

Long-term survival after xenograft versus homograft aortic root replacement: Results from a prospective randomized trial



Giovanni Melina, MD, PhD,^{a,b} Fabio De Robertis, MD,^a Jullien A. Gaer, MS, FRCS(C-th),^a Emiliano Angeloni, MD, PhD,^b Ismail El-Hamamsy, MD, PhD, FRCSC,^c Toufan Bahrami, MD,^a John R. Pepper, OBE, MA, MChir, FRCS,^a Johanna J. M. Takkenberg, MD, PhD,^d and Magdi H. Yacoub, OM, FRS^e

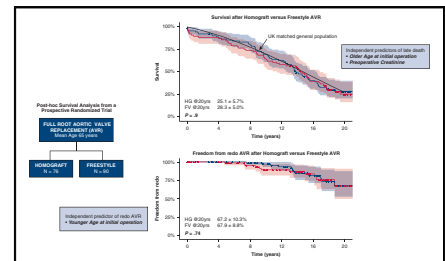
ABSTRACT

Objective: The study objective was to investigate the long-term survival of patients undergoing xenograft versus homograft full root aortic valve replacement.

Methods: A total of 166 patients requiring aortic valve surgery were randomized to undergo the Freestyle (Medtronic Inc, Minneapolis, Minn) bioprosthesis (N = 90) or a homograft (N = 76) full root aortic valve replacement between 1997 and 2005 in a single institution. Six patients randomly assigned to the homograft crossed over to the Freestyle bioprosthesis because of the unavailability of suitably sized homografts. All surgeons were required to adhere to the standard surgical technique for homograft root implantation previously described. Follow-up was 98.5% complete.

Results: The mean age of the study population was 65 ± 8 years. Coronary artery bypass grafting was associated with root aortic valve replacement in 76 of 166 patients (46%, $P =$ not significant between groups), and overall hospital mortality was 4.8% (8/166, $P =$ not significant between groups). Median follow-up was 13.8 years (range, 0-21.8 years; 2033 patient-years). The Kaplan–Meier survival analysis showed that there was no significant difference in overall survival between the 2 arms at 5, 10, and 15 years. Twenty-year survival was $28.3\% \pm 5\%$ for the Freestyle group versus $25.1\% \pm 5.7\%$ for the homograft group ($P = .90$), which was comparable to the age- and sex-matched UK general population. The freedom from aortic valve reoperation at 20 years was comparable for the Freestyle group versus the homograft group ($67.9\% \pm 8.8\%$ vs $67.2\% \pm 10.3\%$, respectively; $P = .74$).

Conclusions: This is the first study to investigate the long-term survival of xenograft versus homograft full root aortic valve replacement from a prospective randomized trial. The observed 20-year overall survival and freedom from aortic valve reoperation serve as a benchmark for future studies on interventions for aortic valve disease in the elderly. (*J Thorac Cardiovasc Surg* 2021;161:57-65)



Long-term results of homograft versus Freestyle (Medtronic Inc, Minneapolis, Minn) full aortic root replacement trial.

Central Message

Long-term survival of patients undergoing surgery for aortic valve disease with Freestyle (Medtronic Inc, Minneapolis, Minn) or homograft full root replacement is comparable to that of the age- and sex-matched UK general population.

Perspective

The results of this prospective randomized trial provide strong evidence of comparable survival after full aortic root replacement using xenografts or homografts. In addition, in the present era of large and expanding TAVR, this study may serve as an important tool of comparison for future analyses.

The number of candidates for aortic valve surgery is increasing progressively, in particular because of the aging population.¹⁻³ In this group of patients, tissue valves are preferred over mechanical prostheses because of quality of

life and the fact that lifelong anticoagulation is not required.⁴ Several biological devices are available,⁴⁻⁷ including those implanted via the recently introduced transcatheter procedures, but the impact of the choice of

From the ^aRoyal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; ^bDepartment of Cardiac Surgery, Ospedale Sant'Andrea, "Sapienza" Università di Roma, Rome, Italy; ^cDivision of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; ^dDepartment of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands; and ^eImperial College, London, United Kingdom.

Read at the 98th Annual Meeting of The American Association for Thoracic Surgery, San Diego, California, April 28-May 1, 2018.

Received for publication April 30, 2018; revisions received Sept 1, 2019; accepted for publication Sept 4, 2019; available ahead of print Oct 4, 2019.

Address for reprints: Giovanni Melina, MD, PhD, The Magdi Yacoub Institute, Harefield Heart Science Centre, Hill End Rd, Harefield UB9 6JH, United Kingdom (E-mail: gmelina@ospedalesantandrea.it).

0022-5223/\$36.00

Copyright © 2019 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.09.119>

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
HR	= hazard ratio
TAVI	= transcatheter aortic valve implantation

▶ Scanning this QR code will take you to the article title page to access supplementary information. To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.



prosthesis on long-term survival is not known. Unstented bioprostheses, particularly when implanted as full roots, are thought to offer more favorable outcomes, allowing for better hemodynamics and durability compared with their stented counterparts.^{4,8} Recently published systematic reviews and meta-analyses on outcomes of biological prostheses implanted in the aortic position show good results in the elderly at midterm follow-up.^{4,9} However, the ideal aortic valve substitute remains undetermined because of the scarcity of prospective randomized trials comparing different surgical options. As we have previously reported the initial results of 2 unstented aortic valves randomly assigned to homograft or Freestyle (Medtronic Inc, Minneapolis, Minn) root replacement,^{10,11} with the present investigation we have looked at the late survival and its determinants, comparing it with the general population. This could guide the choice of operation and might even act as a benchmark for the new-generation valves.

MATERIALS AND METHODS

Study Population

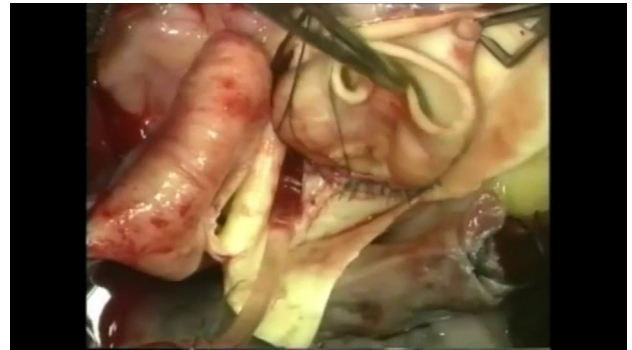
The protocol of the present prospective randomized trial was approved by the local ethics committee. Every patient was informed, and written consent to participate in the study was obtained.

Through the period 1997 to 2005, a total of 166 patients scheduled for aortic valve surgery were prospectively randomly allocated to receive a homograft ($n = 76$) or a Medtronic Freestyle (Medtronic Inc, Minneapolis, Minn) full root replacement ($n = 90$). Inclusion criteria were age 40 years or more and the need for aortic valve surgery; thus, previous cardiac surgery, active endocarditis, and the need for concomitant procedures did not preclude enrollment in the study. Exclusion criteria were known systemic illness affecting long-term survival and age less than 40 years.

During the study period, 6 patients randomized to the homograft group crossed over to the Freestyle group in the operating room because a suitable homograft was not available. Patients were then analyzed according to the treatment received.

Surgical Technique

The standard surgical technique for homograft or Freestyle root replacement has been described.^{10,11} In short, a full aortic root replacement



VIDEO 1. Full aortic root replacement technique. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)32134-8/fulltext](https://www.jtcvs.org/article/S0022-5223(19)32134-8/fulltext).

with coronary artery reimplantation was performed using the largest implantable prosthesis. There was no subcoronary implantation procedure, and no reinforcement techniques or synthetic material were used to support the surgical anastomoses. As shown in **Video 1**, the proximal anastomosis between the prosthetic root and the patients' aortic annulus was performed using multiple interrupted 3/0 or 4/0 braided polyester nonabsorbable sutures. The native coronary ostia were implanted in their respective aortic sinuses. Because the height and angle between the native porcine coronary ostia in Freestyle prostheses may be different from that in normal human anatomy, new ostia were fashioned to avoid tension, torsion, or kinking of the proximal coronary arteries (**Video 1**).

Homograft Procurement

Two types of homografts were used: "homovital" homografts ($N = 30$) and cryopreserved antibiotic-sterilized homografts ($N = 46$). Homovital homografts were obtained from heart transplantation recipients and immediately placed in sterile culture medium with a low-concentration antibiotic solution for 72 hours at 4°C (1% penicillin/1% streptomycin). The median time from dissection to implantation was 7 days (range, 1-30 days). The remaining homografts were harvested from routine postmortem examination and processed at the Royal Brompton Tissue Bank. Homografts were dissected using a sterile technique and sterilized using a nutrient antibiotic solution (Gaya 5¹⁰), followed by cryopreservation and storage at -130°C for up to 5 years until use.

Follow-up

All patients were followed up at a single institution (The Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom) at regular intervals between 6 and 9 months. In the case of patients not attending, the families were contacted, rendering the follow-up to be 98.5% complete. Completeness of follow-up was calculated with Clark's C.¹²

Statistical Analysis

Analyses of data were performed using the statistical package SPSS Statistics, version 24 (IBM Corp, New York, NY). Data are expressed as mean \pm standard deviation or median (range) for continuous variables and as absolute number (percentage) for categorical variables.

Survival analysis was performed using the Kaplan–Meier method, and the log-rank test was used to compare curves. Kaplan–Meier estimates of the survival of all patients were compared with a matched cohort for age, sex, and year of surgery.

Univariable and multivariable Cox regression models were constructed to study determinants of survival. All variables in **Table 1** and data in **Table 2** regarding operative details were considered for the univariable analysis, and those with a P value less than .1 were included in the multivariable analysis.

TABLE 1. Baseline characteristics

Variable	Homograft (N = 76)	Freestyle (N = 90)	P value
Age, y	64.1 ± 9.2	66.0 ± 8.2	.2
Sex, male	49 (64)	61 (68)	.6
BSA, m ²	1.89 ± 0.22	1.88 ± 0.21	.8
Creatinine, mmol/L	102.1 ± 27.5	99.7 ± 28.8	.7
LVEF, %	57.2 ± 24.8	64.0 ± 13.6	.1
Aortic stenosis	51 (67)	63 (70)	.5
Previous surgery	14 (18)	16 (18)	.9
Comorbidities			
Coronary artery disease	37 (49)	46 (51)	.8
Diabetes	11 (14)	6 (7)	.5
Dyslipidemia	5 (7)	4 (4)	.5
Renal failure	9 (12)	11 (12)	.8
Hypertension	24 (32)	19 (21)	.2
Previous CVA	1 (1)	3 (3)	.6
Previous TIA	8 (11)	5 (6)	.4
Peripheral vascular disease	1 (1)	0 (0)	.4
Infective endocarditis	2 (3)	2 (2)	.9
Aortic valve pathology			
Degenerative	51 (67)	57 (63)	1.0
Congenital	17 (22)	23 (26)	.7
Rheumatic	8 (11)	10 (11)	1.0

Values are mean ± standard deviation, n (%). BSA, Body surface area; LVEF, left ventricular ejection fraction; CVA, cerebrovascular accident; TIA, transient ischemic attack.

RESULTS

Baseline Characteristics

Patient characteristics, as previously reported,¹⁰ are listed in Table 1. The mean age at the time of operation was 65.1 ± 8.7 years (range, 40–82 years). Overall, there were 110 of 166 men (66.3%) and 56 of 166 women (33.7%). The original aortic valve pathology was senile degeneration in 108 of 166 patients (65%), congenital in 40 of 166 patients (24%), and rheumatic in 18 of 166 patients (11%). The main indication for surgery was aortic valve stenosis (114/166, 69%).

Early Results

As shown in Table 2, operative data were similar between groups. In the homograft group, the homografts implanted were cryopreserved in 61% of the patients and fresh, or “homovital,” in 39% of the patients. The use of the Freestyle valve as a root permitted oversizing of the valves; the 2 most common sizes were 25 and 27 mm (N = 68/90, 76%). Concomitant procedures were associated with root replacement in 76 of 166 patients (46%). In particular, coronary artery bypass grafting (CABG) was performed in 43% of both homograft and Freestyle recipients. Overall, there were 8 of 166 hospital deaths (4.8%). The hospital

TABLE 2. Operative and postoperative outcomes

Variable	Homograft (N = 76)	Freestyle (N = 90)	P value
Overall hospital mortality	4 (5.3)	4 (4.5)	.5
Isolated root replacement	1/40 (2.7)	0/50 (0)	
Concomitant procedures			
CABG	33 (43)	39 (43)	1.0
AAR	3 (4)	1 (1)	.8
Crossclamp time, min	90 ± 30	94 ± 24	.8
CPB time, min	131 ± 37	139 ± 42	.2
Mechanical ventilation >48 h	13 (17)	15 (17)	.9
Inotropes >48 h	25 (33)	29 (32)	.8
Postoperative complications			
Reexploration	5 (7)	8 (9)	.8
Sternal infection	2 (3)	4 (4)	.7
Stroke	4 (5)	2 (2)	.4
TIA	3 (4)	2 (2)	.7
Acute renal failure	4 (5)	11 (12)	.2
Heart block	0 (0)	8 (9)	<.01
Atrial fibrillation	13 (17)	20 (22)	.6
Valve-related complications			
Endocarditis	1 (1)	2 (2)	.9
Thromboembolic event	2 (3)	2 (2)	.8
Major bleeding	0 (0)	0 (0)	1.0
Thrombosis	0 (0)	0 (0)	1.0

Values are mean ± standard deviation, n (%). CABG, Coronary artery bypass grafting; AAR, ascending aorta replacement; CPB, cardiopulmonary bypass; TIA, transient ischemic attack.

mortality rate for isolated root replacement was 2.7% in the homograft group versus 0% in the Freestyle group. Complication rates are listed in Table 2.

Long-term Survival

After a median follow-up of 13.8 years (range, 0–21.8 years; 2033 patient-years), there were a total of 49 late deaths in the homograft group and 57 in the Freestyle group. The Kaplan–Meier analysis of survival showed no significant differences between the 2 study groups at 5, 10, and 15 years (Figure 1). Estimate of 20-year survival was 26.8% ± 3.8% for the overall population (25.1% ± 5.7%, 95% confidence interval [CI], 0.16–0.39, for the homograft group vs 28.3% ± 5%, 95% CI, 0.2–0.4, for the Freestyle group, P = .86; Figure 1). The expected survival for an age- and sex-matched UK population is 27.1% at 20 years (Figure 1). Of the 49 late deaths in the homograft group, 7 were valve related, 16 were cardiac, 16 were noncardiac, 6 were sudden, unexpected, unexplained, and 4 were of unknown causes. Of the 57 late deaths in the Freestyle group, 6 were valve related, 17 were cardiac, 20 were noncardiac, 10 were sudden, unexpected, unexplained, and 4 were of unknown causes. Independent predictors of late mortality were older age at operation (hazard ratio

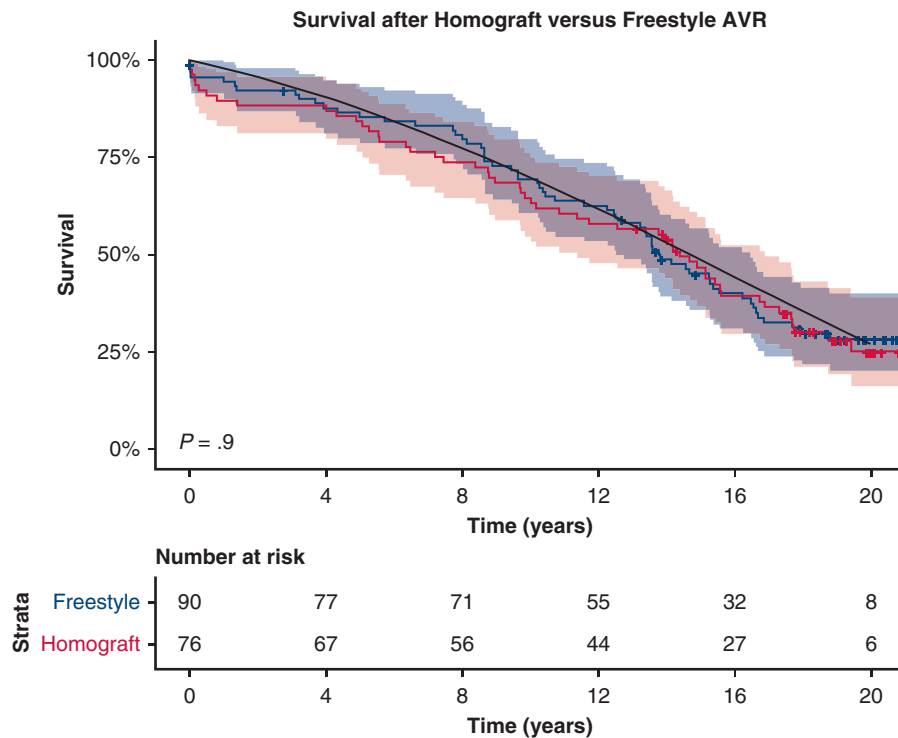


FIGURE 1. Kaplan–Meier survival analysis after homograft versus Freestyle (Medtronic Inc, Minneapolis, Minn) full root aortic valve replacement. The corresponding age- and sex-matched United Kingdom population is plotted in *black*. AVR, Aortic valve replacement.

[HR], 1.07; 95% CI, 1.04-1.11; $P = .000$) and preoperative creatinine levels (HR, 1.01; 95% CI, 1.00-1.02; $P = .003$) (Table 3). No survival differences were found between homograft and cryopreserved homograft recipients.

A total of 23 patients required reoperation on the aortic valve. The actuarial freedom from aortic valve redo was $67.2\% \pm 10.3\%$ (95% CI, 0.5-0.91) for the homograft group and $67.9\% \pm 8.8\%$ (95% CI, 0.53-0.88) for the Freestyle group after 20 years ($P = .81$, Figure 2). Indication for reoperation was aortic valve degeneration in 10 of 11 patients in the homograft group and in 11 of 12 patients in the Freestyle group. One patient in each group was reoperated for aortic valve endocarditis. The reoperations included 20 aortic valve replacements (stented tissue valves 15, mechanical prostheses 3, stented biological conduit 1, aortic homograft 1) and 3 transcatheter aortic valve implantations (TAVIs). At redo, concomitant procedures were CABG ($N = 3$), mitral valve repair ($N = 3$), mitral valve replacement ($N = 2$), tricuspid valve

repair ($N = 1$), and pulmonic valve replacement in ($N = 1$). Younger age at initial operation was an independent predictor of increased aortic valve reoperation rates (HR, 0.92; CI, 0.88-0.97; $P = .001$) (Table 4), whereas the diagnosis of rheumatic heart disease was independently associated with a lower rate of aortic valve reoperation (HR, 0.92; 95% CI, 0.88-0.97; $P = .001$).

For an additional 8 patients, a redo-sternotomy was required for indications other than prosthetic aortic valve degeneration; 3 patients underwent mitral valve repair, and 5 patients underwent replacement (biological prostheses 4, mechanical 1). Concomitant procedures included CABG ($N = 1$), tricuspid valve repair ($N = 2$), and Maze ($N = 1$).

DISCUSSION

This post-hoc analysis of the landmark Freestyle homograft trial shows that relatively elderly patients who undergo Freestyle and homograft total aortic root implantation have comparable late survival and freedom from reintervention on the aortic valve up to 20 years after the initial operation (Figure 3). In addition, the survival trends observed were comparable to those expected for the general UK population matched for age and sex (Figure 3).

A wide variety of mechanical, bioprosthetic, and human tissue valves are available for clinical use. With the aging of the general population, the number of elderly patients

TABLE 3. Independent predictors of very long-term death after aortic root replacement

Variable	Hazard ratio (95% CI)	P value
Older age at operation	1.07 (1.04-1.11)	.000
Preoperative creatinine	1.01 (1.00-1.02)	.003

CI, Confidence interval.

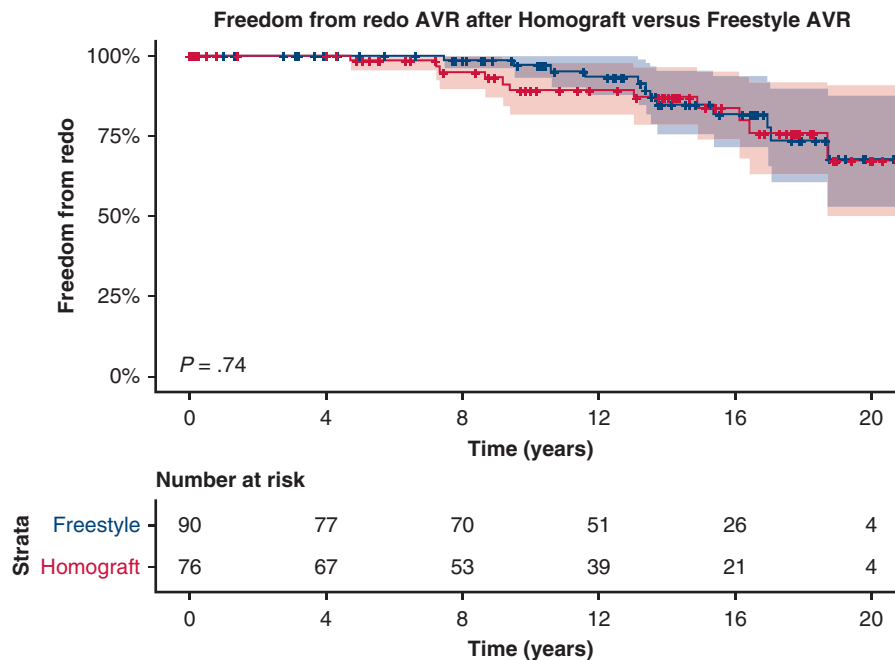


FIGURE 2. Kaplan–Meier freedom from reoperation on the aortic valve analysis after homograft versus Freestyle full root replacement. AVR, Aortic valve replacement.

requiring aortic valve replacement has increased rapidly in the past 10 years,¹³ with a trend toward a higher rate of biological aortic valve replacements.^{14,15} In addition, since the introduction of TAVI for use in patients at high surgical risk, this procedure is now being increasingly used in patients at low to intermediate risk, reaching approximately 50% of all aortic implants.¹³ However, the long-term survival and determinants of outcome for these patients remain unknown. Aortic homografts used to be regarded as the “gold standard” for aortic valve replacement in the 1980s and 1990s because of the good long-term results, particularly when implanted as freestanding aortic roots.^{16–18} Compared with other prostheses, they showed excellent hemodynamics and other valve-related complications.^{18–20} In addition, aortic allografts were found to be useful in complex aortic root pathology with aortic annular destruction because of the flexible allograft tissue properties that allow for reconstruction of destroyed tissue.²¹ A recent large single-center prospective study on homograft implantation started in 1987 has shown that the indication for use has become more selective, mainly because of the progressive structural valve deterioration over time.^{21,22} This finding is reflected in the current

guidelines for surgical management of patients with valvular heart disease by major cardiac surgery and cardiology committees that have no specific recommendations in favor of allografts for aortic valve replacement, except for active endocarditis with perivalvular lesions.^{23,24} In addition, the limited availability of homografts has stimulated the search for other substitutes with similar hemodynamic characteristics and comparable durability.

The Freestyle prosthesis is a complete porcine aortic root treated with a specific preparation, which has been extensively used in many centers showing excellent outcomes.^{10,25,26} In the light of its similar characteristics and mindful of the need to seek alternatives to homografts, we started a comparison of the 2 prostheses in a prospective randomized trial in 1997, which was formally closed in 2005. The technique of implantation was the full root replacement because of the anticipated advantages of better hemodynamic performance. In a previous report, we showed some advantages of the Freestyle roots over homografts, at least at 8 years, in terms of lower need for reoperation and less progressive dysfunction.¹⁰ The large experience with surgical valves has shown the importance of long-term follow-up surveillance for all bioprostheses.¹³ We have now investigated the survival outcome of this series of full root replacements 20 years after the first implants. Our findings showed excellent survival after 2 decades with a median survival of approximately 14 years for these relatively

TABLE 4. Independent predictors of very long-term reoperation after aortic root replacement

Variable	Hazard ratio (95% CI)	P value
Younger age at operation	0.92 (0.88-0.97)	.001

CI, Confidence interval.

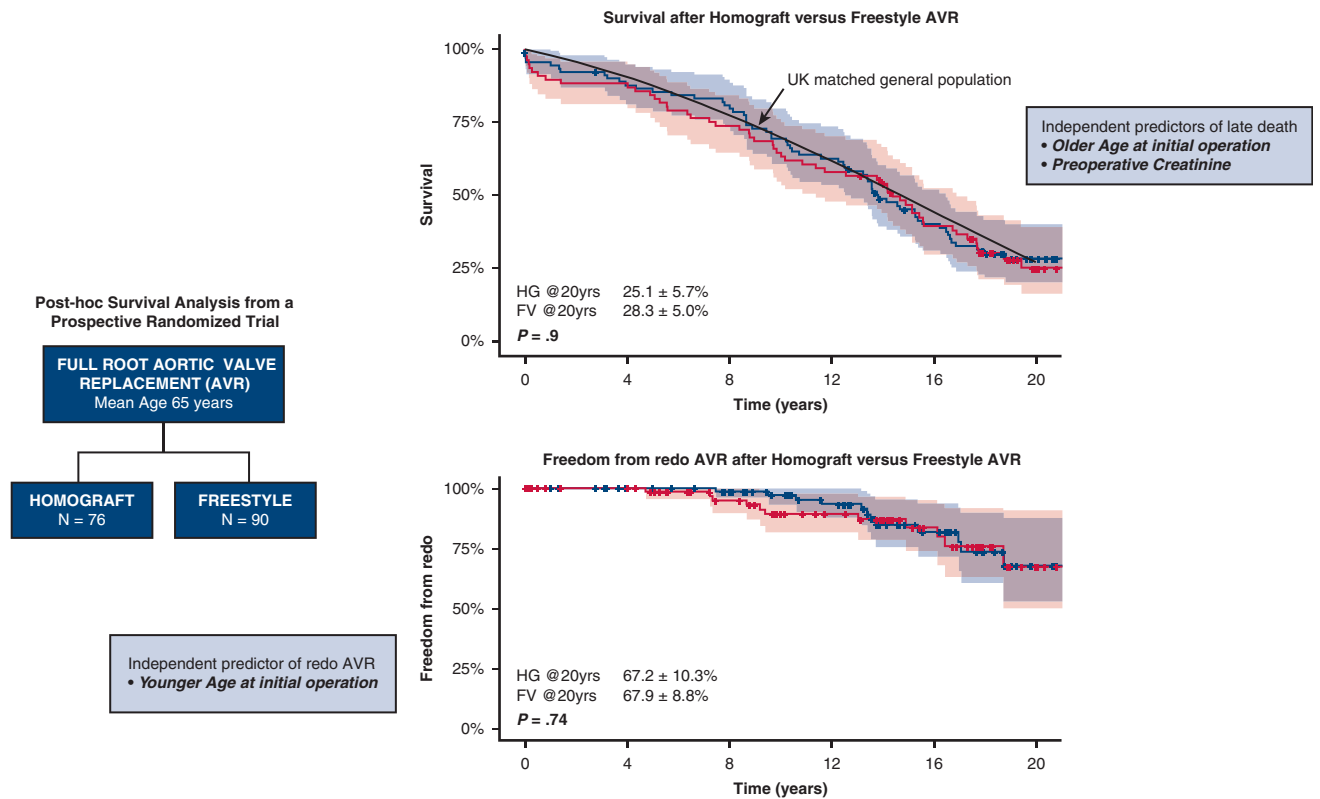


FIGURE 3. Long-term results of homograft versus Freestyle full aortic root replacement trial. AVR, Aortic valve replacement; HG, homograft; FV, Freestyle valve.

elderly patients (14.6 years for homograft recipients and 13.7 years for Freestyle recipients). As previously shown,¹⁰ survival was comparable to those of the age- and sex-matched UK general population. Older age and preoperative creatinine were independent predictors of late mortality. This important survival information compares favorably with other large studies with similar age groups and follow-up duration.²⁷⁻³⁰

Both the homograft and Freestyle valves showed a better freedom from reoperation compared with other available stented or stentless bioprosthesis implanted using subcoronary techniques.²⁷⁻³⁰ On the basis of our overall experience with total root replacement, we think that all patients with aortic valve or root disease benefit from this approach compared with stented bioprosthetic valve replacement. This approach is based on the knowledge that this technique preserves the exact relationship between the different component parts of the valve mechanism, including the sinuses of Valsalva and the sinotubular junction.³¹ In addition, when compared with different techniques of stentless prosthesis implantation, it appears that the total root replacement could be associated with less mechanical stress on the cusps and therefore might lead to better long-term durability of the valve. Nevertheless, there have been reports of pseudoaneurysm

formation after the Freestyle valve replacement.³² However, none of our Freestyle recipients experienced this complication. We can only speculate that the implantation technique can be an important contributing factor, and we suggest that surgeons adhere to the technique of implantation shown in [Video 1](#).

Study Limitations

This study was a post hoc analysis of a prospective randomized trial completed in 2005 and comparing 2 types of unstented tissue valves. It did not involve the currently and commonly used stented valve options and TAVI. In addition, results of prosthetic valve and ventricular function were not included because of incomplete echocardiographic data. However, it does provide a benchmark for comparison as the results of survival of these other valve options become available. As with any randomized controlled trial, selection bias may have affected the results, and it may not be directly applicable to current clinical practice.

CONCLUSIONS

This is the first study to investigate the long-term survival of xenograft versus homograft full-root aortic valve replacement from a prospective randomized trial, which appears to be comparable to that of the general age-matched

population. The long-term survival and determinants of outcome for more recently introduced valve procedures are not yet known. This study should serve as a benchmark for future investigations in elderly patients with aortic valve disease.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: [https://aats.blob.core.windows.net/media/18Apr29/20ABC%20Adult%20Cardiac%20SS%20\(PM\)/S51%20-%20Part%202/S51_1.mp4](https://aats.blob.core.windows.net/media/18Apr29/20ABC%20Adult%20Cardiac%20SS%20(PM)/S51%20-%20Part%202/S51_1.mp4).



Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The authors thank Drs Elena Bellazzi and Ahmed Abdulsalam for their invaluable assistance in collecting the data and Drs Kevin Veen and Shehab Anwer for help with the construction and graphical reproduction of the figures.

References

- Nkomo VT, Gardin JM, Skelton TB, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
- Kostis V, Bennet JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet*. 2017;389:1323-35.
- Yacoub MH, Takkenberg JJM. Will heart valve tissue engineering change the world? *Nat Clin Pract Cardiovasc Med*. 2005;2:60-1.
- Huygens SA, Mokhles MM, Hanif M, Bekkers JA, Bogers AJ, Rutten-van Mölken MP, et al. Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2016;50:605-16.
- Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Bogers AJ, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation*. 2001;103:1535-41.
- Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Jamieson WR, Grunkemeier GL, et al. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement. *Eur J Cardiothorac Surg*. 2006;29:374-9.
- Johnston DR, Soltész EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF III, et al. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. *Ann Thorac Surg*. 2015;99:1239-47.
- Kobayashi J. Stentless aortic valve replacement: an update. *Vasc Health Risk Manag*. 2011;7:345-51.
- Huygens SA, Etnel JRG, Hanif M, Bekkers JA, Bogers AJJC, Rutten-van Mölken MPMH, et al. Bioprosthetic aortic valve replacement in elderly patients: meta-analysis and microsimulation. *J Thorac Cardiovasc Surg*. 2019;157:2189-97.
- El-Hamamsy I, Clark L, Stevens LM, Sarang Z, Melina G, Takkenberg JJ, et al. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. *J Am Coll Cardiol*. 2010;55:368-76.
- Melina G, De Robertis F, Gaer JA, Amrani M, Khaghani A, Yacoub MH. Mid-term pattern of survival, hemodynamic performance and rate of complications after Medtronic freestyle versus homograft full aortic root replacement: results from a prospective randomized trial. *J Heart Valve Dis*. 2004;13:972-5.
- Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359:1309-10.
- Arsalan M, Walther T. Durability of prostheses for transcatheter aortic valve implantation. *Nat Rev Cardiol*. 2016;13:360-7.
- Dunning J, Gao H, Chambers JB, Moat NE, Murphy G, Pagano D, et al. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use - an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland national database. *J Thorac Cardiovasc Surg*. 2011;142:776-82.
- Beckmann A, Funkat AK, Lewandowski J, Frie M, Ernst M, Hekmat K, et al. Cardiac surgery in Germany during 2014: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. *J Thorac Cardiovasc Surg*. 2015;63:258-69.
- Svensson LG, Pillai ST, Rajeswaran J, Desai MY, Griffin B, Grimm R, et al. Long-term survival, valve durability, and reoperation for 4 aortic root procedures combined with ascending aorta replacement. *J Thorac Cardiovasc Surg*. 2016;151:764-74.
- Palka P, Harrocks S, Lange A, Burstow DJ, O'Brien MF. Primary aortic valve replacement with cryopreserved aortic allografts: an echocardiographic follow-up study of 570 patients. *Circulation*. 2002;105:61-6.
- Lund O, Chandrasekaran V, Grocott-Mason R, Elwidaa H, Mazhar R, Khaghani A, et al. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. *J Thorac Cardiovasc Surg*. 1999;117:77-91.
- Lim E, Ali A, Theodorou P, Sousa I, Ashrafian H, Chamageorgakis T, et al. Longitudinal study of the profile and predictors of left ventricular mass regression after stentless aortic valve replacement. *Ann Thorac Surg*. 2008;85:2026-9.
- Yacoub M, Rasmi NR, Sundt TM, Lund O, Boyland E, Radley-Smith R, et al. Fourteen-year experience with homovital homografts for aortic valve replacement. *J Thorac Cardiovasc Surg*. 1995;110:186-94.
- Arabkhani B, Bekkers JA, Andrinopoulou ER, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ. Allografts in aortic position: insights from a 27-year, single-center prospective study. *J Thorac Cardiovasc Surg*. 2016;152:1572-9.
- Bekkers JA, Klieverik LM, Raap GB, Takkenberg JJ, Bogers AJ. Re-operations for aortic allograft root failure: experience from a 21-year single-center prospective follow-up study. *Eur J Cardiothorac Surg*. 2011;40:35-42.
- Habib G, Lancellotti P, Antunes MJ, Bongiorno MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2015;36:3075-128.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91.
- Bach DS, Kon ND. Long-term clinical outcomes 15 years after aortic valve replacement with the Freestyle stentless aortic bioprosthesis. *Ann Thorac Surg*. 2014;97:544-51.
- Sherrah AG, Edelman JJ, Thomas SR, Brady PW, Wilson MK, Jeremy RW, et al. The freestyle aortic bioprosthesis: a systematic review. *Heart Lung Circ*. 2014;23:1110-7.
- Mohammadi S, Tchana-Sato V, Kalavrouziotis D, Voisin P, Doyle D, Baillet R, et al. Long-term clinical and echocardiographic follow-up of the Freestyle stentless aortic bioprosthesis. *Circulation*. 2012;126(11 Suppl 1):S198-204.
- Biglioli P, Spampinato N, Cannata A, Musumeci A, Parolari A, Gagliardi C, et al. Long-term outcomes of the Carpentier-Edwards pericardial valve prosthesis in the aortic position: effect of patient age. *J Heart Valve Dis*. 2004;13(Suppl 1):S49-51.
- Banbury MK, Cosgrove DM III, White JA, Blackstone EH, Frater RW, Okies JE. Age and valve size effect on the long-term durability of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg*. 2001;72:753-7.
- David TE, Feindel CM, Bos J, Ivanov J, Armstrong S. Aortic valve replacement with Toronto SPV bioprosthesis: optimal patient survival but suboptimal valve durability. *J Thorac Cardiovasc Surg*. 2008;135:19-24.
- Yacoub MH, Kilner PJ, Birks EJ, Misfeld M. The aortic outflow and root: a tale of dynamism and crosstalk. *Ann Thorac Surg*. 1999;68(3 Suppl):S37-43.

32. Englum BR, Pavlisko EN, Mack MC, Ganapathi AM, Schechter MA, Hanna JM, et al. Pseudoaneurysm formation after Medtronic freestyle porcine aortic bio-prosthesis implantation: a word of caution. *Ann Thorac Surg.* 2014;98:2061-7.

Key Words: aortic valve surgery, xenografts, homografts, survival

Discussion



Dr Neal D. Kon (*Winston-Salem, NC*). I congratulate Dr Melina and colleagues on an outstanding study with superb results. In particular, I would like to praise the dedication and commitment they have shown in completing a randomized trial and following each group for 20 years.

The results are outstanding. The patients at our center have enjoyed the benefits of both these natural valves implanted as root replacements since 1992. This is when we started implanting the Freestyle as part of the initial worldwide study. Unfortunately, we have not shown the same commitment to following these patients long-term.

Stentless valves have been abandoned by many surgeons despite their optimal hemodynamics and superior durability. There are a host of reasons why other surgeons have not adopted stentless valves using a full root technique. First, it's technically more challenging to implant than the standard stented valve; second, studies in the literature show higher mortality when doing a root replacement compared to stented valves. Studies also suggest poor durability of stentless valves when using a subcoronary technique, although you had not used the subcoronary technique in your study. For many surgeons, they have encountered coronary artery reimplantation challenges. There are also articles in the literature that describe pseudoaneurysm formation in Freestyle roots, both in the sinuses and beneath the valve. I have also heard many surgeons complain about how challenging a redo operation is with a previously implanted homograft or Freestyle root.

Could you address each of the issues I just described in your series, whether or not you have encountered any of these problems, and what you have done to address them?

Second, you must have an outstanding approach to redo root replacement with homografts and Freestyles. Could you share with us some of the pearls that you might have developed over the years for doing redo root replacements?

I also can't help but ask you if you have used TAVR in any redo stentless valves or homografts, and if so, some people say that's more difficult. So could you share with us some pearls with regard to that.



Dr Giovanni Melina (*London, United Kingdom*). The main reason why these results are interesting is because we had the opportunity to see these patients constantly, and this thanks to Professor Yacoub, who left us with a legacy to follow them up.

To answer your questions, yes, technically a full root replacement is more challenging than a standard stented valve and should be done by experienced aortic surgeons, but once learned, including careful coronary mobilization and reimplantation, it becomes a routine operation. In particular in case of Freestyle implantation, there is no need to rotate the valve, only a nice hole in the right position to avoid tension or torsion or kinking of the proximal coronary artery, and it is done. Pseudoaneurysm formation has never been an issue in the present series or in any other Freestyle implantation outside this study.

Regarding the higher mortality, if one looks at the early mortality rate for this study, for isolated root replacement this was only 1%, 0% in the Freestyle and 2.5% in the homograft recipients, which is not worse than any other routine aortic valve replacement.

Regarding durability, I fully agree with your observation. No subcoronary implantations have been performed, and we believe that this could be one of the reasons for the good results for these valves over a true long follow-up, which compares well with other commercially available counterparts. Redos for these patients, like any other redo, are challenging, I agree.

Indeed, the root at reoperation is often a bunch of calcium, but once you have carefully removed it, you have a skeletonized root, which you can easily replace and the native coronary ostia are always free of calcium.

Finally, 3 patients underwent TAVI. I am not a TAVI surgeon, but it is known that this procedure with the Freestyle is more challenging because of the absence of a stent, probably the same for homografts. However, it was possible with success in all of them, and they did well.



Dr Joseph E. Bavaria (*Philadelphia, Pa*). This was a beautiful study and is a nice update from the midterm and early studies that were previously reported. I tend to agree completely with the results, especially the comments about the fact that the Freestyle is as good and probably better than a homograft, and I think that's the reason why we have adopted the full root Freestyle.

I am a disciple of Dr Kon regarding the full root implantation and stopped doing subcoronary implants after about 20 and have done 400 to 500 of the full-root Freestyles.

We have used TAVI, and it's okay, but what's really nice is the sutureless valves are a really good indication for this.

My question to you is about failure modes. It seems to me looking at our large series of homografts and Freestyles, which we started in 1997, is that the homografts tend to fail a little slower than the Freestyles. The Freestyles are fantastic, and then when they start to fail with aortic insufficiency, they fail within 6 months, whereas the homografts, just like you showed, there are a lot of them that have 2 or 3+ aortic insufficiency for a little while and then they finally just fall off the cliff. Can you just describe for me what your experience is in your center, which is the original center, for the failure modes?

Dr Melina. The main failure mode for the Freestyles is calcification of the aortic root wall. In the homografts, there is calcification of both the root and the leaflets.

Dr Bavaria. A quick follow-up question. I will put you on the spot. In your experience after all these years, is there any bioprosthetic valve that lasts as long as a Freestyle full root?

Dr Melina. As a full root?

Dr Bavaria. Is there any bioprosthetic aortic valve that lasts as long as the Freestyle full root?

Dr Melina. We have shown excellent long-term results for the Freestyle bioprosthesis with survival curves comparable to the sex- and age-matched UK population. To answer your question, only a prospective randomized trial designed to compare different prostheses, as we did here for Freestyle and homograft roots, will clarify which one performs better, especially in the long-term.