Progress in Late Results Among Pediatric Cardiac Surgery Patients
A Population-Based 6-Decade Study With 98% Follow-Up
Alireza Raissadati, MD; Heta Nieminen, MD, PhD; Eero Jokinen, MD, PhD; Heikki Sairanen, MD, PhD

Background—Surgical treatment of congenital cardiac defects in Finland started >60 years ago. We analyzed the survival of all the pediatric cardiac surgery patients operated on before 2010.

Methods and Results—Data were obtained retrospectively from a pediatric cardiac surgery database. Patient status was received from the Finnish Population Registry. Survival was determined with the Kaplan–Meier method, and the survival rate was compared with a sex- and age-matched general population. Between 1953 and 2009, 13 876 cardiac operations were performed on 10 964 pediatric patients in Finland. Follow-up coverage was 98%. The 60-year survival for the entire study was 70% versus 86% for the general population. The number and proportion of severe cardiac defects increased in the 2000s. The long-term survival of patients with severe defects improved significantly across decades. For instance, the 22-year survival rate of patients with transposition of the great arteries operated on in 1953 to 1989 and in 1990 to 2009 improved from 71% to 93% (hazard ratio for death, 0.29; 95% confidence interval, 0.17–0.49; P<0.0001), respectively. The mean patient age at operation decreased from 8.9 to 2.2 years (95% confidence interval, 6.2–7.1; P<0.0001). The early mortality of patients decreased from a maximum of 7% in the 1970s to 3% in the 2000s (95% confidence interval, 0.05–0.08; P<0.0001).

Conclusions—Patients are diagnosed and treated at an increasingly younger age. Advanced diagnostics, surgical methods, and postoperative intensive care have led to substantial improvements in both early and late results among pediatric cardiac surgery patients. (Circulation. 2015;131:347-353. DOI: 10.1161/CIRCULATIONAHA.114.011190.)

Key Words: cardiac surgical procedure ■ cardiology ■ heart defects, congenital ■ pediatrics ■ survival

Although many studies have been published on pediatric cardiac surgery results, most have been limited to operations from a single center, on 1 type of defect, in a small patient population, with a short follow-up time, or with limited follow-up coverage.1–6

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Systematic screening of children and newborns in the Finnish healthcare system has secured exceptional accuracy in detecting and diagnosing pediatric cardiac defects. All children are treated equally regardless of socioeconomic status or place of residence. The nationwide Finnish Population Registry allows a unique and comprehensive follow-up of practically all patients (98%).

The aim of this study was to establish the postoperative mortality and long-term survival of all pediatric patients (≤15 years of age) operated on for cardiac defects in 1953 to 2009 in Finland. This population-based study includes 10 964 patients and 13 876 pediatric cardiac operations during 60 years of follow-up. To evaluate progress in patient care, we compared the results of operations performed across decades.

Methods

Patients and Data Collection
We obtained patient and operational data from the custom-built ProCardio version 11 database: the Research Registry of Pediatric Cardiac Surgery (Melba Group, Helsinki, Finland) running on FileMaker Pro version 11.0v1 (FileMaker Inc, Santa Clara, CA). The database contains the records for all pediatric patients who have undergone surgery for congenital heart defects in Finland. All pediatric cardiac operations were performed at 5 university hospitals (Helsinki, Turku, Tampere, Oulu, and Kuopio) and 1 district hospital (Aurora Hospital, Helsinki) in Finland. Since 1997, all operations in Finland have been centralized to and performed in the Helsinki university children’s hospital. We received status and date of death or emigration of patients from the Finnish Population Registry.

This study includes all operations performed between 1953 and 2009 in Finland. The only procedures excluded were patent ductus arteriosus (PDA) closures in children <1 month old because of the vast majority of their deaths being caused by prematurity. We defined children <15 years of age as pediatric patients.

Diagnoses were arranged hierarchically according to the severity of the defect (Table 1), as published previously.7,8 Each patient was assigned 1 primary diagnosis to facilitate data comparison and statistical analysis. In patients with several congenital heart defects, we chose the hierarchically higher defect.
Mortality and Survival
All patient deaths within 30 days after the operation were defined as early operative mortalities. Early mortality after the first operation for PDA, atrial septal defect (ASD), coarctation of aorta (COA), ventricular septal defect (VSD), tetralogy of Fallot (TOF), transposition of the great arteries (TGA), hypoplastic left heart syndrome (HLHS), and univentricular heart (UVH) was analyzed separately. All other diagnoses were categorized as miscellaneous.

Long-term follow-up started immediately after the patient’s first operation and ended at the patient’s death or October 24, 2012. For patients who emigrated, the day of emigration was marked as the last day of follow-up. Separate survival curves were created for the 6 most severe defects operated on in 1990 to 2009. The follow-up for these patients excluded early mortality. Each individual patient survival was compared with that of the age-, time-, and sex-matched population.

This research was conducted with permission from the Ministry of Social Affairs and Health and the institutional review board and ethics committee of Helsinki University Hospital for Children and Adolescents.

Statistics
Survival statistics and Kaplan–Meier data were obtained and analyzed with the R program and IBM SPSS statistics version 21.0 (SPSS, Inc, Chicago, IL).

The nonparametric Mann–Whitney test was used for 2-group comparisons, and the 1-way ANOVA with the least-significant-difference method. The proportional hazards assumption was tested by inspecting log(-log) survival plots and by plotting Schoenborn residuals over time. Variables that failed both tests were deemed nonproportional. The univariate Cox regression model was used to estimate the hazard ratio (HR) for death in patients operated on during different decades. The univariate Cox regression model with time-dependent covariates was used to estimate the HR for death when proportionality was not met. For this model, the cutoff point was chosen manually according to where the hazards crossed, and HRs were reported before and after that specific point in time. Values of $P<0.05$ were considered significant.

<table>
<thead>
<tr>
<th>Table 1. Hierarchy of Diagnoses</th>
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<tbody>
<tr>
<td>Univentricular heart</td>
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<tr>
<td>Hypoplastic left heart syndrome</td>
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<tr>
<td>Truncus arteriosus</td>
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<tr>
<td>Interrupted aortic arch</td>
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<tr>
<td>Transposition of the great arteries</td>
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<tr>
<td>Atrioventricular septal defect</td>
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<tr>
<td>Total anomalous pulmonary venous drainage</td>
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<tr>
<td>Pulmonary atresia</td>
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<tr>
<td>Tetralogy of Fallot</td>
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<tr>
<td>Ventricular septal defect</td>
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<tr>
<td>Coarctation of the aorta</td>
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<tr>
<td>Aortic stenosis</td>
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<tr>
<td>Pulmonary stenosis</td>
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<tr>
<td>Mitral valve disease</td>
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<tr>
<td>Partial anomalous pulmonary venous drainage</td>
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<tr>
<td>Atrial septal defect</td>
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<tr>
<td>Patent ductus arteriosus</td>
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<tr>
<td>Miscellaneous</td>
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</tbody>
</table>

Patients
A total of 13876 operations were performed on 10964 patients during 56 years (1953–2009) of pediatric cardiac surgery in Finland. The study period ended on October 24, 2012. Follow-up was complete in 98% of patients and ended prematurely for 177 patients (1.6%) who emigrated. Only 86 patients (0.4%) and 90 operations were excluded from analyses as a result of insufficient patient and surgical data. Thus, 99.6% of all patients were included in the survival analysis.

The sex distribution was male dominant in nearly all groups. The proportion of male patients fell between 56% and 67% in the more severe defect groups of TOF, TGA, HLHS, and UVH, with the TGA group having highest proportion of male patients.

Patient Age at Operation
Both the median age and mean age at operation have decreased significantly in all diagnostic groups. Mean age at operation was 8.9 years in the 1950s, gradually decreasing to 2.2 years in the 2000s (95% CI, 6.2–7.1; $P<0.0001$ for the decrease in age; Table 2 and Figure 1). Similarly, the median patient age at operation has decreased from 9.0 years in the 1950s to 0.5 years in the 2000s.

The age at which patients underwent their first operation decreased substantially in all diagnostic groups, especially in the groups with severe cardiac defects ($P<0.0001$ for all diagnoses; Table 3). Patients with TGA, HLHS, and UVH underwent their first operation at 28, 7, and 153 days of age, respectively, in 1990 to 2009 (Table 3).

Operations and Early Mortality (<30 Days After the Operation)
The number of operations for severe cardiac defects increased throughout the follow-up years (Table 4). Practically no HLHS patients were operated on before 1995. In the 2000s, surgical palliation of HLHS accounted for 10% of all operations performed (Table 4). The number of operations for minor defects decreased.

The average early mortality (<30 days) for all operations conducted in 1953 to 2009 was 6% (Tables 2 and 3). Nearly all patients operated on for PDA, ASD, and COA survived their procedures, even those operated on during earlier decades.

<table>
<thead>
<tr>
<th>Table 2. Mean Age at All Operations and Early Mortality (&lt;30 Days After the Operation)</th>
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<tbody>
<tr>
<td><strong>Time</strong></td>
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<tr>
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</tr>
<tr>
<td>1950</td>
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<td>1960</td>
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<td>1970</td>
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<td>1980</td>
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<td>1990</td>
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<tr>
<td>2000</td>
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<tr>
<td>Total</td>
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* $P<0.0001$ for comparison of the mean age of patients operated on in each decade and those operated on in previous decades.
For other diagnosis groups, the operative mortality decreased significantly across years (Table 3). The operative mortality of TGA operations was 13% in 1953 to 1989 and only 4% in the 2000s (P <0.0001; Table 3). Operative mortality of HLHS decreased from 79% in 1953 to 1989 to 7% in the 2000s (P <0.0001; Table 3). Similarly, the early mortality of UVH operations decreased from 20% for those conducted in 1953 to 1989 to 5% in the 2000s for all surgical stages of UVH palliation (P <0.0001; Table 3).

Survival
The vast majority of patients (8976, 82%) were alive on the last day of the study with the follow-up time extending up to 60 years. The mean age of living patients was 30 years, ranging from 3 to 73 years. The average length of follow-up time was 25 years, ranging from 2 to 60 years (Table 5). Eleven percent of patients (1115) who survived their first operation had died. The average follow-up time for these patients was 14 years (range, 0.3–55 years). Patients with severe cardiac defects who survived their first operation died on average at a much younger age, eg, 0.8 years in the HLHS group versus 30 years in the PDA or ASD group.

At the end of the 60-year follow-up period, the survival rate was 86% for the general population and 70% for patients (Figure 2A). After the exclusion of operative mortality, the study group survival increased to 72%.

Patients with surgically corrected ASD or PDA had on average a normal life span (Figure 2A and Table 5). The 50-year survival rate for COA, VSD, and TOF patients was 70%, 77%, and 53%, respectively (Figure 2A and Table 5). Patients in the TGA and UVH groups had 45-year survival rates of 59% and 33%, respectively. There was a significant decrease in the survival curve for TGA patients at 40 years of follow-up from 66% to 59%, which was caused by a single death. Additionally, patients operated on for TOF had a sharp decrease in survival rate, from 58% to 53%, at 49 years, caused by only 4 deaths: 2 accidental, 1 related to Down syndrome, and 1 case of severe retardation. HLHS patients had the shortest follow-up time of 17 years with a 15-year survival rate of 53%.

To measure progress in late results, we compared the long-term survival (without early mortality) of patients operated on in 1953 to 1989 and 1990 to 2009 (Figures 2B and 3A–3F). We found that the long-term survival of patients operated on for VSD in 1990 to 2009 was significantly higher than for those operated on in 1953 to 1989, with 95% and 87% survival at 22 years, respectively (HR for death in 1990–2009, 0.36; 95% CI, 0.24–0.54; P <0.0001 for log-rank test; Figure 3B). Moreover, patients operated on for TOF in 1990 to 2009 had significantly improved late results compared with those operated on during 1953 to 1989, with 90% versus 87%, respectively, at 22 years after their operation (HR for death in 1990–2009, 0.52; 95% CI, 0.28–0.94; P =0.037 for log-rank test; Figure 3C). The long-term survival rate of patients operated on for TGA in 1990 to 2009 was also significantly higher than for those operated on in 1953 to 1989 with values of 93% and 71% at

Table 3. Early Mortality (<30 Days), Number of Operations, and Mean Age at the First Operation

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<tbody>
<tr>
<td>PDA</td>
<td>21 (1)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>22 (1)</td>
<td>1.0</td>
<td>5.9 y</td>
<td>1.8 y</td>
</tr>
<tr>
<td>ASD</td>
<td>6 (1)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>1.0</td>
<td>8.2 y</td>
<td>4.5 y</td>
</tr>
<tr>
<td>COA</td>
<td>47 (5)</td>
<td>10 (3)</td>
<td>2 (1)†</td>
<td>59 (4)</td>
<td>1.1</td>
<td>5.4 y</td>
<td>1.5 y</td>
</tr>
<tr>
<td>VSD</td>
<td>85 (9)</td>
<td>24 (3)</td>
<td>3 (1)‡</td>
<td>112 (5)</td>
<td>1.2</td>
<td>4.1 y</td>
<td>1.7 y</td>
</tr>
<tr>
<td>TOF</td>
<td>53 (9)</td>
<td>7 (3)</td>
<td>3 (1)‡</td>
<td>63 (6)</td>
<td>1.4</td>
<td>4.9 y</td>
<td>0.9 y</td>
</tr>
<tr>
<td>TGA</td>
<td>53 (13)</td>
<td>34 (14)</td>
<td>7 (4)‡</td>
<td>94 (1)</td>
<td>1.4</td>
<td>1.1 y</td>
<td>28 d</td>
</tr>
<tr>
<td>HLHS</td>
<td>11 (79)</td>
<td>28 (42)</td>
<td>21 (7)‡</td>
<td>60 (17)</td>
<td>3.4</td>
<td>49 d</td>
<td>7 d</td>
</tr>
<tr>
<td>UVH</td>
<td>44 (20)</td>
<td>41 (12)</td>
<td>11 (5)‡</td>
<td>96 (12)</td>
<td>3.0</td>
<td>1.6 y</td>
<td>153 d</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>186 (15)</td>
<td>112 (11)</td>
<td>31 (4)‡</td>
<td>329 (10)</td>
<td>1.4</td>
<td>4.6 y</td>
<td>2.3 y</td>
</tr>
<tr>
<td>All</td>
<td>506 (7)</td>
<td>258 (7)</td>
<td>78 (3)</td>
<td>842 (6)</td>
<td>1.2</td>
<td>5.2 y</td>
<td>2.0 y</td>
</tr>
</tbody>
</table>

ASD indicates atrial septal defect; COA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart; and VSD, ventricular septal defect.

*P <0.0001 in all diagnostic groups when comparing the mean age of patients operated on in 1990 to 2009 with those operated on in 1953 to 1989.
†P =0.017, ‡P <0.0001 vs early mortality in 1953 to 1989.
22 years, respectively (HR for death in 1990–2009, 0.29; 95% CI, 0.17–0.49; P < 0.0001 for log-rank test; Figure 3D). The long-term survival of patients who underwent surgery for UVH improved significantly only after the eighth postoperative year for those operated on in 1990 to 2009 (HR for death in 1990–2009, 0.17; 95% CI, 0.06–0.50; P = 0.001 for χ² test; Figure 3E).

HLHS was a practically inoperable cardiac defect before the latter half of the 1990s, rendering the comparison of patient survival in 1953 to 1989 and 1990 to 2009 to only 3 years. Nevertheless, the 3-year survival rate of patients operated on for HLHS during 1990 to 2009 was significantly higher than for those operated on in 1953 to 1989 at 81% versus 50%, respectively (HR for death in 1990–2009, 0.16; 95% CI, 0.033–0.67; P = 0.0004 for log-rank test; Figure 3F). Eighty-nine percent (64 of 72) of all deaths in the HLHS group occurred before the second-stage operation, and 93% (67 of 72) of deaths occurred within 1 year of the first operation.

### Number of Operations per Patient

Of all patients alive at the closing day of the study, 15% needed reoperation surgery before 15 years of age. One third of patients with TOF or TGA needed >1 operation (Table 3). Ninety-nine percent (99%) of the HLHS patients and 95% of the UVH patients alive at the end of the study had >1 operation (Table 3).

### Discussion

We previously reported long-term results of a 45-year follow-up of pediatric cardiac surgery. However, the present study is unique in terms of the sheer size of the study population, the long follow-up time of 60 years, and the nearly complete follow-up coverage of 98%.

The number of pediatric cardiac operations increased substantially throughout the follow-up time. The birth rate in Finland remained relatively constant, but the improved diagnosis of cardiac defects led to this increase in operations. However, the number of operations for all defects except HLHS decreased in the 2000s. The number of children born with congenital malformations in Finland remained constant throughout the 1990s and 2000s, thus failing to explain this. On the other hand, the steady increase in the number of catheter interventions compensated for cardiac surgery, especially for less complicated defects.

### Patient Age and Number of Operations

Surgical skills and techniques, as well as screening for cardiac defects, have improved dramatically throughout the years. In effect, both mean and median patient age at operation decreased steadily during the follow-up period. The average age of the patients at their first operation was highest in the ASD group and lowest in the HLHS group in the 2000s because untreated HLHS patients are not able to live long after birth.

The rise in the number of severe defects from the 1950s to 2000s led to an increase in the average number of operations per patient. Fifteen percent of all patients who were alive at the end of the study had undergone >1 operation for their defect. Patients with HLHS and UVH required 3 operations to palliate their cardiac defect. In contrast, patients with simpler defects such as PDA and ASD required practically no subsequent procedures.

### Operative Results and Early Mortality

The risk of early mortality correlated with the severity of the defect in that more severe defects experienced higher early mortality. Our results show that early mortality accounted for an increasingly smaller number of deaths within all diagnostic groups, especially those with severe defects.

Enhanced surgical skills and the development of catheter techniques have contributed to the improved operative results. Moreover, the development of new inotropes (eg, milrinone) or therapeutic drugs (eg, nitric oxide and Sildenafil) for the treatment of pulmonary hypertension and technical advances in pediatric extracorporeal membrane oxygenators and ventricular assist devices have improved the postoperative care of patients. In addition, advanced prenatal screening methods and diagnostic procedures have improved the results of fetal cardiac surgery.
tools have led to the detection and treatment of cardiac defects at an earlier stage in life, potentially contributing to improved surgical outcomes.11–14 Finally, centralization of pediatric cardiac surgery into 1 center (ie, Helsinki university central hospital) was completed toward the end of the 1990s and has most probably contributed to improved results during the 1990s and 2000s.

Survival
Older patients dying as a result of natural, age-related factors caused the declining feature of the survival curves. The oldest patient alive at the end of the study was 73 years of age. Altogether, 367 patients were >60 years old at the end of the study period.

This study proves that the vast majority of patients with simpler defects are expected to survive up to 60 years after corrective surgery. More important, according to these results, the surgical treatment of PDA and ASD can be considered a curative procedure. Additionally, the majority of late deaths in these patient groups were caused by noncardiovascular events. The late survival of COA and VSD patients has improved significantly over time. Nonetheless, after the exclusion of early mortality, COA and VSD patients operated on in 1990 to 2009 experienced nearly identical survival rates as the general population after 20 years of follow-up. The survival rate of patients operated on for HLHS, TGA, and UVH decreased significantly during the first year of follow-up, which was caused mainly by the high rate of early mortality. However, both early and late results of all patients operated on between 1990 and 2009 have improved significantly compared with those of patients operated on between 1953 to 1989. The explanation is most likely multifaceted, including improvements in preoperative diagnostics and care, operative treatment, postoperative care, and patient follow-up.

The long-term survival of TOF patients improved significantly to 90% at 22 years for those operated on after 1990 (excluding early mortality) and compares well with those of previous studies.11–14 In this study, TGA included both simple and complex forms of the defect. The 22-year survival rate of simple TGA patients was nearly 100% (early mortality excluded). Until 1984, the atrial switch procedure was the primary surgical method for the correction of TGA in our institution; since 1990, the arterial switch operation has been used for the correction of all TGA defects. Several studies have found the arterial switch operation method to improve late results compared with the
Accordingly, in our study, the 22-year survival of TGA patients operated on after 1990 improved significantly, confirming the results from other studies.

Previous studies have reported a survival rate of 84% to 86% at 10 years and 74% to 82% at 15 years after surgical correction of UVH (including early mortality). In our study, one third of patients were alive after 45 years of follow-up, with the majority of patients dying at a young age. The late survival of patients operated from 1953 to 1989 and 1990 to 2009 was comparable until 8 years after the operation; thereafter, the late survival of patients operated on from 1990 to 2009 was significantly higher than that for patients operated on from 1953 to 1989.

Previous studies have reported a 39% survival rate after stage 1 (including early mortality) and a 90% survival rate after stage 3 (early mortality excluded) HLHS operations at 10 years. In our study, the long-term survival of HLHS patients was 81% at 15 years after all operative stages (excluding early mortality) for those who underwent surgery after 1990. Almost all of the HLHS patients were <1 year of age at the time of death. The majority of deaths in the HLHS group occurred before the second operation. These results suggest that if HLHS patients survive their first operation, their chance of long-term survival increases significantly. These results correspond well with previous studies in which mortality after stage 1, but not stage 2 or 3, surgery remained high. However, we observed a 6-fold decrease in early operative mortality after stage I Norwood operations for HLHS from the 1990s to the 2000s. Similarly, the early mortality of patients operated on for UVH decreased significantly from the 1990s to the 2000s, showing a potential toward improved long-term results in both the HLHS and UVH groups in the future.

**Conclusions**

The number of children operated on for severe cardiac defects increased steadily throughout the study period. The defects were diagnosed and treated at increasingly younger ages. Improved diagnostic methods, combined with advancements in surgical, cardiologic, and intensive care skills, contributed to profoundly improve operative results and the long-term survival of patients.

**Acknowledgments**

We thank the Finnish Cancer Registry for assisting us with the statistical survival analyses and for providing us with the age-, time-,
and sex-matched population data used as the comparison group in the survival study. We also extend our gratitude to the Finnish Institute for Molecular Science for their statistical advice.

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This work was funded by the Finnish Foundation for Cardiovascular Research.

Disclosures
None.

References

CLINICAL PERSPECTIVE
Although many studies have been conducted on the late outcome of pediatric cardiac surgery patients, the majority of them are single centered, have a short follow-up or small patient population, or focus on a single cardiac defect. This population-based study of 13,876 cardiac operations on 10,964 pediatric patients shows the actual survival of pediatric cardiac surgery patients up to 60 years after their operation. The operative age has decreased in all cardiac defect groups, and the late survival of patients with severe cardiac defects has improved significantly in recent years. The mortality rate for patients with transposition of the great arteries, hypoplastic left heart syndrome, and univentricular heart was highest during the first postoperative year but remained stable thereafter. The number of operations has increased steadily during the last 6 decades, but the number of operations on simple cardiac defects decreased after the 2000s as a result of the increase in invasive cardiologic procedures. The follow-up is practically complete (98%), offering practicing clinicians a clear and reliable understanding of how these patients are managing during the short and long term. This information is valuable in planning the treatment and follow-up of these patients. A similar comprehensive study on this subject is not yet available.
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