

Temporal Trends in Survival to Adulthood Among Patients Born With Congenital Heart Disease From 1970 to 1992 in Belgium

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Background—Over the past decades, the life expectancy of individuals with congenital heart disease (CHD) has increased significantly. However, precise estimates for survival to adulthood are scarce for patients with CHD. We investigated the proportion of CHD patients born between 1990 and 1992 who survived into adulthood. We also compared their survival with that of CHD patients born in earlier eras and evaluated survival as a function of the type of heart defect.

Methods and Results—We reviewed the CHD program administrative and clinical database at the University Hospitals Leuven (Leuven, Belgium) and analyzed the records of 7497 CHD patients born from 1970 to 1992. Survival to 18 years of age in patients born between 1990 and 1992 was 88.6% (95% confidence interval [CI], 86.3% to 90.5%), which was significantly greater than that of patients born in previous decades ($P < 0.0001$). For patients born between 1990 and 1992, survival into adulthood for those with mild heart defects was 98.0% (95% CI, 95.8% to 99.1%), whereas survival for those with moderate- and severe-complexity heart defects was 90.0% (95% CI, 86.8% to 92.5%) and 56.4% (95% CI, 47.4% to 64.5%), respectively. Analysis per heart defect confirmed these findings, demonstrating that patients with univentricular heart (49.1% [95% CI, 30.8% to 65.1%]) and hypoplastic left heart syndrome (7.5% [95% CI, 0.6% to 26.6%]) had the poorest survival rate.

Conclusion—This study demonstrates that almost 90% of children with CHD have the prospect of surviving into adulthood. (*Circulation*. 2010;122:2264-2272.)

Key Words: epidemiology ■ heart defects, congenital ■ mortality ■ pediatrics

In Western societies, congenital heart disease (CHD) is the most frequent birth defect in newborns.¹⁻³ The internationally accepted prevalence of CHD at birth is 0.8%.⁴ Since the 1960s, the life expectancy of patients with congenital heart defects has increased significantly owing to progress in pediatric and interventional cardiology, cardiac surgery, and intensive care medicine.

Editorial see p 2231 Clinical Perspective on p 2272

About a decade ago, an estimated 85% of patients with CHD survived into adulthood.^{5,6} This estimate was based largely on anecdotal data obtained during the 1980s and 1990s. Although this number is still commonly referred to in discussions of survival into adulthood,⁷⁻⁹ some authors have suggested that as many as 95% of patients can survive through childhood.¹⁰

Precise estimates of survival into adulthood for the broad population of CHD patients, however, are lacking. Hence, to

date, the prospects of survival into adulthood cannot be projected accurately. The aims of this study were to investigate the proportion of patients who have survived to date into adulthood (ie, those born from 1990 to 1992), to compare the survival of these patients with that of patients born in previous decades, and to evaluate survival as a function of the type of heart defect.

Methods

Setting and Data Source

The setting of the present study was the Department of Pediatric Cardiology and the Adult CHD Program at the University Hospitals Leuven (Leuven, Belgium). This center follows up $\approx 27\%$ of all patients born with CHD in Belgium.¹¹ The center uses a common database that contains the records of all individuals examined, treated, and followed up at the center. The database comprises demographic information (date of birth, gender, home address, and treating physicians) and clinical information (type of heart defect, noncardiac diagnoses, cardiac interventions, date of death, date of last follow-up, etc).

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Although this database was constructed in 1992, it contains the records of all patients seen in the center since the inception of the pediatric cardiology program in 1960. Since 1992, data have been prospectively entered and updated. Data obtained before 1992 were retrospectively entered from the patient medical records and were updated during consecutive follow-up visits after 1992, if any. Hence, the database contains all available information of all patients who have visited the pediatric cardiology and the adult CHD programs, including patients who died before 1992 and those who are still alive. As of June 4, 2010, the database contained the records of 35 651 individuals.

Study Population

We reviewed administrative and clinical data found in this database. For the present study, patients were included if they had a congenital heart defect, defined as a structural abnormality of the heart or intrathoracic great vessels that has actual or potential functional significance.¹² Patients were excluded if they had a morphologically normal heart (eg, functional heart murmur or cardiotoxicity in cancer patients receiving chemotherapy), cardiac arrhythmias without structural abnormalities, patent foramen ovale diagnosed after cryptogenic stroke, patent foramen ovale or isolated ductus arteriosus not receiving treatment, hereditary conditions without cardiac effects, mesocardia without other structural cardiac anomalies, electrolyte disturbances, pectus excavatum without additional heart defect, and pulmonary arterial hypertension without structural heart disease. Patients were also excluded if they were fetuses with a normal echocardiogram. Finally, duplicate records were removed. This procedure yielded 19 381 patients with structural heart defects, 193 of whom were fetuses.

For this study, we analyzed the data of 7497 live-born or stillborn patients who were born between 1970 and 1992. Hence, all subjects in this study have or would have reached adulthood to date.

Measurements and Definitions

Date of birth, gender, cardiac diagnosis, date of death, reason of death, and date of last outpatient or inpatient visit were extracted from the database on June 4, 2010. CHD is often characterized by a combination of different heart defects. Therefore, to categorize patients according to their primary cardiac defect, we used a modified version of the classification of heart defects that was previously developed for the Dutch Congenitale cor Vitia project.¹³ Modifications were based on its use in a recent epidemiological study in Belgium.¹¹ To classify patients by the complexity of their heart defect, we used the categories outlined by Task Force 1 of the 32nd Bethesda Conference: mild-, moderate-, or severe-complexity heart lesions.⁵ Pulmonary arterial hypertension was defined as a mean pulmonary arterial pressure >25 mm Hg on cardiac catheterization.

Patients were stratified by birth into half-decade groups, starting from 1970 to 1989; patients born between 1990 and 1992 constituted a final group. We defined 18 years 0 days as the cutoff age for adulthood.

Data on mortality included both in-hospital and out-of-hospital mortality. Belgium is a small country with easy access to tertiary care¹⁴; thus most CHD patients remain under surveillance at our center for routine checkups. For example, 55.9% of patients born in the 1990s last visited our center as outpatients <5 years ago. Other patients visit satellite centers, which are regional hospitals where one of our pediatric cardiologists has an outpatient clinic. Some patients prefer to go to local cardiologists. These cardiologists are asked to send an examination report after each outpatient visit.

In general, the follow-up recommendations of Task Force 4 of the 32nd Bethesda Conference are followed.¹⁵ If hospitalization for cardiac reasons is needed, patients are most frequently referred to our hospital. Therefore, most of our patients who expired from CHD-related reasons died in our hospital. With respect to out-of-hospital deaths, treating physicians, general practitioners, or the patients' families typically inform the CHD team of the patients' death. Cross-checking patients against the national death registry is disallowed by Belgian law for privacy reasons.

To account for temporal improvements in survival rates in recent decades, we calculated net survival relative to survival rates of the overall Belgian population. We relied on mortality tables for Belgium provided by the National Institute for Statistics. Mortality tables for the following years were used: 1972 to 1976, 1979 to 1982, 1988 to 1990, 1991 to 1993, 1995, 1999, 2003, and 2007.

This study was evaluated and approved by the Institutional Review Board of the University Hospitals Leuven. Because we used existing data that were extracted by a clinical team member (P.M.) and remained anonymous, informed consent was neither required nor sought.

Statistical Analysis

The Statistical Package of the Social Sciences 12.0 (SPSS Inc, Chicago, Ill), SAS software (version 9.2 of the SAS System for Windows), and R version 2.6.2 (R Foundation for Statistical Computing, Vienna, Austria) computer programs were used for data analysis. Descriptive statistics for nominal data were presented in absolute numbers and percentages. Kaplan–Meier curves were plotted to describe the survival rates of the entire sample and those of the subgroups. Patients for whom no death was recorded were censored at the last date for which they were known to be alive. Group comparisons in terms of survival were performed with the log-rank test and the log-rank test for trends. The 95% confidence intervals for survival estimates were calculated with the log-log method.

To determine whether differences in survival across birth cohorts were independent from other confounding factors, we performed multivariable Cox regression analysis. An epidemiological approach was used, and all potential confounding factors were entered into the Cox model regardless of their statistical significance: decade of birth, gender, disease complexity, type of heart defect, presence of pulmonary arterial hypertension, and the advent of echocardiography as a diagnostic tool (cardiac ultrasound has been available at our pediatric cardiology department since 1980). We calculated hazard ratios and 95% confidence intervals. The proportional hazards assumption was checked by using the graphical methods described by Lin and coworkers.¹⁶ They showed no deviations for the variables of interest.

Because survival in our study could be confounded by secular trends in all-cause mortality in the general population, we determined net survival relative to the general Belgian population. For each patient, we calculated expected survival by matching the patient to a Belgian patient from the general population by year of birth and age using Belgian mortality tables. The expected survival probability was calculated. Improvement across decades was assessed by means of a Poisson regression, as described by Dickman et al,¹⁷ using exact survival times on grouped data.

All tests were 2 sided and evaluated at the 5% significance level. No adjustments were made to the significance level because of the exploratory nature of the study.

Results

Sample Characteristics

This study included 7497 patients (50.9% male, 49.1% female). The distributions of heart defect complexity and history of cardiac surgery were significantly different across birth eras (Table 1).

The most prevalent heart defects were ventricular septal defects (VSDs; 26.2%), pulmonary valve abnormalities (10.7%), and secundum atrial septal defects (9.1%). Overall, 48.6% of the patients had a mild-complexity heart defect, 39.5% had a moderate-complexity heart defect, and 11.9% had a severe-complexity heart defect. Table 2 shows the frequency of the different heart defects in our sample and categorization by disease complexity.

Table 1. Demographic and Clinical Characteristics of 7497 Patients With CHD According to Birth Era

| Heart Defect | Overall, n (%) | 1970–1974, n (%) | 1975–1979, n (%) | 1980–1984, n (%) | 1985–1989, n (%) | 1990–1992, n (%) | χ^2 | P |
|----------------------------|----------------|------------------|------------------|------------------|------------------|------------------|----------|-------|
| n (%) | 7497 | 1132 (15.1) | 1598 (21.3) | 1677 (22.4) | 1831 (24.4) | 1259 (16.8) | | |
| Gender | | | | | | | 2.626 | |
| Male | 3818 (50.9) | 563 (49.7) | 820 (51.3) | 845 (50.4) | 958 (52.3) | 632 (50.2) | | 0.622 |
| Female | 3679 (49.1) | 569 (50.3) | 778 (48.7) | 832 (49.6) | 873 (47.7) | 627 (49.8) | | |
| Complexity of heart defect | | | | | | | 23.762 | |
| Mild | 3647 (48.6) | 596 (52.7) | 819 (51.2) | 798 (47.6) | 827 (45.2) | 607 (48.2) | | 0.003 |
| Moderate | 2960 (39.5) | 404 (35.7) | 589 (36.9) | 678 (40.4) | 785 (42.9) | 504 (40.0) | | |
| Severe | 890 (11.9) | 132 (11.6) | 190 (11.9) | 201 (12.0) | 219 (12.0) | 148 (11.8) | | |
| History of cardiac surgery | | | | | | | 13.03 | |
| No cardiac surgery | 4766 (63.6) | 721 (63.7) | 1031 (64.5) | 1039 (62.0) | 1128 (61.6) | 847 (67.3) | | 0.011 |
| Cardiac surgery | 2731 (36.4) | 411 (36.3) | 567 (35.5) | 638 (38.0) | 703 (38.4) | 412 (32.7) | | |

Survival Into Adulthood

Of the 1259 patients born between 1990 and 1992, 110 had died. Survival at 1, 5, 10, 15, and 18 years of age was 92.7% (91.0% to 94.2%), 90.9% (89.0% to 92.5%), 90.3% (88.4% to 92.0%), 89.1% (87.0% to 90.9%), and 88.6% (86.3% to 90.5%), respectively. The reasons for death were cardiac failure (n=61, 55.5%), postoperative complications (n=19, 17.3%), perioperative complications (n=17, 15.5%), cerebral complications (n=3, 2.7%), pulmonary complications (n=2, 1.8%), noncardiac problems (n=1, 0.9%), or other reasons (n=7, 6.4%).

Survival According to Birth Era

Survival of patients into adulthood was 81.0% (77.6% to 83.9%) for individuals born in 1970 to 1974, 82.0% (79.6% to 84.1%) for those born in 1975 to 1979, 81.7% (79.4% to 83.8%) for those born in 1980 to 1984, and 86.6% (84.6% to 88.3%) for those born in 1985 to 1989. These percentages were significantly lower than those of patients born in 1990 to 1992 (88.6% [86.3% to 90.5%]; log rank=28.2; *df*=1; *P*<0.0001). Figure 1 (left) shows a Kaplan–Meier survival curve calculated from birth to 18 years of age according to the birth era. Regardless of the birth era, the most vulnerable

Table 2. Primary Diagnoses in 7497 Patients With CHD

| Heart Defect | n (%) | Mild, n (%) | Moderate, n (%) | Severe, n (%) |
|--|-------------|-------------|-----------------|---------------|
| Hypoplastic left heart syndrome | 143 (1.9) | | | 143 (100) |
| Univentricular physiology | 202 (2.7) | | | 202 (100) |
| Tricuspid atresia | 5 (0.1) | | | 5 (100) |
| Tetralogy of Fallot | 434 (5.8) | | 434 (100) | |
| Pulmonary atresia with VSD | 7 (0.1) | | | 7 (100) |
| Pulmonary atresia without VSD | 21 (0.3) | | | 21 (100) |
| Double-outlet right ventricle | 117 (1.6) | | | 117 (100) |
| Double-inlet left ventricle | 3 (0.04) | | | 3 (100) |
| Truncus arteriosus | 70 (0.9) | | | 70 (100) |
| TGA | 230 (3.1) | | | 230 (100) |
| Congenitally corrected TGA | 39 (0.5) | | | 39 (100) |
| Coarctation of the aorta | 458 (6.1) | | 458 (100) | |
| Marfan syndrome | 20 (0.3) | | 20 (100) | |
| Atrioventricular septal defect | 251 (3.3) | | 251 (100) | |
| Atrial septal defect, type I | 82 (1.1) | | 82 (100) | |
| Ebstein malformation | 29 (0.4) | | 29 (100) | |
| Pulmonary valve abnormality | 802 (10.7) | 523 (65.2) | 279 (34.8) | |
| Aortic valve abnormality | 609 (8.1) | 356 (58.5) | 253 (41.5) | |
| Aortic abnormality | 78 (1.0) | | 78 (100) | |
| Left ventricular outflow tract obstruction | 118 (1.6) | | 118 (100) | |
| Atrial septal defect, type II | 682 (9.1) | 477 (69.9) | 205 (30.1) | |
| VSD | 1965 (26.2) | 1691 (86.1) | 274 (13.9) | |
| Mitral valve abnormality | 455 (6.1) | 382 (84.0) | 73 (16.0) | |
| Pulmonary vein abnormality | 103 (1.4) | | 103 (100) | |
| Other | 574 (7.7) | 218 (38.0) | 303 (52.8) | 53 (9.2) |

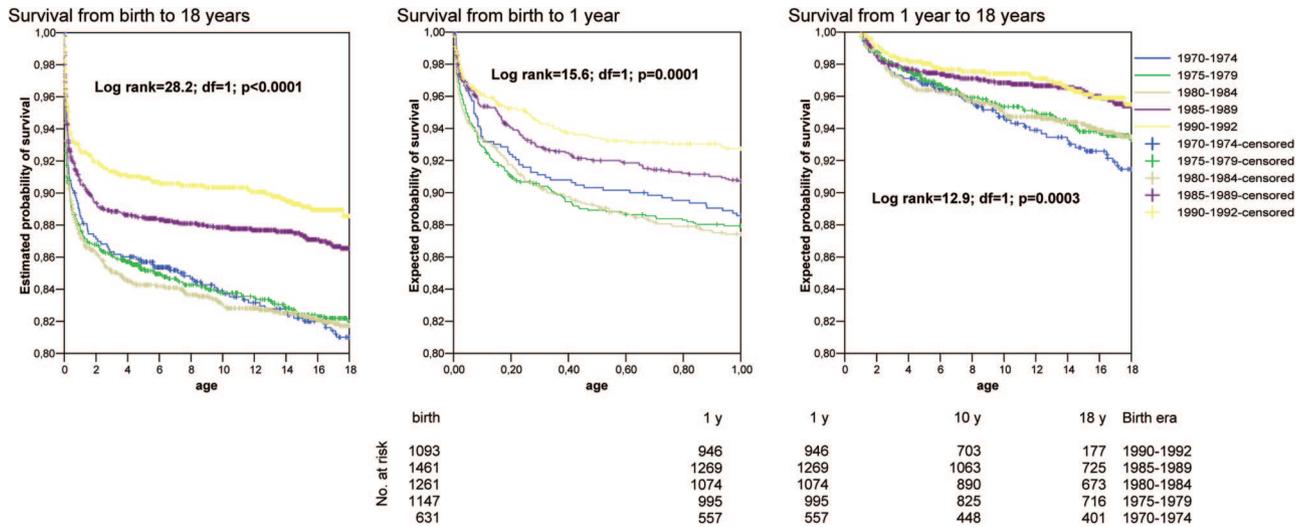


Figure 1. Estimated survival according to the era of birth.

period for mortality was the first year of life. Therefore, we refined the survival analysis as follows: from birth to 1 year of age (Figure 1, middle) and from 1 to 18 years of age (Figure 1, right). Survival was significantly different for these 2 periods, indicating that improved survival was not only a function of lower mortality in infancy.

Multivariable Cox regression analysis demonstrated that the improvement in survival across the birth era was independent of other known risk factors. Indeed, after adjusting for differences between the cohorts in disease complexity, type of heart defect, presence of pulmonary arterial hypertension, availability of echocardiography, and gender, we found that patients born in the eras of 1970 to 1974, 1975 to 1979, and 1980 to 1984 had a significantly higher mortality risk than patients born in the 1990 to 1992 era (Table 3).

To adjust for temporal trends in mortality, we performed a trend test for half-decades in the Poisson regression of death, which yielded $P=0.0002$. This provided evidence that the survival of CHD patients improved across the 5 birth-era cohorts regardless of improved survival in the general population (Figure I in the online-only Data Supplement).

Survival According to the Type of Heart Defect

We computed survival curves according to the complexity of heart lesions and curves for each type of heart defect for patients born between 1990 and 1992. Survival to 18 years of age in patients with mild-, moderate-, and severe-complexity heart defects was 98.0% (95.8% to 99.1%), 90.0% (86.8% to 92.5%), and 56.4% (47.4% to 64.5%), respectively (log rank=158.4; $df=1$; $P<0.0001$; Figure 2).

For the per-defect survival analysis, we included only heart defects that were documented in >20 patients. Figure 3 shows heart defects linked to an estimated survival to 18 years of age of $<90\%$ (left) and heart defects linked to an estimated survival of $>90\%$ (right). This figure shows that survival to the age of 18 years was 89.0% (78.3% to 94.6%) for patients with coarctation of the aorta, 78.1% (64.6% to 86.9%) for tetralogy of Fallot, 76.5% (60.3% to 86.7%) for atrioventricular septal defect, 70.7% (55.6% to 81.5%) for transposition of the great arteries (TGA), 49.1% (30.8% to

65.1%) for a univentricular heart, and 7.5% (0.6% to 26.6%) for hypoplastic left heart syndrome. Survival to the age of 18 years was 100% for left ventricular outflow tract obstruction, 98.4% (89.3% to 99.8%) for mitral valve abnormality, 98.0% (92.2% to 99.5%) for secundum atrial septal defect, 97.0% (90.0% to 99.0%) for aortic valve abnormality, 96.9% (90.8% to 99.0%) for pulmonary valve abnormality, 96.7% (91.8% to 98.7%) for VSD, and 95.0% (69.5% to 99.3%) for pulmonary vein abnormality. Obviously, survival rates across the diagnostic categories was significantly different (log rank=462.7; $df=12$; $P<0.0001$). After adjustments for potential confounding factors, we identified several complex anomalies that were significantly associated with higher mortality (Table 3).

Survival According to Birth Era per Heart Defect

For univentricular heart, truncus arteriosus, TGA, VSD, and pulmonary vein abnormality, we observed a significant difference in survival into adulthood across various birth eras (Figure 4). Survival of patients born during the 1970s was consistently worse than that of patients born during the following decades. For other heart lesions, no significant trends in survival over the respective era were found.

Furthermore, we assessed potential interaction effects between birth era and heart defect complexity with respect to survival. Using the Wald test, we found a significant interaction ($P=0.014$). When analyzing the changes in survival up to 18 years separately for mild-, moderate-, and severe-complexity heart defects, we found no effect for the group of patients with mild defects ($P=0.3687$). However, we found statistically significant effects (ie, improved survival) for the groups of patients with moderate- and severe-complexity heart defects ($P=0.0006$ and $P=0.0002$, respectively).

Survival Beyond 18 Years of Age

Although the focus of this article is on survival to adulthood, our database also allowed us to explore survival beyond the age of 18 years. This analysis revealed that, once a patient reaches 18 years of age, no significant difference in survival occurred for the different birth eras (log rank=0.01; $df=1$; $P=0.91$; Figure 5). The steep decline in the 1985 to 1989

Table 3. Multivariable Cox Regression Analysis

| Determinants | HR (95% CI) |
|--|-----------------------------------|
| Birth era | |
| 1990–1992 | 1.00 |
| 1985–1989 | 1.11 (0.87–1.41) |
| 1980–1984 | 1.76 (1.40–2.22)* |
| 1975–1979 | 1.78 (1.40–2.25)* |
| 1970–1974 | 1.50 (1.15–1.95)* |
| CHD complexity | |
| Mild | 1.00 |
| Moderate | 4.19 (2.99–5.86)* |
| Severe | 3.94 (1.78–8.72)* |
| Type of heart defect | |
| VSD | 1.00 |
| Hypoplastic left heart syndrome | 27.26 (11.89–62.52)* |
| Pulmonary atresia without VSD | 19.98 (7.77–51.38)* |
| Pulmonary atresia with VSD | 17.51 (5.36–57.25)* |
| Truncus arteriosus | 12.57 (5.37–29.43)* |
| Univentricular physiology | 9.46 (4.11–21.74)* |
| Tricuspid atresia | 6.59 (1.32–32.99)* |
| TGA | 4.00 (1.74–9.20)* |
| Congenitally corrected TGA | 3.29 (1.23–8.80)* |
| Double-outlet right ventricle | 2.77 (1.14–6.73)* |
| Aortic abnormality | 2.52 (1.38–4.60)* |
| Atrioventricular septal defect | 2.36 (1.57–3.53)* |
| Pulmonary vein abnormality | 2.24 (1.29–3.89)* |
| Tetralogy of Fallot | 1.72 (1.15–2.58)* |
| Coarctation of the aorta | 1.27 (0.83–1.93) |
| Mitral valve abnormality | 1.10 (0.63–1.91) |
| Ebstein malformation | 1.06 (0.33–3.44) |
| Aortic valve abnormality | 0.92 (0.58–1.48) |
| Pulmonary valve abnormality | 0.87 (0.53–1.41) |
| Atrial septal defect, type II | 0.79 (0.47–1.34) |
| Marfan syndrome | 0.43 (0.06–3.14) |
| Left ventricle outflow tract obstruction | 0.40 (0.14–1.12) |
| Atrial septal defect, type I | 0.14 (0.02–1.00) |
| Double-inlet left ventricle | 0.002 (0.00–4.92 ⁺⁶⁰) |
| Other | 1.88 (1.23–2.86)* |
| Presence of pulmonary arterial hypertension | |
| No pulmonary arterial hypertension | 1.00 |
| Pulmonary arterial hypertension | 1.82 (1.47–2.27) |
| Availability of echocardiography | † |
| Gender | |
| Male | 1.00 |
| Female | 0.89 (0.78–1.03) |

HR indicates hazard ratio; CI, confidence interval.

*Significant.

†No results because of multicollinearity with era of birth.

cohort is due to 1 patient who died at 24.99 years of age. When considering all the birth cohorts together, the estimated survival at 20, 25, 30, 35, and 40 years of age was 99.4% (99.0% to 99.6%), 97.6% (96.8% to 98.2%), 95.3% (94.0% to

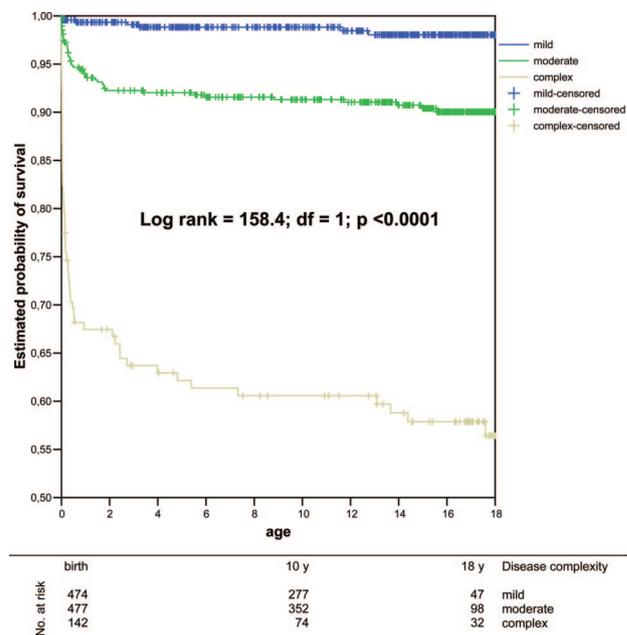


Figure 2. Estimated survival in patients born between 1990 and 1992 by disease complexity.

96.4%), 92.5% (90.2% to 94.3%), and 84.1% (71.5% to 91.4%), respectively.

Discussion

To expand on existing mortality studies,^{11,18–22} we investigated to what extent children with CHD survive to adulthood. Nearly 90% of CHD patients born between 1990 to 1992 survived to 18 years. This survival rate was significantly better than the 81.0% to 86.6% of patients born in prior decades. After adjustment for potential confounding factors, Cox regression modeling showed that the higher survival rate of patients born in the 1990 to 1992 era was independent of other known prognostic factors. Moreover, comparison with temporal trends in mortality in the general population showed that improved survival was greater than could be attributed to the secular reduction of all-cause mortality in the population alone.

We observed that survival improved particularly since 1985. This might be due to cardiac surgery improvements in our center. In the early 1970s, our center performed cardiac operations mainly on patients with mild heart defects. Complex cases were referred to centers in other countries that practiced more advanced surgical procedures. In the mid 1970s, our center began to take on complex surgical cases. By the mid 1980s, complex operations were performed routinely and perioperative management was optimal, thus improving survival.

The first year of life is obviously the most critical period, regardless of decade of birth. Therefore, we performed subanalyses to determine to what extent children with CHD survive during infancy (birth to 1 year) and childhood/adolescence (1 to 18 years). We observed significant differences in survival across these 2 birth cohorts. Hence, improved survival in patients born in 1990 to 1992 is not merely a function of better outcomes in the first year of life but may

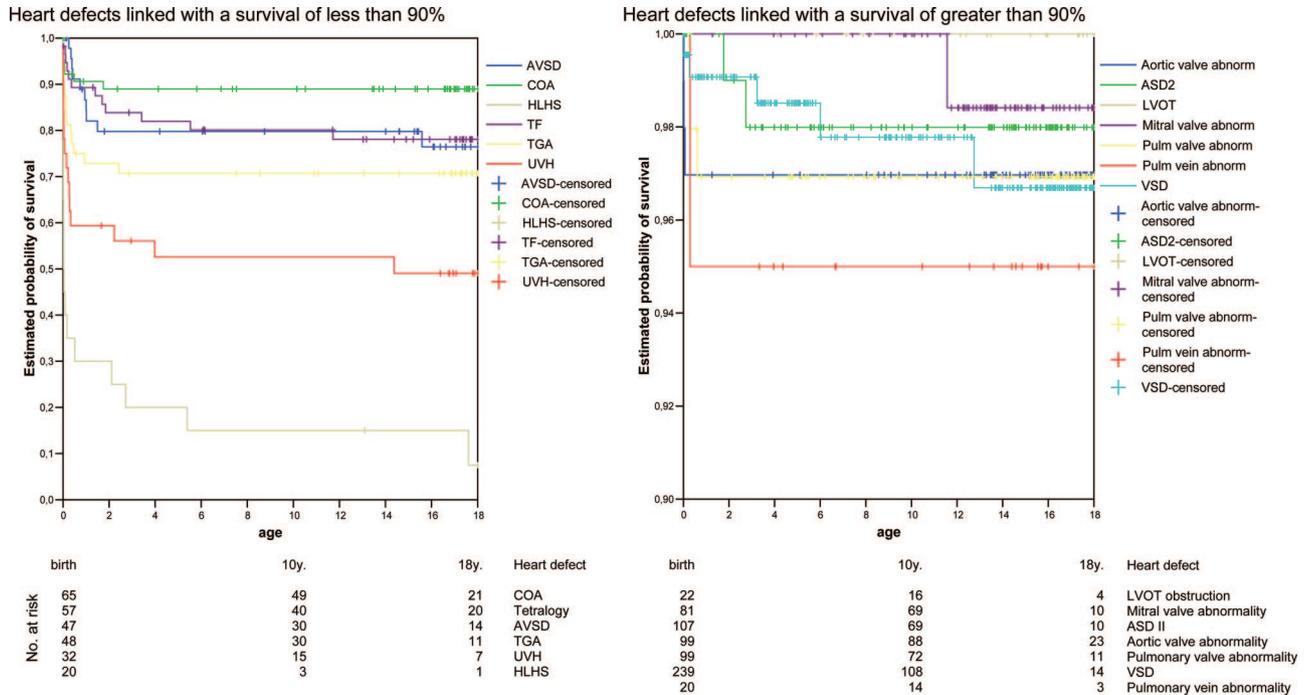


Figure 3. Estimated survival in patients born between 1990 and 1992 by type of heart defect. AVSD indicates atrioventricular septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; TF, tetralogy of Fallot; UVH, univentricular heart; LVOT, left ventricular outflow tract; and ASD, atrial septal defect.

suggest the success of continuing follow-up by experienced pediatric cardiologists during childhood. Beyond 18 years of age, no differences in survival were found, indicating that patients who reached 18 years of age have a similar probability of survival, regardless of the era of birth.

Survival for patients with mild-, moderate-, and severe-complexity lesions differed from previous estimates. For patients born in the 1980s, Task Force 1 of the 32nd Bethesda Conference predicted a survival to adulthood of 95%, 90%, and 80% for mild-, moderate-, and severe-complexity heart defects, respectively.⁵ Compared with the Task Force’s predictions, we found higher (98.0%), equivalent (90%), and lower (56%) survival rates in patients with mild-, moderate-, and severe-complexity heart defects, respectively. The survival differences for complex heart defects are particularly striking. Given the facts that patients with hypoplastic left heart syndrome and univentricular heart represent a high proportion of all patients with complex heart defects and that the survival of such patients is poor if both operated and nonoperated patients are taken into account, survival to adulthood is expected to be <80%. Indeed, perinatal mortality is already as high as 50% in hypoplastic left heart syndrome²² and is ≈40% in univentricular heart.¹¹

The information obtained in the present study not only is important for estimating survival into adulthood for youngsters with CHD living today but also may be useful for future workforce planning. About a decade ago, Wren and O’Sullivan²³ used the estimated survival data available to calculate the need for follow-up in adult life. At present, we can estimate the need for outpatient facilities and required manpower by using published prevalence rates,^{24,25} the survival

numbers from the present study, and the suggested follow-up frequency proposed by Task Force 4 of the 32nd Bethesda Conference.¹⁵ By doing so, we would be able to organize care in line with the demands of the population and to improve the delivery of care in North America and Europe.^{26–29}

Methodological Issues

The merit of this study is that it was based on an extensive database of a large tertiary care center in Belgium, which includes ≈7500 patients. Belgium is a small country (11 787 sq miles) with a high population density (10.4 million inhabitants), limited migration of the population, and easy access to tertiary care.¹⁴ Thus, nearly all patients with CHD in Belgium have been evaluated by pediatric cardiology or adult CHD programs, which are all located in university hospitals. On the basis of an epidemiological study comprising 111 225 births in Belgium,¹¹ we calculated that 27% of all patients with CHD in Belgium are diagnosed, treated, and followed up at the University Hospitals Leuven. Hence, we believe that the results of this study are fairly representative of the population of CHD patients in Western societies.

Studies like ours can be subject to ascertainment bias in CHD detection over time. Since the 1980s, the detection rate for mild heart lesions has increased as a result of the availability of cardiac ultrasound. Hence, the growing number of mild defects could inflate the denominator for all events defined as death in the analyses. We dealt with this issue by performing multivariable Cox regression analysis, adjusting for disease complexity, type of heart defect, presence of pulmonary arterial hypertension, availability of echocardiography, and gender. Furthermore, ascertainment bias

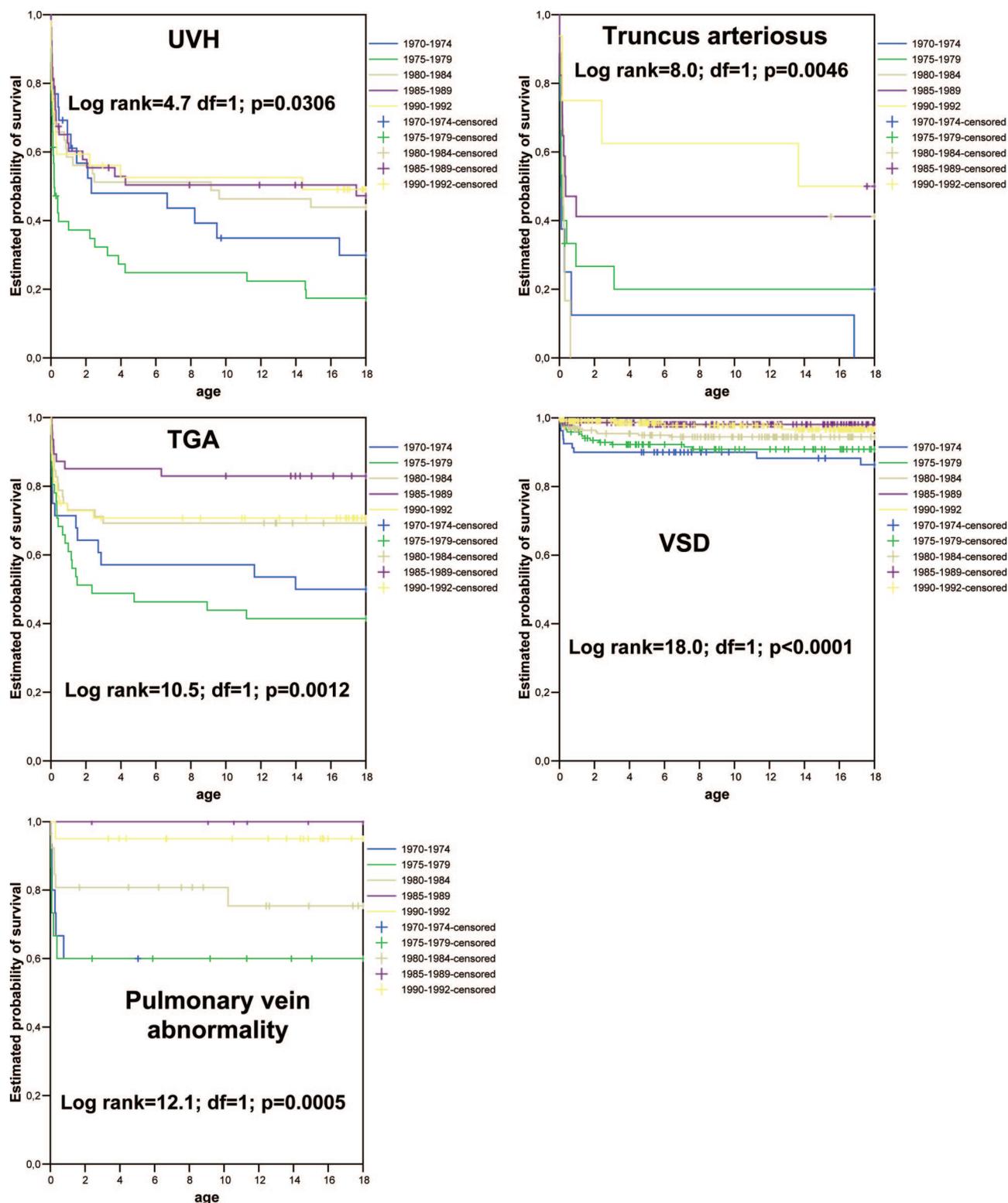


Figure 4. Estimated survival according to half-decade of birth by type of heart defect.

related to diagnosis, according to family income or locality, was not likely to be present because health care in Belgium is universal and the country is very small.

Belgian privacy laws prohibited us from linking our clinical database to the national mortality registry. Thus, a possible limitation of this study is that our mortality data might be incomplete. However, we believe that our data are

fairly complete because Belgium is a small country and because our center maintains good contact with local treating cardiologists.

Another possible limitation could stem from the fact that we performed our analysis on data recorded in an administrative and clinical database. Since the time of its construction in 1992, data have been prospectively entered into the

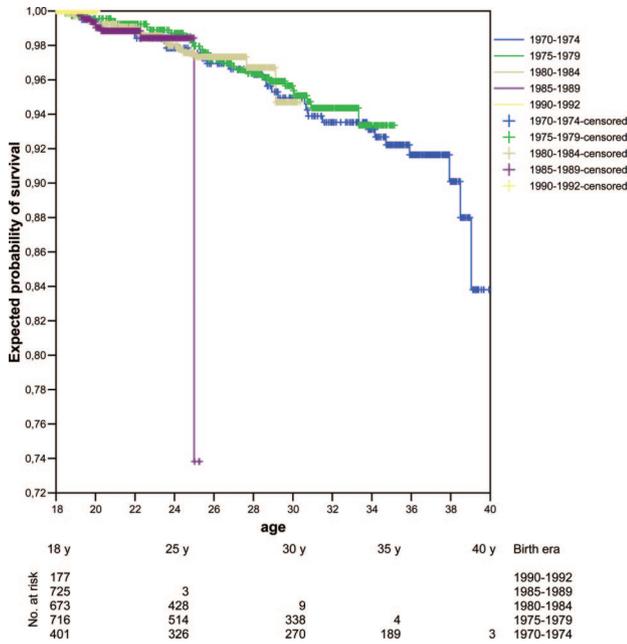


Figure 5. Estimated survival beyond 18 years of age.

database and regularly updated. Data obtained before 1992 were retrospectively entered. Together with incomplete mortality data, this may have resulted in informative censoring of the data; patients might not have returned to our center because they died or because they no longer felt the need for routine checkups. Informative censoring can introduce bias into the results of survival analyses. However, we believe that the assumption of noninformative censoring is largely met because ≈80% of patient follow-up visits are routine follow-ups. In addition, as mentioned, we believe that our mortality data are fairly accurate. Furthermore, we recently reported that only 7.1% of our adolescents who leave pediatric cardiology after the age of 16 years are no longer in cardiac follow-up.³⁰ However, some bias resulting from informative censoring cannot be excluded.

Our database does not permit us to specifically assess the impact of care or social changes on the outcome of CHD patients. For instance, although it would be interesting to investigate the effects of loss to follow-up on patient outcomes,³¹ our database does not contain the frequency of follow-up at the time of death. Thus, we cannot infer such associations. In a specifically designed study, we recently found that 7.1% of the patients who have left pediatric cardiology are either no longer in follow-up or not traceable.³⁰ This is substantially less than percentages reported for other countries.³² Our previous study can serve as a basis for future follow-up studies endeavoring to elaborate on the impact of loss to follow-up on patient outcomes.

Finally, it should be noted that for the 1990 to 1992 cohort, the last death was recorded for a patient who was 17.6 years old at the time of death. In this cohort, there were still 177 patients at risk for death. So theoretically, we cannot estimate an 18-year mortality. However, it is unlikely that mortality would change dramatically in the 3 months before a patient's 18th birthday.

Disclosures

None.

References

- Dastgiri S, Stone DH, Le Ha C, Gilmour WH. Prevalence and secular trend of congenital anomalies in Glasgow, UK. *Arch Dis Child.* 2002;86:257-263.
- Tagliabue G, Tessandori R, Caramaschi F, Fabiano S, Maghini A, Tittarelli A, Vergani D, Bellotti M, Pisani S, Gambino ML, Frassoldi E, Costa E, Gada D, Crosignani P, Contiero P. Descriptive epidemiology of selected birth defects, areas of Lombardy, Italy, 1999. *Popul Health Metr.* 2007;5:4.
- Tan KH, Tan TY, Tan J, Tan I, Chew SK, Yeo GS. Birth defects in Singapore: 1994-2000. *Singapore Med J.* 2005;46:545-552.
- Hoffman JJ, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.* 2002;39:1890-1900.
- Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JJ, Somerville J, Williams RG, Webb GD. Task Force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol.* 2001;37:1170-1175.
- Grown-up congenital heart (GUCh) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK. *Heart.* 2002;88(suppl 1):i1-i14.
- Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, Del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation.* 2008;118:e714-e833.
- Spence MS, Balaratnam MS, Gatzoulis MA. Clinical update: cyanotic adult congenital heart disease. *Lancet.* 2007;370:1530-1532.
- Bédard E, Shore DF, Gatzoulis MA. Adult congenital heart disease: a 2008 overview. *Br Med Bull.* 2008;85:151-180.
- Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
- Moons P, Sluysmans T, De Wolf D, Massin M, Suys B, Benatar A, Gewillig M. Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. *Acta Paediatr.* 2009;98:472-477.
- Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births: incidence and natural history. *Circulation.* 1971;43:323-332.
- Vander Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol.* 2005;20:549-557.
- Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart.* 2004;90:307-313.
- Landzberg MJ, Murphy DJ Jr, Davidson WR Jr, Jarcho JA, Krumholz HM, Mayer JE Jr, Mee RB, Sahn DJ, Van Hare GF, Webb GD, Williams RG. Task Force 4: organization of delivery systems for adults with congenital heart disease. *J Am Coll Cardiol.* 2001;37:1187-1193.
- Lin D, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. *Biometrika.* 1993;80:557-572.
- Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med.* 2004;23:51-64.
- Dadvand P, Rankin J, Shirley MDF, Rushton S, Pless-Mulloli T. Descriptive epidemiology of congenital heart disease in northern England. *Paediatr Perinat Epidemiol.* 2009;23:58-65.
- Dastgiri S, Gilmour WH, Stone DH. Survival of children born with congenital anomalies. *Arch Dis Child.* 2003;88:391-394.
- Calzolari E, Garani G, Cocchi G, Magnani C, Rivieri F, Neville A, Astolfi G, Baroncini A, Garavelli L, Gualandi F, Scorrano M, Bosi G. Congenital heart defects: 15 years of experience of the Emilia-Romagna Registry (Italy). *Eur J Epidemiol.* 2003;18:773-780.
- Garne E. Congenital heart defects: occurrence, surgery and prognosis in a Danish County. *Scand Cardiovasc J.* 2004;38:357-362.
- Khoshnood B, De Vigan C, Vodovar V, Goujard J, Lhomme A, Bonnet D, Goffinet F. Trends in prenatal diagnosis, pregnancy termi-

- nation, and perinatal mortality of newborns with congenital heart disease in France, 1983–2000: a population-based evaluation. *Pediatrics*. 2005;115:95–101.
23. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart*. 2001;85:438–443.
 24. Hoffman JJ, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147:425–439.
 25. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–172.
 26. Moons P, Engelfriet P, Kaemmerer H, Meijboom FJ, Oechslin E, Mulder BJ. Delivery of care for adult patients with congenital heart disease in Europe: results from the Euro Heart Survey. *Eur Heart J*. 2006;27:1324–1330.
 27. Davidson WR Jr, Warren GH, Verstappen A, Kuehl KS, Graham TP. US resources for care of adults with congenital heart disease. *Circulation*. 2006;114(suppl):II-681. Abstract.
 28. Marelli AJ, Therrien J, Mackie AS, Ionescu-Ittu R, Pilote L. Planning the specialized care of adult congenital heart disease patients: from numbers to guidelines; an epidemiologic approach. *Am Heart J*. 2009;157:1–8.
 29. Moons P, Meijboom FJ, Baumgartner H, Trindade PT, Huyghe E, Kaemmerer H. Structure and activities of adult congenital heart disease programmes in Europe. *Eur Heart J*. 2010;31:1305–1310.
 30. Goossens E, Stephani I, Hilderson D, Gewillig M, Budts W, Van Deyk K, Moons P. Transfer destinations and risk factors for “no follow-up” and “no appropriate follow-up” in young adults with congenital heart disease after leaving pediatric cardiology. *J Am Coll Cardiol* 2010;55:A42.E399. Abstract.
 31. Moons P, Hilderson D, Van Deyk K. Implementation of transition programs can prevent another lost generation of patients with congenital heart disease. *Eur J Cardiovasc Nurs*. 2008;7:259–263.
 32. Moons P, Hilderson D, Van Deyk K. Congenital cardiovascular nursing: preparing for the next decade. *Cardiol Young*. 2009;19(suppl 2):106–111.

CLINICAL PERSPECTIVE

This study investigated the actual prospects to survive into adulthood, explored temporal trends in survival over the past decades, and evaluated survival according to the type of heart defect. The information provided is important for clinicians to gain insight into the survival rates of different groups of patients with congenital heart disease. Furthermore, this article shows that survival is determined by decade of birth, disease complexity, type of heart defect, and pulmonary hypertension. This finding can assist clinicians in estimating the risk of mortality in their patients. In addition, this study can be used for future workforce planning. Based on the prevalence of heart defects and survival curves presented in this study, the need for outpatient facilities and required manpower can be estimated at the program, hospital, or country level.