# CHAPTER III

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## EVOLUTION OF ALLOGRAFT AORTIC VALVE REPLACEMENT OVER 13 YEARS: RESULTS OF 275 PROCEDURES

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## Abstract

**Objective:** We describe our center's experience with the use of allografts for aortic valve or root replacement, illustrating the impact on outcome of the changes made in surgical and preservation techniques.

**Methods:** Between 4/1987 and 1/2001 275 allografts were used in 267 consecutive patients to replace the aortic valve or root. All patients were prospectively followed over time. Mean patient age was 46 years (SD 16; range 0.06-83), male/female ratio was 201/74. Prior cardiac operations took place in 73 patients; 49 patients presented with active endocarditis. Pre-op NYHA-class was ≥ III in 51%. Initially, the subcoronary technique was used (SC; N=95) while in recent years root replacement (ARR; N=180) became the technique of choice. Seven fresh (2 pulmonary and 5 aortic) and 268 cryopreserved (4 pulmonary and 264 aortic; 35 glycerol and 233 DMSO) allografts were implanted. Concomitant procedures took place in 133 (48%).

**Results:** Operative mortality was 5.5% (N=15) and during follow-up (99% complete) 29 more patients died. Overall cumulative survival was 73% (95% CI 65-81%) at 9 years postop and significantly better for SC compared to ARR patients (p=0.005). Freedom from allograft-related reoperation (N=34) was 77% (95% CI 69-85) at 9 years, and worse in the SC compared to ARR group due to increased early technical failure (p=0.03). Freedom from reoperation for structural failure (SVD; N=22) was 81% (95%CI 73-89) at 9 years and did not differ between SC and ARR (p=0.51). Independent predictors of degenerative SVD were younger patient age (HR 0.93 with age as continuous variable; 95% CI 0.90-0.97), older donor age (HR 1.06 with age as a continuous variable; 95% CI 1.00-1.11), larger allograft diameter (HR1.38; 95% CI 1.11-1.71) and the use of pulmonary allografts (HR 10.72; 95% CI 3.88-29.63). Calculated median time to reoperation for structural valve deterioration ranged from 23 years in a 65-year-old patient to 12 years in a 25-year-old.

**Conclusions:** Aortic valve replacement with allografts yields adequate midterm results. Although important changes have been made over the years to improve durability, allografts still have a limited life span especially in young patients.

**Key words:** allograft, aortic valve replacement, surgical technique, preservation technique

## Introduction

The use of allografts for replacement of the aortic valve was initiated by Ross in 1962[1] and over the past decades the allograft has become a well-known aortic valve substitute. During this time period several changes in surgical techniques have been attempted to improve durability, and different preservation techniques have been employed to increase shelf half-life time and improve durability.

Ross initially employed the subcoronary implantation technique with good results. However, in the hands of less experienced surgeons early technical failure requiring reoperation was observed[2, 3]. Nowadays, most centers use cryopreserved aortic allografts and employ the root replacement implantation technique with reimplantation of the coronary arteries[4-6]. A major advantage of this technique is the preservation of the aortic root geometry, minimizing initial regurgitation[7]. On the other hand, it requires radical root resection with the risk of complications associated with the reimplantation of the coronary arteries. In addition, on the long term the root may calcify and cause loss of aortic root compliance and an increased risk of leaflet damage caused by contact with the calcified root. Finally, replacement of allograft roots may be more complicated compared to subcoronary implanted allografts.

Also with regard to preservation and sterilization techniques changes have taken place over the years. Most centers now use cryopreserved valves, with the advantage of a long shelf half-life time. Whether the durability of cryopreserved valves is better compared to fresh 4ºC antibiotic stored allograft valves remains unclear[4]. The role of immunologic processes in allograft valve failure is still under debate, and although both cryopreserved and fresh allografts elicit a donor-reactive immune response there is (yet) no clear clinical evidence of associated increased allograft valve failure[8, 9].

We present our center's experience with the use of allografts for aortic valve or root replacement, illustrating the impact on outcome of the changes made in surgical and preservation techniques.

## Materials and methods

**Patients.** From April 1987 until January 2001 275 allografts were used in 267 consecutive patients to replace the aortic valve or root. Eight patients had 2 aortic valve replacements with an allograft. In Table 1 the patient characteristics at the time of operation

Table 1. Pre-operative patient characteristics.

| | All patients (N=275) | SC group (N=95) | ARR group (N=180) |
|---|---|---|---|
| **Patient age (yrs)** | | | |
| Mean (SD; range) | 46.1 (16; 0.06-83.7) | 45.9 (15; 14.2-83.7) | 46.1 (17; 0.06-75.7) |
| **Gender (M/F ratio)** | 201/74 | 67/28 | 134/46 |
| **NYHA class** | | | |
| I | 23% (N=62) | 13% (N=12) | 28% (N=50) * |
| II | 26% (N=72) | 27% (N=26) | 26% (N=46) |
| III | 32% (N=88) | 48% (N=46) | 23% (N=42) |
| IV-V | 19% (N=53) | 12% (N=11) | 23% (N=42) |
| **Heart rhythm** | | | |
| Sinus | 93% (N=256) | 91% (N=86) | 94% (N=170) |
| Atrial fibrillation | 2.5% (N=7) | 3% (N=3) | 2% (N=4) |
| Other | 4.5% (N=12) | 6% (N=6) | 3% (N=6) |
| **Etiology** | | | |
| Endocarditis | 29% (N=81) | 33% (N=31) | 28% (N=50) * |
| *Active endocarditis* | *N=49* | *N=13* | *N=36* |
| Congenital | 29% (N=80) | 32% (N=30) | 28% (N=50) |
| Aneurysm | 8% (N=23) | -- | 12% (N=23) |
| Dissection | 7% (N=18) | -- | 10% (N=18) |
| Rheumatic/degenerative | 16% (N=44) | 26% (N=25) | 11% (N=19) |
| Other | 11% (N=29) | 9% (N=9) | 11% (N=20) |
| **Ischemic heart disease** | 9.5% (N=26) | 12% (N=11) | 9% (N=16) |
| **Hypertension** | 15% (N=41) | 15% (N=14) | 15% (N=27) |
| **Diabetes** | 3.3% (N=9) | 4% (N=4) | 3% (N=5) |
| **Previous CVA** | 5% (N=14) | 8% (N=8) | 3% (N=6) |
| **Prior cardiac operation** | 27% (N=73) | 20% (N=19) | 30% (N=54) |
| **Mean creatinin (μmol/L)** | 104 (SD 88) | 113 (SD 107) | 98 (SD 75) |
| **Left ventricular function** | | | |
| Good | 73% (N=201) | 79% (N=75) | 70% (N=126) |
| Impaired | 19% (N=52) | 17% (N=16) | 20% (N=36) |
| Moderate-bad | 7% (N=18) | 4% (N=4) | 8% (N=14) |
| Missing | 1% (N=4) | -- | 2% (N=4) |

SC= subcoronary implantation, ARR= root replacement; * $p<0.05$ Pearson Chi-square test SC versus ARR group; SD= standard deviation.

are displayed for all 275 operations, and separately for the subcoronary implantation group (SC group; N=95) and the root replacement group (ARR group; N=180).

**Allograft characteristics.** Of the 275 allografts, 95 were implanted using the subcoronary implantation technique and 180 using the aortic root replacement technique. Initially the subcoronary technique was used, while in recent years the root replacement technique has become the technique of choice. In Table 2 the allograft characteristics are displayed. Most of the allografts were provided by the Rotterdam Heart Valve Bank (N=234), as allocated by Bio Implant Services, Leiden, The Netherlands.

Table 2. Allograft properties.

| | **All patients (N=275)** | **SC group (N=95)** | **ARR group (N=180)** |
|---|---|---|---|
| **Type allograft** | | | |
| Aortic | 269 | 90 | 179 * |
| Pulmonary | 6 | 5 | 1 |
| **Preservation** | | | |
| Fresh | 7 | 6 | 1 * |
| Cryopreserved | 268 | 89 | 179 |
| *DMSO* | *233* | *58* | *175* * |
| *Glycerol* | *35* | *31* | *4* |
| **Diameter (mm; N=273)** | | | |
| Mean (SD) | 22.8 (2.2) | 23.4 (2.3) | 22.6 (2.1)# |
| <25 mm | 220 | 64 | 156 * |
| ≥ 25 mm | 53 | 29 | 24 |
| **Type donor** | | | |
| Non-heart-beating | 71 | 13 | 58 |
| Heart-beating | 135 | 47 | 88 |
| Domino heart | 61 | 29 | 32 |
| **Donor age** | | | |
| Mean (SD; range) | 39.7 (12; 9-63) | 36.0 (13; 12-61) | 41.6 (12; 9-63) |
| **Quality code (N=263)** | | | |
| 1-2 | 114 | 59 | 55 * |
| 3-5 | 149 | 29 | 120 |

SC= subcoronary implantation, ARR= root replacement; * Pearson Chi-square test or Fisher Exact test and #ANOVA ($p<0.05$ SC versus ARR group); SD= standard deviation.

The remaining allografts were shipped from the Deutsches Herz-zentrum, Berlin, Germany (N=17), the National Heart Hospital, London, United Kingdom (N=9), the Hospital Clinic I, Barcelona, Spain (N=8), the Karolinska Homograft Bank, Stockholm, Sweden (N=4), the Homograftbank AKH, Linz, Austria (N=1), the Oxford Heart Valve Bank, Oxford, United Kingdom (N=1), and the Heart Center North Rhein Westphalia, Bad Oeynhausen, Germany (N=1). No attempt was made to achieve ABO blood type or HLA type matching.

**Operation.** Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Deep hypothermia and circulatory arrest were used in 32 patients with ascending aorta or arch pathology. Subcoronary implantation was initially done with scalloping of the sinus of Valsalva (N=32), while later on the non-coronary sinus was preserved (N=53)[10]. Root replacement was performed as a freestanding root with reimplantation of the coronary arteries[11]. Surgical techniques were applied as described previously[10, 11]. At the end of the operation routine echocardiography was done to assess allograft function.

**Follow-up.** All patients were prospectively followed over time either through the outpatient clinic and/or by means of an annual telephone survey. Standardized echocardiographic follow-up was done as described previously[3]. Mean duration of follow-up was 4.8 years (SD 3.6 years), ranging from 0 days- 13.8 years. Total follow-up was 1315 patient years, and 99% complete. Morbidity and mortality during follow-up were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations[12].

**Statistical methods.** Data are expressed as mean ± 1SD. Means were compared by the unpaired T-test. The $\chi^2$-test or Fisher's Exact test was used to compare categorical variables. All tests were 2-sided, with an $\alpha$-level of 0.05. Logistic regression was used to study potential determinants of early mortality (death during hospitalization or within 1 month after operation). Multiple logistic regression was used to study independent determinants for early mortality. The final model was obtained using the stepwise backward method with criteria for entry $P<0.05$ and removal $P>0.10$. Cumulative survival and freedom from reoperation were analyzed using the Kaplan-Meier method. The survival of a patient started at the time of aortic valve operation and ended at death (event) or at last follow-up (censoring). The analysis of allograft survival started at the time of implantation and ended with reoperation (event) or last follow-up or patient death (censoring). The differences between Kaplan-Meier curves were evaluated using the log-rank test. Multivariate analysis of time-related events (death, reoperation, and reoperation for structural valve deterioration) was done using the Cox proportional hazard regression model. Backward stepwise selection of potential predictors (criteria for entering variables: log-rank $\chi^2$-test P<0.05) was employed. Covariables were examined by complete case analysis. The incidence of structural valve deterioration requiring reoperation was described by a Weibull curve, which is a generalization of the exponential distribution that accommodates a changing risk over time[13-15]. An age parameter that was based on the observed relationship between patient age and structural valve deterioration was added to the Weibull model, allowing for patient age-specific calculations for structural valve deterioration[16, 17].

## Results

**Early morbidity and mortality.** Peri-operative data of all 275 patients and of the subcoronary implantation (N=95) and root replacement groups (N=180) are displayed in Table 3. In the root replacement group there were more urgent operations (within 24 hours after diagnosis), perfusion time was longer, and there were more patients who underwent concomitant procedures compared to the subcoronary implantation group. In addition, in the root replacement group circulatory arrest was employed in 32 patients (mean age 45 years; SD 17, range 5-75 years) for aortic arch surgery, in comparison to no patients in the subcoronary implantation group. Coronary artery bypass grafting for complications related to reimplantation of the coronary arteries was necessary in 6 root replacement patients, of which 2 subsequently died. In one patient the left coronary artery button was too small, causing ostium stenosis. Another patient had annular calcifications extending up to the right coronary artery ostium that was very thin-layered and ruptured after reimplantation. A third patient had an acute endocarditis of an aortic bioprosthesis with abscesses, and the edematous right coronary artery button ruptured after reimplantation. Another 2 patients experienced right ventricular dysfunction due to kinking of the reimplanted right coronary artery. In one patient the coronary artery buttons were very big, probably causing malperfusion of both the right and left coronary artery. Important postoperative complications were permanent pacemaker insertion in 8 patients, and reoperation for persistent bleeding in 33 patients.

During the procedure 4 patients died, and 11 more patients died during the same hospitalization or within 30 days postoperative (operative mortality 5.5%). The 4 operative deaths were caused by persistent massive bleeding in 3 patients (1 with an active endocarditis with abscesses, 1 with an acute dissection, and 1 patient who underwent a reoperation for paravalvular leakage of a Bjork-Shiley mechanical valve) and left ventricular failure in 1 patient who presented with acute endocarditis with fistula to the left atrium. Causes of death in the 11 patients who died during the same hospitalization or within 30 days postoperative were registered as cardiac and not valve-related in 8 patients, 1 patient died of a major intracerebral bleeding, 1 patient of a myocardial infarction caused by a kink in the reimplanted right coronary artery, and 1 patient with an acute endocarditis as a result of a stroke caused by septic emboli. Independent risk factors for early mortality were patient age>40 at operation (OR 8.8, 95% CI 1.1-70.8; p=0.04), preoperative kidney dysfunction (expressed as preoperative creatinin level (continuous variable), OR 1.0, 95% CI 1.0-1.0; p=0.007), and procedure-related CABG (OR 12.1, 95% CI 1.2-119.0; p=0.03). In addition, longer perfusion times showed an association with impaired early survival (P=0.07).

Table 3. Peri-operative data.

| | **All patients (N=275)** | **SC group (N=95)** | **ARR group (N=180)** |
|---|---|---|---|
| **Urgent operation (<24h)** | 11% (N=30) | 2% (N=2) | 16% (N=28) * |
| **Valve pathology** | | | |
| Stenosis | 26% (N=70) | 26% (N=25) | 25% (N=45) |
| Regurgitation | 61% (N=168) | 58% (N=55) | 63% (N=113) |
| Combined | 13% (N=37) | 16% (N=15) | 12% (N=22) |
| **Perfusion time (min)** | | | |
| Mean (SD; range) | 196 (74; 79-589) | 175 (40; 116-316) | 206 (85; 79-589)# |
| **Cross clamp time (min)** | | | |
| Mean (SD; range) | 136 (43; 0-326) | 132 (30; 79-248) | 138 (48; 0-326) |
| **Circulatory arrest** | N=32 | N=0 | N=32* |
| **Concomitant procedures** | | | |
| No | 52% (N=142) | 68% (N=65) | 43% (N=78)* |
| Yes | 48% (N=132) | 32% (N=30) | 57% (N=102) |
| **Early mortality** | 5.5% (N=15) | 5.3% (N=5) | 5.6% (N=10) |
| **Perioperative stroke** | 3% (N=8) | 2% (N=2) | 3% (N=6) |
| **Reoperation bleeding** | 12% (N=33) | 14% (N=13) | 11% (N=20) |
| **Permanent pacemaker** | 3% (N=8) | 4% (N=4) | 2% (N=4) |
| **Procedure-related CABG** | 2% (N=6) | -- | 3% (N=6) |

SC= subcoronary implantation, ARR= root replacement; * Pearson Chi-square test or Fisher Exact test and #ANOVA ($p<0.05$ SC versus ARR group); SD= standard deviation.

**Long-term mortality.** During follow-up another 29 patients died. Of these patients 21 died of non-valve-related causes. Six patients died sudden unexpected and unexplained deaths, 1 patient died due to a major bleeding, and 1 patient died of acute heart failure caused by severe aortic insufficiency while waiting for reoperation of a degenerated aortic allograft 7.9 years after the initial procedure. Overall cumulative survival including early survival was 93% at 1 year (95% CI 90-96%), 87% at 5 years (95% CI 83-92%), and 73% at 9 years postoperative (95% CI 66-81%). In Figure 1 cumulative survival for patients operated with the subcoronary implantation technique and the root replacement technique is displayed separately (Log-rank test p=0.006). Independent risk factors for overall mortality were older patient age>40 years (HR 3.6, 95% CI 1.7-7.5; p=0.001), root replacement technique (HR 2.2, 95% CI 1.1-4.7; p=0.04), preoperative heart rhythm other than sinus rhythm (HR 1.9, 95% CI 1.3-2.7; p<0.001), longer perfusion time (in minutes, HR 1.0, 95% CI 1.0-1.0, p=0.02), diabetes mellitus (HR 3.0, 95% CI 1.1-8.3; p=0.03), and preoperative ventilatory support (HR 4.1, 95% CI 1.3-12.9; p=0.02).

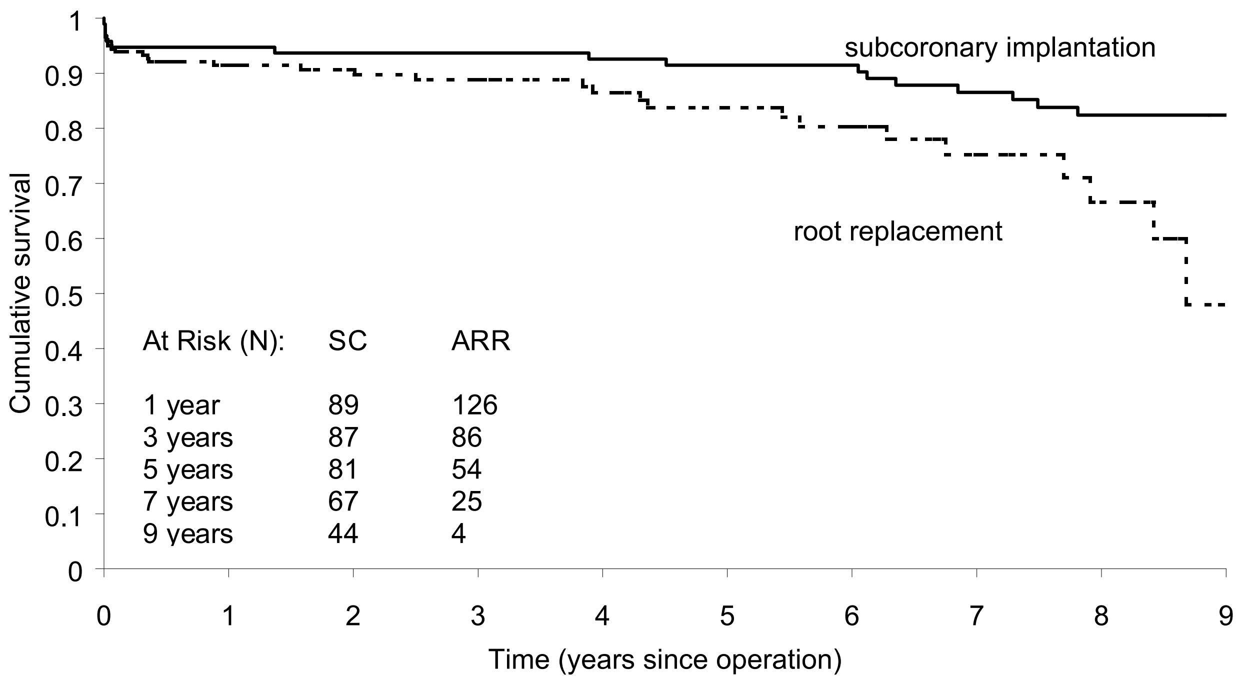


Figure 1. Cumulative survival of patients operated using the subcoronary implantation technique (solid line; SC) and the root replacement technique (interrupted line; ARR); Log-rank test p=0.005.

**Reoperation.** Reoperation for allograft related causes was necessary in 34 patients. Reason for reoperation was structural valve deterioration in 22 patients (early technical in 3 SC patients at 0.5, 0.8 and 1.1 years postop; degenerative in 19 patients at 0.4, 4.4, 4.9, 5.0, 5.7, 5.7, 6.0, 6.2, 6.4, 6.7, 6.8, 8.1, 8.3, 8.4, 8.5, 9.8, 10.0,and 10.9 years postoperative). Non-structural valve failure required reoperation in 11 (paravalvular leakage in 8 patients from the SC group at 0.05, 0.2, 0.5, 1.1, 1.2, 1.3, 2.0 and 3.7 years postop, 1 replacement of an allograft root for pseudo-aneurysm at 2.6 years, 1 closure of a false aneurysm in a ARR patient at 1.9 years, 1 removal vegetation from proximal suture line of an allograft root at 0.06 years postop), and persistent endocarditis in 1 patient at 0.06 years. Freedom from reoperation for allograft-related causes was 97% at 1 year (95% CI 95-99%), 90% at 5 years (95% CI 86-94%), and 77% at 9 years (95% CI 69-85%), and worse in the SC compared to ARR group due to increased early technical failure (Figure 2; Log-rank test p=0.03).

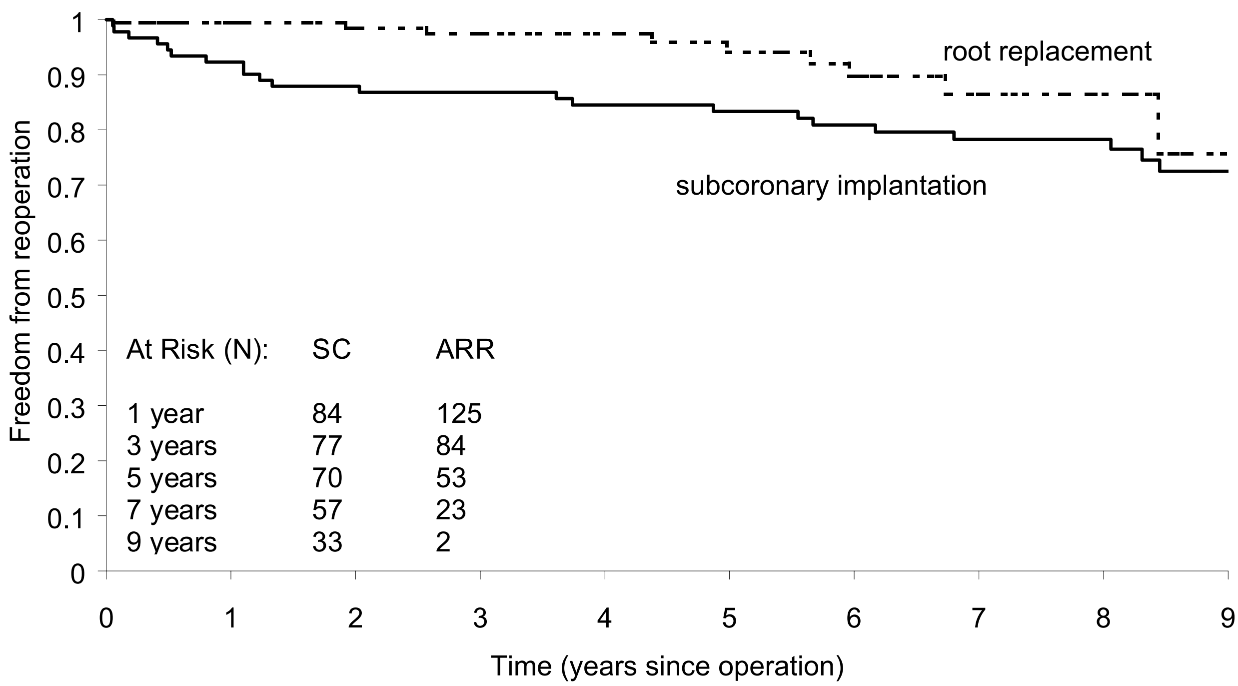


Figure 2. Cumulative freedom from allograft-related reoperation of patients operated using the subcoronary implantation technique (solid line; SC) and the root replacement technique (interrupted line; ARR); Log-rank test p=0.03.

**Structural valve deterioration.** Structural valve deterioration requiring reoperation and replacement of the allograft occurred in 22 patients. In 3 patients in the SC group allograft replacement occurred early after operation due to technical valve failure related to the implantation technique. In 2 of these patients a prolapse of one of the cusps caused moderate to severe regurgitation that was already noticed at discharge by means of echocardiography and necessitated replacement with a bioprosthesis and a mechanical valve at 0.8 and 1.1 year postop. The prolapse of the cusps was most likely caused by imperfect positioning of the allograft valve in the aortic annulus. The third patient developed progressive dyspnea with severe aortic regurgitation 4 months postoperative and at reoperation (6 months postoperative) the non-coronary cusp was noted to be fused with the aortic wall and the allograft was replaced with a mechanical valve. The fusion of the cusp with the aortic wall was most likely caused by oversizing of the allograft valve.

In the other 19 patients structural valve deterioration caused by degeneration of the allograft was the reason for replacement of the allograft. This occurred in 12 patients in the SC group and in 7 patients in the ARR group. The allograft was replaced by a mechanical valve in 14 patients, an allograft in 3 patients (1 subcoronary implantation; 2 root replacement), and a modified autograft procedure was performed in 2 patients. Freedom from reoperation for structural valve deterioration caused by degeneration of the allograft (N=19) was 97% at 5 years (95% CI 93-100), 89% at 7 years (95% CI 85-95%) and 83% at 9 years postoperative (95% CI 75-91%). The results of the univariate and multivariate analyses of potential determinants of degenerative structural valve deterioration are displayed in Table 4.

Table 4. Risk factor analysis for degenerative structural valve deterioration requiring reoperation (N=19).

| | **Univariate model** | | **Multivariate model** | |
|---|---|---|---|---|
| | **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** |
| **Patient age (yrs)** | 0.96 (0.93-0.98) | 0.002 | 0.93 (0.90-0.97) | <0.001 |
| **SC vs ARR technique** | 1.41 (0.51-3.92) | 0.51 | -- | -- |
| **Donor age (yrs)** | 1.04 (1.00-1.08) | 0.05 | 1.06 (1.00-1.11) | 0.045 |
| **Diameter allograft (mm)** | 1.41 (1.13-1.76) | 0.003 | 1.38 (1.11-1.71) | 0.004 |
| **Pulmonary vs aortic allograft** | 4.43 (2.01-9.74) | <0.001 | 10.72 (3.88-29.63) | <0.001 |
| **Cryopreserved vs fresh allograft** | 0.63 (0.14-2.88) | NS | -- | -- |
| **Cryo method*** | 1.38 (0.71-2.69) | NS | -- | -- |

*Cryo method = Glycerol versus DMSO preservation; NS = not significant (p>0.20).

Independent predictors of structural valve deterioration requiring reoperation were younger patient age at the time of operation, the use of fresh allografts, larger allograft diameter, and older donor age. Mean age at the time of operation of those patients requiring reoperation for degenerative structural valve deterioration (N=19) was 33 years (SD 12; range 14-57 years). In Figure 4 the Weibull function representing the effect of patient age on freedom from structural valve deterioration is displayed. For example, for a 45-year-old patient median time to reoperation for structural allograft valve deterioration was 16.5 years.

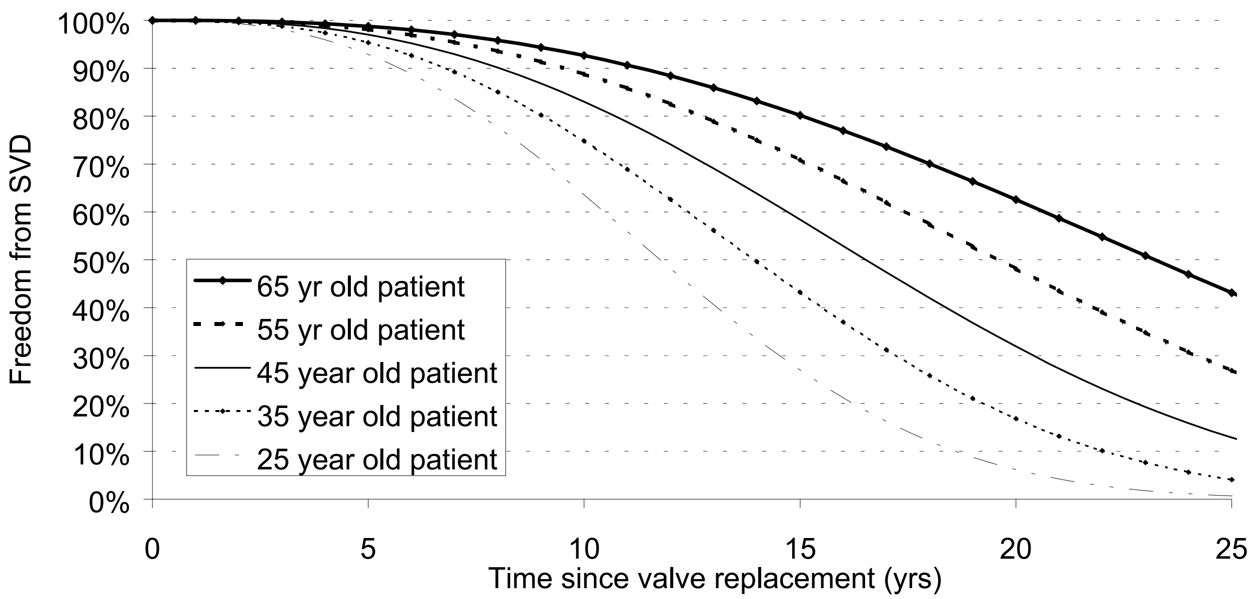


Figure 3. Weibull estimate of age-dependent freedom from structural valve deterioration (SVD) after allograft aortic valve or root replacement for patients aged 25, 35, 45, 55 and 65 years at the time of operation.

**Other valve-related complications.** One patient had a non-fatal ischemic stroke of the right hemisphere 2.5 years postoperative of which he recovered partially. Another patient, who had a perioperative stroke, developed a non-fatal ischemic stroke 3 years postoperative. The linearized annual occurrence rate (LOR) for stroke was 0.15%/patient year. One patient had a reversible neurological deficit (RIND), and 6 patients had one or more episodes of transient ischemic attacks. One patient who received cumarin therapy because of a mechanical valve in mitral position had a major kidney bleeding 2.2 years postoperative, of which he recovered completely (INR 4.8 at the time of the event). Another patient, who received cumarin therapy for atrial fibrillation, developed a lethal intracerebral bleeding 4.8 years postoperative (INR>8.0 at the time of the event). The LOR for major bleeding was 0.15%/patient year. One patient developed an endocarditis with intracranial abscesses 5 years postoperative that was treated medically (LOR 0.08%/patient year). No valve thrombosis or peripheral embolism was observed.

## Discussion

During the past 13 years major changes have taken place in allograft aortic valve replacement in our center, not only in surgical and preservation techniques but also with regard to patient profile. Root replacement has become the preferred surgical technique, and solely cryopreserved aortic allografts are used nowadays. With the shift of surgical technique from subcoronary implantation to root replacement, the patient profile also changed. While isolated disease of the aortic valve leaflets requiring elective surgery was most common when the subcoronary implantation technique was still in use, nowadays a considerable proportion of patients presents with complex aortic root disease and/or active endocarditis often requiring urgent surgery. Also, concomitant procedures are more common and circulatory arrest is employed more often in the root replacement technique group compared to patients operated using subcoronary implantation. Surprisingly, this has not resulted in an increase in early mortality and reflects the growing surgical expertise with allograft aortic root replacement in our center. On the downside, procedure-related coronary artery bypass grafting has emerged as an important complication of the root replacement technique.

Important predictors of early mortality were patient age and impaired preoperative renal function, and confirm the findings by Lund et al[5]. Procedure-related coronary artery bypass grafting was also associated with increased early mortality (2 of the 6 patients; OR 13.1). This operative complication is restricted to root replacement and related to the reimplantation of the coronary arteries that is necessary using this technique.

Overall survival was better in patients operated with the subcoronary technique compared to the root replacement technique, reflecting the change in patient profile that took place over the years. This is contradictory to what Lund et al report[5], and also not supported by the experience from O'Brien's group[4]. It can be explained by the fact that the patient populations of these other centers consist of relatively more patients with isolated valve disease, while only a minority presents with aortic root disease and/or endocarditis.

As has been reported previously[3-5] younger patient age is the most important predictor of structural valve deterioration. This is confirmed by our findings. In addition, we used a

Weibull model to calculate long-term freedom from reoperation for structural valve deterioration based on our current midterm results. It should be stressed that the estimates from the Weibull model are based on the assumption that the risk of structural valve deterioration increases with time. Therefore, the estimates beyond 13 years are still hypothetical and will require regular validation and refinement using the growing experience with allografts worldwide. Currently, using the Weibull model the calculated median time to reoperation for structural valve deterioration varies from 23 years in a 65-year-old patient down to 12 years in a 25 year old (Figure 3). This reflects the need for improvement of the durability of the allograft, and also raises the question whether allografts are the preferred aortic valve substitute in the younger age groups. In these patients other valve substitutes should be seriously considered. In our center, children who require surgical treatment of their aortic valve disease preferably undergo valvotomy or a modified autograft procedure. We reported previously that in patients after autograft aortic root replacement calculated median time to explantation of the autograft for structural valve deterioration was 25 years[18], much better than the estimates derived from our allograft population. Also, no relation between autograft structural valve deterioration and patient age was observed. On the other hand, there is yet little information on the durability of the allograft in the right ventricular outflow tract after autograft aortic root replacement. This is a factor that may be of influence when considering the durability of the autograft procedure. In selected patients a mechanical valve is also a good alternative to the allograft. We previously showed that in younger patients with mechanical bileaflet prostheses the impact of bleeding and thrombo-embolic complications is relatively low, since the life expectancy of these patients is markedly reduced and they will not reach older age where these events become important determinants of outcome[19].

According to our findings, older donor age is also a predictor of structural valve deterioration. Lund et al previously described that the difference between donor age and patient age is the most important determinant for tissue failure after aortic valve replacement with 'homovital' allografts[5]. We did not attempt to investigate this factor in our model, since in our opinion it combines two separate risk factors for allograft structural valve deterioration. Younger patient age is an approximation of an increased workload on the allograft and possibly an increased immune response, while older donor age represents the aging and wear out of the valve substitute. Although donor age is not (yet) a very strong risk factor for structural valve deterioration, it may be advisable to preferably use allografts from younger donors, at the least in the younger patient group.

Other well-known risk factors for structural valve failure in our series were large diameter of the allograft and the use of pulmonary allografts. With the introduction of the root replacement technique, matching of the size of the allograft to the recipient aortic annulus has become less important. Nevertheless, in the multivariate analysis larger allograft size still was an important predictor of allograft structural valve failure independent of patient age and surgical technique. Further investigation into the possible causes that could explain this observation is necessary.

Our experience with fresh wet-stored allograft valves (N=7) is limited, and we find no difference in the durability of fresh compared to cryopreserved allografts. Previous reports tended to be in favor of cryopreserved over fresh valves with regard to durability[20, 21]. However, a recent publication from O'Brien and colleagues[4] shows that in their extensive experience with over 1,000 implantations the freedom from structural valve deterioration at 20 years is similar for cryopreserved and 4ºC anti-biotic stored valves.

Another issue that is often being raised is the influence of surgical technique on the durability of the allograft in aortic position. We have shown previously that the subcoronary implantation technique has a surgeon's learning curve that results in more initial aortic regurgitation and early reoperation compared to the root replacement technique[3]. The progression of aortic regurgitation over time is small in both techniques and it yet remains unclear whether and how the surgical technique will influence durability. The high incidence of early technical failure with the subcoronary implantation technique in our center, and the potential advantage of the preservation of the aortic root geometry using aortic root replacement, has led us to nowadays only use the root replacement technique. It is however a more extensive operation that requires reimplantation of the coronary arteries with the potential complication of coronary malperfusion. Therefore it is essential to pay close attention to the sizing of the coronary buttons and to carefully select the reimplantation site to avoid kinking or stretching of the reimplanted coronary artery. From our current study, we still observe the early increased reoperation rate due to technical failure in the subcoronary implantation group, and thereafter progression of structural valve deterioration is similar to that of the root replacement group. There may however be evidence in favor of the subcoronary implantation technique over the root replacement technique with regard to long-term freedom from reoperation, when carefully studying O'Brien's most recent update of the pioneer series from Australia[4].

With regard to the other valve-related events after allograft aortic valve replacement that were observed in this prospective ongoing study, it can be stated that these occur infrequently. In this respect the allograft is far superior to mechanical and bioprosthetic valves.

In conclusion, we have shown that aortic valve replacement with allografts yields adequate midterm results. Although important changes have been made over the years to improve durability, allografts still have a limited life span especially in young patients. Effort should be made to improve the durability of this valve substitute and to optimize the use of allografts. Most importantly, given the current evidence other aortic valve substitutes should be seriously considered in younger patients.

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