Long-Term Survival After Arterial Versus Atrial Switch in d-Transposition of the Great Arteries

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Background. **The arterial switch operation (ASO) became the procedure of choice for dextro-transposition of the great arteries (d-TGA) nearly 30 years ago, but the long-term results of this operation are unknown. We aimed to compare the long-term transplant-free survival of patients with d-TGA who underwent ASO versus atrial switch in the Pediatric Cardiac Care Consortium.**

Methods. **We performed a retrospective cohort study of d-TGA patients undergoing ASO or atrial switch in the United States between 1982 and 1991. Long-term transplant-free survival was obtained by linking Pediatric Cardiac Care Consortium data with the National Death Index and the Organ Procurement and Transplant Network. Kaplan-Meier survival plots were constructed, and multivariable regression was used to compare long-term transplant-free survival.**

Results. **Of 554 d-TGA patients who underwent ASO (n = 259) or atrial switch (n = 295), the 20-year overall transplant-free survival was 82.1% for those undergoing ASO and 76.3% for those who had atrial switch procedure. Adjusted overall transplant-free survival beyond 10 years after operation was superior for ASO compared with atrial switch (hazard ratio 0.07, 95% confidence interval: 0.01 to 0.52, $p = 0.009$). During this period, the ASO had higher in-hospital mortality than the atrial switch (21.6% versus 12.9%, $p = 0.007$). After excluding patients with in-hospital mortality, the transplant-free survival 20 years after repair was 97.7% for the ASO patients versus 86.3% for the atrial switch patients.**

Conclusions. **Despite initial higher in-hospital mortality for ASO during the study period, there is a significant long-term transplant-free survival advantage for ASO as compared with atrial switch for d-TGA surgery. Ongoing monitoring is required to assess late risk of cardiovascular disease.**

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Dextro-transposition of the great arteries (d-TGA) is the second most common cyanotic congenital heart defect, with an estimated annual incidence of 860 cases in the United States [1]. In 1960, the Mustard and Senning atrial switch procedures became the first corrective surgeries available for d-TGA [2, 3]. Although the atrial switch had good perioperative survival, complications of the repair were common [4].

In 1975, Jatene and colleagues [5] introduced the arterial switch operation (ASO), but their initial experience was notable for a high perioperative mortality (71%), much greater than the well-established atrial switch procedure [4, 6]. At this time some surgeons recommended ASO only for complex d-TGA, citing the potential unknown long-term complications of the ASO [7]. Others sought to perform the ASO in most cases of d-TGA despite poor initial results, anticipating improved results with increasing experience [8]. In 1990, with the improved perioperative ASO experience, the ASO superseded the atrial switch as the preferred corrective surgery for d-TGA [9, 10].

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Although the ASO has been shown to have better mid-term results, long-term results beyond the second decade of life are unknown for those undergoing the procedure in the United States [10–14]. Common ASO complications include neopulmonary stenosis and neoaortic dilation, which may impact long-term results [9]. In addition, reports of ASO follow-up show that coronary artery obstructions are found at a low persistent rate [11, 12, 15], but late deaths due to myocardial infarction and sudden cardiac death in ASO patients are rare [11, 16, 17]. Nevertheless, coronary lesions and other ASO complications underlie concerns about the long-term results of the operation. Our objective, therefore, was to compare the long-term transplant-free survival of patients with d-TGA between the ASO and atrial switch performed in the decade when the surgery preference transitioned.

Patients and Methods

Study Design

We performed a retrospective cohort study using data from the Pediatric Cardiac Care Consortium (PCCC), an international registry for interventions for pediatric heart diseases established in 1982 to allow collaboration between pediatric cardiovascular centers [18, 19]. Cardiovascular centers voluntarily participated in the PCCC, with 47 US centers participating from 1982 to 2011.

Patients were included in this study if they were US residents who had surgery for d-TGA with an ASO or an atrial switch (Mustard or Senning) during infancy at a PCCC center in the United States during the decade from 1982 to 1991, the period during which the transition from atrial to arterial switch type of correction for d-TGA took place in the United States. The Mustard and Senning procedures were considered together as the atrial switch group in the initial analyses, with supplemental analyses then performed considering these operations separately. Complex d-TGA was defined as d-TGA accompanied by any combination of ventricular septal defect, coarctation, native pulmonary outflow tract obstruction, or native systemic outflow tract obstruction. Simple d-TGA included patients with an atrial septal defect, patent ductus arteriosus, or no accompanying defects. Available PCCC forms were reviewed for the collection of variables such as cardiopulmonary bypass and cross-clamp times, as well as coronary artery anatomy. In-hospital deaths were defined as postoperative death during the admission for d-TGA repair. Among hospital survivors, those who had adequate identifiers (first name, middle initial [if available], last name, birth day, birth month, birth year, sex, and state of birth) were submitted to the National Death Index (NDI) and the Organ Procurement and Transplant Network [20]. Ascertainment of vital status and cause of death with NDI and transplant status with the Organ Procurement and Transplant Network was complete through December 31, 2014. The study was approved by the Institutional Review Board of Emory University.

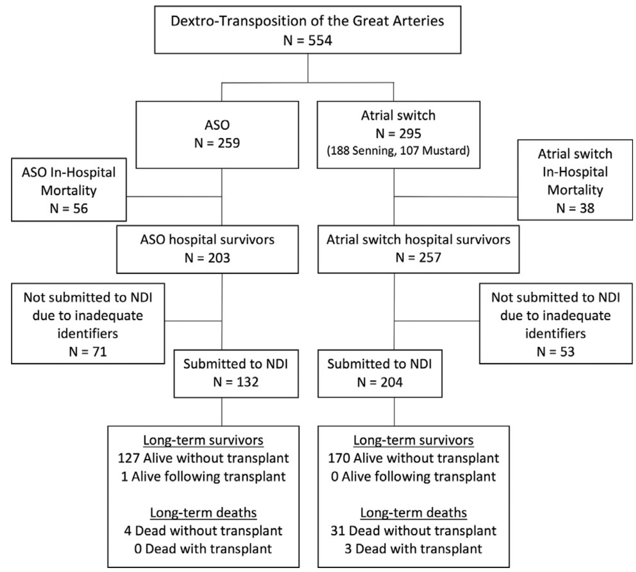

Fig 1. Patient inclusion diagram. (ASO = arterial switch operation; NDI = National Death Index.)

Statistical Methods

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC), and statistical significance was assessed at the 0.05 level, unless otherwise noted. Normality of continuous variables was assessed with histograms, normal probability plots, and the Anderson-Darling test for normality. Descriptive statistics are presented as counts and percentages for categoric variables, and median (25th to 75th percentile) for continuous data with skewed distributions. Continuous data were compared between surgical groups with the use of Wilcoxon rank sum tests and comparisons between categoric variables were performed with χ^2 tests, or Fisher's exact tests when the expected cell counts were less than 5. Unadjusted and adjusted in-hospital mortality was compared between surgical interventions using generalized linear mixed models (controlling for sex and transposition complexity and treating surgical center as a random effect). Kaplan-Meier survival plots were constructed to display long-term transplant-free survival data, with statistical comparisons performed using the log rank test. These plots were created for overall transplant-free survival and for long-term transplant-free survival, conditional on survival to hospital discharge after d-TGA repair.

Survival without transplant after d-TGA intervention was treated as a time-dependent outcome and analyzed using survival analysis methods. Before modeling, the proportional hazard assumption was assessed using log-log survival curves and by formally testing the interaction between time and d-TGA intervention group using an extended Cox model. For both overall and conditional long-term survival, the proportional hazard assumption was violated. As a result, we utilized Heaviside functions in the extended Cox model. When such a function is used, the hazard ratio (HR) formula

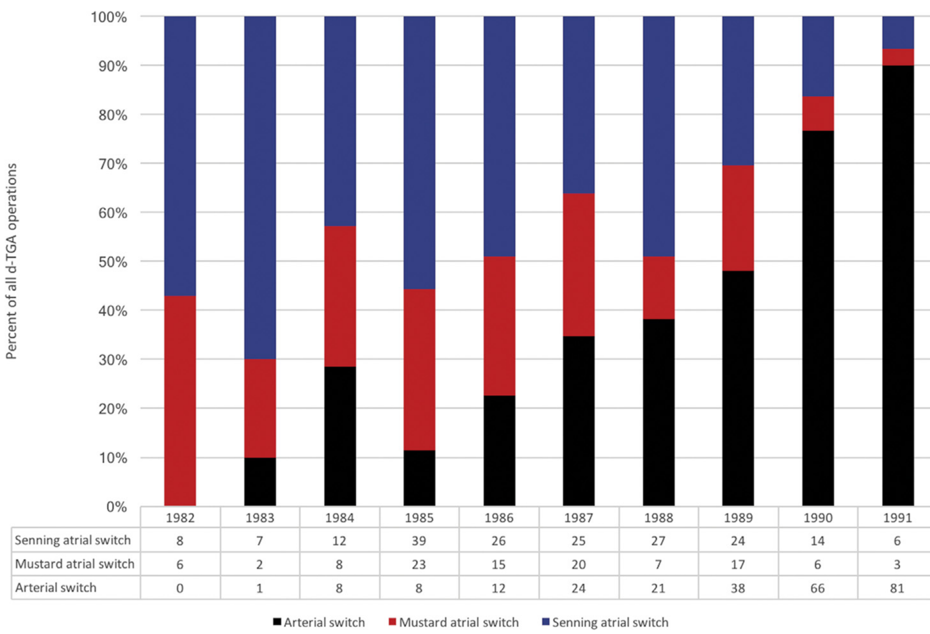

Fig 2. Operations for dextro-transposition of the great arteries (d-TGA) in the Pediatric Cardiac Care Consortium, expressed as percent of total d-TGA operations in the bar graph (arterial switch, black; Mustard atrial switch, red; Senning atrial switch, blue) as well as raw number of each operation.

Table 1. Characteristics of All Dextro-Transposition of the Great Arteries Patients (Including In-Hospital Deaths), Overall and Stratified by Operation

Characteristics	n	Overall (N = 554)	ASO (n = 259)	Atrial Switch (n = 295)	*p* Value
Sex	554				0.65
Female		157 (28.3)	71 (27.4)	86 (29.2)	
Male		397 (71.7)	188 (72.6)	209 (70.8)	
Genetic defect	554	2 (0.4)	0 (0)	2 (0.7)	0.50
Type of transposition	554				0.55
Simple d-TGA		394 (71.1)	181 (69.9)	213 (72.2)	
Complex d-TGA		160 (28.9)	78 (30.1)	82 (27.8)	
Accompanying defect	554				
VSD		151 (27.3)	76 (29.3)	75 (25.4)	0.30
Coarctation		16 (2.9)	10 (3.9)	6 (2)	0.20
ASD		115 (20.8)	65 (25.1)	50 (16.9)	0.02
Native POTO		13 (2.3)	2 (0.8)	11 (3.7)	0.02
Coronary anatomy	116				0.43
Usual		97 (83.6)	57 (81.4)	40 (87)	
Abnormal		19 (16.4)	13 (18.6)	6 (13)	
Prior balloon atrial septostomy	554	347 (62.6)	129 (49.8)	218 (73.9)	<0.001
Birth weight, kg	531	3.4 (3–3.8)	3.4 (3.1–3.7)	3.3 (2.9–3.8)	0.009
Age at index operation, days	554	72 (7–177)	7 (4–12)	167 (97–215)	<0.001
Weight at TGA operation, kg	489	4.2 (3.5–6.1)	3.6 (3.2–3.9)	6.0 (4.9–7.1)	<0.001
CPB time, minutes	90	117 (85–152)	123 (80–150)	106 (88–180)	0.35
Cross-clamp time, minutes	84	66 (56–87)	67 (56–86)	62 (52–94)	0.97
Median follow-up, years	394	25.2 (23.3–27.5)	24.3 (23.3–25.6)	26.5 (23.4–28.7)	<0.001

Values are n (%) or median (interquartile range, 25th to 75th percentiles). Continuous variables are compared using Wilcoxon rank sum tests, and categoric variables using χ^2 tests or Fisher's exact test if expected cell count less than 5.

ASD = atrial septal defect; ASO = arterial switch operation; CPB = cardiopulmonary bypass; d-TGA = dextro-transposition of the great arteries; POTO = pulmonary outflow tract obstruction; VSD = ventricular septal defect.

yields constant HR for different time intervals. Our intervals were chosen so that (1) an event occurred in both groups so that the hazard ratio was estimable; and (2) the hazard function was relatively stable within each window of time. Stability of the hazard function was assessed using kernel smoothed hazard plots with bandwidth of 2 years. The date of intervention was used as our starting point, and the effects of ASO intervention on the probability of survival in the models are given as HR with 95% confidence interval (CI), unadjusted and adjusted.

Results

Baseline Characteristics

There were 554 patients with d-TGA who met the study inclusion criteria. Among those, 259 patients underwent surgical correction with ASO and had a median follow-up time of 24.3 years; there were 295 patients with atrial switch and a median follow-up time of 26.5 years. The Senning procedure accounted for 63.7% (n = 188) of all atrial switch procedures. There were 460 patients discharged alive after surgical correction, and 336 of the hospital survivors (73.0%) had sufficient identifiers to be submitted to NDI. The patient flow diagram is depicted in Figure 1. The number of ASO performed each year increased until 1990 when the ASO outpaced the atrial switch (Fig 2).

The characteristics of all d-TGA patients are shown in Table 1. There were no differences between the two groups with regards to sex, anatomic complexity, or presence of an accompanying ventricular septal defect or coarctation. Those who underwent ASO were more likely to have an atrial septal defect and less likely to have pulmonary outflow tract obstruction. Of the 116 total patients who had documented coronary artery anatomy, atypical coronary anatomy was present in a similar percentage of ASO and atrial switch patients (18.6% versus 13.0%, $p = 0.43$). Not surprisingly, given the nature and timing of the two operations, age and weight at index operation were both lower among patients who underwent ASO compared with patients undergoing atrial switch (7 days versus 167 days, respectively, $p < 0.001$; and 3.6 kg versus 6.0 kg, respectively, $p < 0.001$); patients undergoing ASO were less likely to have had prior balloon atrial septostomy than patients undergoing atrial switch (49.8% versus 73.9%, respectively, $p < 0.0001$). Patient characteristics stratified by hospital discharge status are shown in Table 2. Hospital survivors were less likely to have an accompanying ventricular septal defect (24.6% versus 40.4%, $p = 0.002$) or an additional cardiac lesion (complex d-TGA) than patients who died before

Table 2. Characteristics of All Dextro-Transposition of the Great Arteries Patients Stratified by Hospital Discharge Status

Characteristics	n	Hospital Survivors (n = 460)	In-Hospital Deaths (n = 94)	*p* Value
Index operation	554			0.006
Arterial switch operation		203 (44.1)	56 (59.6)	
Atrial switch operation		247 (55.9)	38 (40.4)	
Sex	554			0.34
Female		127 (27.6)	30 (31.9)	
Male		333 (72.4)	64 (68.1)	
Genetic defect	554	1 (0.2)	1 (1.1)	0.31
Type of transposition	554			0.003
Simple d-TGA		339 (73.7)	55 (58.5)	
Complex d-TGA		121 (26.3)	39 (41.5)	
Accompanying defect	554			
VSD		113 (24.6)	38 (40.4)	0.002
Coarctation		13 (2.8)	3 (3.2)	0.74
ASD		90 (19.6)	25 (26.6)	0.13
POTO		13 (2.8)	0 (0)	0.14
Coronary anatomy	116			0.36
Usual		74 (81.3)	23 (92)	
Abnormal		17 (18.7)	2 (8)	
Prior balloon atrial septostomy	554	297 (64.6)	50 (53.2)	0.04
Birth weight, kg	531	3.4 (3–3.8)	3.3 (3–3.7)	0.92
Age at index operation, days	554	83 (7–182)	21 (5–134)	0.02
Weight at TGA operation, kg	489	4.5 (3.6–6.3)	3.8 (3.2–5.2)	0.001
CPB time, minutes	90	123 (86–152)	86 (78–146)	0.28
Cross-clamp time, minutes	84	65 (57–88)	67 (43–86)	0.42

Values are n (%) or median (interquartile range, 25th to 75th percentiles). Continuous variables are compared using Wilcoxon rank sum tests, and categoric variables using χ^2 tests or Fisher's exact test if expected cell count less than 5.

ASD = atrial septal defect; CPB = cardiopulmonary bypass; d-TGA = dextro-transposition of the great arteries; POTO = pulmonary outflow tract obstruction; VSD = ventricular septal defect.

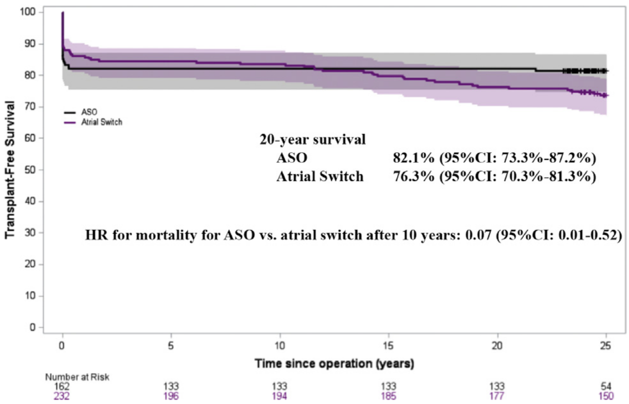

Fig 3. Kaplan-Meier curves for overall transplant-free survival of patients with detro-transposition of the great arteries are shown by operation group: arterial switch operation (ASO [black line]) or atrial switch (purple line). For the period after 10 years, mortality hazard ratio (HR) for ASO versus atrial switch is displayed, adjusted for sex, transposition complexity, and surgical center. (CI = confidence interval.)

discharge (26.3% versus 40.4%, $p = 0.003$). Sex, coronary anatomy, cardiopulmonary bypass time, or cross-clamp time were not significantly different between hospital survivors and patients who died in-hospital. Demographic information stratified by hospital discharge status for each specific surgical group is shown in Supplemental Tables 1 and 2.

Overall Survival

As shown in Figure 3, the 20-year overall transplant-free survival for children who had surgery for d-TGA was 82.1% for those undergoing ASO and 76.3% for those who had atrial switch procedure (log rank $p = 0.14$). Given that the hazard of transplant/mortality changed over time, we determined time intervals where the hazard was proportional to establish mortality HR (Table 3). Overall transplant-free survival was initially similar between the two surgical groups, but 10 years after d-TGA repair, the ASO had better long-term transplant-free survival as compared with the atrial switch (adjusted mortality HR 0.07, 95% CI: 0.01 to 0.52, $p = 0.009$).

In comparing the overall transplant-free survival by type of atrial switch, patients who underwent Mustard and Senning atrial switch procedures had similar long-term results. There was an initial difference in early mortality, with Mustard having a lower hazard of transplant/mortality within the first month after the operation (adjusted mortality HR 0.27, 95% CI: 0.09 to 0.81, $p = 0.02$). Beyond this early period, there was no difference in overall transplant-free survival, with both atrial switch procedure groups experiencing a steady survival decline (Supplemental Fig 1, Supplemental Table 3).

Conditional Survival

Much of the mortality in this population was in-hospital mortality. For the ASO, in-hospital mortality was 21.6%; for the atrial switch, it was 12.9% (odds ratio 1.87, 95% CI: 1.19 to 2.93, $p = 0.007$). Among patients who survived to hospital discharge, 20-year transplant-free survival was 97.7% for those with ASO and 86.3% for those with atrial switch, as shown in Figure 4 ($p < 0.001$). Again, time intervals were established where the hazard of transplant/mortality remained proportional (Table 4). Within the first 10 years after the operation there was no significant difference between the transplant-free conditional survival of the two surgical groups. Beyond 10 years, however, the advantage of the ASO became clear, with an adjusted mortality HR of 0.07 (95% CI: 0.01 to 0.52, $p = 0.009$).

In examining the atrial switch outcomes by subtype, patients with a Senning operation had significantly higher in-hospital mortality than patients with a Mustard (16.5% versus 6.5%, odds ratio 2.82, 95% CI: 1.19 to 6.67, $p = 0.02$). Among survivors of these initial operations, patients had similar long-term outcomes, with transplant-free survival at 20 years of 87.6% for those with a Senning and 84.0% for those with a Mustard ($p = 0.99$; Supplemental Fig 2). When comparing the conditional survival of the ASO with each individual atrial switch procedure, the results were similar (Supplemental Table 4).

Cause of Death

There were 38 late deaths in our cohort, with 4 occurring in ASO patients and 34 in atrial switch patients (Table 5). The vast majority of these deaths (66%) were noted to have cardiac etiology. The low numbers of late deaths in the ASO group prohibited any cause of death comparisons between the two groups.

Comment

In this study, the largest of its kind comparing surgical techniques in d-TGA patients with at least 20 years of

Table 3. Effect of Treatment Strategy on Overall Survival of Dextro-Transposition of the Great Arteries Patients During Periods After Surgical Correction That Have Proportional Hazards

Period After Surgical Correction	Unadjusted Mortality HR (95% CI)	*p* Value	Adjusted Mortality HR (95% CI)[a]	*p* Value
ASO versus atrial switch				
Between 0 and 1 month	1.39 (0.81–2.37)	0.23	1.62 (0.93–2.85)	0.10
Between 1 month and 10 years	0.45 (0.12–1.64)	0.23	0.52 (0.14–1.90)	0.32
After 10 years	0.06 (0.01–0.46)	0.007	0.07 (0.01–0.52)	0.009

[a] Adjusted for sex, transposition complexity, and surgical center.

ASO = arterial switch operation; CI = confidence interval; HR = hazard ratio.

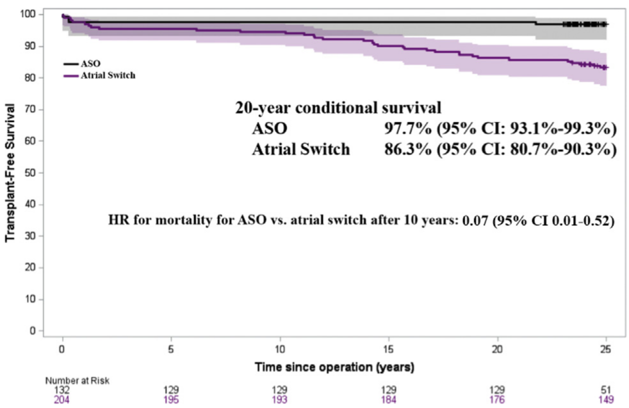

Fig 4. Kaplan-Meier survival curves for transplant-free survival of patients with d-transposition of the great arteries are shown by operation group—arterial switch operation (ASO [black line]) or atrial switch (purple line)—conditional on survival to hospital discharge after initial operation. For the period after 10 years, mortality hazard ratio (HR) of ASO versus (vs.) atrial switch is displayed, adjusted for sex, transposition complexity, and surgical center. (CI = confidence interval.)

follow-up, we found that long-term transplant-free survival among patients with d-TGA was superior in patients who received an ASO as compared with an atrial switch. This finding was true both with and without consideration of the in-hospital mortality associated with the initial operation. Prior survival modeling of the two groups of operations using mortality parameters from this era predicted that the overall survival curves would intersect at approximately 30 years, beyond which ASO survival would be superior [21]. Our study reveals that this cross-over point actually took place around 10 years after the operation in the transitional era between the two procedures in the United States. Our results are consistent with many other studies of smaller size or shorter duration of follow-up [10–14, 16].

In the current era of the ASO, with extremely low in-hospital mortality, the 20-year survival of d-TGA patients likely approximates the greater than 97% 20-year survival of the ASO hospital survivors shown here. The ASO is clearly the better long-term strategy, but in the 1980s that outcome was not a certainty. The delay between the first successful ASO and its widespread use was primarily due to the concern for the high in-hospital mortality of the operation. The ASO results improved throughout the 1980s with the advent of the Lecompte maneuver, the neonatal ASO, and improvements in coronary implantation techniques [22]. Our study shows the gradual transition in d-TGA repair preference throughout the decade. More than half of the ASOs that were included in this study occurred in 1990 and 1991. However, despite the surgical innovations, our results reveal that during this period the ASO, compared with atrial switch, remained a risk factor for early mortality. Greater than 20% of patients who underwent an ASO were not discharged from the hospital alive. This in-hospital mortality for the ASO is slightly higher than other reports from the same era [11, 13]. In the current era, in-hospital mortality after ASO is considered a rare event. Villafañe and colleagues [9] reported that the in-hospital mortality after ASO in the PCCC was only 2.9% from 2003 to 2007, similar to other present day reports that are consistently below 5% [11, 13].

There are many factors which may contribute to the increased long-term mortality among the atrial switch cohort. The atrial baffles diverting venous inflow to the contralateral ventricle in the atrial switch procedure are prone to baffle leaks and obstructions. In addition, the process of atrial reconstruction predisposes these patients to atrial arrhythmias. Finally, the systemic right ventricular function deteriorates over time, also leading to tricuspid regurgitation [23]. These complications give rise to a high rate of reinterventions [4]. Our study agrees with prior estimates of overall long-term survival in atrial switch patients, with approximately 70% to 80% remaining alive 25 years after their operation [23]. Despite the difference in in-hospital mortality between the Senning and Mustard procedures, patients undergoing these operations in our study had similar overall survival to beyond 20 years.

Our study has several limitations in addition to those inherent to a retrospective cohort study. First, a proportion of hospital survivors did not contain adequate identifiers to be submitted to the NDI. Our previous work with this linked registry demonstrated that younger patients were less likely to have adequate identifiers [20]. This limitation did not affect our ability to detect a difference in transplant-free survival, but it may have prohibited us from comparing causes of death. Second, in 1990 there was a rapid shift from the atrial switch to the ASO, a shift that resulted in more than half of the ASO group occurring in the last 2 years of our study. This timeframe somewhat limits our ability to compare exactly contemporaneous outcomes between groups.

Table 4. Effect of Treatment Strategy on Long-Term Mortality Among Dextro-Transposition of the Great Arteries Hospital Survivors During Periods After Surgical Correction That Have Proportional Hazards

Period After Surgical Correction	Unadjusted Mortality HR (95% CI)	*p* Value	Adjusted Mortality HR (95% CI)[a]	*p* Value
ASO versus atrial switch				
Between 0 and 10 years	0.42 (0.12–1.51)	0.18	0.47 (0.13–1.71)	0.25
After 10 years	0.06 (0.01–0.47)	0.007	0.07 (0.01–0.52)	0.009

[a] Adjusted for sex, transposition complexity, and surgical center.

ASO = arterial switch operation; CI = confidence interval; HR = hazard ratio.

Table 5. Late Causes of Death Among Dextro-Transposition of the Great Arteries Hospital Survivors Stratified by Surgical Operation

Cause of Death	Overall	ASO	Atrial Switch
Cardiac failure/CHD related	25	2	23
Sepsis	2	0	2
Multiple system organ failure	1	0	1
Pulmonary hypertension	1	0	1
Pneumonia/other respiratory	3	1	2
Neurologic	1	0	1
External cause of injury	4	1	3
Unknown	1	0	1

ASO = arterial switch operation; CHD = congenital heart defect.

Third, there was limited data collection or ascertainment for some of our variables of interest such as coronary artery anatomy. However, we believe that this is unlikely to have affected our overall results as this potential misclassification would have been equally distributed between the two groups. Finally, the PCCC database does not collect information regarding long-term complications. Therefore, we cannot assess whether there are differences in complications between the surgical groups other than mortality or transplant. Nevertheless, our study describes the late survival of a large nationally representative cohort of d-TGA patients who underwent surgery when the superiority of the ASO was uncertain.

Our study shows that among d-TGA patients, the survival into the third decade of life of those who underwent ASO is superior to that of atrial switch patients. That is particularly true among patients who survived to discharge after the initial hospitalization. In the current era of the operation with low ASO perioperative mortality, the overall ASO survival to 20 years of age likely closely approximates the greater than 97% 20-year survival of ASO hospital survivors reported here. As patients with ASO age and are exposed to the cardiovascular complications of aging, future efforts should be directed at continued surveillance of this cohort for coronary artery disease and sudden cardiac death.

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