Medtronic freestyle valves in right ventricular outflow tract reconstruction. The Annals of thoracic surgery. 2003; 76: 1896-900.
17. Erez E, Tam V, Doublin N, Stakes J. Repeat right ventricular outflow tract reconstruction using the Medtronic Freestyle porcine aortic root. The Journal of heart valve disease. 2006; 15: 92-6.
18. Erek E, Yalcinbas YK, Salihoglu E, Ozturk N, Arat S, Sarigolu A, et al. Fate of stentless bioprostheses on right side of the heart. Asian Cardiovascular and Thoracic Annals. 2003; 11: 58-62.
19. Niwaya K, Knott-Craig CJ, Lane MM, Chandrasekaren K, Overholt ED, Elkins RC. Cryopreserved Homograft Valves In The Pulmonary Position: Risk Factor Analysis For Intermediate-Term Failure. The Journal of thoracic and cardiovascular surgery. 1999; 117: 141-7.

20. Shinkawa T, Anagnostopoulos PV, Johnson NC, Watanabe N, Sapru A, Azakie A. Performance of Bovine Pericardial Valves in the Pulmonary Position. Ann Thorac Surg. 2010; 90: 1295-300.

21. Fiore AC, Brown JW, Turrentine MW, Ruzmetov M, Huynh D, Hanley S, et al. A Bovine Jugular Vein Conduit: A Ten-Year Bi-Institutional Experience. Ann Thorac Surg. 2011; 92: 183-92.

22. Breymann T, Blanz U, Wojtalik MA, Daenen W, Hetzer R, Sarris G, et al. European Contegra multicentre study: 7-year results after 165 valved bovine jugular vein graft implantations. The Thoracic and cardiovascular surgeon. 2009; 57: 257-69.

23. Schmid FX, Keyser A, Wiesenack C, Holmer S, Birnbaum DE. Stentless Xenografts and Homografts for Right Ventricular Outflow Tract Reconstruction During the Ross Operation. Ann Thorac Surg. 2002; 74: 684-8.

24. Hawkins JA, Sower CT, Lambert LM, Kouretas PC, Burch PT, Kaza AK, et al. Stentless porcine valves in the right ventricular outflow tract: improved durability? European Journal of Cardio-Thoracic Surgery. 2009; 35: 600-5.

25. Schiralli MP, Cholette JM, Swartz MF, Vermilion R, Meagher C, Alferis GM. Carpentier Edwards Porcine Valved Conduit for Right Ventricular Outflow Tract Reconstruct. J Card Surg. 2011; 26: 643-9.

26. Rüffer A, Wittmann J, Potapov S, Purbojo A, Glöckler M, Koch AM, et al. Mid-term experience with the Hancock porcine-valved Dacron conduit for right ventricular outflow tract reconstruction. Eur J Cardiothorac Surg. 2012; 48: 988-95.

27. Jang W, Kim YJ, Choi K, Lim HG, Kim WH, Lee JR. Mid-term results of bioprosthetic pulmonary valve replacement in pulmonary regurgitation after tetralogy of Fallot repair. Eur J Cardiothorac Surg. 2012; 42: 1-8.

28. Gillespie MJ, Rome JJ, Levi DS, Williams RJ, Rhodes JF, Cheatham JP, et al. Melody Valve Implant Within Failed Bioprosthetic Valves in the Pulmonary Position A Multi-center Experience. Circ Cardiovasc Interv. 2012; 5: 862-70.

29. Meadows JJ, Moore FM, Berman DP, Cheatham JP, Cheatham SL, Porras D, et al. Use and Performance of the Melody Transcatheter Pulmonary Valve in Native and Postsurgical, Nonconduit Right Ventricular Outflow Tracts. Circ Cardiovasc Interv. 2014; 7: 374-80.

30. McElhinney DB, Hellenbrand WE, Zahn EM, Jones TK, Cheatham JP, Lock JE, et al. Short-and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation. 2010; 122: 507-16.

31. Neukamm C, Lindberg HL, Try K, Dohlen G, Norgard G. Pulmonary Valve Replacement With a Bovine Pericardial Valve: A Five Year Follow-Up Study. World J Pediatr Congenit Heart Surg. 2014; 5: 534-40.

32. Black MD, Ley SJ, Regal AM, Shaw RE. Novel approach to right ventricular outflow tract reconstruction using a stentless porcine valve. Ann Thorac Surg. 2008; 85: 195-8.

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