Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial

Ismail El-Hamamsy, Zeynep Eryigit, Louis-Mathieu Stevens, Zubair Sarang, Robert George, Lucy Clark, Giovanni Melina, Johanna J M Takkenberg, Magdi H Yacoub

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Department of Cardiac Surgery, Royal Brompton and Harefield NHS Trust, London, UK (I El-Hamamsy MD, R George MD, G Melina MD, Prof Sir M H Yacoub FRS); **National Heart and Lung Institute, Imperial College London, London, UK** (I El-Hamamsy, Z Eryigit MD, Z Sarang BSc, R George, L Clark PhD, Prof Sir M H Yacoub); **Department of Cardiac Surgery and Epidemiology, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada** (L-M Stevens MD); **and Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Rotterdam, Netherlands** (Z Eryigit, J J M Takkenberg MD)

Correspondence to:
Prof Sir Magdi H Yacoub, Magdi Yacoub Institute, Hill End Road, Harefield, Middlesex, London UB9 6JH, UK
m.yacoub@imperial.ac.uk

Summary

Background **The ideal substitute for aortic valve replacement in patients with aortic valve disease is not known. Our hypothesis was that the regulatory and adaptive properties of a living valve substitute could improve the long-term outcomes in patients. We therefore compared these outcomes after autograft aortic root replacement (Ross procedure) versus homograft aortic root replacement in adults.**

Methods **Male and female patients (<69 years) requiring aortic valve surgery were randomly assigned in a one-to-one ratio to receive an autograft or a homograft aortic root replacement in one centre in the UK. The random allocation sequence was computer generated. Treatment was not masked. The primary endpoint was survival of patients at 10 years after surgery. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN03530985.**

Findings **228 patients were randomly assigned to receive an autograft or a homograft aortic root replacement. 12 patients were excluded because they were younger than 18 years; 108 in each group received the surgery they were assigned to and were analysed. There was one (<1%) perioperative death in the autograft group versus three (3%) in the homograft group (p=0·621). At 10 years, four patients died in the autograft group versus 15 in the homograft group. Actuarial survival at 10 years was 97% (SD 2) in the autograft group versus 83% (4) in the homograft group. Hazard ratio for death in the homograft group was 4·61 (95% CI 1·71–16·03; p=0·0060). Survival of patients in the autograft group was similar to that in an age-matched and sex-matched British population (96%).**

Interpretation **Our findings support the hypothesis that a living valve implanted in the aortic position can significantly improve the long-term outcomes in patients.**

Funding **Magdi Yacoub Institute.**

Introduction

Aortic valve replacement has been shown to improve the natural history of patients with severe symptomatic aortic valve disease.[1,2] With the increase in the global population and improved access to health care, the number of aortic valve surgeries worldwide is estimated to triple within the next 30 years.[3] So far, surgery remains the only effective solution for improvement of the natural history of the disease; however, survival after surgery is often worse than in the general population[4] and the degree of improvement seems to depend on the type of aortic valve substitute used.[5] Randomised controlled trials are a robust way to enable rational, evidence-based decision making with respect to the choice of valve substitute. Nevertheless, the long-term outcomes (survival and quality of life) after different valve replacement procedures in patients with aortic valve disease have been compared in only a few randomised studies.[6,7] Results of several observational studies have shown an excellent pattern of survival after autograft aortic root replacement (Ross operation) in adults that might be attributed to selection bias.[8–10] The aortic valve has several sophisticated functions that are dependent on its viability.[11–13] The Ross operation is the only surgical procedure that provides continued long-term viability of the valve tissue. We postulated that the regulatory and adaptive properties of a living valve substitute could translate into improved long-term outcomes in patients. Our aim therefore was to assess the late outcomes in patients after autograft versus homograft aortic root replacement.

Methods

Patients

All male and female patients (<69 years) presenting from 1994 to 2001 at the Royal Brompton and Harefield NHS Trust, London, UK, with aortic valve disease requiring surgery were eligible for enrolment in the study. Patients presenting with concomitant aortic root dilatation or ascending aortic dilatation (>5 cm), bicuspid aortic valve disease, active endocarditis requiring surgery, rheumatic heart disease, decreased ejection fraction, requiring emergent surgery, or who had previous cardiac surgery were not excluded from the study. In the initial study period (1994–97), children (<18 years) were included (n=12). Because of early homograft failure in two children, all patients younger than 18 years of age were excluded from

the trial. Other exclusion criteria were the presence of Marfan's syndrome, rheumatoid arthritis, Reiter's syndrome, and age older than 69 years.

Approval for the study was obtained from the local ethics committee, and all patients provided written informed consent before enrolment to the study.

Randomisation and masking

Patients were assigned in a one-to-one ratio, and the random allocation schedule was computer generated by a dedicated research nurse. We used sequentially numbered opaque sealed envelopes to conceal treatment allocation. Patients were enrolled by a dedicated research nurse and the main consultant surgeon (MHY). Treatment was not masked.

Surgical procedures

One surgeon (MHY) undertook all the procedures using the same technique during the study period. All patients underwent total aortic root replacement. For autograft root replacement, the pulmonary root was harvested in a scalloped fashion, leaving 1–2 mm below the attachment of the cusps. Close interrupted sutures were used for the proximal aortic anastomosis. The left-facing sinus was positioned in the left coronary sinus and the autograft was placed in an intra-annular position to provide external fibrous support to the muscular pulmonary root. The coronary ostia were anastomosed to their respective sinuses. The distal anastomosis was completed 2–3 mm above the level of the commissures to reduce the risk of autograft dilatation. No foreign material was used to support the proximal or distal anastomoses. A pulmonary homograft was placed in the pulmonary position. The largest available size was always used. Strict blood pressure control (systolic blood pressure <110 mm Hg) was maintained perioperatively and for the first 6 months, to allow adaptive remodelling of the autograft. For patients undergoing homograft aortic root replacement, a previously described standard technique was used.[14]

Follow-up

Follow-up of patients was actively done on a yearly basis and consisted of outpatient appointments, patient call-ups, or contact with the patient's family physician. Overall, 80% of patients were followed up regularly in our outpatient department with complete clinical and echocardiographic examinations. For personal and professional reasons, some patients moved during the study period. These were contacted by phone or through their family doctors, and echocardiographic reports were obtained when possible. Mean duration of clinical follow-up was 10·2 years (SD 3·2; 2173 total patient-years) and was 97% complete within 12 months of study closure. Indications for reintervention were symptomatic valve dysfunction (moderate or severe) or progressive ventricular dilatation. Perioperative death was defined as death in hospital or within 30 days after surgery.

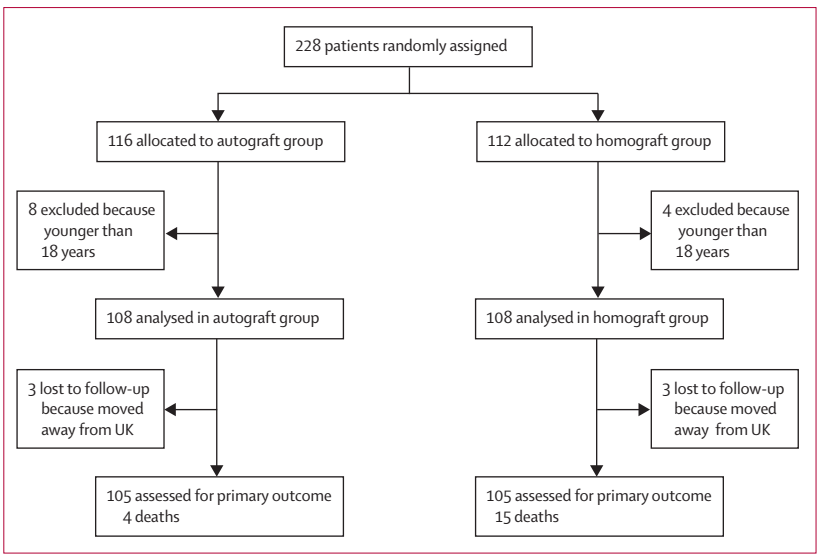

Figure 1: **Trial profile**

Serial echocardiogram examinations were done every 2 years if patients were asymptomatic and the previous echocardiogram showed no signs of valvular or ventricular dysfunction, and more frequently in the remaining patients. Completeness of echocardiogram follow-up was 80% within 24 months of study closure. A total of 1505 complete echocardiogram examinations were analysed to produce mixed-effect models of aortic

	Homograft (n=108)	Autograft (n=108)
Age (years; median, range)	39 (19–68)	38 (19–66)
Age (years)		
18–34	46 (43%)	47 (44%)
35–49	28 (26%)	39 (36%)
50–59	24 (22%)	13 (12%)
≥60	10 (9%)	9 (8%)
Sex (male)	89 (82%)	92 (85%)
Body-surface area (m^2; mean, SD)	1·9 (0·2)	1·9 (0·2)
Smoking status		
Smoker	23 (21%)	18 (17%)
Ex-smoker	26 (24%)	18 (17%)
Never smoked	59 (55%)	72 (67%)
Comorbidities		
Hypertension	29 (27%)	21 (19%)
Dyslipidaemia	4 (4%)	3 (3%)
Diabetes	2 (2%)	1 (1%)
Renal failure*	7 (6%)	6 (6%)
Preoperative aortic regurgitation		
0	14 (13%)	8 (7%)
1	5 (5%)	1 (1%)
2	16 (15%)	21 (19%)
3	28 (26%)	34 (31%)
4	44 (41%)	44 (41%)

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	Homograft (n=108)	Autograft (n=108)
(Continued from previous page)		
Surgical indication		
Primary isolated aortic stenosis	35 (32%)	30 (28%)
Primary isolated aortic regurgitation	46 (43%)	49 (45%)
Mixed aortic stenosis and regurgitation	27 (25%)	29 (27%)
Thoracic aortic aneurysm	1 (1%)	2 (2%)
Cause		
Degenerative	48 (44%)	48 (44%)
Congenital	54 (50%)	53 (49%)
Rheumatic	6 (6%)	7 (6%)
Endocarditis		
None	86 (80%)	89 (82%)
Active	9 (8%)	9 (8%)
Treated	13 (12%)	10 (9%)
Previous intervention†	48 (44%)	45 (42%)
Homograft	33 (31%)	24 (22%)
Mechanical or tissue prosthesis	12 (11%)	13 (12%)
Aortic valve repair	9 (8%)	12 (11%)
Coarctation repair	2 (2%)	9 (8%)
New York Heart Association		
I	22 (20%)	33 (31%)
II	48 (44%)	49 (45%)
III	29 (27%)	21 (19%)
IV	9 (8%)	5 (5%)
Heart rhythm		
Sinus rhythm	101 (94%)	103 (95%)
Atrial fibrillation	5 (5%)	1 (1%)
Pacemaker	1 (1%)	4 (4%)
Type of surgery		
Emergent	8 (7%)	5 (5%)
Urgent	8 (7%)	5 (5%)
Elective	92 (85%)	98 (91%)

Data are number (%), unless otherwise indicated. *Defined as estimated creatinine clearance of less than 0·835 mL/s. †Refers to the last surgery before enrolment; some patients had more than one procedure at the last intervention.

Table 1: **Characteristics of patients**

valve function, ventricular dimensions and function, and aortic or autograft sinus diameter. Aortic or autograft sinus diameter was systematically measured in the long-axis view at the level of the aortic sinus of Valsalva.[15] Aortic regurgitation was quantified by measurement of the ratio of the maximum regurgitant jet diameter to the systolic left ventricular outflow tract diameter directly under the aortic valve in the parasternal long-axis view (jet diameter ratio).[16]

Quality of life

Short-form 36 health survey questionnaires (SF-36) were used to assess the quality of life of patients.[17] The questionnaires were sent to all surviving patients between September and December, 2008. Questionnaires were resent to non-responders. 76 (75%) of 102 eligible patients responded in the autograft group and 64 (71%) of 90 in the homograft group at a mean of 11 years (SD 2) after surgery.

Statistical analysis

Calculation of the sample size was based on an estimated 80% of patients surviving after homograft root replacement at 10 years,[18] 97% of the population surviving at 10 years,[19] and the assumption that the Ross procedure would restore the population survival. A total of 85 patients in each group would be needed to show a 15% survival difference at 10 years, with α less than 0·05, β greater than 0·80, and a dropout rate of 10%. The primary endpoint was survival at 10 years. Secondary endpoints were freedom from reoperation, valve-related morbidity, quality of life, and changes in valvular and ventricular function assessed by use of echocardiogram. Data were reported according to the latest guidelines for reporting mortality and morbidity after cardiac valve interventions.[20]

Data were presented as mean (SD) for continuous variables and analysed by use of the student's *t* test. Categorical variables were presented as number (%) and compared by use of Fisher's exact test. The Kaplan-Meier method was used to do the survival analyses, and the log-rank test was used to compare the survival curves. Kaplan-Meier survival estimates were compared with survival of the general population matched for age, sex, and year of surgery by use of UK interim lifetables for 1996–98 to 2005–07.[19] Variables with a $p<0·2$ in the univariate analyses were assessed in the multivariate analyses. The effect of each variable was assumed to be constant with time. A stepwise backward elimination process was used and, as for all other analyses, variables with a $p<0·05$ were judged to be significant. Hazard ratios were presented with 95% CIs. Mixed-effects models were used to assess changes in echocardiographic measurements with time and account for the correlation between repeated follow-up measurements (the MIXED and NLMIXED procedures in SAS software, version 9.1). Fully parameterised mixed-effect models were built including a coefficient for each timepoint for each group (preoperatively [baseline, B], postoperatively before discharge [A], and yearly thereafter). Since most patients had an echocardiogram every 2 years, piecewise linear random-effect models with time as a continuous measurement were constructed with time knots at 1 month, 1 year, and every 2 years. We used the same time knots for aortic regurgitation grade, piecewise multinomial ordinal random-effect model. Between-group differences and changes with time were assessed. For patients with missing echocardiogram measurements at any timepoint, the outcome data were judged to be missing at random.

SF-36 scores for all eight domains were normalised by use of the Oxford healthy life survey UK population estimates[21] with a mean of 50 (SD 10). Physical component scores (which correlate with six of eight domains) and mental component scores (which correlate with five of eight domains) were computed by use of UK-corrected weights.[21] Quality-of-life scores

were expressed as median (IQR), and group differences were assessed by use of the Wilcoxon signed-rank test.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN03530985.

Role of the funding source

The funding source did not influence the design, data gathering, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility to submit for publication.

Results

Figure 1 shows the trial profile. From September, 1994, to May, 2001, 228 patients undergoing aortic root replacement for aortic valve disease were randomly assigned to receive a homograft or an autograft aortic root replacement; 216 were included in the analysis. Table 1 shows the characteristics of the patients in the autograft and homograft groups. Although more perioperative deaths occurred in the homograft group, the difference was not significant (table 2). Three of four perioperative deaths were caused by low-output syndromes in patients operated on for acute infectious endocarditis. The fourth patient had undergone successful homograft root replacement and died suddenly at home on postoperative day 6. Post-mortem examination showed no valvular dysfunction, but severe left ventricular hypertrophy and intramyocardial fibrosis were present.

In the autograft group, the cumulative number of deaths that occurred at up to 1 year, 5 years, 10 years, and 13 years after surgery were three, three, three, and four, respectively; in the homograft group, the cumulative number of deaths were four, five, 15, and 15, respectively. Actuarial survival was greater in the autograft group than in the homograft group at 10 years and 13 years (figure 2). There was one early death, and three late deaths (sudden cardiac death 6 months after surgery [n=1], non-cardiac new-onset motor neuron disease 5 years after surgery [n=1], and unknown cause [n=1]) in the autograft group, and three early deaths and 12 late deaths in the homograft group (valve related [n=2], cardiac [n=3], non-cardiac [n=4], and unknown cause [n=3]) during 13 years. In the homograft group, the valve-related deaths were caused by late infective endocarditis (10 years after surgery) complicated by sudden myocardial infarction and death before surgery could be undertaken; and admission of a patient with acute aortic regurgitation to another hospital (9 years after surgery) and death from decompensated left heart failure before transfer for surgery. The cardiac deaths were secondary to progressive heart failure in the absence of significant valve dysfunction. The non-cardiac deaths were due to metastatic breast cancer (10 years after surgery), rectal cancer (3 years after surgery for infective endocarditis), chronic renal failure with alcohol misuse and heavy smoking (13 years after surgery), and primary lung disease (2 years after surgery). The proportion of patients surviving in the autograft group was similar to an age-matched and sex-matched UK population (figure 2). In the multivariate analysis, the only independent predictor of late mortality was homograft use (hazard ratio 8·64, 95% CI 2·76–27·06) whereas high creatinine clearance was protective (0·97, 0·96–0·99).

In the autograft group, one patient who had undergone surgery for prosthetic valve dysfunction needed pulmonary autograft reoperation 9·5 years after surgery. The indication was mild autograft dilatation (44 mm) with moderate aortic regurgitation and progressive left ventricular enlargement. In the autograft group, the cumulative number of aortic valve reoperations at up to 1 year, 5 years, 10 years, and 13 years after surgery were 0, 0, one, and one, respectively; in the homograft group, the cumulative number of these reoperations were one, two, 16, and 27, respectively. Overall, actuarial freedom from aortic valve reoperation in the autograft group was excellent at 13 years (figure 3A). Additionally, seven patients had eight pulmonary

	Homograft (n=108)	Autograft (n=108)	p value
Perioperative deaths*	3 (3%)	1 (1%)	0·6215
Concomitant procedures			..
Coronary artery bypass graft	3 (3%)	2 (2%)	>0·99
Mitral valve	4 (4%)	5 (5%)	>0·99
Bypass time (min; mean, SD)	117 (49)	163 (37)	<0·0001
Ischaemia time (min)	85 (23)	110 (21)	<0·0001
Cardioplegia			>0·99
Blood	41 (38%)	42 (39%)	..
Crystalloid	67 (62%)	66 (61%)	..
Aortic homograft			..
Homovital	36 (33%)	..	..
Antibiotic sterilised	41 (38%)	..	..
Cryopreserved	32 (30%)	..	..
Inotrope drugs			0·9605
<24 h	68 (63%)	69 (64%)	..
24–48 h	23 (21%)	21 (19%)	..
>48 h	17 (16%)	18 (17%)	..
Ventilatory support			0·8151
<24 h	93 (86%)	96 (89%)	..
24–48 h	5 (5%)	4 (4%)	..
>48 h	10 (9%)	8 (7%)	..
Complications			..
Re-exploration for bleeding	4 (4%)	13 (12%)	0·0405
Pacemaker	2 (2%)	2 (2%)	>0·99
Atrial fibrillation	17 (16%)	17 (16%)	>0·99
Cerebrovascular accident or transient ischaemic attack	3 (3%)	2 (2%)	0·6816
Renal failure	2 (2%)	3 (3%)	>0·99
Sternal wound infection	1 (1%)	4 (4%)	0·3692
Intensive care unit length of stay (days; median, range)	1 (0–9)	1 (1–14)	0·7744
Hospital stay (days; median, range)	9 (0–46)	9 (4–44)	0·4510

Data are number (%) unless otherwise indicated. *Includes death in hospital or within 30 days of surgery.

Table 2: **Operative and perioperative characteristics of patients**

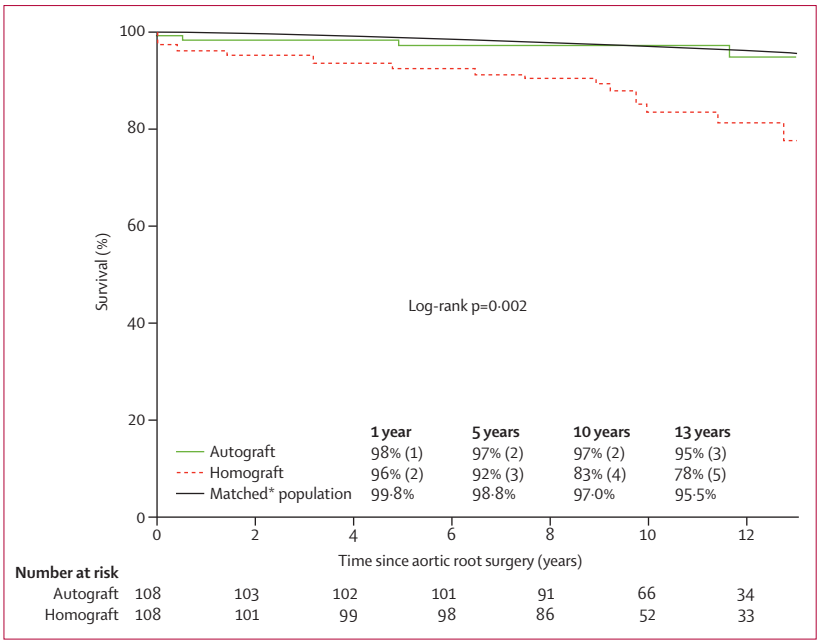

Figure 2: **Actuarial survival after autograft versus homograft aortic root replacement**
Data are percentage (SD). *For age and sex.

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homograft reoperations for stenosis (n=6) and endocarditis (n=2). Four (50%) of the pulmonary reoperations were done within the first 18 months after surgery. Actuarial freedom from pulmonary homograft reoperation in the autograft group was 95% (SD 2) at 10 years and 94% (3) at 13 years (webappendix p 1). In the autograft group, the cumulative number of aortic or pulmonary valve reoperations up to 1 year, 5 years, 10 years, and 13 years after surgery were two, four, seven, and nine, respectively; in the homograft group, the cumulative number of these reoperations were one, two, 16, and 27, respectively. Overall freedom from any reoperation in the autograft group was also high at 10 years and 13 years (figure 3B).

By contrast, the rate of actuarial freedom from reoperation was lower in the homograft group than in the autograft group at 10 years and 13 years (figure 3A). 18 of 27 re-operations in the homograft group were for structural valve deterioration and nine were for infective endocarditis. Use of a homograft was an independent predictor of the need for reoperation in the multivariate analysis (hazard ratio 5·69, 95% CI 2·46–13·15), whereas older age at surgery was a negative predictor (0·74, 0·57–0·97).

No cases of aortic endocarditis and two late cases of pulmonary homograft endocarditis were reported in the autograft group. By contrast, nine cases of infective endocarditis arose in the homograft group at a median of 10 years (range 2–12) after surgery. Actuarial freedom from all endocarditis was 98% (SD 1) at 10 years and 97% (2) at 13 years in the autograft group versus 94% (3) at 10 years and 82% (6) at 13 years in the homograft group (p=0·002; webappendix p 2). One patient (age 59 years) in the autograft group had a stroke 4 years after surgery versus three patients (ages 23 years, 30 years, and 31 years) in the homograft group at 2 years, 10 years, and 11 years after surgery (webappendix p 3). One of these cases of stroke occurred in the perioperative period after repeat surgery for homograft endocarditis. No cases of bleeding or thrombosis were reported in either group. Overall, actuarial freedom from the composite endpoint of endocarditis, stroke, bleeding, or thrombosis was 97% (2) at 10 years and 96% (2) at 13 years in the autograft group, versus 93% (3) at 10 years and 82% (6) at 13 years in the homograft group (p=0·075; webappendix p 4).

Transaortic gradients did not change in the autograft group for up to 13 years after surgery (gradients <10 mm Hg) versus a steady increase in the homograft group (p<0·0001; figure 4A). Figure 4B shows time-related changes in aortic regurgitation in the two groups. Overall, actuarial freedom from aortic regurgitation grade 3–4 was 94% (SD 3) in the autograft group versus 82% (5) in the homograft group at 10 years (p=0·029). Figure 4C shows the progression of echocardiographically measured transpulmonary gradients across the pulmonary homograft in the autograft group (mean 25 mm Hg [SD 5] at 13 years).

In both groups, left ventricular end-systolic and end-diastolic dimensions substantially decreased after surgery and remained fairly stable thereafter (figure 4D). No differences were noted between the two groups (figure 4D). Similarly, in both groups, the left ventricular ejection fraction showed a striking improvement for up to 3 years after surgery that remained stable for up to 10 years, and was then followed by a slight decrease (p=0·047 for change with time for both groups; figure 4E).

From the outset, the autograft sinus diameter was slightly larger than the homograft sinus diameter (p=0·004; figure 4F). However, in each group, the sinus diameter remained stable and did not show a significant change for up to 13 years after surgery (p=0·463 for change with time in both groups).

Data consistency for quality-of-life questionnaires, measured by use of Cronbach's α, was greater than 0·8 (range 0·81–0·93) for all domains, indicating high reliability of the questionnaire. Median SF-36 physical functioning scores were higher in recipients of autograft aortic root replacement than in those given homograft aortic root replacement (51·0 [IQR 45·9–56·1] *vs* 48·5 [38·3–56·1]; p=0·041), and so were the general health domain scores (51·9 [43·1–55·4] *vs* 48·0 [35·8–52·9]; p=0·019), resulting in a higher physical component score in the autograft group than in the homograft group (53·5 [47·3–56·5] *vs* 49·1 [33·9–54·8]; p=0·018).

Discussion

The Ross procedure, compared with homograft aortic root replacement, improved survival in adults, and was associated with improved freedom from reoperation and quality of life. The proportion of patients who survived after the Ross operation was similar to that in the general population.

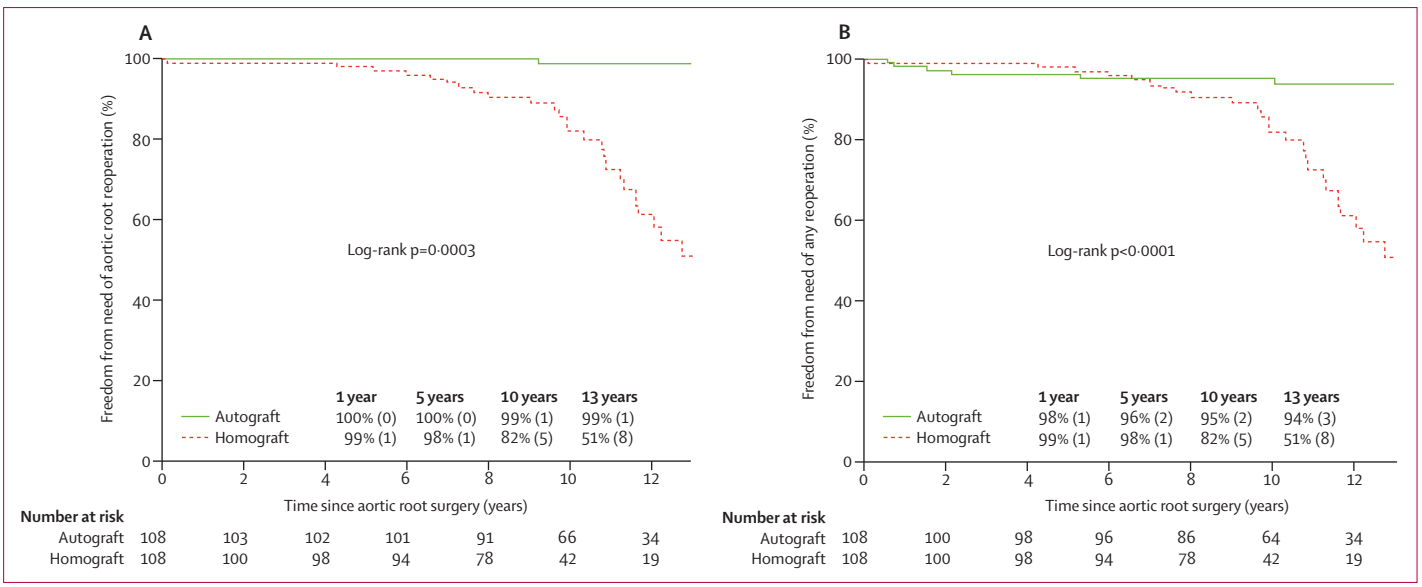

Figure 3: **Actuarial freedom from need of (A) aortic valve reoperation and (B) any (aortic or pulmonary) reoperation in patients after autograft versus homograft aortic root replacement**
Data are percentage (SD).

The two valve substitutes used in this study were chosen on the basis that both provide excellent haemodynamic function and do not require anticoagulation.[18,22,23] Aortic root replacement with implantation of the coronary arteries was used for all patients to ensure that the aortic orifice was maximum and to preserve the exact spatial and functional relation of the component parts of the aortic valve mechanism.[24] The Ross procedure is the only operation with which long-term viability of the aortic root is guaranteed, which could explain the enhanced survival in this study.[25,26] Rapidly increasing evidence suggests that the aortic root has several sophisticated functions in which its constituent parts change their shape and size during the different parts of the cardiac cycle.[11,27] This ability to change shape can affect left ventricular workload and possibly coronary flow, and stress distribution on the cusps.[28,29] Additionally, living aortic cusps modify their stiffness in response to humoral and endothelial signals, allowing them to adapt to changes in haemodynamic conditions.[12]

Apart from survival, patient quality of life is the most important endpoint after valve surgery. In this study, although some patients did not respond to the questionnaire, the quality-of-life scores were significantly better after the Ross operation. The reason for this improvement in the scores could be due to the ability of the living valve to rapidly adapt to changing haemodynamic conditions during exercise in addition to the higher rate of reoperations in the homograft group.

The incidence of progressive autograft root dilatation and neoaortic regurgitation has been reported after the Ross operation.[30,31] In the current study, with the follow-up being complete in 97% of patients, freedom from reoperation was 99% at 13 years. In addition, by use of mixed-effects models, no significant change in autograft sinus diameter was noted during the study period. The reasons could be attributable to specific technical elements and postoperative management of the patients. Unlike the aortic valve, the pulmonary valve has no fibrous annular support; therefore, it is critical to trim the infundibular muscle to 1–2 mm below the cusps and to position the root inside the annulus, ensuring adequate fibrous support. Strict blood pressure control (systolic blood pressure ≤100–110 mm Hg) is critical in the immediate postoperative period and for 6–12 months thereafter to allow adaptive remodelling of the autograft root to systemic pressures.

Pulmonary allograft stenosis has been another cause for concern after the Ross procedure. The incidence, pathological appearance, and location have previously been described and are characterised by intimal hyperplasia at the distal anastomosis and an inflammatory-mediated external compression by fibrous tissue.[32] On the basis of this experience, our approach consists of systematic oversizing of the pulmonary homograft, interrupted sutures for the distal anastomosis, and the use of anti-inflammatory drugs to reduce the haemodynamic effect of this inflammatory reaction. The overall freedom from all reoperations at 13 years in the autograft group compares favourably with available alternatives for tissue valve replacement in a similar patient population.[5]

Freedom from the composite endpoint of endocarditis, bleeding, thrombosis, and thromboembolism in this study is better than that reported in other series after aortic valve replacement.[33]

In this single-centre randomised trial, the number of patients was small. However, sample size was adequate and standardised techniques were used to support the

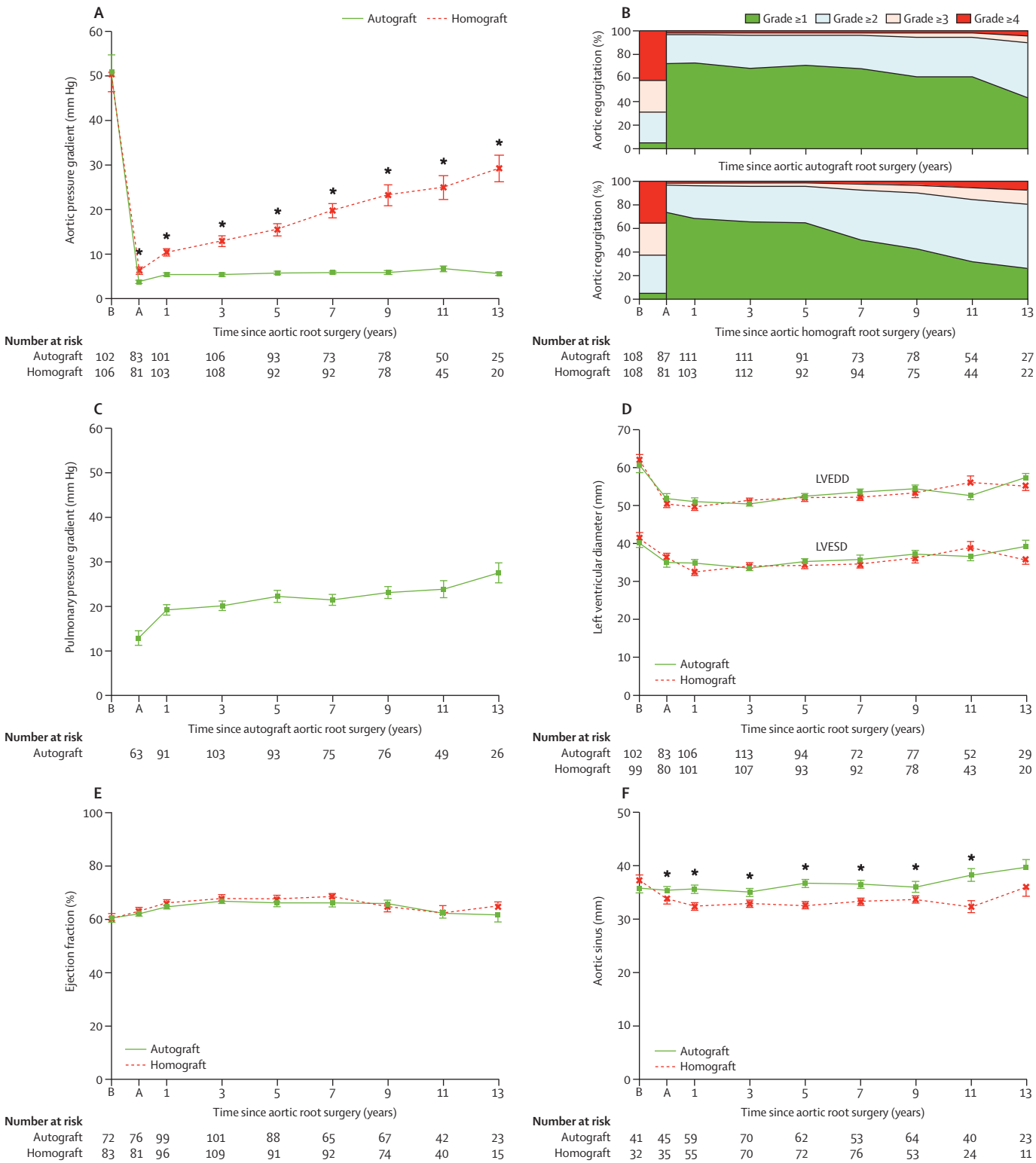

Figure 4: **Mixed-effect models of echocardiogram variables after autograft versus homograft aortic root replacement**
(A) Transaortic gradients; (B) aortic regurgitation; (C) transpulmonary gradient; (D) left ventricular end-diastolic diameters (LVEDD) and end-systolic diameters (LVESD); (E) left ventricular ejection fraction; and (F) aortic sinus diameter. *For parts (A) and (F), p<0·05 between groups at all timepoints. B=preoperative measurement. A=1 month after surgery.

main findings. Although the mean follow-up was 10·2 years, not all patients were followed up for 10 years (figure 2). Longer-term results (>20 years) are not yet available. Continued follow-up of our cohort should address this limitation. All patients were systematically invited to undergo regular echocardiogram follow-up, but completeness of follow-up was 80% mainly because of patients moving, particularly the younger ones. Although patients moving could have had an effect on echocardiogram data, clinical follow-up was available for 97% of patients. In this study, autograft roots were compared only with homograft roots. Xenogenic tissue valves (both stented and stentless) and mechanical prostheses should be compared with autograft implantation in a randomised trial.

In conclusion, our results support the hypothesis that a living valve implanted in the aortic position can lead to significantly improved clinical outcomes in patients.

Contributors

IEH contributed to data gathering, patient follow-up, data analysis and interpretation, and writing of the report. ZE contributed to data gathering, patient follow-up, and editing of the report. LMS was the lead statistician for the study, and also contributed to data analysis and writing of the report. ZS contributed to data gathering and analysis. RG contributed to data analysis and editing of the report. LC contributed to data gathering and patient follow-up. GM contributed to patient recruitment and editing of the report. JJMT contributed to data analysis, statistical analysis, and editing of the report. MHY contributed to concept and design of the trial, scientific overview, patient recruitment, data interpretation, and writing and editing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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References

1 Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968; **38:** 61–67.
2 Iivanainen AM, Lindroos M, Tilvis R, Heikkilä J, Kupari M. Natural history of aortic valve stenosis of varying severity in the elderly. *Am J Cardiol* 1996; **78:** 97–101.
3 Yacoub MH, Takkenberg JJ. Will heart valve tissue engineering change the world? *Nat Clin Pract Cardiovasc Med* 2005; **2:** 60–61.
4 Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000; **35:** 747–56.
5 Svensson LG, Blackstone EH, Cosgrove DM. Surgical options in young adults with aortic valve disease. *Curr Probl Cardiol* 2003; **28:** 417–80.
6 Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000; **36:** 1152–58.
7 Stassano P, Di Tommaso L, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol* 2009; **54:** 1862–68.
8 Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. *J Thorac Cardiovasc Surg* 2008; **136:** 623–30.
9 Sievers HH, Hanke T, Stierle U, et al. A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? *Circulation* 2006; **114:** I504–11.
10 Yacoub MH, Klieverik LM, Melina G, et al. An evaluation of the Ross operation in adults. *J Heart Valve Dis* 2006; **15:** 531–39.
11 Dagum P, Green GR, Nistal FJ, et al. Deformational dynamics of the aortic root: modes and physiologic determinants. *Circulation* 1999; **100:** II54–62.
12 El-Hamamsy I, Balachandran K, Yacoub MH, et al. Endothelium-dependent regulation of the mechanical properties of aortic valve cusps. *J Am Coll Cardiol* 2009; **53:** 1448–55.
13 Yacoub M, Nerem R. Introduction. Bioengineering the heart. *Philos Trans R Soc Lond B Biol Sci* 2007; **362:** 1253–55.
14 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.
15 Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol* 1989; **64:** 507–12.
16 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:** 952–59.
17 SF-36.org. A community for measuring health outcomes using SF tools. http://www.sf-36.org (accessed Jan 25, 2010).
18 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.
19 ONS. Office for National Statistics annual life tables. 1980–82 to 2005–07. http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459 (accessed Jan 25, 2010).
20 Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *J Thorac Cardiovasc Surg* 2008; **135:** 732–38.
21 Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993; **306:** 1437–40.
22 O'Brien MF, Harrocks S, Stafford EG, et al. The homograft aortic valve: a 29-year, 99.3% follow up of 1,022 valve replacements. *J Heart Valve Dis* 2001; **10:** 334–44.
23 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.
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:** S37–43.
25 Rabkin-Aikawa E, Aikawa M, Farber M, et al. Clinical pulmonary autograft valves: pathologic evidence of adaptive remodeling in the aortic site. *J Thorac Cardiovasc Surg* 2004; **128:** 552–61.
26 Mitchell RN, Jonas RA, Schoen FJ. Pathology of explanted cryopreserved allograft heart valves: comparison with aortic valves from orthotopic heart transplants. *J Thorac Cardiovasc Surg* 1998; **115:** 118–27.
27 Lansac E, Lim HS, Shomura Y, et al. A four-dimensional study of the aortic root dynamics. *Eur J Cardiothorac Surg* 2002; **22:** 497–503.
28 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:** 1545–47.
29 Katayama S, Umetani N, Sugiura S, Hisada T. The sinus of Valsalva relieves abnormal stress on aortic valve leaflets by facilitating smooth closure. *J Thorac Cardiovasc Surg* 2008; **136:** 1528–35.
30 David TE, Omran A, Ivanov J, et al. Dilation of the pulmonary autograft after the Ross procedure. *J Thorac Cardiovasc Surg* 2000; **119:** 210–20.
31 Takkenberg JJ, van Herwerden LA, Galema TW, et al. Serial echocardiographic assessment of neo-aortic regurgitation and root dimensions after the modified Ross procedure. *J Heart Valve Dis* 2006; **15:** 100–06.
32 Carr-White GS, Kilner PJ, Hon JK, et al. Incidence, location, pathology, and significance of pulmonary homograft stenosis after the Ross operation. *Circulation* 2001; **104:** I16–20.
33 Kulik A, Bedard P, Lam BK, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. *Eur J Cardiothorac Surg* 2006; **30:** 485–91.