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Transplant-Free Survival After Intervention for Mild Congenital Heart Disease: Long-Term Outcomes from the PCCC

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2019

Abstract

Transplant-Free Survival After Intervention for Mild Congenital Heart Disease: Long-Term Outcomes from the PCCC

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Background

Mild congenital heart diseases [CHDs] such as patent ductus arteriosus [PDA], atrial septal defect/patent foramen ovale [ASD], mild pulmonary stenosis [PS], and ventricular septal defect [VSD] have, historically, been considered "cured" after percutaneous or surgical intervention. Studies with sufficient participation and duration to describe the long-term outcomes after surgical or percutaneous intervention are lacking.

Methods

The Pediatric Cardiac Care Consortium database was queried for US patients with intervention for any combination of mild CHDs before 21 years. Patients with additional cardiac comorbidities, prematurity, or inadequate identifies for death certificate linkage. Outcomes included transplant, death, and cause of death. Product-limit survival analysis was performed for time to transplant or death among those surviving first intervention. Standardized mortality ratios [SMRs] with the general population were calculated using the CDC WONDER vital statistics database. Cox Proportional Hazards models were generated to assess risk factors for transplant or death.

Results

The cohort for survival analysis included 14,861 patients. Survival at 25 years after first intervention was greater than 97 % for all defects. Survival was significantly greater for PS and ASD than VSD (log-rank $p < 0.0001$). SMRs were significantly greater than 1 until 18 years after first intervention. The presence of extracardiac comorbidities, being underweight, male sex, and younger age at first surgery are associated with greater risk for transplant or death during follow-up. Cardiovascular- and CHD-related causes of death were most frequent among those in younger age groups at death.

Conclusions

While transplant-free survival after intervention for mild CHDs is excellent, risk for death remains elevated over the general population up to 18 years after first intervention. Extracardiac comorbidities confer significantly greater risk, along with several biometric factors. This study provides pediatric cardiologists with long-term data for advising patients and families, and prompts a deeper analysis of causes of death in mild CHD.

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Introduction

Mild CHDs such as isolated patent ductus arteriosus (PDA), atrial septal defect/patent foramen ovale (ASD), mild pulmonary stenosis (PS), and ventricular septal defect (VSD) account for about one third of all patients with CHD (1,2) and therefore constitute a significant public health problem. We and others have demonstrated that patients with CHD have increased mortality compared to the general population even after successful and relatively uneventful surgical repair (3–9). However, these studies do not account for the impact of additional extracardiac comorbidities (ECCs) including chromosomal, syndromic and other non-syndromic ECCs that are frequently associated with the presence of a CHD (1,2,10,11). ECCs can occur in up to 25% of patients with mild CHDs such as PDA, ASD and VSD and can significantly increase the mortality in patients with CHD (2). The only study assessing survival of isolated mild CHD in otherwise healthy children comes from the Danish National Registry, but in this cohort less than a third had undergone surgical or percutaneous intervention (12).

We used a large, multi-center, clinical registry, linked with national registries of death and transplant, to evaluate the long-term, transplant-free survival of children with mild CHD (ASD, VSD, PDA and PS) without any significant comorbidities after percutaneous or surgical repair of their defect.

Methods

Cohort Selection

We performed a retrospective cohort study to describe the long-term outcomes in children (<21 years of age) after percutaneous or surgical interventions for mild CHD, including those with combinations of mild defects. Data were obtained from the PCCC, a US-based, multi-institutional registry including data from 47 US centers, enrolling patients between 1982 and 2011 (13–15). We queried the PCCC registry for patients enrolled in the PCCC between 1982 and April 15, 2003 (at which time stricter Health Insurance Portability and Accountability privacy rules precluded the collection of direct identifiers) and underwent a percutaneous or surgical intervention for at least one of ASD/PFO, PDA, PS, or VSD before 21 years of age.

Non-US residents, patients undergoing interventions in a non-US center, patients with prior cardiac interventions in a non-PCCC participating center, or patients with incomplete or conflicting data were excluded. In addition, we excluded patients with additional cardiac comorbidities besides the above mentioned CHDs; chromosomal defects and genetic syndromes known to affect survival; and preterm infants with isolated ductal closure at a weight of less than 2.5 kg because of the significant mortality associated with these conditions rather than the CHD itself. Special scenarios (e.g. mitral valve abnormalities in ostium primum type ASD) were explored, leading to a small number of additional exclusions (Supplemental Table 1). Patients with ECCs at the time of first intervention that were deemed not to significantly affect survival were included as a risk factor in the multivariable analysis.

Patient Classification

Mild CHD was defined as the presence of ASD, PDA, PS, or VSD or any combination thereof and the absence of any additional CHD. All types of ASD were included (secundum and primum types, as well sinus venosus) as long as no mitral valve regurgitation and/or partial anomalous pulmonary venous return was present. Coronary sinus type ASDs were excluded. All types of VSDs were included (muscular, perimembranous and inlet types).

Patients were assigned to the diagnosis groups "ASD", "PDA", "PS", and "VSD" using a hierarchical scheme wherein defects were prioritized VSD > PS > ASD > PDA, detailed as follows: any patient with intervention for VSD was assigned to the "VSD" group regardless of the presence of additional mild CHD (ASD, PDA, or PS); any patient with intervention for PS and without intervention for VSD, was assigned to the "PS" group regardless of the presence of ASD or PDA. Any patient with intervention for ASD and without intervention for VSD or PS, was assigned to the "ASD" group regardless of intervention for a PDA. Isolated intervention for PDA was assigned to the "PDA" group. A sensitivity analysis was performed using only the four defects above in isolation.

Ascertainment of Outcomes

Direct identifiers of patients enrolled between 1982 and 2003 were matched against the National Death Index (NDI) and the Organ Procurement and Transplantation Network (OPTN) datasets up to the end of 2014 (16,17). The OPTN data system includes data from all donors, wait-listed candidates, and transplant recipients in the US, submitted by the member organizations. The Health Resources and Services

Administration, US Department of Health and Human Services provides oversight of the activities of the OPTN contractor.

End-points for survival analysis were transplant or death. Additional outcomes included cause of death (COD) as reported by the NDI. COD data are reported from NDI-supplied ICD-9/10 codes of death records. Transplants and deaths during the hospitalization for the first intervention were excluded from the survival analysis. Follow-up time was calculated from the end of the hospitalization for the first intervention to transplant, death, or December 31, 2014. Transplant-free survival was estimated from the first intervention and compared with the general population using standardized mortality ratios (SMRs) with CDC WONDER vital statistics data, adjusted for age, sex, and calendar year.

Statistical Analyses

Categorical data are reported as counts with percentages within diagnosis groups. Age at first intervention is reported in the following biologically significant groups: neonates (less than 28 days), infants (28 days to 1 year), young children (1-5 years), and older children/young adults (5-21 years). Weight at first intervention is reported in three groups based on age- and sex-specific z-scores: “underweight” for z-scores less than -2, “normal weight” for z-scores between -2 and 2, and “overweight” for z-scores greater than 2. Normally distributed continuous data are reported as mean and standard deviation (SD) and are otherwise reported as median and interquartile range (IQR). Time to transplant or death is reported using the product-limit (Kaplan-Meier, KM) method. Differences in transplant-free survival as a function of follow-up time were analyzed by the log-rank test for homogeneity with Sidak adjustment for multiple comparisons (18).

SMRs, adjusted for age, sex, and calendar year, were reported as point estimates with 95 % confidence intervals. Univariable and multivariable analyses for potential predictors of increased risk of transplant or death were conducted using Cox Proportional Hazards (PH) models. Time varying risk factors in violation of the proportional hazards assumption were identified using analysis of Schoenfeld residuals (19). Models were then adjusted to report hazard ratios for various risk factors during certain intervals of follow-up where the proportional hazards assumption was satisfied. COD data are reported as frequencies and percentages of the total cohort by age group at death. Frequencies and percentages by diagnosis group can be found in the Data Supplement. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) using an alpha of 0.05 for determining statistical significance.

This study was approved by the Emory University Institutional Review Board without the need for informed consent.

Results

Patient Characteristics

In the PCCC we identified 71,623 patients with ASD, PDA, PS, or VSD or any combination thereof. After exclusions the final study cohort was comprised of 14,919 patients. Of this cohort, 58 died or were transplanted during their first intervention, leaving 14,861 for survival analysis (Figure 1). Patient characteristics and types of intervention stratified by diagnosis group are shown in Table 1. The majority (74.7%) underwent surgical intervention and the rest percutaneous intervention with significant variations in the treatment modality among diagnosis groups.

The majority of patients were female (58 %), varying from 65 % for PDA to 49 % for VSD. The mean age at first intervention was 2.9 years (IQR 1.0, 5.9), with the highest among those with ASD at 4.6 years (IQR 2.9, 8.9) and lowest among those with VSD 1.0 year (IQR 0.4, 3.3). Overall median follow-up was 18.0 years (IQR 15, 22 and maximum 33) and essentially equal across diagnosis groups. The majority of patients were within the normal weight z-score group (78 %), with the most underweight being among those with VSD (41 %) and the most overweight among those with PS (5.4 %). ECCs were documented in 1.3 % of patients overall, with the greatest frequency among those with VSD (1.8 %) and the least among those with ASD (1.1 %).

Outcomes

The outcomes at first intervention and long-term outcomes are shown in Table 1. Overall transplant-free survival at discharge after first intervention for mild CHD was 99.6 % with a total of 53 deaths and 5 heart transplants. The proportion of deaths at first intervention was greatest among those with VSD (0.8 %) and least among those with

ASD (0.2 %). Transplants at the first intervention were performed among those with ASD (n=3) and VSD (n=2).

The cumulative 25-year transplant-free survival was 97.2 % for all mild CHDs in the PCCC (Figure 2). The distribution of time to death or transplant after first intervention shows an initial peak as well as later peaks at 6, 12, and 16 years. Detailed distribution of deaths and transplants by age of occurrence of the event and time after intervention is shown in Supplement Figure 1. Survival was observed to be significantly greater for PS and ASD compared to VSD (log-rank $p < 0.0001$) (Figure 3). Differences among the remaining pairwise comparisons were non-significant. Life tables are presented in Table 2 for each primary defect including secondary defects as per the hierarchical scheme discussed in methods and in Supplemental Table 2 for the isolated mild defects as sensitivity analysis.

SMRs were calculated based on the expected US deaths for age-, sex-, and calendar year-matched subjects from the CDC WONDER database of vital statistics (Figure 4). The risk for death for patients who had intervention for mild CHD was significantly greater than that of the general population until 18 years of age, at which point risk of death for surviving patients resembles the general population

Cox Proportional Hazards Models

Cox Proportional Hazards models were constructed for assessing the association between each of the following categorical predictors and the odds of transplant or death: presence of ECC, weight z-score group, sex, and age group at first intervention. Results from the multivariable model are shown in Table 3 (univariable results are shown in Supplemental Table 4). Each predictor was categorized and hazard ratios (HRs) were

estimated for various time intervals after the first intervention. The method for the selection of time intervals during follow-up for the estimation of HR is detailed in Supplemental Figure 2.

After adjustment for the other risk factors, the presence of ECC was significantly associated with transplant or death both in the early (<1 year) post-intervention period (HR 16, 95% CI 7.2, 33) and later period (>1 year) (HR 4.1, 95% CI: 1.9, 8.8). Being underweight at time of intervention was also shown to be an independent risk factor for death or transplant (HR of 2.4, 95 % CI 1.6, 3.6) at <5 years after the intervention and (HR 1.81, 95% CI 1.26,2.60) at >5 years respectively. Intervention within neonatal period and the first year of life was significantly associated with risk for transplant or death during the first five years after first intervention (HR for young children 0.25, 95 % CI 0.11, 1.6 and for older children/young adults 0.28, 95% CI 0.12, 0.64). Age at first intervention is no longer significantly associated with transplant or death beyond five years after first intervention. Finally, there was an age dependent effect of sex on post intervention outcomes with male sex becoming a significant risk factor for death or transplant at >5 years after the corrective intervention (HR 2.4, 95 % CI 1.8, 3.3), but this is a general effect observed in the general population as well.

Inclusion of the secondary defects did not meaningfully affect the survival (Supplemental Table 3), SMRs (Supplemental Figure 4), multivariable analysis, nor cause of death analysis.

Cause of Death (COD)

Underlying COD among all patients by age group at death are shown in Figure 5. Deaths attributed to “CHD” and to “Cardiovascular Diseases” (CVD) accounted for less

than 30 % of the total deaths and, despite some fluctuation over time, there was a decreasing trend in these deaths up to 15-20 years of age. There was some heterogeneity in COD by diagnosis group, with CHD being more frequent in VSD compared to the others (Supplemental Figure 3). “Congenital, non-CHD” was relatively more frequent in PDA and PS. Accidents/Trauma were most frequent in PS and ASD, and were a large proportion of CODs in all diagnosis groups.

Discussion

Our registry-based study provides a large-scale, analysis of long-term outcomes after intervention for a full spectrum of mild CHDs in the US. Survival after first intervention for mild CHD is excellent at greater than 97 % for all diagnosis groups after 25 years of follow-up, however the risk of death for mild CHD remains increased compared to the general population until 18 years after first intervention. Patients with combinations of mild CHDs have similar outcomes compared to patients having only isolated defects.

Risk factors for increased odds of transplant or death include the presence of ECCs, being underweight at first intervention, and being less than one year of age at first intervention. Some of these events are likely to be explained by the procedures themselves, which carry a small but real incidence of complications such as ventricular dysfunction, valve dysfunction, tissue erosion and arrhythmias (20). However, some may reflect more chronic implications of abnormal hemodynamics.

The worse early outcomes with intervention in infancy may reflect the greater technical challenge of interventions in patients who are young and small, but they may also indicate some residual risk from the earlier exposure to hemodynamically more significant abnormalities. A similar argument can be made for the effect of being underweight at time of surgery. It is notable that, in this case, correction of the hemodynamics does not eliminate the risk for premature mortality for the length of the follow up of this cohort. The worse outcomes with ECCs is likely due to the increased contribution to morbidity from other systems in the presence of CHD, even without known a chromosomal or syndromic condition (1,2,10,20). In these cases, the additional

morbidity due to the dysfunction of the involved systems may contribute to worsened long-term outcomes. The worse outcomes for males will need to be verified by comparison to the general population, in whom increased risk for death is greater at the corresponding age group.

Reviewing a subset of the relevant literature for outcomes after intervention for mild CHDs supports and contextualizes the findings of our study. The most directly comparable study to ours was reported by Videbaek et al. and leveraged mandatory nationwide registry health in Denmark, supplemented with medical record review (12). Long-term results included mortality, COD, morbidity, and medical follow-up. Important distinctions are the inclusion of patients without intervention, the earlier era of this cohort (1963-1973) and diagnostic, therapeutic and socioeconomic context in the northern European cohort, as well as the exclusion of patients with end-stage presentations, combinations of defects, and ECCs. The resulting cohort in Videbaek et al. is healthier and less representative of "all comers" with mild defects. A discussion of our results compared with Videbaek et al. and additional, defect-specific studies follows.

Overall survival at 30 years of age in Videbaek et al., a comparable time point to our 25 years follow-up, was 98.4 % compared to our estimate of 97.2 %. The lower survival in our study may be explained by the inclusion of only patients that had a defect clinically significant enough to require intervention.

Overall transplant-free survival after both percutaneous and surgical intervention for PDA in our study was 98.9 % at 25 years. Survival estimates in the literature were similar: 100 % (21–27) and 97.8 - 100 % (28) for percutaneous and surgical interventions respectively at up to five years, improved to 100 % at 10 years for interventions

performed more recently (29). Overall transplant-free survival among those with ASD was 97.2 % at 25 years, similar to literature estimates: 98.9 - 100 % (30–35) and 99.2 - 100 % (36–39) for percutaneous and surgical interventions respectively up to five years, 100 % (40,41) and 98.0 - 100 % (41–43) at 10 years, and 74 - 100 % (44–46) for surgical intervention beyond 25 years, with older studies taking place as early as 1990, reflecting interventions in the 1950s and 1960s (46). Overall transplant-free survival for VSD was 96.5 % at 25 years, better than prior studies with outcomes for surgeries performed prior to the modern era in which survival ranged from 94.6 % (47) at five years, 87.0 - 90.9 % (48,49) at 10 years, and 96 % (50) at 25 years (the most recent study). Percutaneous methods were more recently developed, and report essentially complete survival at 5 (51–55) and 10 years (56).

Using age-, sex-, and calendar year-matched data, the SMR for the full cohort was 2.2 (95 % CI 1.9, 2.5). This significantly increased risk for death persists until 18 years after the first intervention. Videbaek et al. report an overall hazard ratio for death of 1.9 (95 % CI 1.5, 2.4) compared to the general population over approximately 35 years of follow-up. While methodological differences prevent direct comparison of these results, both suggest residual risk for death with mild CHD, especially after intervention, decades after diagnosis and/or intervention. Few studies in the literature report such comparisons to the general population after intervention for mild CHD. Cuypers et al. report survival “comparable” to the general population after surgery for ASD (44), and survival “comparable to...nearly the same” as the general population after surgery for PS (57). Kopecky et al. report survival beyond 21 years after surgery for PS as “comparable” to the general population. Both studies of PS after surgery featured less than 200 patients,

and Kopecky et al. were studying a cohort who had surgery in earlier decades. Discrepancies between this study and those by Cuypers et al. may be explained by lower participation, while the finding of similar residual mortality in Kopecky may be due to overall higher surgical morbidity and mortality of the era, a factor less likely to be explanatory in our cohort.

Presence of ECC, being underweight at first intervention, being male, and being younger at first intervention were associated with increased risk for transplant or death in our cohort using Cox proportional hazards modeling. There was variation in the hazard rate throughout follow-up, necessitating the use of heaviside functions to estimate hazard ratios for various intervals of follow-up. Videbaek et al. found no significant difference by sex or age at first intervention, and did not consider ECCs or weight in their multivariable modeling. Few studies in the literature incorporate these methods, primarily due to sample size limitations. Murphy et al. report older age at first surgery for ASD as a risk factor for death during follow-up (46). Kopecky et al. report older age at first surgery for PS as a risk factor for death during follow-up (58). These contradictory results are likely due to the earlier era during which the majority of patients in each study had their surgery, and the missing contribution of patients having less risky percutaneous interventions. Younger age being associated with transplant or death in our study may be indicative of greater pre-intervention mild CHD severity, the assessment of which was not feasible beyond the covariates already included in our models due to the large sample size.

Using ICD-9/10 COD data, we were able to make three important observations that necessitate further study. CHD and Congenital, non-CHD make up the greatest

proportion of deaths in the younger age groups (<1 to 5 years), whereas Accidents/Trauma and "Other Diseases" make up the greatest proportion of deaths in the older age groups (5 to 20+ years). The change in proportional COD is greatest between the younger age groups and the older groups. Videbaek et al. did not report COD stratified by age of death. Overall, "cardiac" and "sudden unexpected death" made up a combined 55 % of deaths, greater than the approximately 32 % of deaths in our study due to CHD or CVD causes. Considering the proportion of deaths due to Accidents/Trauma our US cohort, overall lower incidents of that sort in the Danish population may account for this difference. In a cohort containing all forms of CHD, the proportion of deaths due to CHD followed a similar trend as our study, with increasing age group at death, thought the magnitude of this proportion was greater in this cohort with more severe defects included (6). Further analysis of contributing CODs, as well as comparisons to the general population, are warranted given the residual increased mortality decades after first intervention found in this study. Should the proportional CODs, especially among those dying in older age group, resemble the general population, investigation into the increased rate of death from non-CHD, non-CVD causes may yield important information about the long-term care of patients having intervention mild CHD.

Strengths and Limitations

Our study employs many strengths that add to the minimal body of literature on long-term outcomes of patients after intervention for mild CHD. These include most notably the large sample size and long-term follow-up of these patients (median 18.0 years, range 0, 33). As a result, the number of patient-years of follow up in our study allows for more precise estimations of survival beyond the more commonly studied post-

intervention period. Finally, inclusion of the full spectrum of mild CHDs as well as combinations thereof, long-term outcomes, and CODs allows for a full picture of these clinical outcomes that can translate to clinical practice and the possibility of pre-intervention counseling of patients and families based on our findings.

Despite significant strengths, limitations to our study still exist. First, the study is subject to the limitations of a registry-based retrospective study that limits the number of available covariates to what is available in this dataset. Secondly, it is possible that patients received additional care outside of PCCC centers in which data were not captured. We assigned diagnosis groups based on the highest order defect (VSD > PS > ASD > PDA) for which intervention was performed, which assumes that the defect was the most severe, and thus would have been the cause of long-term morbidity and mortality. While there may be a small number of patients for whom the defect on which intervention was not performed caused long-term morbidity and mortality, we believe that, on balance, our approach to diagnosis group designation is most appropriate. In addition, our PCCC-NDI-OPTN linkage for those with adequate identifiers had a sensitivity of 88.1 % for death events which is within the expected range for this methodology but not perfect (17) Lastly, underlying COD as reported on NDI-linked death certificates may not be a reliable measure for the relationship between COD and intervention for mild CHD. However, the NDI is the current “gold standard” for assessment of these outcomes measures in the US (59).

Conclusion

Our study provides the first US-based, large-scale, registry-based analysis of long-term outcomes after intervention for a full spectrum of mild CHDs. Long-term transplant-free survival is excellent, but residual annual risk for death remains elevated long after first intervention. These results emphasize the importance of cardiologists discussing the prognosis and benefits of intervention for a variety of mild CHDs, incorporating various demographic and biometric risk factors for transplant or death to better inform and treat patients and families.

Acknowledgements

Thanks to Drs. Kochilas and Oster for guidance, to Dr. Moller for his seminal work, to the faculty and staff at the Pediatric Research Alliance, to the Emory University Rollins School of Public Health and School of Medicine, and to the patients.

Sources of Funding

National Heart, Lung, and Blood Institute, RO1HL122392

Emory University Department of Pediatrics

Disclosures

The authors have no relevant disclosures.

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Figures

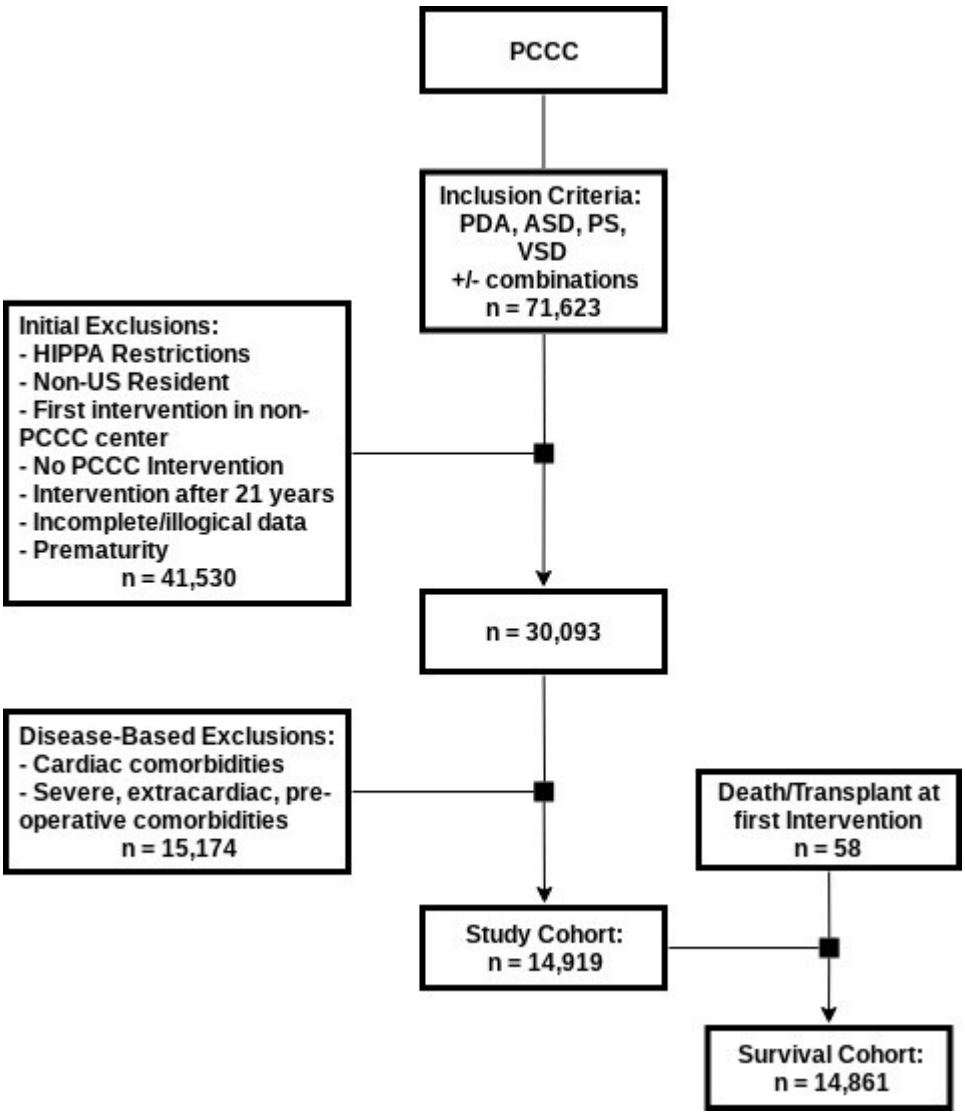


Figure 1: Study Population.

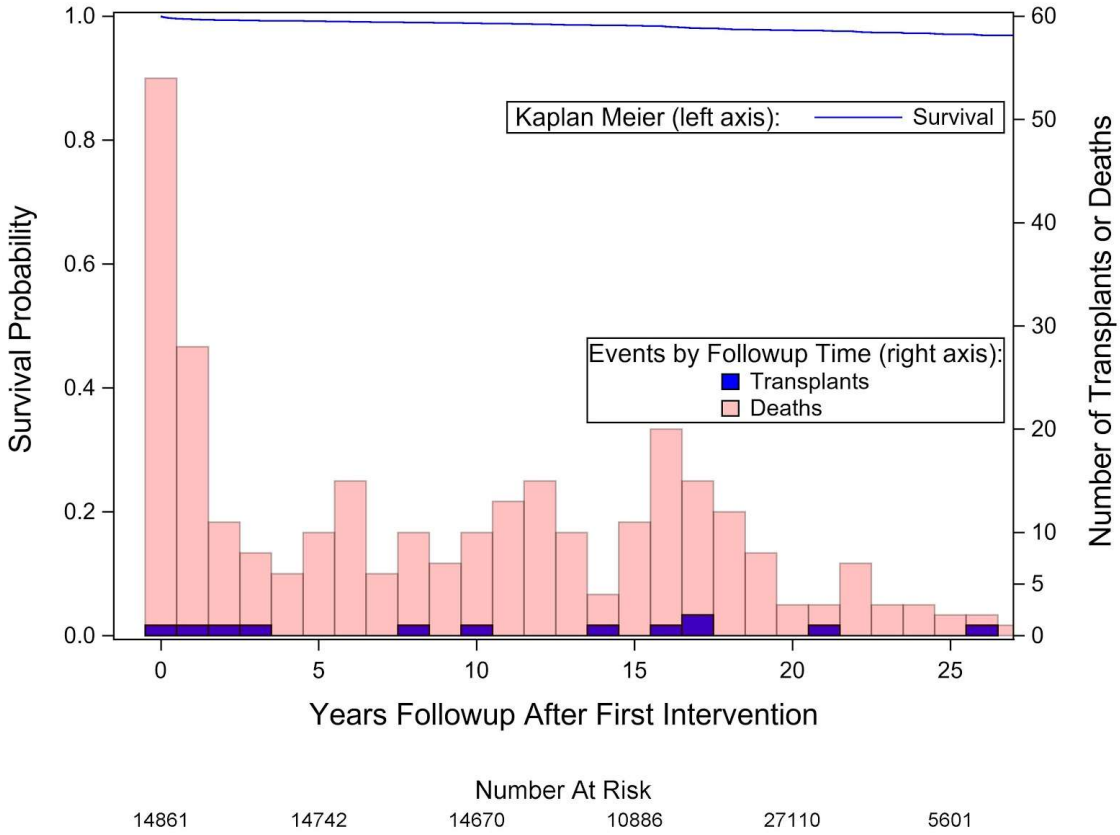


Figure 2. Overall Transplant-Free Survival After First intervention and Events by Follow-up Time. Transplant-free survival was excellent (97.2 %, blue curve). Superimposed histograms show deaths (red) and transplants (blue) by years after first intervention.

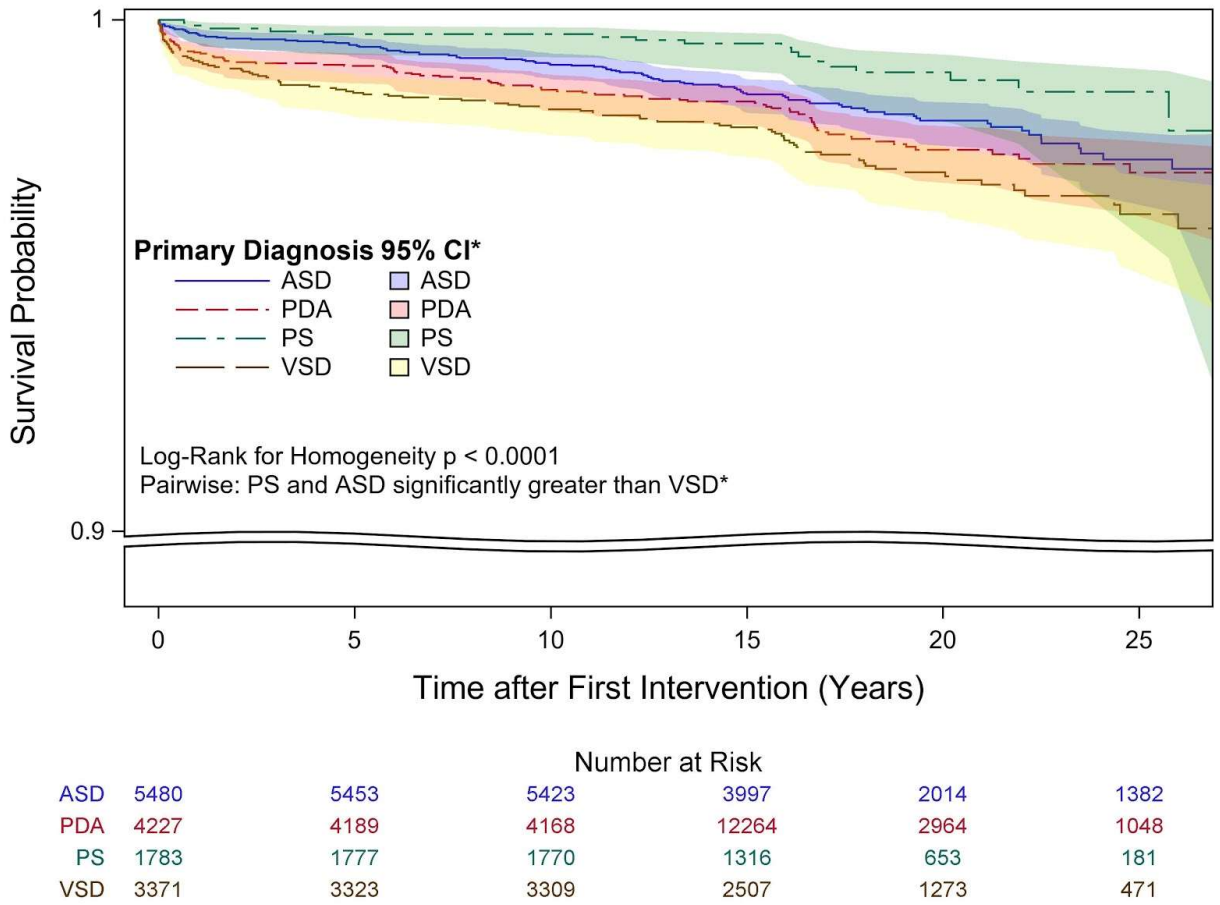


Figure 3. Transplant-free Survival by Primary Diagnosis. NOTE: broken y-axis. When stratified by primary diagnosis group, transplant-free survival is essentially equal among the groups, though transplant-free survival for PS and ASD were slightly, statistically significantly higher than VSD. All other pairwise comparisons were not statistically significantly different. Number at risk shows greater than 10 % of each original diagnosis remaining at 25 years follow-up, validating estimates at this long-term time point.

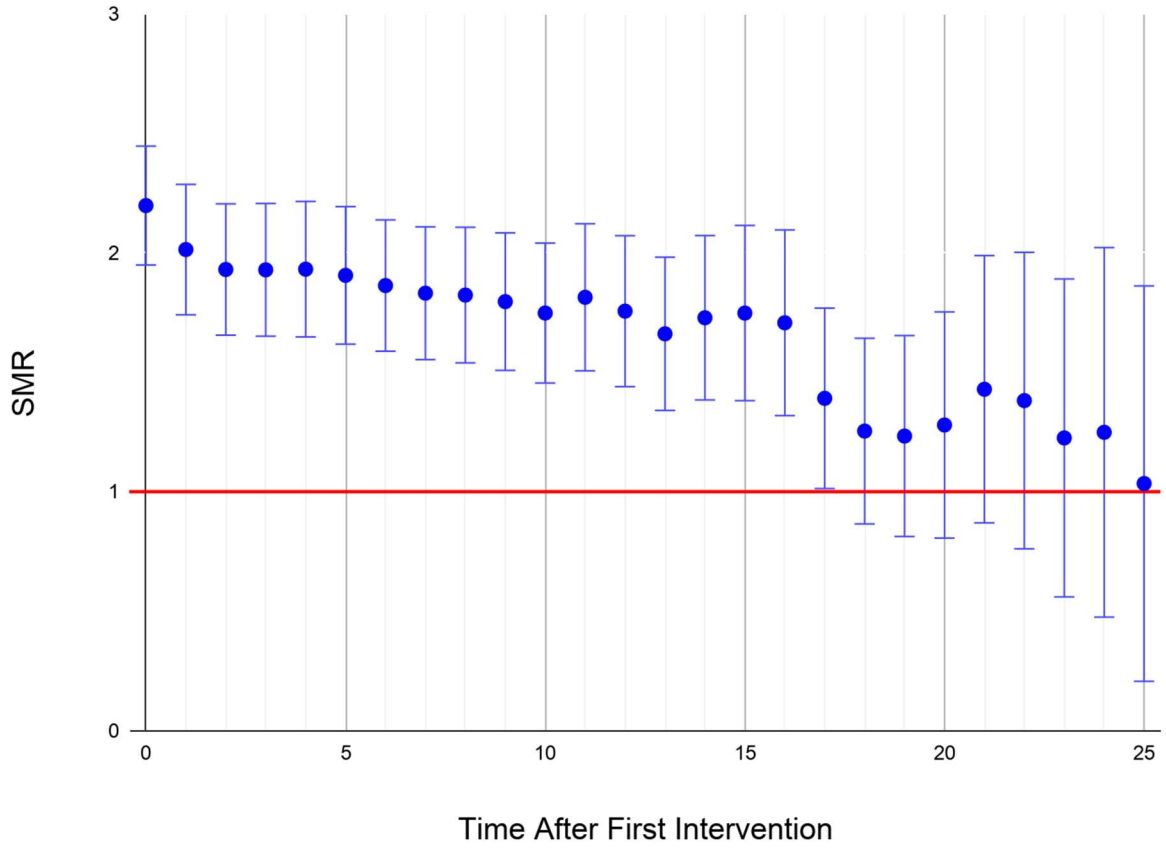


Figure 4. SMRs Conditional on Survival Time After First intervention. CDC WONDER vital statistics data were used to compare our cohort to age-, sex- and calendar year-matched subjects in the general population. Error bars indicate 95 % confidence limits. At 18 years after first intervention, annual mortality matches that of the general population.

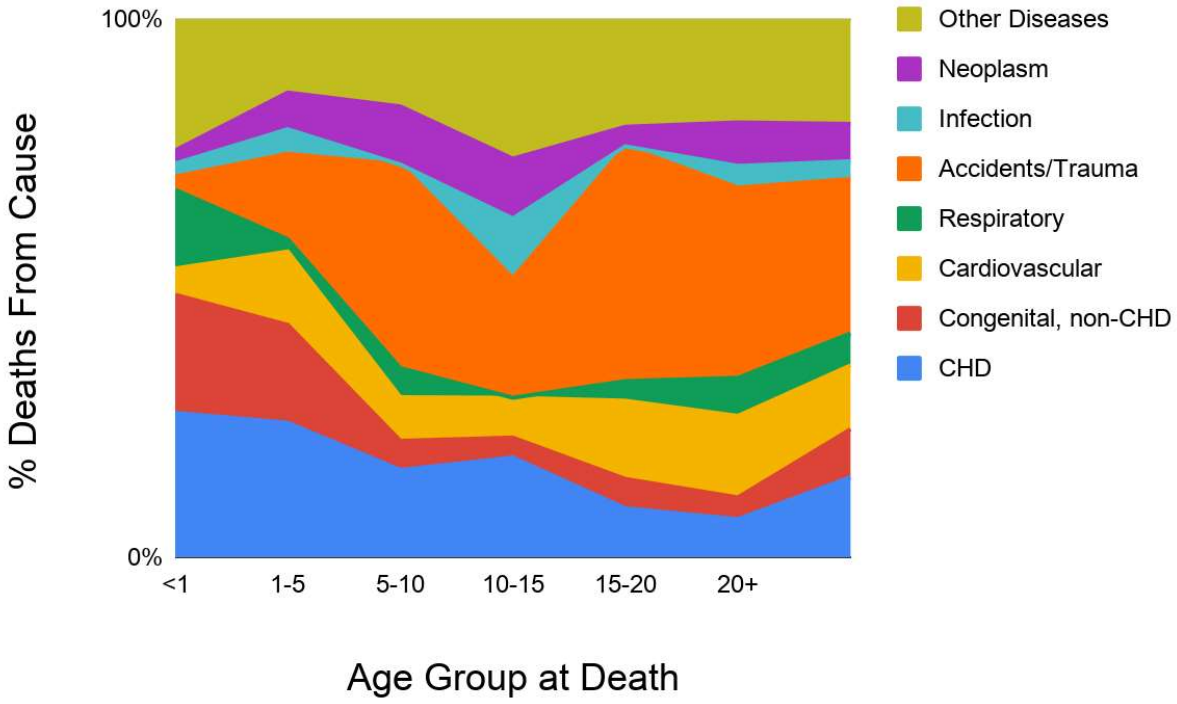


Figure 5. Underlying Cause of Death by Age of Death. Age categories at death on the x-axis represent the age at which a patient died after intervention for mild CHD. The width of each colored COD represents the proportion of that COD among all CODs for that age category at death. CHD and CVD represent a large but diminishing proportion of deaths as the age at death increases. The proportion of Accidents/Trauma increases as age at death increases, a phenomenon observed in the general population as well.

Tables

Table 1. Patient Characteristics and Outcomes by Diagnosis Group at First Intervention

	Total	PDA	ASD	PS	VSD
Number of Patients	14,919	4,239	5,492	1,789	3,399
Surgical, n (%)	11,142 (74.7)	2,547 (60.1)	4,866 (88.6)	354 (19.8)	3,375 (99.3)
Percutaneous, n (%)	3,777 (25.3)	1,692 (39.9)	626 (11.4)	1,435 (80.2)	24 (0.7)
Median Age	2.85	2.11	4.62	1.17	0.97
(IQR)	(0.95, 5.85)	(0.98, 4.89)	(2.92, 8.86)	(0.17, 4.02)	(0.42, 3.29)
Age Group			n (%)		
< 28 days	476	97	9	340	30
28 days - 1 year	3393	995	208	499	1691
1 - 5 years	6582	2119	2774	587	1102
5 - 21 years	4468	1028	2501	363	576
Median Follow-up, years	18.0	17.9	17.9	18.1	18.3
(IQR)	(15, 22)	(15, 22)	(15, 22)	(14.8, 22)	(15, 22)
Sex, n (% female)	8,706 (58.4)	2,765 (65.2)	3,328 (60.6)	960 (53.7)	1,653 (48.6)
Weight			n (%)		
Underweight	2,636 (17.7)	539 (12.7)	561 (10.2)	130 (7.3)	1,406 (41.4)
Overweight	421 (2.82)	132 (3.11)	153 (2.79)	96 (5.37)	40 (1.18)
Normal Weight	11,666 (78.2)	3,516 (85.4)	4,690 (78.2)	1,542 (82.9)	1,918 (86.2)
Decade of Intervention			n (%)		
1980	1,957 (13.1)	551 (13.0)	713 (13.0)	186 (10.4)	507 (14.9)
1990	9,160 (61.4)	2,581 (60.9)	3,353 (61.1)	1,140 (63.7)	2,086 (61.4)
2000	3,802 (25.5)	1,107 (26.1)	1,426 (26.0)	463 (25.9)	806 (23.7)
ECC, n (%)	195 1.31	63 1.49	62 1.13	9 0.50	61 1.79
Outcome			n (%)		
In-Hospital Transplant	5 (0.03)	0 (0.00)	3 (0.05)	0 (0.00)	2 (0.06)
In-Hospital Death	53 (0.36)	12 (0.28)	9 (0.16)	6 (6.00)	26 (0.76)
Follow-Up Transplant	12 (0.08)	1 (0.02)	3 (0.05)	1 (0.06)	7 (0.21)
Follow-Up Death	300 (2.01)	94 (2.22)	99 (1.80)	17 (0.95)	90 (2.65)

Table 2. Percent Survival Estimates by Follow-up Time and Diagnosis Group

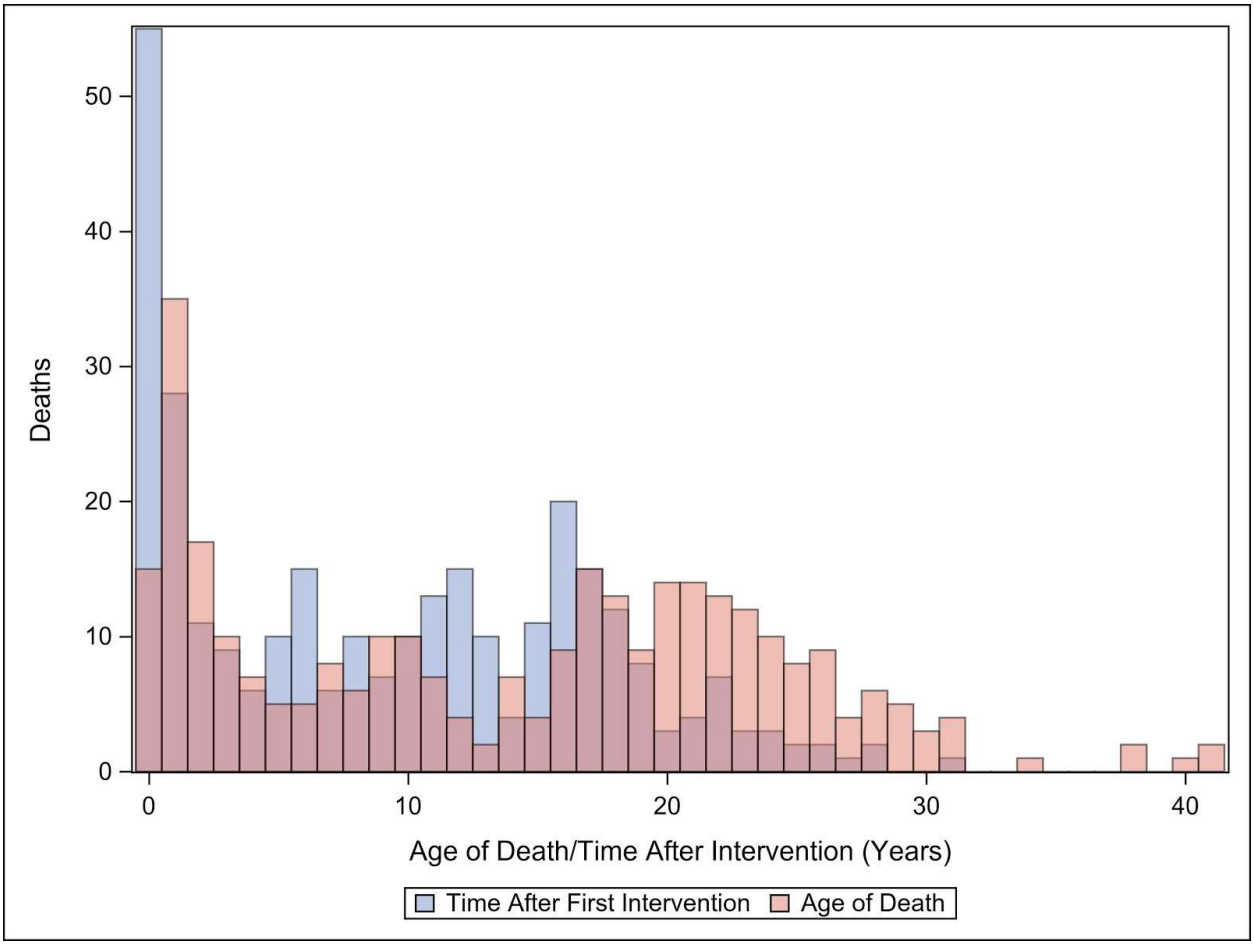
Follow-up Time (years)	Total Cohort	PDA	ASD	PS	VSD
1	99.61	99.36	99.72	99.93	99.59
5	99.36	99.10	99.51	99.72	99.24
10	98.98	98.63	99.13	99.72	98.77
15	98.62	98.40	98.55	99.65	98.47
20	97.85	97.46	98.02	99.06	97.35
25	97.22	97.01	97.24	98.85	96.47

Table 3. Multivariable Analysis Using Cox Proportional Hazards model with heaviside functions to account for violations of proportional hazards assumption

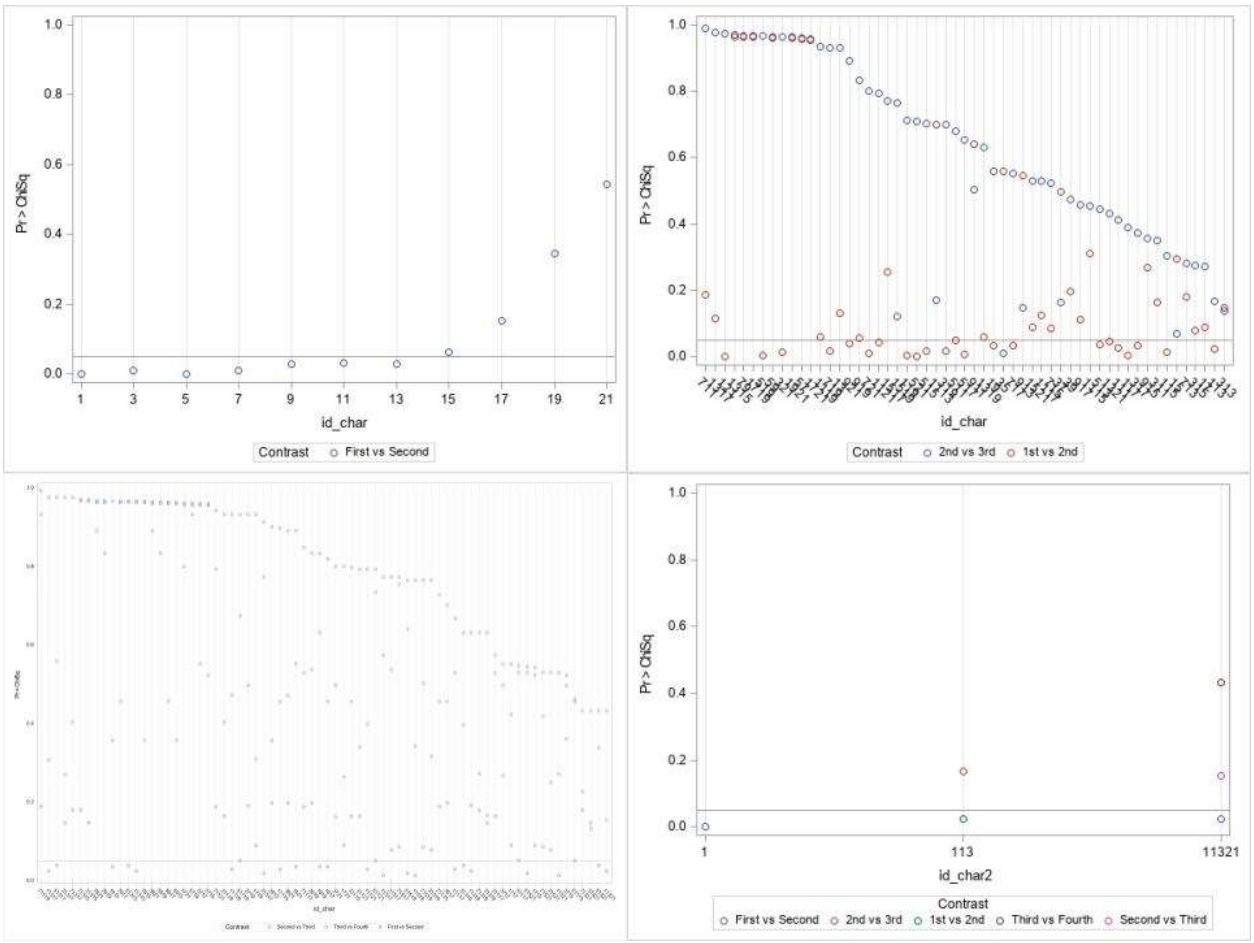
	Range of Follow-Up Years					
	Hazard Ratio for Death/Transplant (95 % Confidence Limits)					
Extracardiac Comorbidity	**0 - 1 year**		**1 - 30 years**			
Yes	15.5	(7.19, 33.3)	4.1	(1.93, 8.84)		
No	(ref)					
Weight	**0 - 5 years**		**5 - 30 years**			
Underweight	2.39	(1.58, 3.63)	1.81	(1.26, 2.60)		
Overweight	1.06	(0.26, 4.33)	1.57	(0.73, 3.36)		
Normal Weight	(ref)					
Sex	**0 - 5 years**		**5 - 30 years**			
Male	1.20	(0.83, 1.74)	2.42	(1.80, 3.26)		
Female	(ref)					
Age	**0 - 5 years**		**5 - 21 years**		**21 - 30 years**	
< 28 days	(ref)					
28 days - 1 year	0.76	(0.35, 1.62)	1.12	(0.34, 3.70)	0.36	(0.08, 1.70)
1 - 5 years	0.25	(0.11, 0.56)	1.25	(0.39, 4.00)	0.28	(0.06, 1.31)
5 - 21 years	0.28	(0.12, 0.64)	2.71	(0.85, 8.61)	0.28	(0.05, 1.43)

Data Supplement

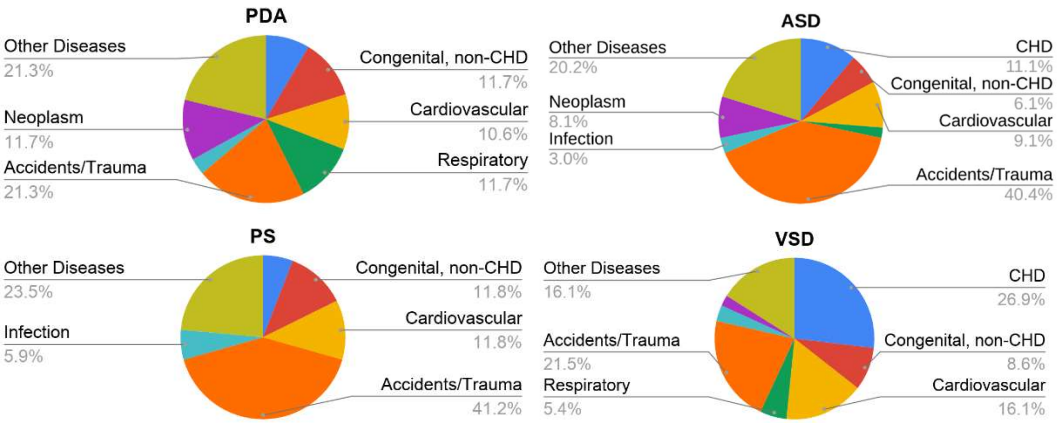
Figures



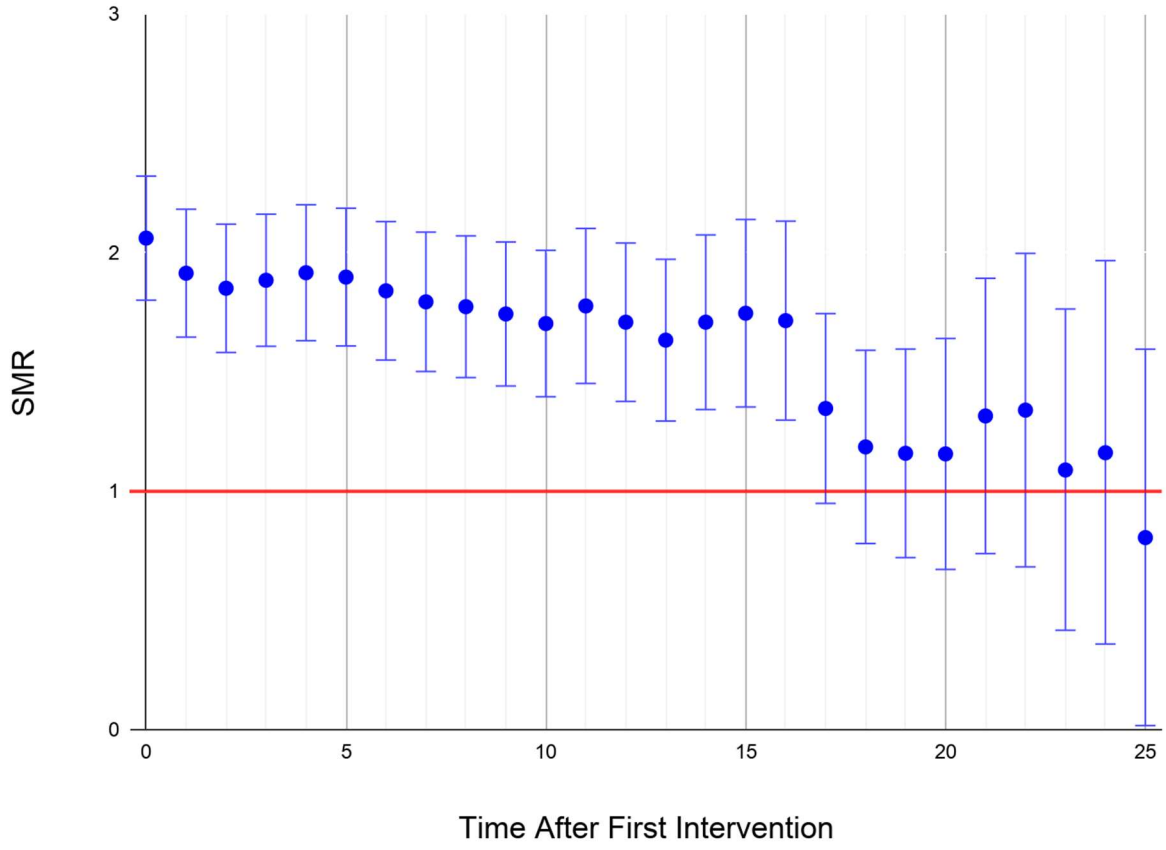
Supplemental Figure 1. Death by Time After intervention and Age of Death. Superimposed histograms show death by time after intervention (blue) and age of death (red). The later distribution by age of death reflects those patients who had their first intervention outside of the neonatal or infant period.



Supplemental Figure 2. Example Schoenfeld Residual Analysis for Cut Points in Heaviside Equations for ECC. Cox proportional hazards models were built using one (**top left**), two (**top right**), or three (**bottom left**) cut points during follow-up. P-values for the difference between hazard ratios estimated for the resulting follow-up time intervals (y-axis) are shown for each combination of cut points (x-axis, cut points in years after first intervention). The cut point combinations with the most significant differences in hazard ratio estimates, with some consideration for biological significance (e.g. early childhood, puberty, adulthood, etc.) were compared (**bottom right**). Determination of final cut points for each risk factor were made in the context of best choices for the other risk factors



Supplemental Figure 3. Cause of Death by Diagnosis Group. CHD and CVD are most frequent among those with VSD and ASD. The variation in Accidents/Trauma warrants further research, including an analysis of the contributing causes of death



Supplemental Figure 4. SMR with Isolated Defects (Sensitivity Analysis).

Supplemental Table 1. Special Cases In Cohort: Inclusion/Exclusion

Case	Inclusion	Exclusion
- Scimitar	Intervention after 1 year	Intervention prior to 1 year
- Mitral valve insufficiency	Ostium primum ASD	All others other defects if pre-intervention
- Cardiac tumors	None	All
- Prematurity	If no isolated PDA	If isolated PDA
- Aortic arch abnormality	Not surgically repaired	Surgically repaired
- Ischemic cardiomyopathy	Post-intervention	Pre-intervention
- Myocardial Infarction	Post-intervention	Pre-intervention
- Pre-intervention pacemaker placement	None	All
- Right ventricular outflow tract procedure	Not associated with tetralogy	Associated with tetralogy

Supplemental Table 2. Diagnosis Group Algorithm

Diagnosis Group and Combinations (Requires Diagnosis AND Intervention for Each Deciding Defect)				
VSD	**VSD**			
	VSD	PS		
	VSD	PS	ASD	
	VSD	PS	ASD	PDA
PS	**PS**			
	PS	ASD		
	PS	ASD	PDA	
ASD	**ASD**			
	ASD	PDA		
PDA	**PDA**			

Supplemental Table 3. Percent Survival Estimates by Follow-up Time and Diagnosis Group With Isolated Defects (Sensitivity Analysis)

Follow-up Time (years)	Total Cohort	PDA	ASD	PS	VSD
1	99.61	99.72	99.36	99.93	99.59
5	99.36	99.51	99.10	99.72	99.24
10	98.98	99.13	98.63	99.72	98.77
15	98.62	98.55	98.40	99.65	98.47
20	97.85	98.02	97.46	99.06	97.35
25	97.22	97.24	97.01	98.85	96.47

Supplemental Table 4. Univariate Analysis Using Cox Proportional Hazards model with heaviside functions to account for violations of the proportional hazards assumption

	Range of Follow-Up Years Hazard Ratio for Death/Transplant (95 % Confidence Limits)					
Extracardiac Comorbidity	**0 - 1 year**		**1 year - end**			
Yes	17.8	(9.35, 33.8)	3.9	(1.99, 7.53)		
No	(ref)					
Weight	**0 - 5 years**		**5 years - end**			
Underweight	3.7	(2.54, 5.36)	1.5	(1.11, 2.14)		
Overweight	0.9	(0.22, 3.72)	1.8	(0.82, 3.78)		
Normal Weight	(ref)					
Sex	**0 - 5 years**		**5 years - end**			
Male	1.3	(0.91, 1.88)	2.4	(1.82, 3.26)		
Female	(ref)					
Age	**0 - 5 years**		**5 - 21 years**		**21 years - end**	
< 28 days	(ref)					
28 days - 1 year	0.83	(0.43, 1.62)	1.40	(0.43, 4.57)	0.47	(0.10, 2.20)
1 - 5 years	0.20	(0.10, 0.40)	1.20	(0.38, 3.84)	0.31	(0.07, 1.40)
5 - 21 years	0.21	(0.10, 0.44)	2.53	(0.80, 8.01)	0.24	(0.05, 1.26)