Journal of the American College of Cardiology Vol. 55, No. 4, 2010
© 2010 by the American College of Cardiology Foundation ISSN 0735-1097/10/$36.00
Published by Elsevier Inc. doi:10.1016/j.jacc.2009.09.030

CARDIAC SURGERY

Late Outcomes Following Freestyle Versus Homograft Aortic Root Replacement

Results From a Prospective Randomized Trial

Ismail El-Hamamsy, MD,* Lucy Clark, PHD,* Louis M. Stevens, MD,† Zubair Sarang, BSC,* Giovanni Melina, MD,* Johanna J. M. Takkenberg, MD, PHD,‡ Magdi H. Yacoub, MD*

London, United Kingdom; Boston, Massachusetts; and Rotterdam, the Netherlands

Objectives The aims of this study were to compare long-term results after homograft versus Freestyle (Medtronic Inc., Minneapolis, Minnesota) aortic root replacement.

Background The ideal substitute for aortic root replacement remains undetermined.

Methods Between 1997 and 2005, 166 patients (age 65 ± 8 years) undergoing total aortic root replacement were randomized to receive a homograft (n = 76) or a Freestyle bioprosthesis (n = 90). Six patients randomly assigned to homograft crossed over to Freestyle because of unavailability of suitably sized homografts. Median follow-up was 7.6 years (maximum 11 years; 1,035 patient-years). "Evolving" aortic valve dysfunction was defined as aortic regurgitation ≥2/4 and/or peak gradient >20 mm Hg.

Results Patient characteristics were comparable between groups. Concomitant procedures were performed in 44% and 47% of Freestyle and homograft patients, respectively (p = 0.5). Overall hospital mortality was 4.8% (1% for isolated root replacement). Eight-year survival was 80 ± 5% in the Freestyle group versus 77 ± 6% in the homograft group (p = 0.9). Freedom from need for reoperation at 8 years was significantly higher after Freestyle root replacement (100 ± 0% vs. 90 ± 5% after homograft replacement; p = 0.02). All reoperations were secondary to structural valve deterioration (n = 6). At last echocardiographic follow-up, actuarial freedom from evolving aortic valve dysfunction was 86 ± 5% for Freestyle bioprostheses versus 37 ± 7% for homografts (p < 0.001). Clinically, freedom from New York Heart Association functional class III to IV and freedom from valve-related complications were similar between groups (p = 0.7 and p = 0.9, respectively).

Conclusions In this patient group, late survival is similar after homograft versus Freestyle root replacement. However, Freestyle aortic root replacement is associated with significantly less progressive aortic valve dysfunction and a lower need for reoperations. (J Am Coll Cardiol 2010;55:368–76) © 2010 by the American College of Cardiology Foundation

The number of patients requiring aortic valve (AV) surgery is constantly increasing and is expected to triple within the next 40 years (1). Yet, the ideal AV substitute remains undetermined, in large part due to the scarcity of prospective randomized studies comparing different surgical options.

From the *Department of Cardiac Surgery, Harefield and Royal Brompton NHS Trust, National Heart and Lung Institute, Imperial College London, London, United Kingdom; †Harvard School of Public Health, Harvard University, Boston, Massachusetts; and the ‡Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands. This study was partly funded by an academic grant from Medtronic to the Harefield Heart Science Center. None of the authors have received any consultancy fees or hold any financial interests in the company. Dr. El-Hamamsy is supported by a Fellowship Award from the Canadian Institute of Health Research and by the Magdi Yacoub Institute. Dr. Stevens is supported by a Fellowship Award from the Canadian Institute of Health Research.

Manuscript received May 26, 2009; revised manuscript received September 28, 2009, accepted September 30, 2009.

Aortic homografts have been used for several decades with good long-term results, particularly when implanted as freestanding aortic roots (2,3). In comparison with more obstructive prostheses, their lower transvalvular gradients are associated with better left ventricular mass regression (4). They also show good resistance to infection and other valve-related complications (2,5). However, in part because of low-grade immunological mechanisms, homografts can undergo late degeneration marked by heavy calcification and valve dysfunction. This finding coupled with limited availability of homografts has stimulated the search for other substitutes with a similar hemodynamic profile and equal or better durability.

See page 377

Xenograft stentless aortic bioprosthetic roots, such as the Medtronic Freestyle bioprosthesis (Medtronic Inc., Minneapolis, Minnesota), were introduced into clinical use almost 2 decades ago. Freestyle prostheses are porcine roots treated with alpha-oleic acid, an anticalcification agent, in an attempt to reduce long-term valve degeneration. Freestyle valves are readily available in different sizes and if shown to have good performance, would offer huge potential for patients requiring aortic root replacement. The objective of this study was, therefore, to compare outcomes after Freestyle versus homograft root replacement in a prospective randomized trial. We have previously reported the shorter-term results showing similar survival, valve performance, and functional status between the 2 groups (6). The purpose of this report was to further analyze the long-term survival, freedom from reoperation, and valvular and ventricular performance after Freestyle versus homograft root replacement.

Methods

Patient population. From 1997 to 2005, 166 patients were prospectively randomly allocated to undergo total aortic root replacement using a homograft (n = 76) or a Medtronic Freestyle aortic root prosthesis (n = 90). Six patients from the homograft group crossed over to the Freestyle group in the operating room because of the unavailability of a suitably sized homograft. Patients were analyzed according to allocated treatment. All patients consented to the study, which was approved by the ethics committee.

All patients ≥40 years of age requiring AV surgery were considered candidates for this study. Previous surgery, active endocarditis, or the need for concomitant procedures did not preclude enrollment in the study. Patients with a known systemic illness affecting long-term survival and patients <40 years of age were excluded from the study. Median follow-up of the patients was 7.6 years (range 0.5 to 10.8 years; 1,035 patient-years). Completeness of clinical follow-up was 87% in the homograft cohort and 88% in the Freestyle cohort (7). Echocardiographic follow-up within 18 months of study closure, redo operation, or death was 83% complete in the homograft group and 76% complete in the Freestyle group. Follow-up was "active" and consisted of direct contact with the patients or their families, by examination or telephone questionnaires. No governmental or administrative databases were used for this study.

Surgical technique. The surgical technique and short-term results of this study have been previously reported (6). Briefly, all patients underwent total aortic root replacement with coronary artery reimplantation. No subcoronary implantations were performed. The largest implantable prosthesis was always used in the aortic root. No reinforcement techniques or synthetic material were used to support the proximal or distal anastomosis. The coronaries were reimplanted in their respective sinuses. As the height and angle between the native porcine coronary ostia in Freestyle prostheses is different from that in normal human anatomy, new ostia were fashioned to avoid tension, torsion, or kinking of the proximal coronary arteries.

Homograft procurement. Two types of homografts were used in this study: "homovital" homografts (n = 30) and antibiotic-sterilized cryopreserved 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 h at 4°C (1% penicillin/1% streptomycin). The median time from dissection to implantation in this study was 7 days (range 1 to 30 days). The rest of the homografts were harvested from routine post-mortem examination and processed at the Royal Brompton Tissue Bank. Homografts were dissected using sterile technique and sterilized using a nutrient antibiotic solution (Gaya 5 [8]), followed by cryopreservation and storage at −130°C for up to 5 years until use.

Echocardiographic studies. Patients were prospectively followed up with yearly echocardiographic examinations. For logistical reasons, some patients were followed up with echocardiographic examinations every 2 years. Transvalvular aortic gradient using the continuity equation and the degree of aortic insufficiency (AI) were evaluated (9). Indices of ventricular function were also evaluated, including left ventricular end-diastolic dimension, ejection fraction, and left ventricular mass regression. In an attempt to accurately assess the occurrence of "evolving" aortic valve dysfunction, we defined it as AI ≥2/4 and/or transvalvular gradient >20 mm Hg.

Symptomatic status and valve-related complications. Symptomatic status of the patients on the basis of New York Heart Association (NYHA) functional classification at last follow-up was assessed and compared between groups. All valve-related complications as defined by the Society of Thoracic Surgeons (10) were prospectively recorded.

Statistical analysis. Data are expressed as mean ± SD or median (range) for continuous variables and as number (percentage) for categorical variables. Univariable analyses included the 2-tailed Wilcoxon rank sum or Student *t* test for continuous variables and Fisher exact test for discrete variables. Univariable and multivariable Cox regression models were constructed to study determinants of survival. All variables in Table 1 were considered for the univariable analysis, and those with $p < 0.2$ were included in the multivariable analysis. Survival analysis (± SD) 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 using 1996 to 1998 and 2005 to 2007 United Kingdom interim life tables (11).

Abbreviations and Acronyms

AI = aortic insufficiency

AV = aortic valve

CI = confidence interval

EF = ejection fraction

HR = hazard ratio

NYHA = New York Heart Association

Table 1 Patient Characteristics (n = 166)

Variable	Homograft (n = 76)	Freestyle (n = 90)	p Value
Age, yrs	64.1 ± 9.2	66.0 ± 8.2	0.2
≤55	12	10	
56–65	22	26	
66–75	30	40	
>75	12	14	
Sex, male	49 (64)	61 (68)	0.6
BSA, m^2	1.89 ± 0.22	1.88 ± 0.21	0.8
Cr clearance, ml/min*	72.6 (29.5–138.2)	70.2 (24.9–128.8)	0.7
LVEF, %	57.2 ± 24.8	64.0 ± 13.6	0.1
Aortic stenosis	51 (67)	63 (70)	0.5
Previous surgery	14 (18)	16 (18)	0.9
Comorbidities			
Coronary artery disease	37 (49)	46 (51)	0.8
IDDM	5 (7)	2 (2)	0.3
NIDDM	6 (8)	4 (4)	0.3
Dyslipidemia	5 (7)	4 (4)	0.5
Renal failure†	9 (12)	11 (12)	0.8
Hypertension	24 (32)	19 (21)	0.2
Previous CVA	1 (1)	3 (3)	0.6
Previous TIA	8 (11)	5 (6)	0.4
Previous syncope	3 (4)	10 (11)	0.1
PVD	1 (1)	0 (0)	0.4
Infective endocarditis			
Active	1 (1)	0 (0)	0.4
Treated	1 (1)	2 (2)	1.0
Valve pathology			
Degenerative	51 (67)	57 (63)	1.0
Congenital	17 (22)	23 (26)	0.7
Rheumatic	8 (11)	10 (11)	1.0

Values are mean ± SD, n, n (%), or median (range). *Creatinine (Cr) clearance was calculated using the Cockroft-Gault formula. †Renal failure was defined as an estimated Cr clearance <50 ml/min.
BSA = body surface area; CVA = cerebrovascular accident; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; NIDDM = noninsulin-dependent diabetes mellitus; PVD = peripheral vascular disease; TIA = transient ischemic attack.

To evaluate the change in echocardiographic values (left ventricular end-diastolic dimension, left ventricular ejection fraction, left ventricular mass) over time, mixed effects models were used to take into account the correlation between repeated follow-up echocardiographic measurements (the MIXED procedure in SAS software version 9.1, SAS Institute, Cary, North Carolina). A fully parameterized mixed-effects model was built, including a coefficient for each time point for each group (baseline pre-operatively, post-operatively before discharge, and yearly thereafter). Overall, 62% of patients (103 of 166) had follow-up echocardiography every year or every other year, and 81% (134 of 166) of patients had ≥3 follow-up echocardiographic measures. Missing data points at each time point were considered to be missing at random for this analysis. Variables with a $p < 0.05$ were considered statistically significant.

Results

Patient demographics. Pre-operative patient characteristics are presented in Table 1. Mean age of the patients was similar in both groups (Freestyle 66.0 ± 8.2 years, and homograft 64.1 ± 9.2 years; p = 0.2). In addition, age distribution within each cohort was comparable between groups (Table 1). The main indication for operation was AV stenosis (Freestyle 67%, and homografts 70%; p = 0.5). Forty-four percent of Freestyle recipients and 47% of homograft recipients underwent a concomitant procedure (p = 0.8) (Table 2).

Operative results. Operative results were similar between groups (Table 2). Overall hospital mortality was 4.5% (4 of 90 patients) in the Freestyle group versus 5.3% (4 of 76 patients) in the homograft group (p = 0.5). The hospital mortality risk for isolated aortic root replacement was 0% in

Table 2 Operative and Post-Operative Results

Variable	Homograft (n = 76)	Freestyle (n = 90)	p Value
Overall hospital mortality	4 (5.3)	4 (4.5)	0.5
Isolated root replacement	1/40 (2.7)	0/50 (0)	
Homografts			
Homovital homografts	30 (39)		
Cryopreserved homografts	46 (61)		
Cross-clamp time, min	90 ± 30	94 ± 24	0.8
CPB time, min	131 ± 37	139 ± 42	0.2
Total blood loss, ml	600 (360–1,140)	600 (370–930)	1.0
Intubation time, h	10 (6–17)	11 (6–18)	0.6
Concomitant procedures	36 (47)	40 (44)	0.8
Coronary bypass	33	39	
Replacement of TAA	3	1	
Inotropes, h			0.8
<24	36 (47)	41 (46)	
24–48	15 (20)	20 (22)	
>48	25 (33)	29 (32)	
Ventilation, h			0.7
<24	63 (83)	72 (80)	
24–48	0 (0)	3 (3)	
>48	13 (17)	15 (17)	
Post-operative complications			
Re-exploration	5 (7)	8 (9)	0.8
Sternal infection	2 (3)	4 (4)	0.7
Stroke	4 (5)	2 (2)	0.4
TIA	3 (4)	2 (2)	0.7
Acute renal failure	4 (5)	11 (12)	0.2
CVVH	1 (1)	8 (9)	0.04
Heart block	0 (0)	8 (9)	<0.01
Atrial fibrillation	13 (17)	20 (22)	0.6
Valve-related complications			
Endocarditis	1	2	
Thromboembolic event	2	2	
Major bleeding	0	0	
Thrombosis	0	0	
Medication at last follow-up			
Warfarin	12/50 (24)	10/54 (18)	0.5
Statin	22/50 (52)	25/54 (46)	0.7
ACE inhibitor	27/50 (54)	23/54 (43)	0.4
Beta-blocker	20/50 (40)	15/54 (28)	0.2

Values are n (%), mean ± SD, median (interquartile range), or n.
ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass; CVVH = continuous venovenous hemofiltration; TAA = thoracic aortic aneurysm; TIA = transient ischemic attack.

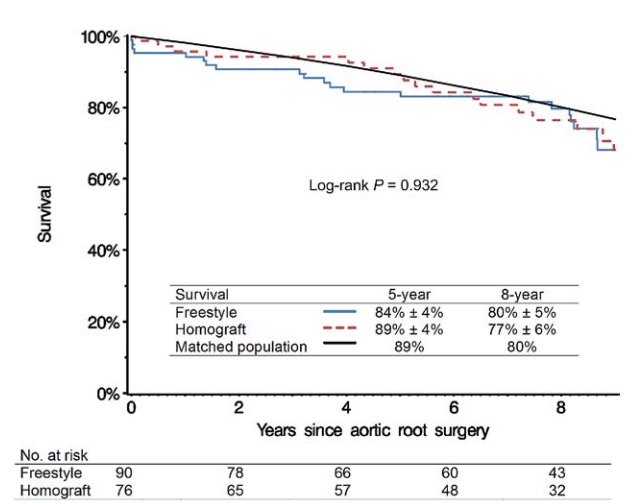

Figure 1 **Actuarial Survival After Freestyle Versus Homograft Root Replacement**

Actuarial survival after Freestyle **(blue)** versus homograft **(red)** aortic root replacement. The corresponding age- and sex-matched United Kingdom population is plotted in **black**.

the Freestyle group and 2.7% in the homograft group. The prevalence of complications is listed in Table 2. No differences were observed between groups. Notably, 15 patients (mean age 69 ± 6 years) suffered post-operative acute renal failure (8.5%). Of those, 7 had pre-operative renal failure (creatinine clearance <50 ml/min) and 5 were redo operations. Eight of the 15 patients had temporary hemofiltration, but none required long-term dialysis. In addition, 8 patients had heart block, 4 transient and 4 that required permanent pacemaker implantation (overall rate 2.4%).

Long-term survival. There were 4 early deaths and 17 late deaths in the Freestyle group and 4 early and 15 late deaths in the homograft group. Actuarial survival at 8 years was 80 ± 5% in the Freestyle group versus 77 ± 6% in the homograft group ($p = 0.9$) (Fig. 1). Expected survival for an age- and sex-matched United Kingdom population is 80% at 8 years. Independent predictors of mortality were concomitant CABG (hazard ratio [HR]: 2.5 [95% confidence interval (CI): 1.3 to 4.9]; $p = 0.008$), pre-operative NYHA functional class III or IV (HR: 2.1 [95% CI: 1.1 to 4.1]; $p = 0.03$), older age (HR: 1.8 [95% CI: 1.1 to 2.9]; $p = 0.02$), and the need for an intra-aortic balloon pump at the time of surgery (HR: 6.6 [95% CI: 3.0 to 14.3]; $p < 0.01$) (Table 3). Of the 17 late deaths in the Freestyle group, 5 were cardiac, 5 were unrelated, and 7 were of unknown causes. Of the 15 late deaths in the homograft group, 7 were cardiac, 6 were unrelated, and 2 were of unknown causes. There were no survival differences between homovital and cryopreserved homograft recipients.

Long-term freedom from reoperation. One patient in the Freestyle group underwent redo surgery for structural valve deterioration manifested by cusp tear and aortic insufficiency at 9.5 years after surgery. No other Freestyle patients had an indication for reoperation. In contrast, 6 patients in the homograft group presented with a redo indication (Table 4). Three of these patients were <55 years of age at the time of initial surgery, the other 3 ranged from 63 to 72 years of age (Table 4). Two of those 6 patients declined reoperation for personal reasons and remained with aortic insufficiency and dilating left ventricles. The remaining 4 patients showed severe structural deterioration of the homografts with varying degrees of calcification in all of them. Of the 6 patients, 2 had homovital homografts (2 of 30 recipients) and 4 had cryopreserved homografts (4 of 45 recipients). Actuarial freedom from the need for reoperation at 8 years was significantly higher after Freestyle root replacement versus homograft root replacement (100% vs. 90 ± 5%; $p = 0.02$) (Fig. 2). Because of the low number of events, no independent factors could be identified to predict the need for reoperation or structural valve deterioration.

Echocardiographic function. AORTIC VALVE. Actuarial freedom from evolving aortic valve dysfunction defined as AI ≥2/4 and/or transvalvular gradient >20 mm Hg was 86 ± 5% at 8 years in the Freestyle group versus 37 ± 7% in the homograft group ($p < 0.001$) (Fig. 3). No differences were observed between both types of homografts used in this study.

LEFT VENTRICLE. Using mixed-effects models to assess changes in left ventricular function and dimensions over time, no differences were observed between both groups. Left ventricular end-diastolic diameter decreased significantly after surgery in both groups, thereafter showing a comparable marginal increase over the years (Fig. 4A). Similarly, there was a significant decrease in left ventricular mass after surgery in both groups, which remained stable for up to 8 years of follow-up (Fig. 4B). Finally, left ventricular ejection fraction showed a significant increase up to 1 year after surgery and remained stable thereafter (Fig. 4C).

Functional assessment. Actuarial freedom from NYHA functional class III or IV was similar between both groups at 8 years: 95 ± 3% ($p = 0.7$) (Fig. 5).

Valve-related complications. Two cases of infective endocarditis were diagnosed in the Freestyle group versus 1 in the homograft group. Two patients in each group had thromboembolic events. In the Freestyle group, 1 patient had a transient ischemic attack during the post-operative period, and the other had a stroke after an orthopedic procedure 6 years

Table 3 **Independent Predictors of Long-Term Death After Aortic Root Replacement**

	Hazard Ratio (95% CI)	p Value
Age	1.8* (1.1–2.9)	0.02
NYHA functional class III or IV	2.1 (1.1–4.1)	0.03
IABP need at time of surgery	6.6 (3.0–14.3)	<0.001
Concomitant CABG	2.5 (1.3–4.9)	0.008

*Per 10-year age increase.
CABG = coronary artery bypass graft surgery; CI = confidence interval; IABP = intra-aortic balloon pump; NYHA = New York Heart Association.

Table 4 Indication, Operative Findings, and Outcomes of Patients Requiring Redo Surgery

	Initial Procedure	Sex/Age (yrs) at Surgery	Delay (yrs)	Indication	Findings	Procedure	Outcome
1	Homograft	M/40	7	Severe AI + LV dilation	Dense aortic wall Ca^{++}	MVR	Alive
2	Homograft	F/52	5	Severe AI	Cusp tear Localized Ca^{++}	TVR	Alive
3	Homograft	M/53	7	Mod AI + LV dilation	Heavy cusp Ca^{++}	MVR	Alive
4	Homograft	M/63	8.5	Severe AI	Heavy cusp Ca^{++} Cusp tear	TVR + TR	Died POD 1 (MOF)
5	Homograft	F/65	8	Severe AI	N/A	Declined	Alive
6	Homograft	M/72	9	Mod–severe AI + symptoms	N/A	Declined	Alive
1	Freestyle	F/63	9.5	Severe AI	Cusp tear	TVR	Died POD 24

AI = aortic insufficiency; LV = left ventricular; Mod = moderate; MOF = multiorgan failure; MVR = mechanical valve replacement; N/A = not available; POD = post-operative day; TR = tricuspid repair; TVR = tissue valve replacement.

post-operatively. Both cases in the homograft group were post-operative transient ischemic attacks.

Actuarial freedom from the composite end point of endocarditis, thromboembolism, thrombosis, and major bleeding was 96 ± 3% at 8 years in the Freestyle group versus 96 ± 2% in the homograft group (p = 0.9) (Fig. 6).

Discussion

The major findings from this study are that use of the Medtronic Freestyle porcine bioprosthesis for total aortic root replacement is associated with a significantly lower rate of structural valve deterioration and reoperation compared with homograft root replacement. These differences did not, however, translate into differences in survival between the 2 groups.

To date, the ideal choice for AV replacement remains largely undetermined because of a lack of prospective randomized studies. The present data suggest that the Freestyle bioprosthesis is a more durable substitute than homografts when implanted as a freestanding total root. Aortic root replacement has been our favored surgical technique for patients with aortic valve or root disease. 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 (Fig. 7). This technique can favorably influence patient survival (2), valve durability (2,12), and possibly coronary flow (13). Other groups have reported similar results with the use of the Freestyle prosthesis as a freestanding root, with overall 10-year freedom from structural deterioration and reoperation of 96% and 92%, respectively (14). These results compare favorably with long-term outcomes after isolated aortic valve replacement using a stented bioprosthesis (15–17). On the basis of our overall experience with total root replacement, we believe that all patients with aortic valve or root disease benefit from this approach compared with stented bioprosthetic valve replacement, particularly

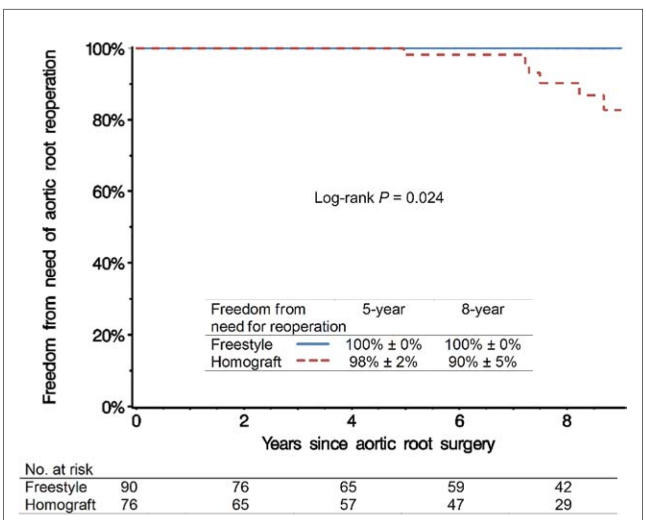

Figure 2 Actuarial Freedom From Reoperation After Freestyle Versus Homograft Root Replacement

Actuarial freedom from need for reoperation (± SD) after Freestyle **(blue)** versus homograft **(red)** aortic root replacement.

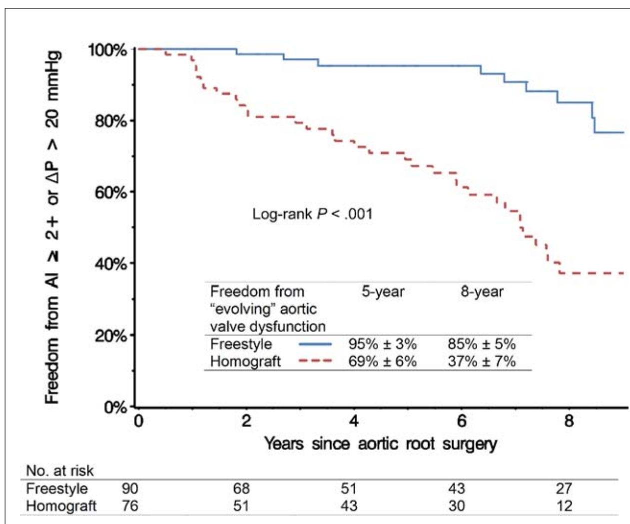

Figure 3 Actuarial Freedom From Aortic Valve Dysfunction After Root Replacement

Actuarial freedom from "evolving" aortic valve dysfunction (aortic insufficiency [AI] ≥2/4 and/or transprosthetic gradient [ΔP] ≥20 mm Hg) after Freestyle **(blue)** versus homograft **(red)** aortic root replacement.

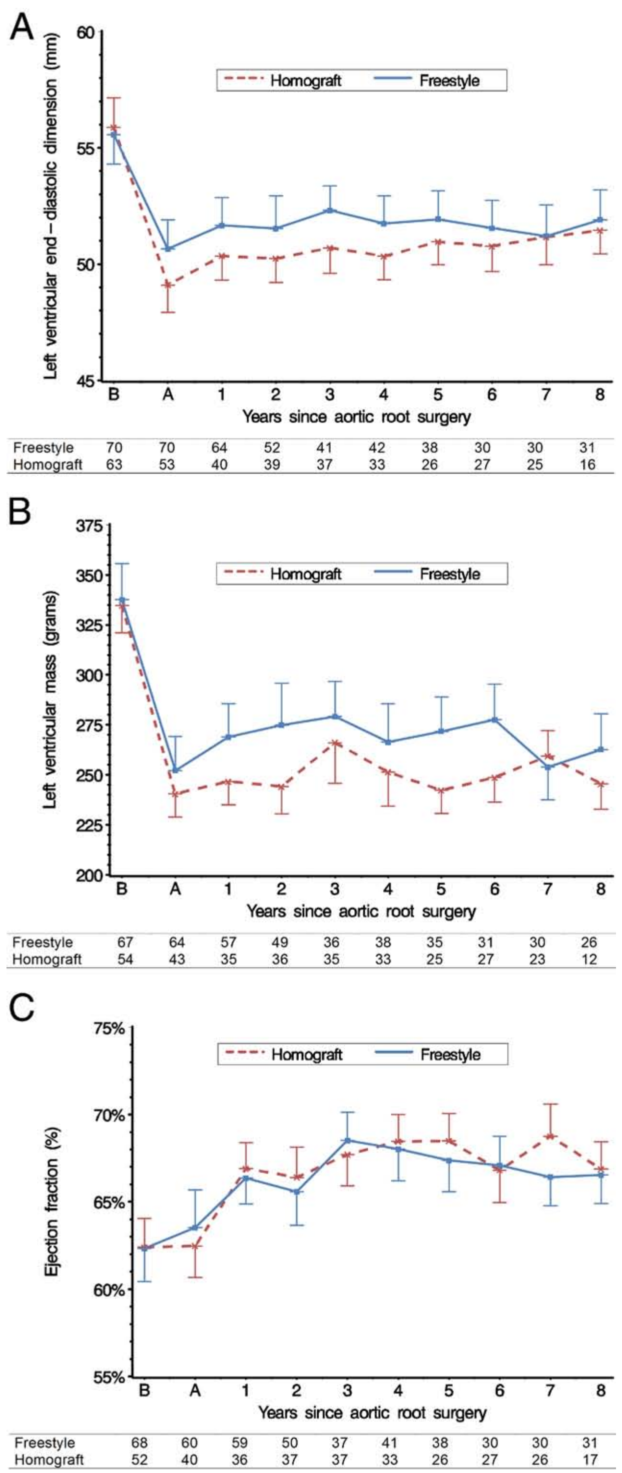

Figure 4 **Time-Dependent Changes After Freestyle Versus Homograft Root Replacement**

(A) Time-dependent changes in left ventricular end-diastolic dimension after Freestyle versus homograft root replacement. **(B)** Time-dependent changes in left ventricular mass after Freestyle versus homograft root replacement. **(C)** Time-dependent changes in ejection fraction after Freestyle versus homograft aortic root replacement. **Blue** = Freestyle; **red** = homograft.

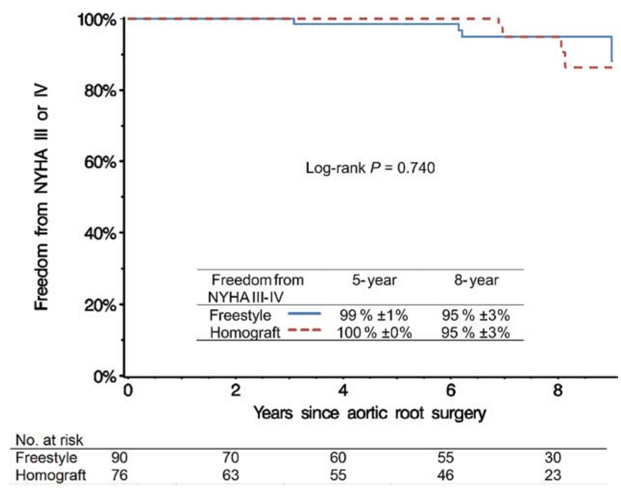

Figure 5 **Actuarial Freedom From NYHA Functional Class III or IV After Freestyle Versus Homograft Root Replacement**

Actuarial freedom from New York Heart Association (NYHA) functional class III or IV after Freestyle **(blue)** versus homograft **(red)** aortic root replacement.

patients with reduced left ventricular function. However, that needs to be evaluated in a prospective randomized trial looking at hemodynamic improvement, valve durability, patient survival, and quality of life.

Mohammadi et al. (18) examined a cohort of 608 patients undergoing Freestyle implantation (78% subcoronary and 22% full roots) and reported a total of 10 cases of cusp tears requiring reoperation at a median time of 8.7 years after surgery. Notably, 9 of the 10 cases of cusp rupture occurred

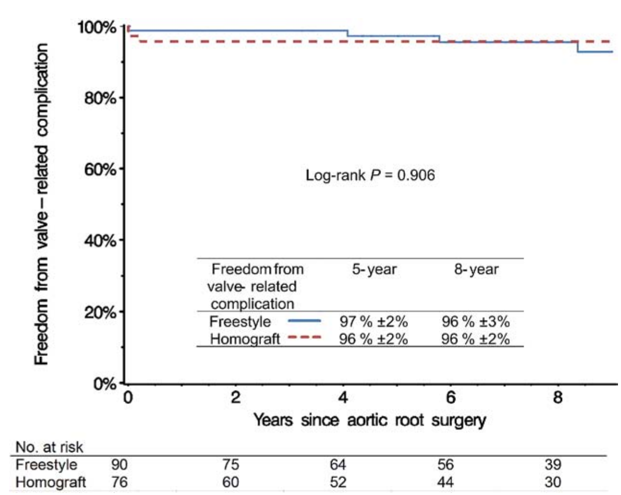

Figure 6 **Actuarial Freedom From Valve-Related Complications After Freestyle Versus Homograft Root Replacement**

Actuarial freedom from the composite end point of endocarditis, thromboembolism, thrombosis, or major bleeding after Freestyle **(blue)** versus homograft **(red)** aortic root replacement.

JACC Vol. 55, No. 4, 2010
January 26, 2010:368–76

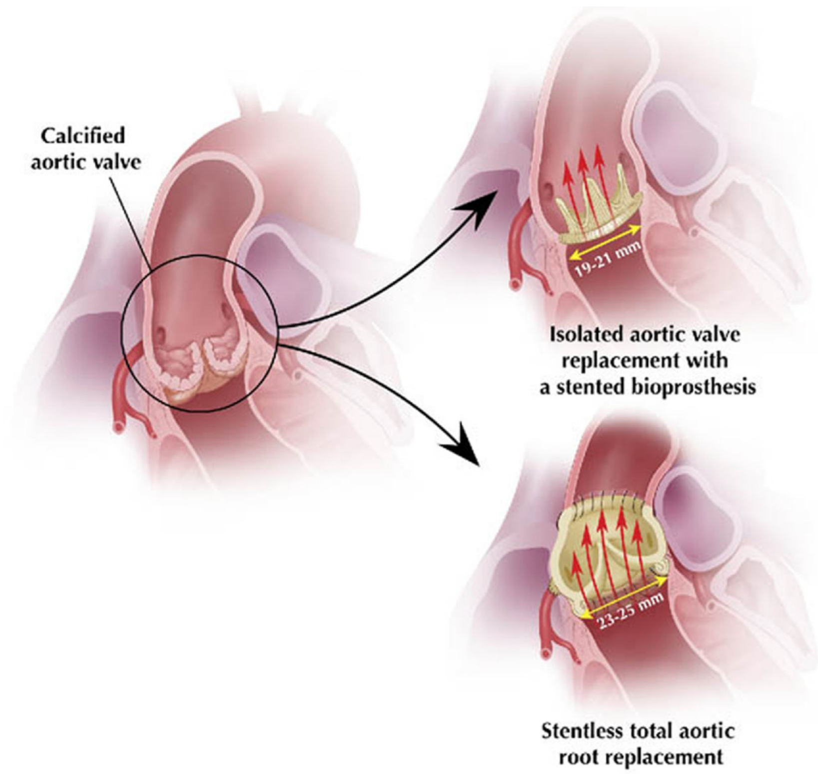

Figure 7 **Rationale for Using Stentless Aortic Prostheses for Aortic Valve Disease**

Rationale for performing total aortic root replacement using a stentless aortic root for patients with aortic valve disease. Replacing the entire root maintains the structural relationship between the different components of the valve mechanism. In addition, it allows marked flexibility in oversizing the annulus thus providing a better effective orifice area. These advantages could have an important impact on ventricular dynamics, long-term valve durability, and patient survival. Figure illustration by Rob Flewell.

after subcoronary implantation with preservation of the noncoronary sinus and were exclusively localized in the right and left coronary cusps. This finding suggests that total root replacement could be associated with less mechanical stress on the cusps and might therefore lead to better long-term durability of the valve. Continued close monitoring of these patients is mandatory to evaluate this hypothesis. We are currently performing computational analysis studies of aortic root biomechanics to define the role of different implantation techniques on the tensile stresses and the aortic and coronary flow patterns.

The increased incidence of homograft degeneration after implantation in this study mirrors that in other reports from different centers (19,20). Importantly, homograft degeneration is often accompanied by varying degrees of cusp and wall calcification (21), sometimes making reoperation a more difficult procedure (22), although in our experience reoperation for homograft root replacement was associated with a similar mortality to first-time operation if reoperation is not unduly delayed, resulting in multiorgan failure (23). In this study, 1 patient undergoing reoperation died of multiorgan failure during the post-operative period. We have recently shown that the rate and extent of calcification measured by electron-beam computed tomography is significantly higher in homograft roots than in Freestyle roots up to 8 years after surgery (24). That is likely a consequence of direct and indirect immune reactions elicited by the persistence of living cells and protein remnants on the homograft cusps and wall. The rate of calcification observed in that study was significantly faster during the first 3 post-operative years. The slower rate of degeneration observed with Freestyle roots is possibly, in part, due to pre-treatment with alpha-oleic acid, which has been shown to mitigate Freestyle wall calcification in animal studies (25). Nevertheless, a slow but steady increase in prosthetic calcification was measured by electron-beam computed tomography up to 8 years after implantation (26). In a recent study of 9 cases of Freestyle reoperation, Butany et al. (27) reported 3 cases of significant calcification (grade 3 or 4) and 3 cases of cusp tear at a median time of 5 years after surgery, further emphasizing the importance of close patient follow-up. Interestingly, these 6 cases had all undergone subcoronary or root inclusion Freestyle implantation at initial surgery.

In the present study, both homovital homografts (n = 30) and antibiotic-sterilized cryopreserved homografts (n = 46) were used. No differences in survival, freedom from reoperation, or valve function were observed between the 2 types of homografts. Nevertheless, the specific source and method of preparation of the homografts could have an influence on outcomes. Therefore, these results cannot be readily generalized to commercially available homografts. Of the 6 patients requiring reoperation in the homograft group, 3 occurred in patients <55 years of age at the time of surgery, supporting the notion of accelerated tissue degeneration in younger patients. Nevertheless, no reoperations were required for that age group in the Freestyle cohort despite a similar age distribution between groups (Table 1).

It appears from the present data that the incidence of evolving valve failure for Freestyle bioprosthetic roots remains low during the first 10 years, as evidenced by an actuarial freedom from evolving valve dysfunction defined as AI ≥2/4 and/or transvalvular gradient >20 mm Hg, of 86% at 8 years. In contrast, freedom from evolving valve dysfunction was found in only 37% of homograft recipients at the same point. Nevertheless, the majority of these patients had grade 2/4 AI, which deteriorates at varying rates in some patients. This study raises important issues regarding the role of homografts in patients with aortic valve disease. Homografts have traditionally been favored over isolated valve replacement for cases of infectious endocarditis, small aortic annuli, and for patients with associated root anomalies. Except for patients with extensive infective endocarditis and root abscesses in whom homografts have a unique benefit due to the mitral flange, the Freestyle bioprosthesis appears to offer the same advantages with the added benefit of a lower rate of reoperations and early valve failure.

The number of children and young adults requiring aortic valve surgery in developing countries is staggering and is constantly increasing because of improved access to health care, better screening programs, and a persistent incidence of rheumatic heart disease. Mechanical valve replacement remains highly risky due to anticoagulation-related problems, and the Ross procedure remains a technically complex operation that requires the presence of homografts. The ready availability of bioprosthetic aortic valves or Freestyle bioprostheses off the shelf in different sizes makes them particularly appealing in this context. The rate of degeneration of both prostheses in young patients requires further assessment. With improving surgical expertise in the developing world, the presence of a durable valve substitute will be critical in these young patients. Therefore, a similar study is mandated with a younger age group to confirm the current results or seek new alternatives. Recruitment of participating centers is now under way for the RAMSES (Randomized Autograft Versus Mechanical Versus Stentless Study) in young patients, and we hope that will further help determine the ideal aortic valve substitute for a potentially larger population of needy patients.

Study limitations. Although clinical follow-up was >85% complete, overall echocardiographic follow-up was lower due to patient-related factors including distance from hospital, compliance with appointments, and lack of mobility. Clinical follow-up was, however, directly obtained from the patients to compensate for this potential bias, ensuring that patients missing to echocardiographic follow-up were clinically well. Mixed-effects models examining echocardiographic measures over time are limited by the number of missing data points. Although these were treated as missing at random, this assumption may be invalid. Therefore, further data are required to validate our findings. The number of potential variables included in the multivariable analysis for predictors of mortality was dictated by the number of deaths. With longer follow-up and additional events, additional predictive factors may emerge. The length of follow-up in this study does not represent "true long-term" follow-up (i.e., ≥20 years). Nevertheless, significant differences were readily apparent between both groups. In this study, we used an age cut-off of 40 years to perform this operation. Similar studies are required for younger patients, in particular to address the large cohorts of young patients in developing countries requiring valve replacement. Finally, although the study was randomized, patient medication was individually prescribed according to current guidelines. Therefore, medication profiles differed slightly between groups at last follow-up, which might have an undetermined effect on outcomes.

Conclusions

Results from this prospective randomized trial indicate significantly better durability of the Medtronic Freestyle bioprosthesis versus homografts after total aortic root replacement. Despite the higher rate of structural valve degeneration and reoperations in the homograft group, overall survival between the 2 groups was nevertheless similar 9 years after surgery. These data have important clinical implications regarding the choice of bioprosthesis for patients requiring aortic valve replacement, particularly in developing countries where storage and availability of homografts remains an important limitation.

Acknowledgment
The authors acknowledge Ms. Sue Edwards, RN, for her invaluable assistance.

Reprint requests and correspondence: Sir Magdi H. Yacoub, Harefield Heart Science Center, Harefield Hospital, Hill End Road, Harefield UB9 6JH, United Kingdom. E-mail: m.yacoub@imperial.ac.uk.

REFERENCES

1. Yacoub MH, Takkenberg JJ. Will heart valve tissue engineering change the world? Nat Clin Pract Cardiovasc Med 2005;2:60–1.
2. Lund O, Chandrasekaran V, Grocott-Mason R, 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;117:77–90, discussion 90–1.

3. Palka P, Harrocks S, Lange A, Burstow DJ, O'Brien MF. Primary aortic valve replacement with cryopreserved aortic allograft: an echocardiographic follow-up study of 570 patients. Circulation 2002;105: 61–6.
4. Lim E, Ali A, Theodorou P, 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.
5. Yacoub M, Rasmi NR, Sundt TM, et al. Fourteen-year experience with homovital homografts for aortic valve replacement. J Thorac Cardiovasc Surg 1995;110:186–93, discussion 193–4.
6. 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, discussion 975–6.
7. Clark TG, Altman DG, Stavola BLD. Quantification of the completeness of follow-up. Lancet 2002;359:1309–10.
8. Hasnat K, Birks EJ, Liddicoat J, et al. Patient outcome and valve performance following a second aortic valve homograft replacement. Circulation 1999;100 Suppl II:II42–7.
9. Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952–9.
10. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732–8.
11. Office for National Statistics. Annual life tables. Available at: http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459. Accessed November 24, 2009.
12. Higashidate M, Tamiya K, Beppu T, Imai Y. Regulation of the aortic valve opening: in vivo dynamic measurement of aortic valve orifice area. J Thorac Cardiovasc Surg 1995;110:496–503.
13. Davies JE, Parker KH, Francis DP, Hughes AD, Mayet J. What is the role of the aorta in directing coronary blood flow? Heart 2008;94: 1545–7.
14. Bach DS, Kon ND, Dumesnil JG, Sintek CF, Doty DB. Ten-year outcome after aortic valve replacement with the freestyle stentless bioprosthesis. Ann Thorac Surg 2005;80:480–6.
15. David TE, Ivanov J, Armstrong S, Feindel CM, Cohen G. Late results of heart valve replacement with the Hancock II bioprosthesis. J Thorac Cardiovasc Surg 2001;121:268–77.
16. Dellgren G, David TE, Raanani E, Armstrong S, Ivanov J, Rakowski H. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. J Thorac Cardiovasc Surg 2002;124:146–54.
17. Rizzoli G, Bottio T, Thiene G, Toscano G, Casarotto D. Long-term durability of the Hancock II porcine bioprosthesis. J Thorac Cardiovasc Surg 2003;126:66–74.
18. Mohammadi S, Baillot R, Voisine P, Mathieu P, Dagenais F. Structural deterioration of the Freestyle aortic valve: mode of presentation and mechanisms. J Thorac Cardiovasc Surg 2006;132:401–6.
19. Smedira NG, Blackstone EH, Roselli EE, Laffey CC, Cosgrove DM. Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft and pericardial prostheses. J Thorac Cardiovasc Surg 2006;131:558–64.
20. Takkenberg JJ, Eijkemans MJ, van Herwerden LA, et al. Prognosis after aortic root replacement with cryopreserved allografts in adults. Ann Thorac Surg 2003;75:1482–9.
21. Koolbergen DR, Hazekamp MG, de Heer E, et al. The pathology of fresh and cryopreserved homograft heart valves: an analysis of forty explanted homograft valves. J Thorac Cardiovasc Surg 2002;124:689–97.
22. Joudinaud TM, Baron F, Raffoul R, et al. Redo aortic root surgery for failure of an aortic homograft is a major technical challenge. Eur J Cardiothorac Surg 2008;33:989–94.
23. Sundt TM, III, Rasmi N, Wong K, Radley-Smith R, Khaghani A, Yacoub MH. Reoperative aortic valve operation after homograft root replacement: surgical options and results. Ann Thorac Surg 1995;60 Suppl:95–9, discussion 100.
24. El-Hamamsy I, Zaki M, Stevens LM, et al. Rate of progression and functional significance of aortic root calcification after homograft versus Freestyle aortic root replacement. Circulation 2009;120 Suppl: 269–75.
25. Chen W, Kim JD, Schoen FJ, Levy RJ. Effect of 2-amino oleic acid exposure conditions on the inhibition of calcification of glutaraldehyde cross-linked porcine aortic valves. J Biomed Mater Res 1994;28:1485–95.
26. El-Hamamsy I, Zaki M, Stevens LM, et al. Rate of progression and functional significance of aortic valve and root calcification after Freestyle versus homograft aortic root replacement: results from a prospective randomized trial. Circulation 2009;120:S269–75.
27. Butany J, Zhou T, Leong SW, et al. Inflammation and infection in nine surgically explanted Medtronic Freestyle stentless aortic valves. Cardiovasc Pathol 2007;16:258–67.

Key Words: homografts ▪ xenografts ▪ survival ▪ structural valve degeneration.