

## 1 **Kriyoprezerve Homogreft İle Aort Kapak Replasmanı Orta Dönem Sonuçları**

2 **Amaç:** Çalışmada kriyoprezerve homogreftler ile kapak replasman sonuçlarının orta dönem  
3 sonuçları incelenmiştir.

4 **Hastalar ve Yöntemler:** Kriyoprezerve homogreft ile 40 olguda aort kapak replasmanı  
5 yapıldı. Endikasyonlar; 20 olguda aort kapak endokarditi, 6 olguda truncus arteriosus ve 14  
6 olguda aort kapak tamir prosedürü sonrası reoperasyonlardı. Kapak çapları 10-27mm idi. Tüm  
7 olgularda kök replasman tekniği kullanıldı.

8 **Bulgular:** Operasyon sonrası 30 günlük mortalite oranı %12,5'ti. Geç dönemde 4 olgu  
9 kaybedildi. Sadece 1 olguda mortalite kardiyak nedenlere bağlıydı. Toplam mortalite oranı  
10 %22,5'ti. 33 olgu ortalama 67±26 aylık süreçte izlendi. Endokardite bağlı aort anevrizması  
11 nedeni ile 2 olgu tekrar ameliyat edildi. Replasman sonrası transvalvular gradiyentlerde  
12 istatistiksel anlamlı düşüş gözlemlendi ( $p<0.03$ ). Son takip sonuçları 27 olgunun normal sol  
13 ventrikül fonksiyonuna sahip olduğunu göstermiştir.

14 **Sonuç:** Kriyoprezerve homogreftler mekanik kapaklara bir alternatif oluşturmaktadırlar ve  
15 uygun endikasyonlarda güvenle kullanılabilirler. Çalışmamızdaki yüksek erken mortaliteye  
16 rağmen; özellikle büyüme çağındakiler ve endokardit gibi ortadan kaldırılması gerekli özel  
17 cerrahi sorunların giderilmesinde kriyoprezerve homogreftler güvenli bir alternatif  
18 oluşturmaktadır.

19 **Anahtar sözcükler:** Aort kapak replasmanı, kriyoprezerve homogreft, endokardit, kalp kapak  
20 bankası

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## 24 **Midterm Results of Aortic Valve Replacement with Cryopreserved Homografts**

25 **Objective:** The aim of this study was to analyze the midterm clinical results of aortic valve  
26 replacement with cryopreserved homografts.

27 **Materials and Methods:** Aortic valve replacement performed in 40 patients with  
28 cryopreserved homograft. The indications were aortic valve endocarditis in 20 patients (50%),  
29 truncus arteriosus in 6 patients (15%), and re-stenosis or regurgitation after aortic valve  
30 reconstruction in 14 (35%) patients. The valve sizes ranged from 10 to 27mm. A full root  
31 replacement technique was used for homograft replacement in all patients.

32 **Results:** The 30-day postoperative mortality rate was 12,5% (5 patients). There were four late  
33 deaths. Only one of them was related to cardiac events. Overall mortality was 22.5%. Thirty-  
34 three patients were followed up for  $67\pm 26$  months. Two patients needed reoperation due to  
35 aortic aneurysm caused by endocarditis. The mean transvalvular gradient significantly  
36 decreased after valve replacement ( $p<0,003$ ). The last follow up showed that the 27 (82 %)   
37 patients had a normal left ventricular function.

38 **Conclusion:** Cryopreserved homografts are safe alternatives to mechanical valves that can be  
39 used in proper indications. Although it has high perioperative mortality rate, cryopreserved  
40 homograft implantation is an alternative for valve replacement particularly in younger patients  
41 and for complex surgical problems such as endocarditis that must be minimized.

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43 **Keywords:** Aortic valve replacement; cryopreserved homograft; endocarditis; heart valve  
44 banking

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## 48           **Introduction**

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50           Since 35 years many mechanical and biological heart valves have been used  
51 successfully for aortic valve replacement (AVR). Despite ongoing investigations and clinical  
52 applications, the ideal aortic valve substitute remains elusive. Stented bioprosthesis  
53 manufactured to provide a standard device that is easily implanted and provide reproducible  
54 results in the aortic position have been associated with good short- and mid-term results (1).  
55 Unfortunately, stented heterograft tissue failures with calcification and cusp rupture becomes  
56 apparent with longer follow-up, particularly in younger patients.

57           Homografts are useful tools for valve replacement, especially in juveniles, in the  
58 presence of contraindications for anticoagulation and in endocarditis. The use of homograft  
59 represents the ideal standard in the aortic valve replacement (2). However, its clinical use is  
60 severely restricted by its limited availability; hence studies demonstrating the clinical results  
61 of these grafts are also limited. The purpose of this study was to examine the durability of  
62 cryopreserved homografts and to determine the clinical outcome.

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## 64           **Materials and Methods**

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66           Patients included in this study were selected from Department of Cardio-Thoracic  
67 Surgery with the diagnosis of isolated aortic valve disease. Informed consent was obtained for  
68 all patients. Cryopreserved homografts were used in 40 patients (26 male, 14 female) (aged 0-  
69 79, median: 40 years). The indications for surgical approach were aortic valve endocarditis in  
70 20 (50%) patients, truncus arteriosus in 6 (15%) patients, re-do surgery for aortic valve  
71 reconstruction in 14 (35%) patients. Eighteen patients (45%) were in a condition of cardiac  
72 decompensation before operation and had class IV angina, the other 14 (35%) had class III,

73 and 8 (20%) had class II angina according to New York Heart association functional  
74 classification. Surgery was performed as an emergency procedure in 14 (35%) patients. The  
75 valve size ranged from 10 to 27mm and median diameter was 21mm. Homograft valves  
76 were harvested under sterile conditions from cardiac transplant recipients, beating-heart or  
77 nonbeating-heart donors, with a maximum age of 65 years. Dissection of the heart was  
78 performed generally within 24 hours after circulatory arrest. After dissection, the valves were  
79 decontaminated by incubation in medium with an antibiotic mixture for 24 hours at 4° C.  
80 Thereafter, valves were cryopreserved in medium containing 10% dimethylsulfoxide (DMSO)  
81 frozen at a controlled rate of  $-1^{\circ}\text{C}/\text{min}$  up to  $-100^{\circ}\text{C}$  and stored on the vapour of liquid  
82 nitrogen ( $-150^{\circ}$  to  $-196^{\circ}\text{C}$ ). All tissues were cryopreserved within 48 hours after circulatory  
83 arrest of the donors. All donors were seronegative for human immunodeficiency virus,  
84 hepatitis B surface and core antigen, cytomegalovirus or treponema pallidum. For  
85 implantation, ABO compatibility or HLA type matching was not required.

86 All operations were performed through a median sternotomy under moderate  
87 hypothermic cardiopulmonary bypass. Myocardial protection was achieved via injection of  
88 antegrade cold blood cardioplegia into the aortic root or into coronary ostia, and in retrograde  
89 fashion through coronary sinus. Root replacement technique (RRT) was used for homograft  
90 replacement in all patients. The hospital records, operative and follow-up notes were reviewed  
91 in this report.

92 A low dose of acetylsalicylic acid (5mg/kg/day) treatment as antithrombotic therapy  
93 was administered to all patients for 3 months postoperatively. All patients were followed up  
94 with serial echocardiographic measurements performed at discharge, at 6 months, at 1 year  
95 and annually thereafter. Graft failure was defined as the need for explantation and valve  
96 related death. The aortic insufficiency (AI) with grade 1 was considered of mild severity.  
97 Mean gradient across the aortic valve was used to define the severity of aortic stenosis (AS)

98 (mild, <25mm Hg; moderate, 25–50 mm Hg; severe,> 50mm Hg). Valve related dysfunction  
99 was defined as an insufficiency of grade 3-4 and a transvalvular gradient of 45 mmHg or  
100 greater.

### 101 **Statistical Analysis**

102 All data analyses were performed with SPSS.13 for windows statistical package.  
103 Continuous variables were expressed as median and range, means and standard deviations.  
104 Categorical data's were given as percentages. Paired and unpaired Student's *t* tests were used  
105 as appropriate to analyse continuous data, and the  $\chi^2$  and Fisher's exact tests were used to  
106 analyse discrete data. In all cases *p* values less than 0.05 were considered to be significant.

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### 108 **Results**

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110 Root technique was used for AVR in all patients. The mean cardiopulmonary bypass  
111 time was  $96 \pm 31.6$  minutes and cross clamp time was  $82 \pm 53$  minutes. Mean intensive care  
112 unit stay and mean total post operative stay durations were 3,8 and 12,1 days, respectively.  
113 The 30-day-operative mortality rate was %12,5 (5 patients). None of these events were valve  
114 related and 4 of them were emergency procedures. 31 patients were examined by Doppler  
115 echocardiography before discharge. Table 1-2 demonstrate the mean gradients and the grade  
116 of valve insufficiency grades with respect to valve sizes.

117 There were 4 (10%) late deaths. Only 1 (%2.5) of them was cardiac related. Overall  
118 mortality rate was 22,5% (9 patients). 33 (82.5%) patients were followed-up for  $67 \pm 26$   
119 months (median: 18 months). 2 (5%) patients needed reoperation for endocarditis and new  
120 developed aortic aneurysm. The mean transvalvular gradient decreased significantly after  
121 valve replacement ( $p < 0,003$ ). The last follow up showed that 27 (82 %) patients had normal

122 left ventricular function. Table1-2-3 demonstrate the mean gradients, the grade of valve  
123 insufficiency and left ventricle end-diastolic diameters according to valve sizes.

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## 125 **Discussion**

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127 Although it has been a half century since Hufnagel implanted the first mechanical  
128 prosthesis; valve surgery continues to have challenges for cardiac surgeons. Ideal aortic valve  
129 prosthesis hasn't been found yet. Theoretically, such a substitute should provide  
130 hemodynamic comparable to the natural human aortic valve, should have the ability to  
131 remodel, should be resistant to infection, must not propagate thromboemboli, should be free  
132 from the hazards of anticoagulation and must be feasible.

133 According to the internationally approved literature, mechanical prosthesis with  
134 diameters smaller than 21mm are not preferred due to the risk of providing suboptimal  
135 hemodynamic (3). Moreover hemolysis and thromboembolic events can occur due to the  
136 mechanical prosthesis applications. Thromboembolic events seen in mechanical valve  
137 replacements are the second leading cause of mortality after cardiac insufficiency (4). Along  
138 with these, complications due to use of anticoagulant agents and postoperative endocarditis  
139 are encountered more often in these patients (1, 5). In our series, we implanted cryopreserved  
140 homografts with diameters smaller than 21mm in twelve patients. During our follow up, we  
141 didn't observe major hemodynamic deterioration or structural valve deterioration. Only two  
142 patients among the survivors had grade II AI. This could be related to the quality of the  
143 harvested donor valve. Since these two valves had diameters greater than 23mm, we may  
144 assume that they might have been harvested from enlarged hearts and had the possibility of  
145 being insufficient initially.

146           The first surgical conduit option in the treatment of endocarditis is homograft (6-13).  
147   One of the main advantages of homograft is its durability in the setting of native or prosthetic  
148   valve endocarditis. Homograft heart valves can be used after several conservation techniques  
149   (14, 15). Cryopreservation technique has improved the durability as compared to other  
150   techniques such as irradiation, fresh or freeze storage in antibiotic solution, and immediate  
151   transplantation (16). In our study, we used cryopreseved homografts and prosthesis  
152   endocarditis was the indication of homograft use in 20 (50%) patients. Three (7.5%) patients  
153   with endocarditis died due to septicemia in the early postoperative period. One (2.5%) patient  
154   had infective endocarditis at the postoperative 15<sup>th</sup> month and had to be reoperated. Riberi and  
155   colleagues and Niwaya and colleagues have reported excellent results with the use of  
156   homografts in these patients, with no recurrent infection (17, 18). Risk of reinfection after  
157   homograft implantation is low (19). We determined 2.5% reoperation rate for infective  
158   endocarditis. However, no clear evidence exists that the homograft is more resistant to  
159   reinfection than other valve types, and the most important issue in the surgical treatment of  
160   patients with severe endocarditis is radical resection of all infected tissues, rather than the type  
161   of valve implanted (20).

162           The potential limiting factor for routine use of homograft is the limited donor supply,  
163   establishing valve banks, and mastering the techniques of homografts. In our study, 28  
164   cryopreserved homografts (70%) were supplied from our own homograft bank. Many centers  
165   do not have experience with these grafts and hence technical mistakes are often made in the  
166   hands of these inexperienced surgeons during operations. However, once the valve banks are  
167   established and the technical skills are improved, the procedure is highly favorable and cost  
168   effective (21).

169           There is debate about the best technique for homograft aortic valve replacement (22,  
170   23). This root replacement technique (RRT) decreases the risks of geometrical distortion due

171 to technical error since the homograft is implanted as a functional unit. The sub coronary  
172 technique (ST) carries the advantage of an easier reoperation in the event of structural  
173 deterioration as compared to the RRT (24). However, the technique is difficult, has a learning  
174 curve, and the technique itself has higher incidence of early reoperation risks if the exact  
175 geometry is not maintained. Willems and colleagues showed that the learning curve associated  
176 with ST is a major reason for early reoperation (24). RRT is easier to perform but reoperations  
177 after this technique are difficult. Most authors advocate use of RRT (25, 26).

178 RRT which was applied in our all procedures was preferred for its low postoperative  
179 valve insufficiency rate. The results for aortic valve insufficiency derived from the similar  
180 studies are in agreement with our study. Another point which is conspicuous is the  
181 discrepancy between the postoperative gradients. Although the sizes of the implanted valves  
182 are same, the mean gradients in our study are higher when compared with other clinics. This  
183 can be due to the chosen implantation technique or the duration of endocarditis infection and  
184 related fibrosis. RRT can be associated with increased gradients across the homograft and  
185 distortion of coronary anastomosis because of a blood filling space between the homograft  
186 and the native aortic wall (27).

187 Despite the improvements in medicine, treatment of valve diseases is still considered  
188 as a problem. There has been a significant increase in the number of aortic valve diseases due  
189 to multifactorial reasons. Investigators are trying to increase the life span and life quality by  
190 the treatment of these diseases. Because of the hemodynamic disadvantages and need for  
191 anticoagulation, there has been many investigations to replace the widely used mechanical  
192 prosthesis. Usage of the biological prosthesis used to be limited because of the resistance  
193 problems, but it has become popular recently. Our experiences showed that, the difficulties of  
194 providing the homografts can be overcome by informing and encouraging the public about  
195 organ donation and increasing the number of tissue banks country wide.

196 Homografts are ideal biological grafts especially for surgical treatments of  
197 endocarditis and young patients because of the physiological characteristics and superior  
198 hemodynamic. As seen in literature, despite high per operative mortality rates, aortic  
199 homograft applications are safe and reliable alternatives for surgical procedures with  
200 favorable short and midterm results. As a surgical technique root implantation is superior  
201 when compared with the aforementioned techniques.

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267 **Table 1:** Early postoperative echocardiography results for aortic insufficiency with respect to  
268 the homograft size

	<b>10-18mm</b>	<b>19-21mm</b>	<b>22-23mm</b>	<b>&gt; 23mm</b>
<b>n: 31</b>	<b>n: 3</b>	<b>n: 13</b>	<b>n: 12</b>	<b>n: 3</b>
<b>Grade 0</b>		1	1	1
<b>Grade 1</b>	3	12	11	2

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289 **Table 2:** Early postoperative echocardiography results for mean gradients

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<b>Mean Gradient</b>	11,3±4,6	291
<b>Peak Gradient</b>	18,6±7,6	292
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336 **Table 3:** Last follow-up echocardiography results for aortic insufficiency with respect to the  
337 valve size

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	<b>10-18mm</b>	<b>19-21mm</b>	<b>22-23mm</b>	<b>&gt; 23mm</b>
<b>n: 33</b>	<b>n: 3</b>	<b>n: 13</b>	<b>n: 13</b>	<b>n: 4</b>
<b>Grade 0</b>	-	1	1	
<b>Grade 1</b>	3	12	12	2
<b>Grade 2</b>	-	-	-	2

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374 **Table 4:** Last follow-up echocardiography results for mean gradients

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<b>Mean Gradient</b>	8,3±3,8	376
		377
<b>Peak Gradient</b>	14,1±7,4	378
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