Redefining Expectations of Long-Term Survival After the Fontan Procedure
Twenty-Five Years of Follow-Up From the Entire Population of Australia and New Zealand

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Background—The life expectancy of patients undergoing a Fontan procedure is unknown.

Methods and Results—Follow-up of all 1006 survivors of the 1089 patients who underwent a Fontan procedure in Australia and New Zealand was obtained from a binational population-based registry including all pediatric and adult cardiac centers. There were 203 atriopulmonary connections (AP; 1975–1995), 271 lateral tunnels (1988–2006), and 532 extracardiac conduits (1997–2010). The proportion with hypoplastic left heart syndrome increased from 1/173 (1%) before 1990 to 80/500 (16%) after 2000. Survival at 10 years was 89% (84%–93%) for AP and 97% (95% confidence interval [CI], 94%–99%) for lateral tunnels and extracardiac conduits. The longest survival estimate was 76% (95% CI, 67%–82%) at 25 years for AP. AP independently predicted worse survival compared with extracardiac conduits (hazard ratio, 6.2; P<0.001; 95% CI, 2.4–16.0). Freedom from failure (death, transplantation, takedown, conversion to extracardiac conduits, New York Heart Association III/IV, or protein-losing enteropathy/plastic bronchitis) 20 years after Fontan was 70% (95% CI, 63%–76%). Hypoplastic left heart syndrome was the primary predictor of Fontan failure (hazard ratio, 3.8; P<0.001; 95% CI, 2.0–7.1). Ten-year freedom from failure was 79% (95% CI, 61%–89%) for hypoplastic left heart syndrome versus 92% (95% CI, 87%–95%) for other morphologies.

Conclusions—The long-term survival of the Australia and New Zealand Fontan population is excellent. Patients with an AP Fontan experience survival of 76% at 25 years. Technical modifications have further improved survival. Patients with hypoplastic left heart syndrome are at higher risk of failure. Large, comprehensive registries such as this will further improve our understanding of late outcomes after the Fontan procedure. (Circulation. 2014;130[suppl 1]S32-S38.)

Key Words: congenital ■ follow-up studies ■ Fontan procedure ■ survival

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Presented at the 2013 American Heart Association meeting in Dallas, TX, November 16–20, 2013.

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.007764
The Fontan procedure has been performed for >40 years, and we are still unclear of the long-term survival of those undergoing this procedure because the only available contemporary data on this topic are limited to small single-center series compromised by small numbers and referral bias.\(^1\) Twenty-year survival estimates have only been delineated for the atrio pulmonary connection (AP), and it is likely that some of these reported poor outcomes have misrepresented the longevity of those treated with more recent surgical strategies.\(^4\)\(^5\)

To clarify these late outcomes, we created the Australia and New Zealand Fontan Registry, which collects health data of all Fontan patients prospectively. During the establishment of the Registry, we collected all clinical data available for all patients who underwent the Fontan operation in Australia and New Zealand. This study describes the long-term outcomes after Fontan surgery in the entire population of both countries and analyzes their risk factors for adverse events.

Methods

The Australia and New Zealand Fontan Registry, created in 2008, includes patients who had their Fontan procedure in either country, as well as patients who had their Fontan procedure overseas who are followed within the region. In 2008 and 2013, all follow-up data were obtained from all hospital databases and private cardiology practices. Ethics approval was granted nationally in Australia and New Zealand and by the institutional review board of participating institutions. Consent to participate in the Registry was obtained prospectively in all patients undergoing the Fontan procedure after 2008 and retrospectively for all remaining patients, including those who did not survive or who required heart transplantation. After 2010, patients undergoing Fontan surgery were enrolled on an opt-out basis. The organization and the governance of the Fontan Registry are described elsewhere.\(^6\)

All 8 pediatric and 7 adult centers overseeing the care of patients with congenital heart disease in Australia and New Zealand participated in the study. Follow-up data were extracted from copies of clinical summaries detailing hospital discharge and outpatient clinic attendances. Patients are reminded to contact their physician after 18 months have elapsed without a visit. At the time of the study, 870 patients were consented, and consent was still being sought for an additional 319 patients. Data for the current analysis were extracted from the Registry for the consented patients and from an audit of the national health information database. A total of 1089 Fontan operations excluding Bjork procedures were recorded between 1975 and 2010. Patients were excluded if they were referred from overseas (27 patients), had early Fontan takedown (defined as takedown during the same hospital stay as the Fontan procedure, 20 patients), or died in hospital (36 patients). The analysis of their early outcomes is published elsewhere.\(^1\)

The 1006 patients surviving to hospital discharge with a Fontan procedure constitute the cohort of this study. There was no follow-up information available in 40 patients (4%). Of the 1006 hospital survivors, 203 had an AP (1975–1995), 271 a lateral tunnel (LT; 1988–2006), and 532 an extracardiac conduit (ECC; 1997–2010). The characteristics of the patients are given in Table 1.

**Definitions**

Hospital mortality was defined as death within 30 days of the procedure or before hospital discharge. Prolonged effusions were defined as effusions lasting for >30 days or requiring reoperation. Fontan failure was defined as death, heart transplantation, Fontan takedown or conversion, protein-losing enteropathy, plastic bronchitis, or New York Heart Association functional class III or IV at follow-up. Thromboembolic events were defined as thrombus within the Fontan circuit, pulmonary embolism, transient ischemic attack/reversible neurological deficit (lasting 1–72 hours), or persistent stroke (lasting >72 hours). Adverse events were defined as failure, sustained episode of supraventricular tachycardia (SVT) including atrial fibrillation and flutter, stroke, or thromboembolism, and requirement for a pacemaker after hospital discharge.

**Statistical Analysis**

The end points examined for the 1006 hospital survivors were death, Fontan failure, occurrence of first adverse event, first SVT, and first instance of protein-losing enteropathy/plastic bronchitis. For the Fontan failure and first adverse event end points, a patient’s experience was censored in the event of death, heart transplantation, or the end of follow-up (occurring before failure or a first adverse event, respectively). For the remaining 3 nonmortality end points, a patient’s experience was censored in the event of death, heart transplantation, Fontan failure, or end of follow-up. Survival and freedom from each of the nonmortality end points were examined using Kaplan–Meier analysis, and risk factors were examined using Cox regression analysis. Equality of survivorship functions was tested using a log-rank test. Testing of the proportional hazards assumption was based on Schoenfeld residuals. The factors analyzed are those listed in Table 1, together with length of hospital stay after Fontan completion (on a log scale), the presence of prolonged effusions, Fontan failure, and the requirement for a pacemaker, each before hospital discharge. Because of the nonlinear relationship of age at Fontan with risk of outcomes, for analysis the data were divided into quartiles (ie, 4 equal-sized groups) according to age at Fontan <3 years, 3 to 5 years, 5 to 7 years, and >7 years, with 3 to 5 years as reference group. For the same reasons, oxygen saturation before Fontan was handled by dividing the data into quartiles according to oxygen saturation <77%, 78% to 81%, 82% to 85%, and >86%, with comparisons made with respect to the 82% to 85% group, and hospital length of stay by dividing the data into tertiles according to length of stay <12 days, 12 to 18 days, and >18 days. Factors with large effect size (eg, hazard ratio [HR] of ≥2 and HR of ≤0.5) and moderate or greater evidence against the null hypothesis (P<0.05) under univariable modeling were considered for inclusion in the multivariable model. Factors with small effect size and weak evidence against the null hypothesis after initial multivariable modeling were subsequently dropped. For the protein-losing enteropathy end point, because of the smaller number of events (32), only the 3 factors most likely to be associated with the end point were included in the initial multivariable model. All covariates in the final models were complete, except for hospital length of stay (13% missing) and pre-Fontan collaterals (24% missing). All analyses were performed on complete cases only. Because fenestration and staging with bidirectional cavopulmonary shunt were only initiated after the introduction of the LT, the effects of these 2 factors could only be assessed on the subgroup of patients who had either a LT or ECC Fontan. Therefore, to assess their effects in relation to other factors, we repeated the entire risk analysis with the atrio pulmonary Fontan subgroup excluded. Data analysis was performed using Stata 11 (Statacorp, College Station, TX).

**Results**

The growth of the Fontan population and its distribution between the 3 types of Fontan techniques are displayed in Figure 1. A median of 34 new Fontan survivors was added to the population of the countries every year, increasing from 31 (between 1985 and 1989) to 49 (between 2005 and 2009). From 2007, the ECC was the sole method of Fontan completion used in Australia and New Zealand. The proportion with hypoplastic left heart syndrome increased from 1/173 (1%) before 1990 to 80/500 (16%) after 2000.
Survival

A total of 55 patients died during follow-up: 37 AP, 12 LT, and 6 ECC. Three of 16 transplanted patients died, one perioperatively and the others after 8 and 15 years. Four of the 7 patients who underwent a late Fontan takedown died. Kaplan–Meier overall estimates of survival at 15, 20, and 25 years were 93% (95% CI, 90%–95%), 90% (95% CI, 86%–93%), and 83% (95% CI, 75%–89%), respectively. Independent predictors of mortality are listed in Table 2. Survival after each type of Fontan is displayed in Figure 2. For each longest estimate,
survival was 76% (95% CI, 67%–83%) at 25 years for AP, 90% (95% CI, 81%–95%) at 20 years for LT, and 97% (95% CI, 94%–99%) at 13 years for ECC. Sixteen patients ultimately underwent an orthotopic heart transplantation (4 AP, 3 LT, and 9 ECC) after a median of 4.8 years (interquartile range [IQR], 2.7–8.4 years). One patient underwent transplantation 1 year after Fontan conversion.

Seven patients underwent Fontan takedown late after hospital discharge after a median of 1.2 years (0.4–9.2). Mortality despite late Fontan takedown was 57% (4/7 patients) and occurred 1 day, 4 days, 15 years, and 18 years after take-down. Thirty-one patients underwent a reoperation to convert an atriopulmonary (26 patients) or a LT (5 patients) Fontan into an ECC. Two patients died in hospital after this procedure (6.5%), and 3 patients died 4, 10, and 11 months after the procedure.

Dysrhythmia

A total of 94 patients ultimately required a pacemaker implantation: 9 before Fontan surgery, 35 during the same hospital stay as the Fontan surgery (11 ECC, 6 LT, 9 AP), and 59 a median of 6.0 years (IQR, 3.1–12.1 years) after the Fontan surgery (0 ECC, 30 LT, 33 AP). Sustained episodes of SVT were reported in 100 patients. Predictors of SVT were atrial isomerism (HR, 2.4, 95% CI, 1.1–5.0) and atriopulmonary and LT Fontan compared with the ECC (HR, 10.7; 95% CI, 4.5–25.6 and HR, 3.1; 95% CI, 1.2–7.8 respectively; Table 2). Freedom from SVT according to Fontan type is presented in Figure 3.

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Thromboembolic Events

Thromboembolic events occurred in 56 patients at a median of 7.6 years (IQR, 1.9–14.0 years) after Fontan, consisting of stroke/transient ischemic attack in 22, thrombus within
the Fontan conduit or AP in 19, pulmonary embolism in 10, non–line-related central vein thrombosis in 3, and other in 3. Overall freedom from thromboembolic events was 82% at 25 years (95% CI, 74%–87%).

**Fontan Failure**
Failure of the Fontan circulation occurred in 122 patients. The first failure event was New York Heart Association class III/IV in 11 patients, protein-losing enteropathy/plastic bronchitis in 15, conversion to ECC in 31, takedown in 7, transplant in 16, and death in 42. Freedom from failure at 15, 20, and 25 years was, respectively, 83% (95% CI, 79%–86%), 70% (95% CI, 63%–76%), and 56% (95% CI, 44%–66%). By multivariable analysis, having hypoplastic left heart syndrome predicted Fontan failure (HR=3.8 compared with LV; 95% CI, 2.0–7.1). Ten-year freedom from failure was 79% (95% CI, 61%–89%) for patients with hypoplastic left heart syndrome versus 92% (95% CI, 90%–94%) for patients with other morphologies (Table 2; Figure 4).

**Late Adverse Events**
Late adverse events (failure, SVT, thromboembolism, or pacemaker) occurred in a total of 308 patients. The 15, 20, and 25 years of freedom from the occurrence of adverse events were, respectively, 59% (95% CI, 54%–63%), 34% (95% CI, 27%–41%), and 29% (95% CI, 21%–37%; Figure 5). Risk factors predicting the late occurrence of adverse events are listed in Table 2. Having an arch intervention (excluding Norwood procedure) before or at Fontan completion predicted late occurrence of adverse events (HR, 1.7; P=0.005; 95% CI, 1.2–2.4; Figure 6). On a logarithmic scale, having a prolonged hospital stay at the time of the Fontan surgery was predictive of both Fontan failure and occurrence of adverse events (HR, 2.2; P<0.001; 95% CI, 1.6–2.8 and HR, 1.7; P<0.001; 95% CI, 1.3–2.1 respectively) with >18 days representing the top tertile of patients with regard to hospital length of stay (Figure 7).

In a multivariable analysis of the risk factors predicting late mortality, Fontan failure, and occurrence of late adverse events in the population of patients who underwent the LT or the extracardiac procedure, no additional independent predictors were identified. Fenestration and staging with bidirectional cavopulmonary shunt were not predictors of these end points even by univariable analysis.

**Analysis of Patients With Incomplete Data**
There were 5 (4%) late deaths among patients excluded from the multivariable analysis of mortality because of missing values. The 25 years of freedom from the occurrence of adverse events were, respectively, 59% (95% CI, 54%–63%), 34% (95% CI, 27%–41%), and 29% (95% CI, 21%–37%; Figure 5). Risk factors predicting the late occurrence of adverse events are listed in Table 2. Having an arch intervention (excluding Norwood procedure) before or at Fontan completion predicted late occurrence of adverse events (HR, 1.7; P=0.005; 95% CI, 1.2–2.4; Figure 6). On a logarithmic scale, having a prolonged hospital stay at the time of the Fontan surgery was predictive of both Fontan failure and occurrence of adverse events (HR, 2.2; P<0.001; 95% CI, 1.6–2.8 and HR, 1.7; P<0.001; 95% CI, 1.3–2.1 respectively) with >18 days representing the top tertile of patients with regard to hospital length of stay (Figure 7).

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hospital length of stay compared with 50 (6%) late deaths among the included patients. Excluded patients had similar distributions to included patients for sex (42% women in both groups), prolonged pleural effusions (7% versus 2%), and age at Fontan (median [IQR], 4.7 [3.7–7.6] versus 4.6 [3.4–6.2]). Excluded patients had a larger proportion of LT Fontan (51%) and a lower proportion of ECC Fontan (19%) patients compared with included patients (23% LT and 58% ECC). However, as Figure 2 illustrates, survival experience for these 2 subgroups was similar. There were 9 (7%) late failures among patients excluded from the multivariable analysis of late failure because of missing hospital length of stay compared with 113 (13%) late failures among the included patients. Excluded patients had similar distributions to included patients for hypoplastic left heart syndrome (9% versus 5%) and for sex and age at Fontan (as reported for late deaths above).

There were 122 (37%) first late adverse events among patients excluded from the multivariable analysis of late adverse event compared with 186 (28%) among the included patients. Distributions of key complete covariates for excluded patients compared with included patients were sex (43% versus 42%), age at Fontan (median=4.8; IQR [3.3–7.6] versus 4.6 [3.5–6.0]), hypoplastic left heart syndrome (3% versus 11%), arch intervention (12% versus 29%), and early pacemaker (3% versus 2%). Although excluded patients had a smaller proportions of patients with hypoplastic left heart syndrome and patients had an arch intervention up to the time of Fontan, an examination of the freedom from adverse event curves for the 2 groups indicated that ≤20 years after Fontan, the 2 curves were almost identical, with some divergence occurring beyond 20 years (log-rank P=0.82).

Discussion

The survival of our population-based group of patients who had undergone a Fontan procedure are excellent by current standards: even the survival of the patients who had undergone the first form of Fontan surgery, the AP, was 76% at 25 years. In a historical study by Francis Fontan, 20-year survival of these patients had been predicted to be limited to 65% in the best candidates. Our longest follow-up for the recent forms of the Fontan operation, the LT and the ECC, was 20 years and 13 years, respectively. The population of patients who had undergone an AP still seems to be subjected to a continuous attrition, but in the time frame of the study there seemed to be no such trend for those who underwent an LT or an extracardiac Fontan.

In the time frame of this study, heart transplantation has not yet become the ultimate solution that is often forecast for these patients, with only 2% of this population reaching this status. It is likely that this small proportion of patients underestimates the number of potential candidates for heart transplantation after Fontan surgery. In this historical review, some patients would have undoubtedly died before being considered appropriate candidates and some would have died only after having been directed to Fontan conversion. As our understanding of failure of the Fontan circulation improves, it is possible that we will see an increase in the proportion of Fontan patients requiring transplantation.

There may be several reasons explaining the excellent survival noted in our region. Fontan surgery was offered only in a relatively late era in Australia and New Zealand, at a time when contraindications for Fontan might have been better delineated. Patient selection is likely the single most important determinant of improved late outcomes after Fontan surgery, and the quality of our results is likely a reflection of our selection process. It is only recently that newborns with hypoplastic left heart syndrome have survived to the point of being eligible for a Fontan procedure in our region, as reflected by their small proportion in our series. We have not yet been able to show that patients with hypoplastic left heart syndrome have worse long-term survival, but we demonstrated that they were at greater risk of failure, and it is therefore likely that their long-term survival will ultimately be affected.

Patients after Fontan surgery may benefit from excellent survival, but close to half of them experience a major adverse event in the 15 years after this surgery, underlining the considerable burden of single-ventricle conditions. Clearly, patients staying longer in hospital with prolonged effusions after Fontan surgery are those who had worse late outcomes. One third of our patients stayed for >18 days in hospital, and for these patients the hazard of late adverse outcomes was greater. Patients requiring arch interventions also had worse outcomes. Reduced aortic distensibility and deficiency in ventricular arterial coupling in single-ventricle patients may partly explain this finding. One could also suspect that a low threshold for arch reintervention should
be applied in patients with single ventricles. It was surprising to note that common atrioventricular morphology did not predict any adverse outcome and one could wonder whether this fact is not a consequence of a progressively more aggressive management of atrioventricular valve regurgitation.

Interestingly, the study also showed that patients who underwent the ECC had significantly less risk of experiencing sustained episodes of SVT, although the difference observed was relatively small.

The finding that survival after Fontan surgery may be better than expected may have several implications for our practice. Better outcomes after single-ventricle palliation may influence decisions for patients who are potential candidates for high-risk biventricular repair. Patients with a Fontan circulation are functioning close to their reserve capacity: they have a decreased cardiac output and increased systemic vascular resistances, and there is growing evidence that their chronically elevated central venous pressures may lead to liver and renal dysfunction.\(^1\)\(^{-14}\) If we expect these patients to survive \(\geq 3\) decades, it should become our priority to optimize all aspects of their circulation before and after the Fontan completion even at the cost of additional procedures.

**Limitations and Strengths**

Some parameters, in particular pre-Fontan pressures obtained by catheterization and some procedural data such as cardiopulmonary bypass time, may not have been adequately analyzed because too many of these data were missing from the files of our older patients. The entry point in this study was survival from the Fontan procedure, and accordingly, the selection process that may have affected their long-term outcomes was not evaluated. We cannot eliminate the possibility that some rare deaths occurring overseas may not have been reported to us. Follow-up outcomes were limited to clinical events reported. The data reported gain strength because they report the entire population of 2 countries, thereby eliminating any selection bias. The quality of the data was enhanced by the creation of the Fontan Registry.

**Conclusions**

In conclusion, the long-term survival of the Australia and New Zealand Fontan population is excellent. Patients with an AP Fontan palliation.

**Sources of Funding**

Dr d’Udekem is a Career Development Fellow of The National Heart Foundation of Australia (CR 10M 5339). The Australia and New Zealand Fontan Registry is funded by grants from the National Heart and Medical Research Council (NHMRC; Project Grants 1012241, 1047923, 1065794), HeartKids, and the Australian and New Zealand (ANZ) Bank Trustees. Dr Iyengar has received postgraduate awards from the Royal Australasian College of Surgeons (Catherine Marie Enright Kelly and Eric Bishop Scholarships) and the NHMRC and The National Heart Foundation of Australia (1038802). The authors acknowledge support provided to the Murdoch Childrens Research Institute by the Victorian Government’s Operational Infrastructure Support Program.

**Disclosures**

None.

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**Acknowledgments**

We thank our research assistants, Ingrid King, Dr Aneta Kotevski, Janina Chapman, Gabriela Abrahamsson, Megan Upjohn, and Lisa Cowcher for their invaluable assistance in the creation and maintenance of the Registry.
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_Circulation_. 2014;130:S32-S38
doi: 10.1161/CIRCULATIONAHA.113.007764

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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