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Long-Term Outcome and Quality of Life in Adult Patients After the Fontan Operation

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The first successful Fontan operation was performed in 1971, and this first cohort of Fontan patients is reaching adulthood with unclear outcome of this palliative procedure. We studied the mortality, morbidity, and quality of life in our adult Fontan patients. We examined all patients (n = 36) who underwent a Fontan procedure and were being seen in an adult outpatient clinic by using electrocardiography, exercise testing, and echocardiography. Quality of life was assessed by the Short Form 36 questionnaire. The mean follow-up period was 15 years (range 0 to 23). Of the initial 36 patients, 10 died (28%) at a mean of 10 years (range 0 to 21) after the Fontan operation and 1 patient underwent cardiac transplantation. Reoperations were performed in 21 patients (58%), and the most common reason was revision of the Fontan connection. Sustained supraventricular tachycardia was observed in 20 patients (56%) with an increased incidence of arrhythmias with longer follow-up. Thromboembolic events were detected in 9 patients (25%), 5 of whom had adequate anticoagulant levels at the time of event. The thromboembolic event was fatal for 3 patients. A total of 195 hospital admissions (mean 3.8 ± 2.7, range 1 to 13) was recorded. Quality-of-life assessment showed physical functioning, mental health, and general health perception to be significantly lower for Fontan patients than for the normal Dutch population. Thus, we found high mortality and very high morbidity in adult patients after the Fontan operation. In particular, reoperations, arrhythmias, and thromboembolic events compromised quality of life. ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;93:1141–1145)

Since Fontan and Baudet's report of the first successful right-side cardiac bypass directing the entire systemic venous blood flow to the pulmonary arteries in a patient with tricuspid atresia, many modifications of this approach have been applied to all forms of functional univentricular heart disease. During the past 2 decades, several modifications of this operation and advances in management after surgery have improved surgical results.[1,2] Unfortunately, late deterioration in functional capacity has been described with longer duration of follow-up.[3] As hospital mortality has decreased substantially, late mortality and especially late morbidity are of great interest.[4–6] The occurrence of late complications such as atrial arrhythmias, ventricular failure, protein-losing enteropathy, and thromboembolic events are increasingly recognized.[7–9] No reports are available concerning quality of life in adult patients with a Fontan circulation. We evaluated the clinical course of adult Fontan patients and assessed their quality of life.

METHODS

Patients: All adult patients who underwent a Fontan procedure and regularly attended the outpatient clinic of the Thoraxcenter at the Erasmus Medical Center were included in this study. In 1978, the first Fontan operation was performed in our institute. We studied the long-term follow-up from Fontan operation until last follow-up or death. In 2002, a cross-sectional study of surviving patients was undertaken. All medical and surgical records of the patients were reviewed for reoperations, arrhythmias, hospitalization, and thromboembolic events. The cross-sectional evaluation consisted of physical examination, electrocardiography, exercise testing, and echocardiography. Quality of life was assessed with the Short Form 36 (SF-36) questionnaire.

Arrhythmias: The presence of an arrhythmia on any recording device was sufficient to code a patient for that rhythm disturbance, excluding arrhythmias related to cardiac catheterization or the period after surgery. Supraventricular arrhythmia included any sustained episode of atrial flutter, atrial fibrillation, or atrial tachycardia occurring at least 30 days after the Fontan operation.

Exercise capacity: Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of 10 W per minute for workload and compared with standardized data based on age, gender, and height.

Echocardiography: Two-dimensional echocardiography with color Doppler, velocity profiles, and M-mode recordings were performed. The Fontan connection was evaluated for obstruction in the conduit. Systemic ventricular function was judged by visual

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0002-9149/04/$–see front matter
doi:10.1016/j.amjcard.2004.01.041

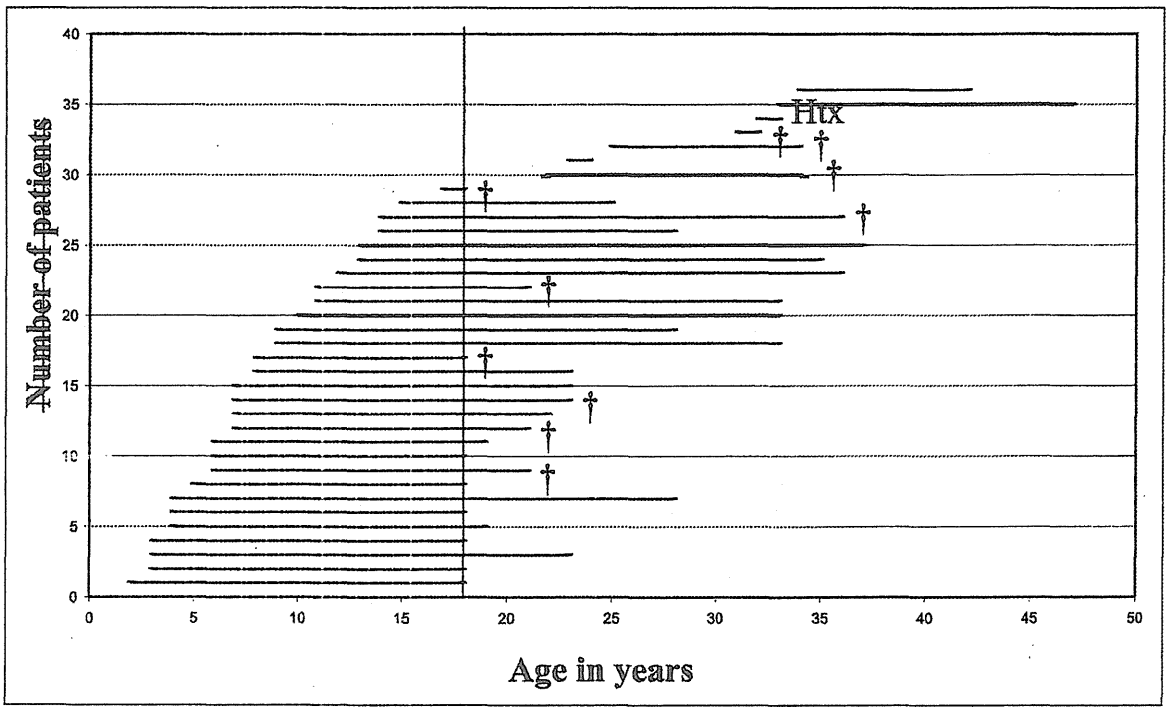

FIGURE 1. Period from age at Fontan operation to final follow-up or death for each patient. †Death; *lost to follow-up. HTx = cardiac transplantation.

estimation of the echocardiographic images and graded as normal, mild, moderate, or severe dysfunction.

Quality of life: A detailed health status questionnaire (SF-36) assessed physical functioning, general health, mental health, role limitations caused by physical health problems, energy and vitality, role limitations caused by emotional problems, social functioning, and bodily pain. For each of these health concepts, scores were in range of 0 to 100, with a higher score indicating a better health state.[10,11] The SF-36 has acceptable internal consistency and test–retest reliability.[12]

Statistical analysis: Data are presented as the mean value (SD) unless otherwise stated. The median value and range are presented if data were not normally distributed.

RESULTS

Patients: Thirty-six adult patients with a Fontan procedure were seen in the outpatient clinic and included in the study. There were 18 men (50%). Mean age at the time of Fontan operation was 12 years (range 2 to 34). Twenty-nine patients were operated in childhood and reached adulthood, and 7 patients underwent the Fontan operation at an adult age. The primary cardiac malformation was tricuspid atresia in 21 patients (58%), double-inlet left ventricle in 9 patients (25%), and other complex congenital cardiac anomalies amenable to a modified Fontan operation in 6 patients (17%). Twenty-eight patients (78%) had ≥1 palliation procedures before the Fontan operation. The surgical technique used for the Fontan procedure was an anastomosis between the right atrium and the pulmonary artery in 20 patients (56%), an atrioventricular connection through a conduit to a rudimentary right ventricle in 12 patients (33%), and a lateral tunnel variant of total cavopulmonary connection in 4 patients (11%).

Mortality: Of the initial 36 patients, 10 died (28%) during follow-up and 1 patient underwent cardiac transplantation. One patient who underwent a Fontan operation in adulthood died soon after surgery. Four patients died suddenly 1, 8, 13, and 14 years after Fontan operation (Figure 1). Three patients died from pulmonary emboli and 2 from severe heart failure. The mean follow-up period of all patients after Fontan operation was 15 years (range 0 to 23). Two patients were lost to follow-up 12 and 15 years after Fontan operation.

Morbidity: Event-free survival 10 and 15 years after the Fontan operation were 48% and 16%, respectively (Figure 2). Twenty-one patients (58%) needed ≥1 reoperations. Thirty-nine cardiac reoperations were performed, consisting of 47 procedures. The most common reoperations were a revision of the atrioventricular connection through a conduit to a rudimentary right ventricle conduit due to obstruction (n = 9), pacemaker insertion (n = 7), and conversion of the modified Fontan circulation to a total cavopulmonary connection (n = 9). Eight patients (22%) needed epicardial pacemaker implantation for sinus node dysfunction (n = 5), surgical related atrioventricular block (n = 2), and atrial flutter with coexisting sinus node dysfunction (n = 1).

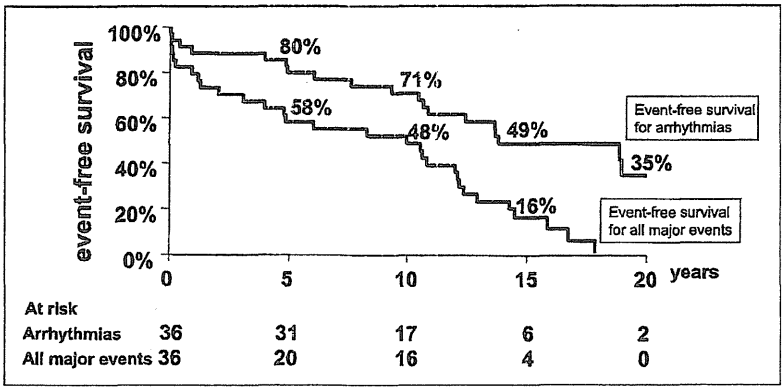

FIGURE 2. Event-free survival rates for all-cause mortality and morbidity, including reoperations, hospitalizations, arrhythmias, and thromboembolic events. There is a separate curve for the incidence of arrhythmias after Fontan operation.

TABLE 1 Multivariables for Patients With and Without Arrhythmias

	No Arrhythmias (n = 16)	Arrhythmias (n = 20)
Morphology		
Tricuspid atresia	10 (62%)	11 (55%)
Double-inlet left ventricle	3 (19%)	6 (30%)
Others	3 (19%)	3 (15%)
Primary Fontan procedure (connection)		
Right atrium–pulmonary artery	10 (62%)	10 (50%)
Right atrium–right ventricle	6 (38%)	6 (30%)
Total cavopulmonary connection	0	4 (20%)
Mean age (yrs) at Fontan operation (mean ± SD)	10 ± 9.5	14 ± 9.8
Deaths	3 (19%)	7 (35%)
Reoperations	7 (44%)	14 (70%)
No. of hospitalizations (mean)	3.4	7.1
Ventricular function		
Good	11 (69%)	8 (40%)
Moderate dysfunction	5 (31%)	9 (45%)
Severe dysfunction	0	3 (15%)
Atrioventricular regurgitation		
None	8 (50%)	11 (55%)
Grade I/II	7 (44%)	4 (20%)
Grade III/IV	1 (6%)	5 (25%)

In 20 patients (56%), a sustained supraventricular tachycardia was present. All 20 patients received antiarrhythmic therapy. The first episode of atrial tachycardia occurred at ±5 years (0 to 19 years) after Fontan operation. Figure 2 shows the incidence of arrhythmia during follow-up. Amiodarone given in 8 patients (47%) was the most effective drug for reducing frequency and duration of the supraventricular tachycardia, with an interval of 1.4 years free of arrhythmias. Electrical cardioversion was performed in 14 patients. Two patients underwent catheter ablation of supraventricular arrhythmias, which was successful in 1 patient. All 4 patients with primary total cavopulmonary connection developed severe atrial tachycardia, and 2 died due to arrhythmias.

As presented in Table 1, mortality and morbidity due to reoperations (70%) and hospitalization occurred more frequently in patients with sustained atrial arrhythmias. In addition, ventricular dysfunction (60%) and severe atrioventricular regurgitation (25%) were more evident in patients with arrhythmias. After the onset of the arrhythmia, a new thrombus in the right atrium was found in 2 patients, and pulmonary embolism was suspected in 2 additional patients. The 4 late sudden deaths in this series were assumed to be arrhythmogenic. Two patients had documented ventricular tachycardia, and 1 of these patients had severe heart failure while waiting for cardiac transplantation. Electrocardiograms at last contact in 23 patients showed 14 (61%) with sinus rhythm, 7 with low atrial rhythm, and 2 with registered pacemaker activity.

Thromboembolic events were detected in 9 patients (25%), 5 of whom had adequate anticoagulant levels at the time of the event. Abnormal coagulation factor, in particular the procoagulation factor protein C, was found in 6 patients (17%), and 1 patient was diagnosed with a deficiency in factor VII. Three (43%) of the 7 patients with abnormal coagulation factor had a thromboembolic event. Two patients had thrombotic obstruction of the Fontan conduit and needed reoperation. Four patients developed pulmonary emboli, 3 of whom died and 1 had a femoral artery thrombosis. Two patients had a cerebral accident with moderate to severe cerebral damage. Protein-losing enteropathy was not reported in our cohort.

All patients needed ≥1 hospitalization after Fontan operation. A total of 195 hospital admissions (mean 3.8 ± 2.7, range 1 to 13) was recorded. Mean duration of hospital stay was 9 ± 11 days (range 1 to 101). The most common reason for hospitalization was an arrhythmia.

New York Heart Association classification before the operation showed 32 patients (89%) in class III or VI. After the Fontan operation, classification indicated more patients in class II or III; however, with longer duration of follow-up, classification indicated most patients in class III (Figure 3).

In 2002, a cross-sectional study of the 23 surviving patients was undertaken. Exercise capacity was tested in 14 patients (58%). Total work performed was 61 ± 11% of the predicted exercise tolerance. Maximal heart rate during exercise was 145 ± 23 beats per minute. Systemic arterial blood pressures showed minimal increases during exercise, with a mean pressure increase of 26 ± 11 mm Hg.

Echocardiographic assessment showed 14 patients (61%) with good systemic ventricular function and 9 patients (38%) with moderate to severe dysfunction of the systemic ventricle. Dilatation of the systemic ventricle was present in 6 patients (25%). Atrioventricular

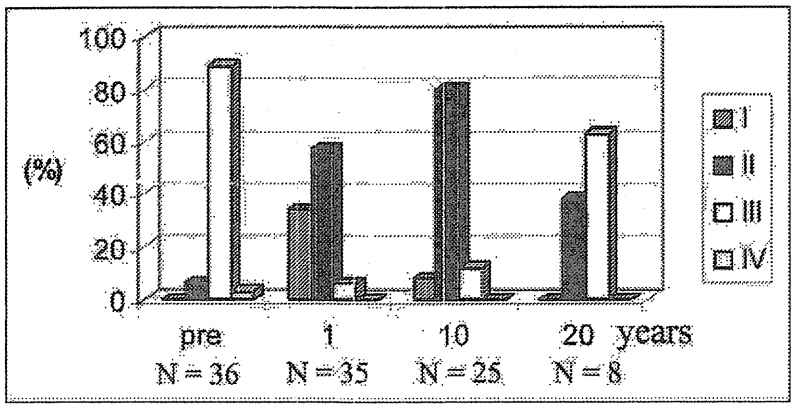

FIGURE 3. New York Heart Association classification before and after Fontan operation. With longer follow-up after Fontan operation, changes in classification indicate a decline in function.

TABLE 2 Current Medications of the 23 Surviving Patients After Fontan Operation

Medication	n (%)
Anticoagulants	
Coumarin	21 (91)
Antiplatelet drugs	1 (4)
None, on own request	1 (4)
Antiarrhythmic drugs	15 (65)
Diuretics	4 (17)
ACE inhibitors	2 (9)

ACE = angiotensin-converting enzyme.

valve regurgitation was seen in 13 patients (57%) and was moderate to severe in 4. The right atrium for most patients was markedly dilated, with pronounced echogenicity of low blood flow.

Medication: Twenty-two patients (96%) were receiving anticoagulant therapy. Thirteen of the 23 patients used other cardiac medications, with amiodarone and diuretics being the most common (Table 2).

Quality of life: The questionnaire was completed by 22 patients (96%). Due to language barriers, 1 patient did not complete the questionnaire. The SF-36 dimensions of physical functioning, mental health, and general health perception were significantly lower for patients with Fontan circulation than for the normal Dutch population (Table 3). For social functioning, vitality, and bodily pain, the patients did not differ from the general population. Five to 10 patients (65%) were gainfully employed. Three were unemployed because of their cardiac problems. None of our patients had children.

DISCUSSION

This study showed a surprisingly high mortality rate in young adults and a high morbidity rate after the Fontan operation. Arrhythmias, reoperations, and thromboembolic events often occurred, and all patients had ≥1 hospital admission during follow-up.

A possible risk factor for late mortality is surgery at older age.[13,14] In our patients who underwent the Fontan operation during adulthood, the mortality rate was as high as 57%. Three of our patients died suddenly after Fontan operation, suggesting arrhythmia as a major factor.

Arrhythmias comprised the most common reason for hospital admission. Our data showed that the prevalence of atrial arrhythmias increased with longer interval after the Fontan operation. A correlation has been found between arrhythmias and reoperations.[15,16] In patients with arrhythmias, moderate to severe ventricular dysfunction was common (60%), and arrhythmias have been associated with right atrial thrombus. The high mortality and morbidity rates associated with arrhythmias make aggressive treatment necessary, and it is urgent to convert these patients to sinus rhythm. The hemodynamic situation and the incidence of arrhythmias seem closely correlated; therefore, if new arrhythmias occur, a thorough evaluation of the total Fontan connection is clearly indicated because arrhythmias can be the first sign of hemodynamic deterioration. Amiodarone was found to be the most effective antiarrhythmic drug in our study. Electrophysiologically guided ablation of an arrhythmogenic substrate has become more successful in morphologically abnormal hearts and must be considered when pharmacologic therapy is insufficient and to avoid lifelong side effects of antiarrhythmic medication.

Thromboembolic events after Fontan operation are a common and serious problem. In this study, the incidence of thromboembolic events during long-term follow-up was 25%, which is higher than in other recent studies reporting an incidence of 10% to 20%. After a thromboembolic event, we found a mortality rate of 38%, which is higher than the 25% reported in the literature.[8,17] Presumably, adult Fontan patients have more severe ventricular dysfunction and therefore cannot cope with the extra hemodynamic burden. Despite the documented frequency and clinical effect of thromboembolic complications, no consensus has been found in the literature regarding anticoagulant therapy, methods (i.e., Coumadin vs antiplatelet agents), or duration of therapy. Coumadin is the most effective prophylactic therapy in preventing thromboembolism. Therefore, our regime is to put all patients on lifelong anticoagulant therapy (international normalized ratio 2.0 to 3.5). Nevertheless, we found a high incidence of thromboembolic events, and more than 50% with adequate levels of anticoagulation. Even higher levels of anticoagulant therapy (international normalized ratio 3.5 to 4.5) or additional antiplatelet drugs may be necessary in this population.

Despite the abnormal hemodynamic situation, clinicians are frequently impressed by the ability of most patients to lead a nearly normal life. In our study, we found most patients to be in New York Heart Association class I or II after 10 years of follow-up, but

TABLE 3 Quality of Life Based on the Short Form 36 Results Compared With Population Normative Data

	Fontan Patients (n = 22)	General Population	p Value
1. Physical functioning	80.2 ± 14.5	93.1 ± 11.8	<0.0001
2. Role — physical	61.9 ± 40.0	86.4 ± 27.6	<0.0001
3. Role — emotional	79.4 ± 34	85.4 ± 30.0	0.4
4. Social functioning	77.6 ± 26.7	87.8 ± 19.1	0.02
5. Mental health	54.5 ± 22.6	78.7 ± 15.2	<0.0001
6. Energy/vitality	68.8 ± 21.2	70.7 ± 16.4	0.6
7. Pain	79.1 ± 23.8	80.9 ± 19.4	0.9
8. General health perception	56.7 ± 21.6	78.2 ± 17.3	<0.0001

Values are mean ± SD.

with time these patients presented a progressive decline in functional status.[3,6,18] Maximal exercise in any patient after Fontan repair is subnormal or, at best, reaches the lower limit of normal. In our adult population, the maximal exercise tolerance was only 61% of the predicted value. In addition, systemic arterial blood pressure did not increase during exercise. This is a known feature of Fontan circulation because it lacks the possibility to significantly accelerate blood flow during exercise.[3] The only mechanism to establish a greater output during exercise is increasing the heart rate. We found an adequate increase of heart rate during exercise.

There have been several studies on the intellectual, social, and emotional developments of children and adolescents with congenital heart disease, but no study has been performed in adults after the Fontan operation.[19–21] Our study showed a significantly lower score for physical functioning, mental health, and general health perception compared with the normal Dutch population. Hospital mortality rate has been reduced and many Fontan patients reach adulthood but at the expense of repeated hospital admissions and surgical procedures. The psychological effect of these repeated procedures must be considered and is very important in adolescence and young adulthood. Social isolation and mental health impairment may be the results of physical incapacity, restricted leisure time activities, or parental overprotectiveness.[22] In addition, patients are usually aware of the potential reduction in their life expectancy and physical capabilities. To enhance the patient's long-term quality of life, psychological aspects must be taken into account. An understanding by health professionals of the subjective experiences and dilemmas in these patients is necessary, and improvement in care may be gained by offering professional psychological or emotional guidance.

Although long-term follow-up information was available for the large majority of patients, the incidence of transient arrhythmias and thromboembolic complications may not be complete because we attended to only clinically relevant events. If so, the numbers of complications have been underestimated, resulting in even higher morbidity rates. A profound bias with a retrospective study can occur (1) when patients are accepted for Fontan operation and (2) with survival after the operation. Therefore, evaluation of this heterogeneous group for long-term consequences of a Fontan circulation has severe limitations.

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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.[1-3] Twenty-year survival estimates have only been delineated for the atriopulmonary 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 hospital and private practice databases for the remaining patients. At the time of the most recent follow-up collection, 166 patients had no concurrent data within the previous 3 years. Eight patients had undergone their Fontan procedure overseas, and the remaining had been operated in the region. Patients from New Zealand were recorded as alive for the purpose of survival analysis as of August 2013, because all deaths in New Zealand are tracked nationally and recorded in 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.[7] 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 analyses. 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 atriopulmonary Fontan subgroup excluded. Data analysis was performed using Stata 11 (Statcorp, 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.

Table 1. Patient Characteristics of Hospital Survivors, AP Versus LT Versus ECC

Characteristic	AP (203 Patients)	LT (271 Patients)	ECC (532 Patients)	Total (1006 Patients)
Male, n (%)	110 (54)	154 (57)	319 (60)	583 (58)
Dextrocardia, n (%)	18 (9)	14 (5)	39 (7)	71 (7)
Isomerism, n (%)	9 (4)	17 (6)	40 (8)	66 (7)
Ventricular morphology, n (%)				
Left	160 (79)	170 (63)	280 (53)	610 (61)
Right	37 (18)	85 (31)	194 (36)	316 (31)
Biventricular/indeterminate	6 (3)	16 (6)	58 (11)	80 (8)
Morphological group				
TA	65 (32)	68 (25)	105 (20)	238 (24)
HLHS	1 (0)	7 (3)	80 (15)	88 (9)
DORV	29 (14)	44 (16)	74 (14)	147 (15)
CAVC	11 (5)	14 (5)	36 (7)	61 (6)
CAVC-DORV	4 (2)	11 (4)	27 (5)	42 (4)
TGA	6 (3)	17 (6)	26 (5)	49 (5)
ccTGA	8 (4)	12 (4)	29 (5)	49 (5)
DILV	46 (23)	62 (23)	76 (14)	184 (18)
PA-IVS	15 (7)	17 (6)	48 (9)	80 (8)
Other	18 (9)	19 (7)	31 (6)	68 (7)
Pre-Fontan procedures				
No. of prior palliations, mean (SD)	1.1 (0.8)	1.6 (0.9)	2.4 (0.9)	1.9 (1.1)
Prior aortic arch intervention, n (%)	10 (5)	36 (13)	177 (33)	223 (22)
Prior pulmonary artery banding, n (%)	46 (23)	84 (31)	135 (25)	265 (26)
Prior staging with BCPS, n (%)	7 (3)	103 (38)	515 (97)	625 (63)
Bilateral BCPS, n (%)	0 (0)	7 (3)	40 (8)	47 (5)
Age at BCPS, y, median (IQR)	1.4 (1.2–3.1)	1.4 (0.8–2.8)	0.9 (0.4–1.5)	1.0 (0.5–1.6)
Atrioventricular valve repair/replacement, n (%)	1 (0)	6 (2)	35 (7)	42 (4)
Pulmonary artery reconstruction or angioplasty, n (%)	5 (2)	16 (6)	108 (20)	129 (13)
Pre-Fontan hemodynamics				
Oxygen saturation, %, mean (SD)	81 (6)	82 (6)	82 (6)	82 (6)
Pulmonary artery pressure, mm Hg, mean (SD)	13 (4.1)	13 (4.5)	11 (2.6)	12 (3.6)
Aortopulmonary or venovenous collaterals, n (%)	2 (1)	16 (6)	130 (24)	148 (15)
Arteriovenous malformations, n (%)	1 (0)	5 (2)	28 (5)	34 (3)
Atrioventricular valve regurgitation ≥ moderate, n (%)	8 (4)	10 (4)	41 (8)	59 (6)
Fontan operative characteristics				
Arch intervention before or at Fontan completion (excluding Norwood procedures), n (%)	13 (6)	35 (13)	99 (19)	147 (15)
Fenestration, n (%)	0 (0)	138 (51)	202 (38)	340 (34)
Age at Fontan, y, median (IQR)	5.5 (3.1–9.3)	3.8 (2.8–5.8)	4.8 (3.9–5.9)	4.6 (3.4–6.4)
Concomitant procedure, n (%)	29 (14)	48 (18)	62 (12)	139 (14)
Concomitant pulmonary artery reconstruction, n (%)	13 (6)	19 (7)	26 (5)	58 (6)
Concomitant atrioventricular valve repair, n (%)	7 (3)	5 (2)	16 (3)	28 (3)

Pre-Fontan hemodynamic data were not available in 56% of atriopulmonary Fontans. AP indicates atriopulmonary connection; BCPS, bidirectional cavopulmonary shunt; CAVC, complete atrioventricular canal; ccTGA, congenitally corrected TGA; DILV, double inlet left ventricle; DORV, double outlet right ventricle; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; IQR, interquartile range; LT, lateral tunnel; PA-IVS, pulmonary atresia with intact ventricular septum; TA, tricuspid atresia; and TGA, transposition of the great arteries.

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,

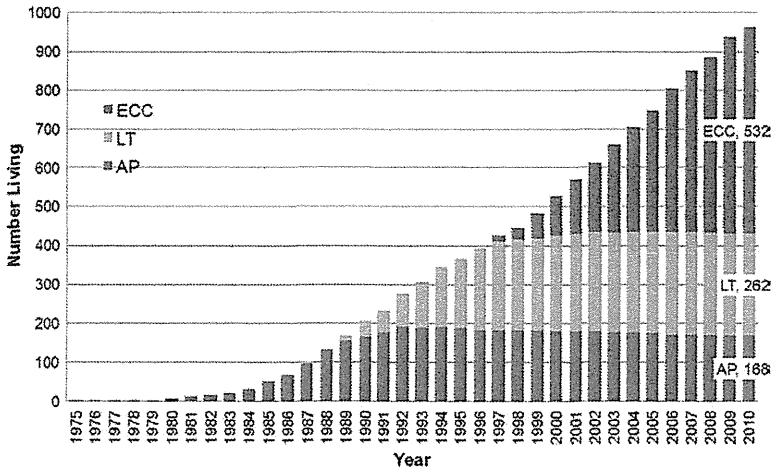

Figure 1. Distribution of the techniques used in the growing population of Fontan patients alive in Australia and New Zealand. AP indicates atriopulmonary connection; ECC, extracardiac conduit; and LT, lateral tunnel.

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.

Table 2. Results of Multivariable Cox Regression Analysis for Long-Term Outcomes

Variable	HR	95% CI	*P* Value
Late mortality (*P**=0.10)			
AP (vs ECC)	6.2	2.4–16.0	<0.001
Age at Fontan > 7 y (vs 3–5 y)	2.7	1.2–5.7	0.012
Prolonged pleural effusions	2.9	1.1–7.4	0.028
Male sex	2.5	1.3–4.6	0.004
Late failure (*P**=0.32)			
Length of stay (on a log scale)	2.2	1.6–2.8	<0.001
HLHS (vs LV morphologies)	3.8	2.0–7.1	<0.001
Age at Fontan > 7 yr (vs 3–5 yr)	2.0	1.2–3.2	0.005
Late adverse events (*P**=0.97)			
Length of stay (on a log scale)	1.7	1.3–2.1	<0.001
HLHS (vs LV morphologies)	1.9	1.1–3.0	0.016
Arch intervention before or at Fontan completion (excluding Norwood)	1.7	1.2–2.4	0.005
Early pacemaker	2.1	1.0–4.2	0.005
Pre-Fontan collaterals	1.8	1.3–2.5	0.001
PLE/plastic bronchitis (*P**=0.67)			
HLHS (vs LV morphologies)	3.8	1.1–13.0	0.035
SVT (*P**=0.06)			
Fontan type			
ECC	Ref		
LT	3.1	1.2–7.8	0.019
AP	10.7	4.5–25.6	<0.001
Isomerism	2.4	1.1–5.0	0.002

AP indicates atriopulmonary connection; CI, confidence interval; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; HR, hazard ratio; LT, lateral tunnel; LV, left ventricular; PA, pulmonary artery; PLE, protein-losing enteropathy; and SVT, supraventricular tachycardia.

*Schoenfeld residuals–based test of proportional hazards assumption.

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 takedown. 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, 3.112.1 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.

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

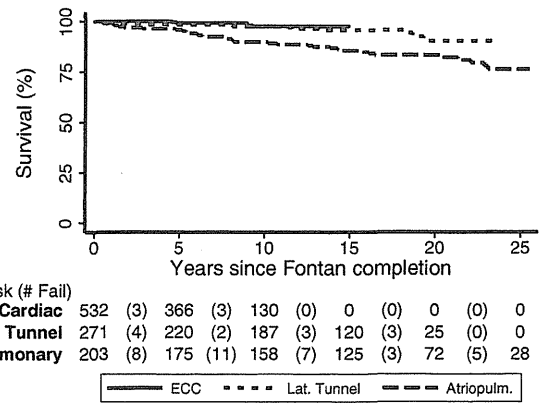

Figure 2. Kaplan–Meier Survival by Fontan type. Log-rank test *P*<0.001. Atriopulm indicates atriopulmonary connection; ECC, extracardiac conduit; and Lat. tunnel, lateral tunnel.

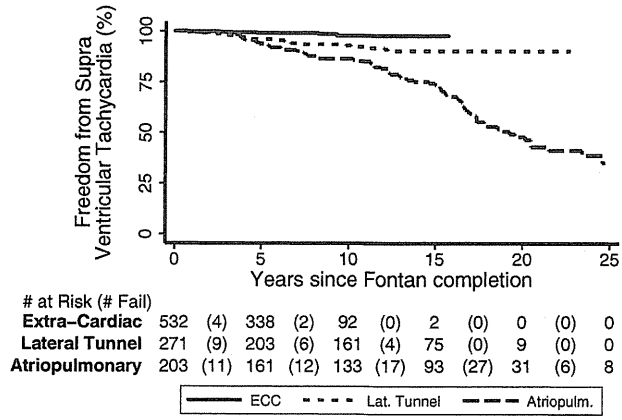

Figure 3. Freedom from late sustained supraventricular tachycardia by Fontan type. Log-rank test $P<0.001$. Atriopulm indicates atriopulmonary connection; ECC, extracardiac conduit; and Lat. tunnel, lateral tunnel.

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

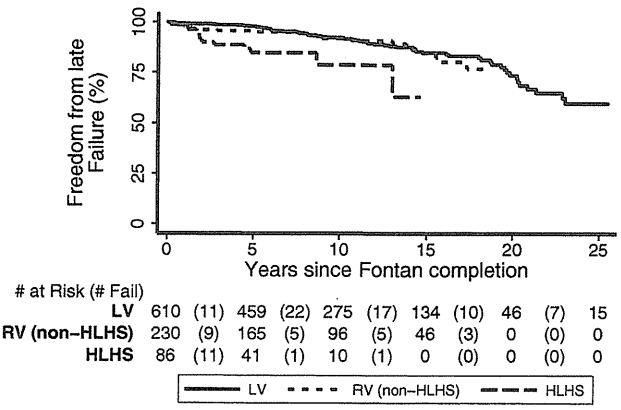

Figure 4. Comparative freedom from failure (death, heart transplantation, reoperation on the Fontan circuit, poor functional status) for patients with and without hypoplastic left heart syndrome (HLHS; log-rank test $P<0.001$). LV indicates left ventricle; and RV, right ventricle.

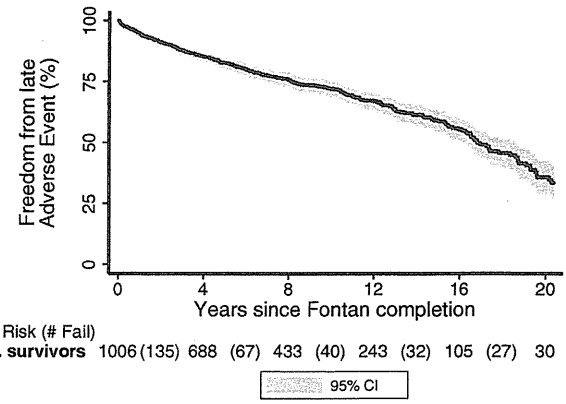

Figure 5. Freedom from adverse events (failure, supraventricular tachycardia, stroke, pulmonary embolism, pacemaker insertion). CI indicates confidence interval; and hosp. survivors, hospital survivors.

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

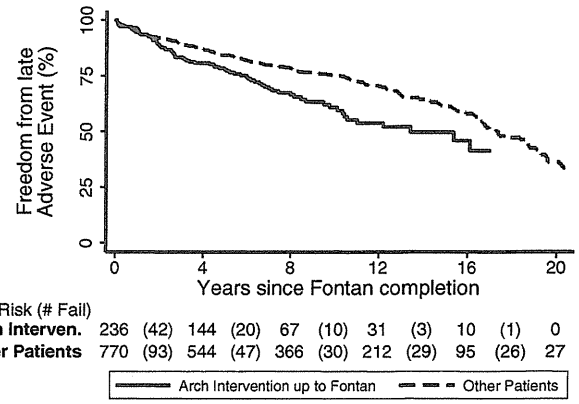

Figure 6. Comparative freedom from adverse events for patients with or without arch intervention before or at Fontan completion (excluding Norwood procedures; log-rank test $P=0.003$).

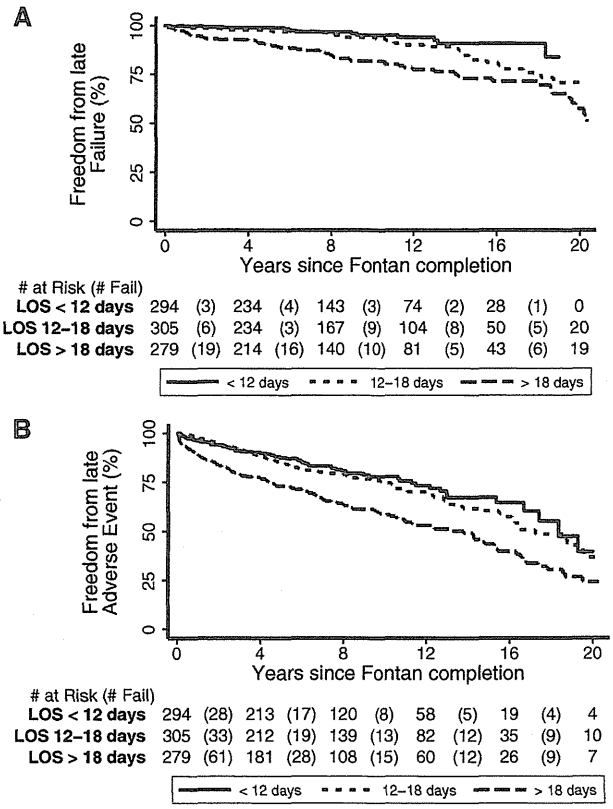

Figure 7. Impact of length of hospital (LOS) stay on late failure (**A**; log-rank test $P<0.001$) and late occurrence of adverse events (**B**; log-rank test $P<0.001$).

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 with186 (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[5,8]: 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.[5] 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.[9] 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.[10] 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.[11–14] If we expect these patients to survive ≥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 experience survival of 76% 25 years after Fontan and contemporary techniques are associated with even better survival. Patients with hypoplastic left heart syndrome have higher rates of adverse events and failure. This large and comprehensive binational registry will continue to track long-term outcomes and shed light on survival, symptoms, and quality of life for these subjects.

Acknowledgments

We thank our research assistants, Ingrid King, Dr Aneta Kotevski, Janina Chapman, Gabriela Abrahamson, Megan Upjohn, and Lisa Cowcher for their invaluable assistance in the creation and maintenance of the Registry.

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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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

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

Yves d'Udekem, Ajay J. Iyengar, John C. Galati, Victoria Forsdick, Robert G. Weintraub, Gavin R. Wheaton, Andrew Bullock, Robert N. Justo, Leeanne E. Grigg, Gary F. Sholler, Sarah Hope, Dorothy J. Radford, Thomas L. Gentles, David S. Celermajer and David S. Winlaw

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

Print ISSN: 0009-7322. Online ISSN: 1524-4539

European Journal of Cardio-Thoracic Surgery 47 (2015) 511–519
doi:10.1093/ejcts/ezu145 Advance Access publication 3 April 2014

ORIGINAL ARTICLE

Cite this article as: Ohuchi H, Yasuda K, Miyazaki A, Ono S, Hayama Y, Negishi J *et al.* Prevalence and predictors of haemostatic complications in 412 Fontan patients: their relation to anticoagulation and haemodynamics. Eur J Cardiothorac Surg 2015;47:511–9.

Prevalence and predictors of haemostatic complications in 412 Fontan patients: their relation to anticoagulation and haemodynamics

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Received 31 October 2013; received in revised form 5 March 2014; accepted 11 March 2014

Abstract

OBJECTIVES: Our aim in the present study was to determine the prevalence of haemostatic events in our Fontan patients, to identify predictive factors and to determine their association with haemodynamics and anticoagulant therapy.

METHODS: We retrospectively evaluated 424 Fontan patients and examined correlations between postoperative haemodynamics and anticoagulant regimens with haemostatic events.

RESULTS: After exclusion of 12 patients with a mechanical valve at the time of Fontan operation, our 412 patients were sub-divided into 21 groups based on the therapeutic duration of warfarin and antiplatelet agent therapy. During the early 5- to 10-year postoperative period, patients receiving warfarin showed higher central venous pressure and lower arterial oxygen saturation (Sat) ($P < 0.05$–0.001). During a mean follow-up of 11.2 years, 29 (7.0%) haemostatic events occurred. With regard to haemorrhagic events, haemoptysis was most common ($n = 13$, 45%), followed by cerebral bleeds in 3 (10%). Of thrombo-embolic events, thrombosis in the Fontan pathway was the most common ($n = 7$, 24%), followed by cerebral infarction in 3. Early haemorrhagic events were associated with late Fontan operation and use of preoperative renin–angiotensin system blockers, while late events were related to heterotaxy syndrome, male gender and low Sat ($P < 0.05$–0.01). A low Sat was the only predictor of early postoperative thrombo-embolic events ($P = 0.0192$). Among the three subgroup analyses of fixed anticoagulant regimens, the most frequent haemorrhagic events were associated with long-term use of warfarin ($P = 0.0033$). None of the anticoagulant regimens that included warfarin and/or antiplatelet agents were independently associated with haemostatic events throughout the follow-up.

CONCLUSIONS: Anticoagulant regimens in Fontan patients varied widely with a significant trend for warfarin use in patients with impaired haemodynamics. Low arterial oxygenation may predict haemostatic events. The relatively high prevalence of haemorrhagic complications indicates the need for individualized anticoagulant administration throughout the follow-up.

Keywords: Fontan procedure • Thrombo-embolism • Haemorrhage • Anticoagulants

CONGENITAL

INTRODUCTION

Thrombo-embolism is one of the major postoperative complications after the Fontan operation and its reported prevalence rate varies from 0 to 28% depending on the study design [1–4]. Virchow's triad has been proposed as a key risk factor for thrombosis formation [5] and several detailed studies of coagulation factors have been undertaken to determine the nature of the post-Fontan hypercoagulability [6–9]. However, these efforts have failed to identify a single culprit among proposed factors and, so far, no prospective studies to identify clinically relevant coagulation factors have been conducted. As for the circulatory stasis, the low cardiac output, impaired ventricular function and presence of a pulmonary stump have been regarded as predisposing to thrombo-embolism [1, 10]. Haematological events may be low during childhood. An intriguing possibility is that they may be based on ethnic differences in the coagulation cascade, which favour a haemorrhagic tendency in oriental patients [11]. A recent randomized controlled study failed to demonstrate any protective benefits of warfarin over acetylsalicylic acid in the first 2 years after the Fontan operation [4]. Furthermore, there has been no comprehensive evaluation of the impact of haemodynamics on thrombo-embolic events. This existing information led us to speculate whether impaired haemodynamics, rather than anticoagulation therapy, might be the predominant precursor of haemostatic events in Fontan patients. In this respect, our policy of serial haemodynamic assessments provided a unique opportunity to study this issue. Accordingly, we planned to clarify the impacts of Fontan

haemodynamics and prescribed anticoagulation regimens on thrombo-embolic events in our large cohort of 424 Fontan patients.

METHODS

Subjects

We retrospectively reviewed all our patients (a total of 424, males 255) who had undergone a Fontan operation in our institute (Table 1). For this study, the last follow-up occurred at the end of February 2013. In our institute, all Fontan survivors had undergone periodic cardiac catheterizations before, and 1, 5, 10 and 15 years after their Fontan operation, except for a few patients excluded for social and/or medical reasons [12]. Of the 424 patients, 19 had been treated with a mechanical valve (12 with the atrioventricular valve and 2 with the aortic valve). Of those, 12 patients who had been treated with a mechanical valve at the time of or before the Fontan operation were excluded from the present study because of a greater risk of haemostatic complications and the remaining 7 were included in our study because they had a certain period of mechanical valve-free postoperative status. Finally, 412 patients were analysed. Of the 367 early (≥6 months) postoperative survivors, 355 had undergone a postoperative cardiac catheterization with cardiovascular imaging by the end of February 2013, 355 before (within 6 months), and 355, 271, 181 and 108 patients 1 (0.5–2.4), 5 (2.5–7.4), 10 (7.5–12.4) and 15 (12.6–17.4) years after the Fontan operation, respectively. The Ethics Committee of the National Cardiovascular Center approved the study protocol.

Table 1: Subject characteristics

	Total	Early survivors
n	412	355
Age at Fontan operation (median) (years)	4.7 ± 5.3 (2.8)	4.4 ± 5.2 (2.5)
Follow-up (median) (years)	11.2 ± 7.6 (10.9)	11.6 ± 6.7 (10.9)
Systemic ventricular type (RV/BV/LV)	176/75/161	149/68/138
First Fontan in 1990	228 (55%)	179 (50%)
Diagnosis		
Heterotaxy syndrome	133 (32%)	104 (29%)
UVH	108	88
TA	88	74
DORV	68	67
MA	40	35
PA	31	28
CAVC	37	25
HLHS	13	12
Others	27	26
Type of first Fontan operation		
APC	62	35
IAR	102	87
ECR	248	233
Previous or additional procedures at Fontan operation		
APS	228	193
PAB	102	95
AAPA	45	45
Glenn	209	194
Fenestration	38	35

Values are mean ± SD.
AAPA: additional aortopulmonary anastomosis; APC: atriopulmonary connection; APS: aortopulmonary shunt; BV: biventricular; CAVC: common atrioventricular canal; DORV: double outlet right ventricle; ECR: extracardiac rerouting; HLHS: hypolastic left heart syndrome; IAR: intra-atrial rerouting; LV: left ventricle; MA: mitral valve atresia; PA: pulmonary valve atresia; PAB: pulmonary artery banding; RV: right ventricle; TA: tricuspid valve atresia; UVH: univentricular heart.

Haemodynamics and systemic ventricular performance

We measured intracardiac and great vessel pressures, including the central venous (CVP) and end-diastolic systemic ventricular pressures. We estimated the oxygen consumption from the age, sex and heart rate and measured the cardiac index (CI; l/min/m^2) using the Fick principle, and assumed that the right and left pulmonary arterial saturations were equal in the patients with either a Glenn or total cavopulmonary connection because it is clinically difficult to measure accurate flow distributions in the bilateral pulmonary arteries. We calculated the systemic and pulmonary arterial resistances and determined the systemic ventricular morphology angiographically as previously described [12]. We used Simpson's rule to estimate the right and left ventricular volumes and divided the end-diastolic ventricular volume by the body surface area to obtain the end-diastolic volume index. We also calculated the systemic ventricular ejection fraction. Bilateral pulmonary artery sizes were measured just proximal to the first branch [13]. The bilateral pulmonary cross-sectional areas were calculated from the corrected pulmonary artery diameter size, after which the areas were summed and divided by the patient's body surface area.

Sub-groups according to anticoagulant regimen

Because warfarin had been used for at least the early postoperative period (≥6 months) until the first cath-based haemodynamic evaluation, we subgrouped the Fontan survivors after the evaluation based on a combination of the duration of warfarin and antiplatelet therapies prescribed. Patients not given warfarin immediately post-evaluation were categorized as W0, those who received warfarin throughout the follow-up as category W1, patients who discontinued warfarin postevaluation after a certain period as W2, intermittent use of warfarin as W3 and receiving current warfarin therapy with a planned discontinuation period as W4. A similar subgrouping based on the antiplatelet prescription pattern was applied to the antiplatelet treatment. Thus, theoretically, 25 patterns were possible. For instance patients currently treated with antiplatelet agent without warfarin were categorized as W0P1 (Fig. 1, left).

Haemostatic events

Haemostatic events consisted of thrombo-embolic and haemorrhagic events. Thrombo-embolic complications included thrombus formation in the Fontan pathway, transient ischaemic attacks, and myocardial or cerebral infarction. Haemorrhagic events included haemoptysis, and cerebral and other bleeding. All of these haemostatic events required hospitalization and asymptomatic patients were not included in this study.

Statistical analysis

Differences in demographics and haemodynamic variables were evaluated using the unpaired *t*-test between two groups and

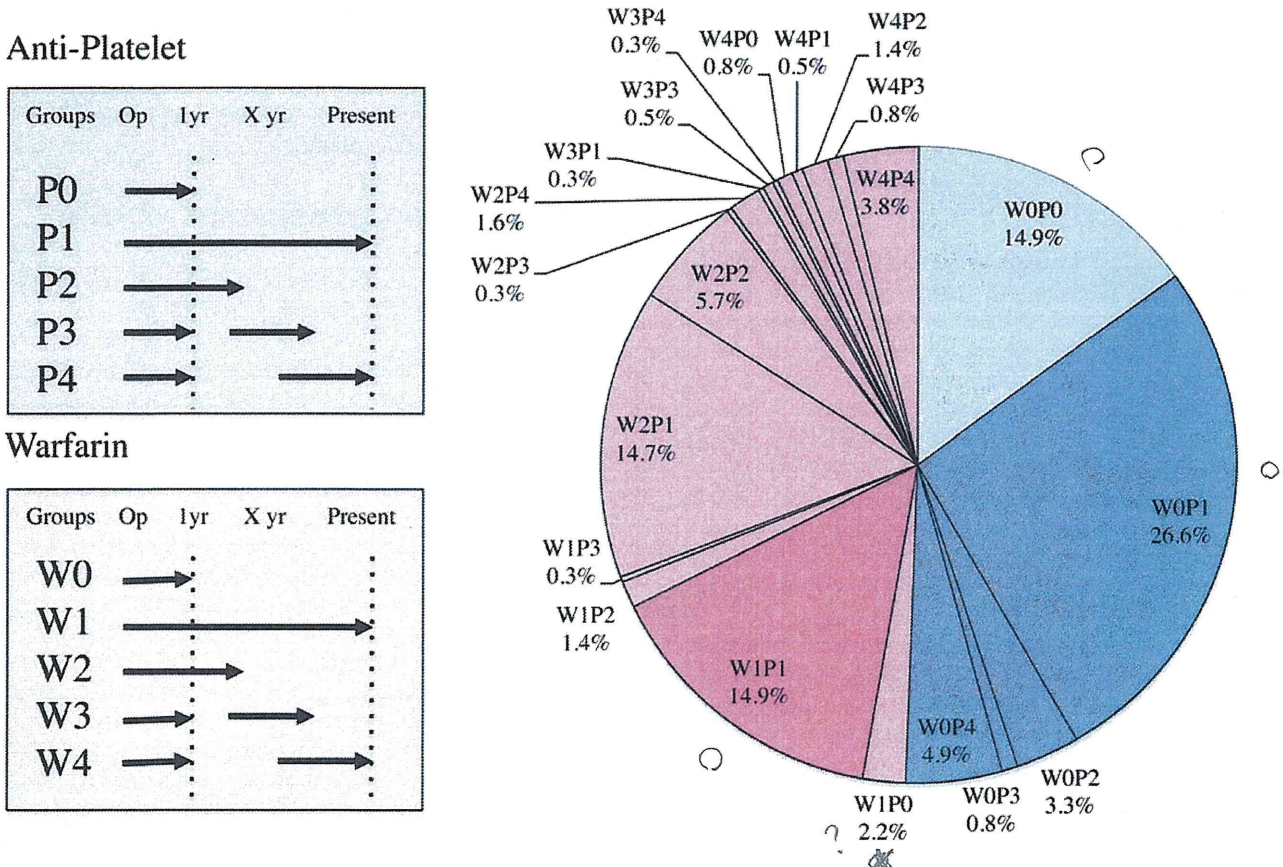

Figure 1: Sub-grouping of anticoagulation regimens according to the therapeutic duration of warfarin and antiplatelet agents. Theoretically, there could be 5 × 5 = 25 regimens. Definitions of groups W and P are described in the text.

one-way ANOVA with Turkey's *post hoc* test among ≥3 groups. Comparisons of the prevalence of clinical profiles, including diagnosis, medications and type of Fontan procedure were evaluated with χ^2 or Fisher's exact test. We used univariate Cox's proportional hazards model to predict the associations of clinical factors with haemostatic events. When the variables had a *P* value of <0.20, they were used in the multivariate Cox's proportional hazards model to identify the independent predictors. We employed the following clinical variables to correlate haemostatic events: preoperative and early postoperative haemodynamics; medications, including anticoagulant regimen; age at first Fontan operation; gender; type of systemic ventricular morphology (LV vs non-LV); heterotaxy syndrome; type of Fontan procedure; and type of palliative operation (s) prior to the Fontan operation. The clinical event-free status was estimated using the Kaplan–Meier method, and differences in the event-free status between groups were assessed using log-rank tests. Analyses were performed with the software JMP 10 pro (SAS Institute, Cary, NC, USA). The data are expressed as the mean ± SD. A *P* value of <0.05 was considered statistically significant.

RESULTS

Of the 412 patients, 367 survived more than 6 months and 8 died (cause of death: heart failure in 3, arrhythmia in 4, unknown in 1) without postoperative haemodynamic assessment. Of the 6-month survivors, 355 patients underwent postoperative catheterization (Table 1). There were 21 patterns of anticoagulant regimen based on our sub-grouping (Fig. 1, right) and the most common four regimens were W0P1 (n = 98, 27%), followed by W1P1 (n = 55, 15%), W0P0 (n = 55, 15%) and W2P1 (n = 54, 15%), totalling 262 patients (73.8%). Of these, the groups of W0P1, W1P1 and W0P0 were patients who received fixed anticoagulant regimens throughout the follow-up period. Warfarin was or is being prescribed in 169 patients (47.8%). Consequently, to determine the impact of anticoagulant therapy on haemostatic events, we focused on the difference between patients with and without warfarin therapy and the characteristics of the three major sub-groups with fixed anticoagulant regimens.

Warfarin therapy and the clinical characteristics

The rate of warfarin use 1, 5, 10 and 15 years post-Fontan was 144 (41%), 51 (19%), 24 (13%) and 17 (16%), respectively. Compared with patients without warfarin therapy, those given warfarin were older (6.5 ± 6.0 vs 5.0 ± 4.5, P = 0.0054) with a significantly higher CVP (11 ± 3 vs 10 ± 2, P = 0.0065) and lower arterial oxygen saturation (92 ± 6 vs 94 ± 3, P = 0.0002). The same trend was observed 5 years after the operation (data not shown), indicating that, in our institution, warfarin was or has been prescribed for sicker patients with impaired haemodynamics.

Major sub-groups and their clinical characteristics

Age and haemodynamics 1, 5, 10 and 15 years after the Fontan operation are summarized in Table 2. As described above, patients

Table 2: Comparison of haemodynamics and functional capacity among three major Fontan groups according to fixed anticoagulant prescription during follow-up

Follow-up		1		5		10	15
Cases		199		135		77	42
W0P0		55		32		24	13
W0P1		96		76		40	25
W1P1		48		27		13	4
Age (years)							
W0P0		5.4 ± 4.3		9.4 ± 4.1		15.6 ± 4.8	18.3 ± 2.9
W0P1	**	4.2 ± 3.0	**	8.1 ± 3.1		13.5 ± 3.2	18.6 ± 3.4
W1P1		7.6 ± 7.5†		12.0 ± 7.1†		15.3 ± 4.8	20.9 ± 6.6
Haemodynamics							
CVP (mmHg)							
W0P0		10 ± 2		11 ± 2		11 ± 2	10 ± 2
W0P1	**	10 ± 2	**	10 ± 2		10 ± 3	10 ± 2
W1P1		12 ± 4$^{\#,\dagger}$		12 ± 3†		12 ± 3	10 ± 3
EF (%)							
W0P0		57 ± 12		59 ± 11		55 ± 14	52 ± 13
W0P1		56 ± 11		57 ± 10		55 ± 8	52 ± 10
W1P1		56 ± 14		57 ± 10		60 ± 11	56 ± 8
CI (l/min/m^2)							
W0P0		3.0 ± 0.7		3.1 ± 0.7		2.7 ± 0.7	2.6 ± 0.8
W0P1		3.1 ± 0.6		3.1 ± 0.6		3.1 ± 0.9	2.7 ± 0.6
W1P1		3.0 ± 1.2		3.2 ± 0.8		3.3 ± 1.1	2.2 ± 0.9
SaO_2 (%)							
W0P0		94 ± 5		94 ± 3		94 ± 4	94 ± 7
W0P1	***	94 ± 2	**	95 ± 2	***	95 ± 2	94 ± 2
W1P1		91 ± 8$^{\#,\dagger}$		93 ± 4†		90 ± 9$^{\#,\dagger}$	94 ± 3

Values are the mean ± SD.
CI: cardiac index; CVP: central venous pressure; EF: ejection fraction of the systemic ventricle; SaO_2: arterial oxygen saturation.
$^{\#}$and †indicate statistically significant vs group of W0P0 and W0P1, respectively.
*, ** and ***indicate $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

receiving continuous warfarin (W1P1) also had impaired haemodynamics (high CVP and hypoxia) for, at least, the last 10 years postoperatively, again indicating that warfarin has been prescribed for sicker patients with impaired haemodynamics.

Predictors of haemostatic events

In all 412 patients, 29 haemostatic events (7.0%) occurred consisting of 11 (2.7%) thrombo-embolic and 18 (4.4%) haemorrhagic events. Thrombo-embolism included thrombus formation in the Fontan pathway in 7, cerebral infarction in 3 and myocardial infarction in 1, while haemorrhagic events included haemoptysis in 13, cerebral bleeding in 3, and intestinal bleeding and bleeding from varicose veins of the lower extremity in 1 each. The incidence of total haemostatic events is shown in (Fig. 2a–d). Overall, the incidence rates were around 1–2% until 15 years after the operation; they then increased up to 5%. Incidences of thrombo-embolic events were relatively high immediately after and remotely after the operation, showing a U-shaped incidence pattern (Fig. 2a). Total haemostatic, thrombo-embolic and haemorrhagic event-free curves are also shown in Fig. 2b–d. Notably, 12 (41%) of the 29 patients eventually died, especially noteworthy being that 8 (73%) of those patients had thrombo-embolic events.

Predictors of haemostatic events in all our patients are summarized in Tables 3 (for the early postoperative phase) and 4 (for the late phase). We separately analysed the predictors of haemorrhagic and thrombo-embolic events in the early phase. However, in the late-phase analysis, we had to focus on the haemorrhagic events because of the small number of thrombo-embolic events late after the Fontan operation.

Predictors of early haemorrhagic events in the very early postoperative phase (before 1 year in Table 1), using preoperative haemodynamics, including pulmonary artery pressure instead of CVP, late Fontan operation and use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker before the Fontan operation, were independent predictors ($P < 0.05$ for both). When the thrombo-embolic events were separately analysed, low cardiac index (systemic flow index in this condition) before Fontan operation emerged as the only predictor ($P = 0.0497$). Although late Fontan operation, heterotaxy syndrome, fenestration, high CVP, use of antiarrhythmic drugs and/or pacemaker implantation, and low Sat were associated with the haemorrhagic events, one year after the operation no independent variables were determined. As for thrombo-embolic events, low Sat was the only independent predictor ($P = 0.0192$) and low cardiac index tended to be associated with the events according to the univariate analysis ($P = 0.0721$). A Kaplan–Meier curve of those with cardiac index ≤2.54 and >2.54 l/min/m^2 and that of those with Sat ≤85 and >85% 1 year after the Fontan operation are shown in Fig. 3a and b, respectively.

Predictors of late haemorrhagic events: based on the data on 5- and 10-year postoperative variables, in addition to heterotaxy syndrome throughout the period, male gender and low Sat were the

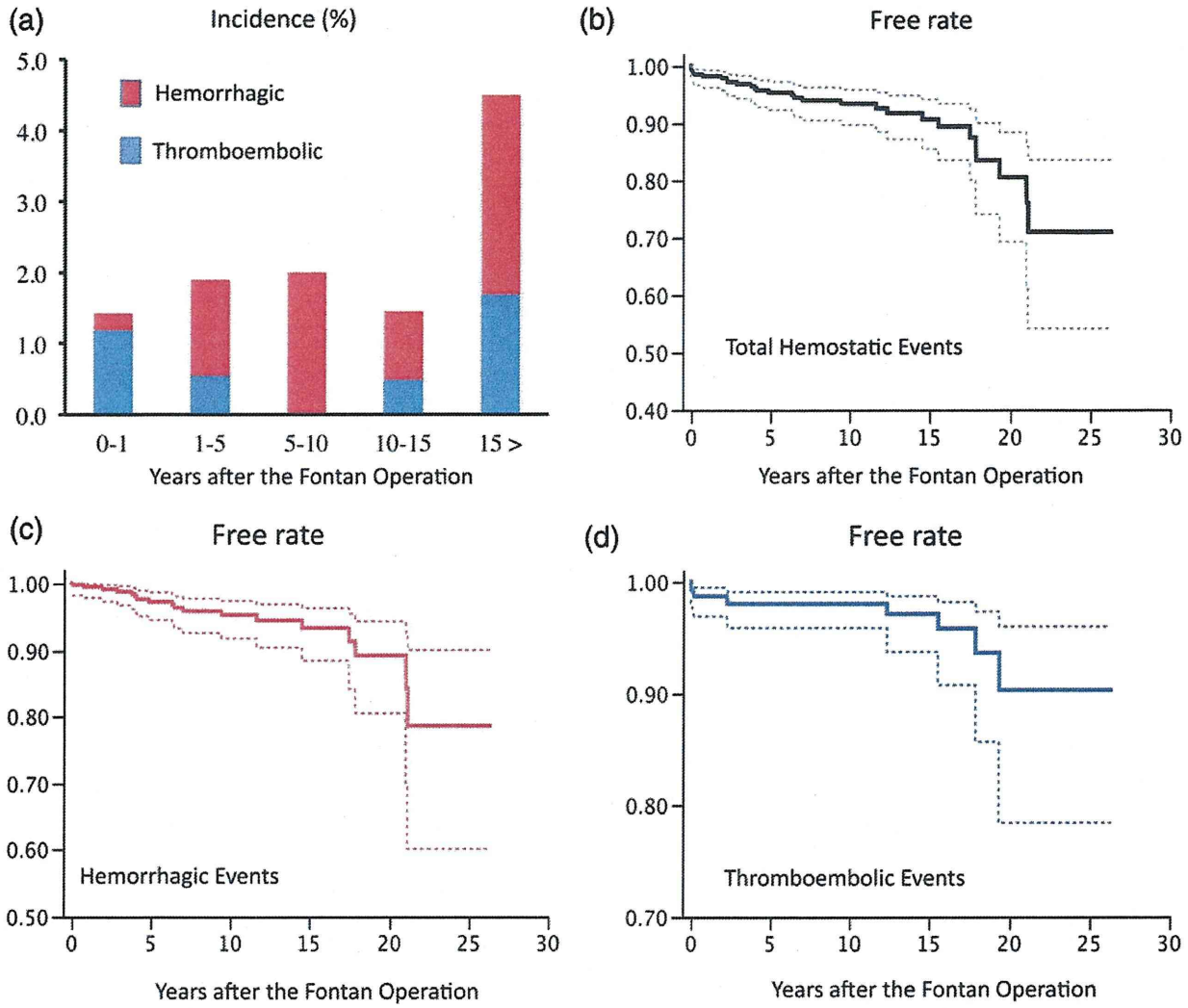

Figure 2: Incidence (**a**) and haemostatic, thrombo-embolic and haemorrhagic event-free curves in Fontan patients. Total event-free curve of thrombo-embolism and haemorrhage (**b**), thrombo-embolic (**c**) and haemorrhagic (**d**) event-free curves are shown. Each dotted line indicates the 95% confidence interval.

independent predictors for the 5- and 10-year analysis, respectively. However, no independent variables were determined in the 15-year analysis although heterotaxy syndrome tended to be predictive ($P = 0.074$). The impact of heterotaxy syndrome on the haemorrhagic events for the 5- and 10-year analysis is shown respectively, in Fig. 3c and d.

Impact of anticoagulation on haemostatic events

We sub-divided the patients into four sub-groups based on anticoagulation with warfarin and the percentages of those regimens at the 1-, 5-, 10- and 15-year phases are shown in Fig. 4a. The rate of warfarin use had gradually decreased and most of the rest were on antiplatelet agents or no treatment. The impact of anticoagulation regimens on haemorrhagic events was analysed in the groups of W0P1, W1P1 and W0P0 (fixed anticoagulation regimens), a long-term use of warfarin was associated with the high prevalence of haemorrhagic events (Fig. 4b). When an intention-to-treat-like approach was applied for the analysis of the impact of anticoagulation regimens at the time of 1- and 5-year postoperative status on the following haemorrhagic events (Fig. 4c and d, respectively), the group W1P1 showed 8.4 times higher haemorrhagic event prevalence than that of group W0P1 (95% confidence interval 1.61–61.1, $P = 0.0123$) based on the analysis of 5-year postoperative anticoagulant regimens.

DISCUSSION

In the present study, we learned the following about our Fontan patients: (i) patients with symptomatic thrombo-embolic events had a high mortality rate (73%, 8 of 11); although the total prevalence rate was relatively low (2.7%, 11 of 412), there were two high prevalence periods: one immediately post-Fontan (45%, <6 months) and the other long term (27%, ≥15 years) (Fig. 2a). Haemorrhagic events, mainly haemoptysis, were more common (4.4%, 18 of 412) than thrombo-embolic events (2.7%) and their prevalence steadily increased during the late follow-up. (ii) No definite risk factor(s) for all haemostatic events were found during the follow-up period although heterotaxy syndrome had a significant impact on the late haemorrhagic events. Furthermore, we were unable to identify predictors for late thrombo-embolic events because of the limited number of events. Finally, (iii) anticoagulant regimens varied widely,

Table 3: Univariate and multivariate predictors of haemorrhagic and thrombo-embolic events in all early Fontan survivors

	Before 1 year						1 year					
	Haemorrhagic (n = 18)			Thrombo-embolic (n = 11)			Haemorrhagic (n = 16)			Thrombo-embolic (n = 5)		
	HR	95% Confidence interval	P value	HR	95% Confidence interval	P value	HR	95% Confidence interval	P value	HR	95% Confidence interval	P Value
Univariate analyses												
Patient characteristics												
Age at first Fontan (years)	1.09	1.01-1.16	**0.0227**	1.06	0.96-1.13	0.2057	1.12	1.03-1.20	**0.0088**	1.08	0.88-1.22	0.4077
Male	1.91	0.72-6.00	0.2010	1.29	0.39-4.96	0.6781	2.21	0.77-7.93	0.1483	3.26	0.48-64.1	0.2452
Non-LV SV	1.05	0.41-2.86	0.9230	0.82	0.25-2.84	0.7409	1.38	0.50-4.38	0.5459	1.04	0.17-7.90	0.9677
Heterotaxy syndrome	2.29	0.89-5.89	0.0828	1.23	0.32-4.09	0.7421	2.72	1.01-7.62	**0.0472**	1.32	0.17-7.97	0.7652
Type of repair												
APC vs TCPC	0.93	0.21-2.88	0.9127	2.86	0.73-9.67	0.1214	0.82	0.13-2.98	0.7881	3.68	0.48-22.7	0.1877
Fenestration	4.70	1.30-13.7	**0.0212**	-	-	-	5.42	1.49-16.1	**0.0135**	-	-	-
Medications												
Wafarin	1.83	0.64-5.47	0.2588	0.50	0.02-3.53	0.5172	2.21	0.82-6.23	0.1162	2.37	0.39-18.1	0.3385
Antiplatelet	1.47	0.54-4.07	0.4494	0.31	0.02-2.07	0.2483	0.70	0.26-1.96	0.4793	0.37	0.05-2.25	0.2717
Diuretics	1.18	0.41-3.48	0.7614	0.57	0.08-3.02	0.5218	0.97	0.35-2.88	0.9488	2.40	0.35-47.2	0.3994
ACEI/ARB	5.60	1.22-19.6	**0.0298**	5.83	0.27-61.0	0.208	2.97	0.66-9.73	0.138	-	-	-
β-Blocker	7.83	0.42-43.1	0.132	-	-	-	-	-	-	-	-	-
Antiarrhythmic/PMI	1.46	0.08-7.50	0.7287	3.53	0.51-15.6	0.1730	3.71	1.02-11.0	**0.0472**	3.68	0.18-28.1	0.3217
Haemodynamics												
PAP[a]/CVP (per 1 mmHg)	1.07	0.96-1.18	0.2394	0.92	0.77-1.07	0.3129	1.23	1.04-1.44	**0.0141**	1.25	0.93-1.65	0.132
PA index (per 10 mm^2/m^2)	0.98	0.93-1.01	0.2255	0.98	0.92-1.03	0.4504	0.96	0.90-1.02	0.247	0.98	0.86-1.08	0.6472
EF (per 1%)	1.00	0.95-1.05	0.9873	0.96	0.91-1.02	0.1867	0.99	0.95-1.04	0.7583	0.95	0.89-1.02	0.1787
Cardiac index (per 1.0 $l/min/m^2$)	1.05	0.65-1.56	0.8347	0.49	0.22-1.00	**0.0497**	1.26	0.65-2.18	0.4697	0.25	0.04-1.12	0.0721
Arterial oxygen saturation (per 1%)	0.96	0.90-1.04	0.3229	1.08	0.97-1.21	0.1645	0.93	0.89-1.00	**0.0429**	0.88	0.82-0.95	0.0044
Multivariate analyses												
Age at first Fontan (years)	1.12	1.03-1.20	**0.012**	-	-	-	-	-	-	-	-	-
ACEI/ARB	7.41	1.46-29.8	**0.0191**	-	-	-	-	-	-	-	-	-
Arterial oxygen saturation (per 1%)	-	-	-	-	-	-	-	-	-	0.88	0.82-0.95	**0.0044**

Bold values indicates statistically significant. Italic values indicates a tendency of statistical significance on the multivariate analysis.
SV: systemic ventricular; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; PAP: pulmonary artery pressure; TCPC: total cavopulmonary connection; PA: pulmonary artery; PMI: pacemaker implantation. Other abbreviations are the same as in Tables 1 and 2.
[a]PAP is only for the analysis of before 1 year.

and warfarin therapy had been applied to sicker patients with impaired haemodynamics. Consequently, warfarin therapy might be associated with a high prevalence of haemorrhagic events.

Thrombo-embolic events

The pathophysiology of thrombo-embolic events in Fontan patients may be explained in the context of Virchow's triad, i.e. abnormal 'blood flow', 'blood constituents' and 'vessel wall' [5]. In the Fontan circulation, venous systemic flow is sluggish, and inappropriate intra- or extracardiac Fontan pathways may cause whirlpool effects, resulting in thrombus formation [14]. Our observations of a high prevalence (45%) immediately after the Fontan operation and the high mortality (73%) do not contradict previous reports [2, 15] although symptomatic thrombo-embolic events were relatively rare (2.7%). Early postoperative hypoxia and low cardiac output were also demonstrated in our thrombo-embolic patients. These unstable 'sluggish blood flow states' in conjunction with the unique features of the Fontan circulation immediately after the operation could have predisposed patients to thrombo-embolic events. In fact, in addition to low Sat, low cardiac index tended to be associated with thrombo-embolic events (P = 0.0721) according to the univariate analysis (Table 3, Fig. 3a). However, use of antiarrhythmic drug(s), including pacemaker implantation, was not associated with the events, as previously reported [16].

We did not evaluate the other two abnormalities, 'blood constituents' and 'vessel wall'. Many investigators have demonstrated that Fontan patients have 'abnormal blood constituents', i.e. coagulation and fibrinolytic factor abnormalities. An association between factor VIII and thrombo-embolic events has been proposed [17]; however, the factor is low in the adult stage [18]. Further confounding the issue is the possibility of ethnic differences in the coagulation abnormalities [11]. In addition, some investigators have demonstrated endothelial dysfunction of the 'abnormal vessel wall' of the triad [19], which may also contribute to thrombo-embolic events in Fontan patients. Furthermore, those abnormal haemostatic profiles may change over time [18], creating a difficulty in employing stereotyped thrombo-prophylactic strategies in growing Fontan patients.

Haemorrhagic events

Interestingly, we found that haemorrhagic events, haemoptysis in particular, were more common than thrombo-embolic events in our Fontan patients. The close association of a high prevalence of