

Factors Associated With Thrombotic Complications After the Fontan Procedure

A Secondary Analysis of a Multicenter, Randomized Trial of Primary Thromboprophylaxis for 2 Years After the Fontan Procedure

Brian W. McCrindle, MD, MPH,* Cedric Manlhiot, BSc,* Andrew Cochrane, MD,† Robin Roberts, MSc,‡ Marina Hughes, DPHIL,† Barbara Szechtman, BA,‡ Robert Weintraub, MBBS,† Maureen Andrew, MD,* Paul Monagle, MD, MSc, MBBS,† for the Fontan Anticoagulation Study Group
Toronto and Hamilton, Ontario, Canada; and Melbourne, Australia

- Objectives** The study sought to identify factors associated with increased risk of thrombosis after Fontan.
- Background** The Fontan procedure is the culmination of staged palliation for patients with univentricular physiology. Thrombosis is an important complication after this procedure.
- Methods** An international multicenter randomized controlled trial of acetylsalicylic acid versus warfarin for thromboprophylaxis after the Fontan procedure was conducted in 111 patients, and did not show a significant difference regarding thrombotic complications. We performed a secondary analysis of this previously published manuscript to identify factors associated with thrombosis in this population. Standardized prospective data collection included independent adjudication of all events.
- Results** At 2.5 years after randomization, time-related freedom from thrombosis was 69% (all venous, no arterial events), with 28% of thrombosis presenting with clinical signs or events. Hazard of thrombosis was highest immediately after Fontan with a gradual increase in risk during late follow-up. In multivariable models, factors associated with higher risk of thrombosis were pulmonary atresia with intact ventricular septum (hazard ratio [HR]: 3.64, 95% confidence interval [CI]: 1.04 to 12.70, $p = 0.04$), pulmonary artery distortion (HR: 2.35, 95% CI: 0.96 to 5.73, $p = 0.06$), lower pre-operative unconjugated bilirubin (HR: 0.84 $\mu\text{mol/l}$, 95% CI: 0.72 to 0.99, $p = 0.04$), use of central venous lines for >10 days or until hospital discharge (HR: 17.8, 95% CI: 3.97 to 79.30, $p < 0.001$), and lower FIO_2 24 h after the procedure (HR: 0.67/10%, 95% CI: 0.45 to 1.00, $p = 0.06$). Patients on warfarin who consistently achieved minimum target international normalized ratio levels or those on acetylsalicylic acid had a decrease in risk of thrombosis compared with patients who often failed to meet target international normalized ratio level (HR: 3.53, 95% CI: 1.35 to 9.20, $p = 0.01$).
- Conclusions** More favorable thromboprophylaxis strategies are needed in light of the difficulties in controlling warfarin therapy and the high prevalence of thrombosis in this population (International Multi Centre Randomized Clinical Trial of Anticoagulation in Children Following Fontan Procedures; NCT00182104) (J Am Coll Cardiol 2013;61:346–53) © 2013 by the American College of Cardiology Foundation

Thrombosis and thromboembolic events are a major cause of morbidity and mortality after the Fontan procedure. Multiple observational studies with various designs and duration of follow-up have reported the prevalence of thrombosis after the Fontan procedure to be between 1%

and 33% (1–8), with the highest prevalence reported in studies using systematic detection protocols with transesophageal echocardiography (TEE) (4,9). Previous studies

See page 354

From the *Labatt Family Heart Centre, Department of Paediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada; †Department of Paediatrics, University of Melbourne, Royal Children's Hospital and Critical Care and Neurosciences Theme, Murdoch Children's Research Institute, Melbourne, Australia; and the ‡McMaster University, Hamilton, Ontario, Canada. This work was supported by a research grant from the Heart and Stroke Foundation of Ontario (grant-in-aid NA-3565), National Heart Foundation of Australia project grant, the Henderson Research Centre, Hamilton, and the CIBC World Markets Children's

Miracle Foundation. Mr. Roberts is a statistical consultant for Coaxia Inc. and Bayer Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. A version of this paper was presented at the 2008 Scientific Sessions of the American Heart Association, November 8 to 12, 2008, New Orleans, Louisiana. Dr. Andrew is now deceased.

Manuscript received May 10, 2012; revised manuscript received July 24, 2012, accepted August 13, 2012.

have shown a high, immediate risk of thrombosis after the procedure, likely related to the surgery and the impact of cardiopulmonary bypass itself (10). There also appears to be an increasing risk over the long term after Fontan (11), culminating in a substantial proportion of late-term (>10 years) mortality in this population being associated with thromboembolic complications (7,12,13).

Multiple studies have explored the effectiveness of thromboprophylaxis strategies in this population (3,14); consensus has yet to be achieved on the matter. This has led to institutional variation in practices, with some centers using low-intensity antiplatelet-based therapy and others using high-intensity anticoagulation-based therapy (15). Therapy is selected on the basis of physician discretion, with decision making being driven by weighing the perceived thrombosis risk for a given patient against the inherent risks of long-term anticoagulation (14). In this context, an evidence-based stratification of patients according to thrombosis risk would be a useful tool in selecting the intensity of thromboprophylaxis strategy warranted in these patients.

Few risk factors have been confirmed from observational studies, including the presence of bilateral bidirectional cavopulmonary shunts, a blind-ended pulmonary artery stump, a hypoplastic chamber with stasis of flow, and previous thrombosis (2,16). An atriopulmonary or Kawashima Fontan connection type, presence of thrombogenic material, dilated atrium, arrhythmias, ventricular dysfunction, patent fenestration, and protein-losing enteropathy have all also been hypothesized as potential risk factors in this population (7,17). Increased presence of thrombophilic risk factors have been described, with uncertain clinical meaning, both before and after Fontan (18–23). As a secondary analysis of a prospective, multicenter randomized clinical trial of thromboprophylaxis strategies for the first 2 years after the Fontan procedure (24), we sought to identify factors associated with increased risk of thrombosis in this population.

Methods

This is a secondary analysis of a previously published randomized controlled trial. Complete details of study intervention and trial results have been previously reported (24).

Study subjects. Patients were recruited between 1998 and 2003 from 6 institutions (242 patients screened, 208 eligible, 111 enrolled and randomized). All patients who underwent Fontan procedure at participating institutions were eligible for inclusion in the trial. Exclusion criteria were a recognized indication for long-term anticoagulation; patient characteristics increasing the risk of hemorrhagic complications; known contraindication for heparin, warfarin, or acetylsalicylic acid (ASA); and the inability to supervise therapy because of social or geographic circumstances.

Randomization and study intervention. Randomization (centrally performed but stratified by center) was performed immediately after completion of the Fontan procedure. Subjects were randomized to either warfarin therapy (0.1

mg/kg titration to achieve and international normalized ratio (INR) of 2 to 3 with heparin lead-in) or ASA (5 mg/kg/day) for a 2-year period after the procedure. INR monitoring was prescribed to be performed at least every 2 to 3 weeks for stable patients and more frequently for patients with dosing challenges. Proportion of INR measurement within the target range was calibrated to risk and then included in risk factor analyses. On the basis of this analysis, we defined controlled warfarin therapy as >30% of INR measurements within the target range (INR 2 to 3).

Measurements. Demographics, underlying cardiac anatomy, previous interventions and complications, and previous and current medical therapy were abstracted for each patient from their respective medical records, including data regarding the Fontan procedure and post-operative complications. Patients were asked to undergo clinical evaluation at 3, 6, 12, 18, and 24 months after randomization and whenever it was clinically indicated regardless of whether they were still taking their assigned study medication and/or had reached a study endpoint. Thrombotic events (venous or arterial) were the study primary endpoint. Thrombosis was defined as the appearance of a space-occupying lesion on ultrasound within the cardiovascular system (mild laminar thickening of the internal surface of the Fontan pathway was not included) or the occurrence of a clinical event known to be strongly associated with thrombus (stroke, pulmonary embolism). Thrombosis with clinical presentation or clinical events known to be strongly associated with thrombus (cardioembolic stroke, pulmonary embolism), were captured for all patients, regardless of whether planned echocardiography or TEE were performed. Trans-thoracic echocardiography and TEE were sought twice at 3 and 24 months post-Fontan procedure. An independent central adjudication committee reviewed all clinically driven and routine echocardiograms. All thrombosis and major adverse clinical events were adjudicated by an expert panel.

Statistics. Data are presented as mean \pm SD, median with minimum and maximum value, and frequency, as appropriate. Time-related risk of thrombosis was modeled in parametric hazard regression model (maximum likelihood method for parameter estimation), which allows for risk of thrombosis to be divided in up to 3 distinct phases of risk, although only an early and a late phase were present in this study. Because of the limited number of events, risk hazard analysis was performed assuming a single phase of risk. A stepwise variable selection strategy was used (forward entry, only variables with univariable p values <0.10 eligible for entry) to create a multivariable parametric survival regression model. All analyses presented in this study combined

Abbreviations and Acronyms

ASA	= acetylsalicylic acid
CI	= confidence interval
CNS	= central nervous system
HR	= hazard ratio
INR	= international normalized ratio
TEE	= transesophageal echocardiography

both groups. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

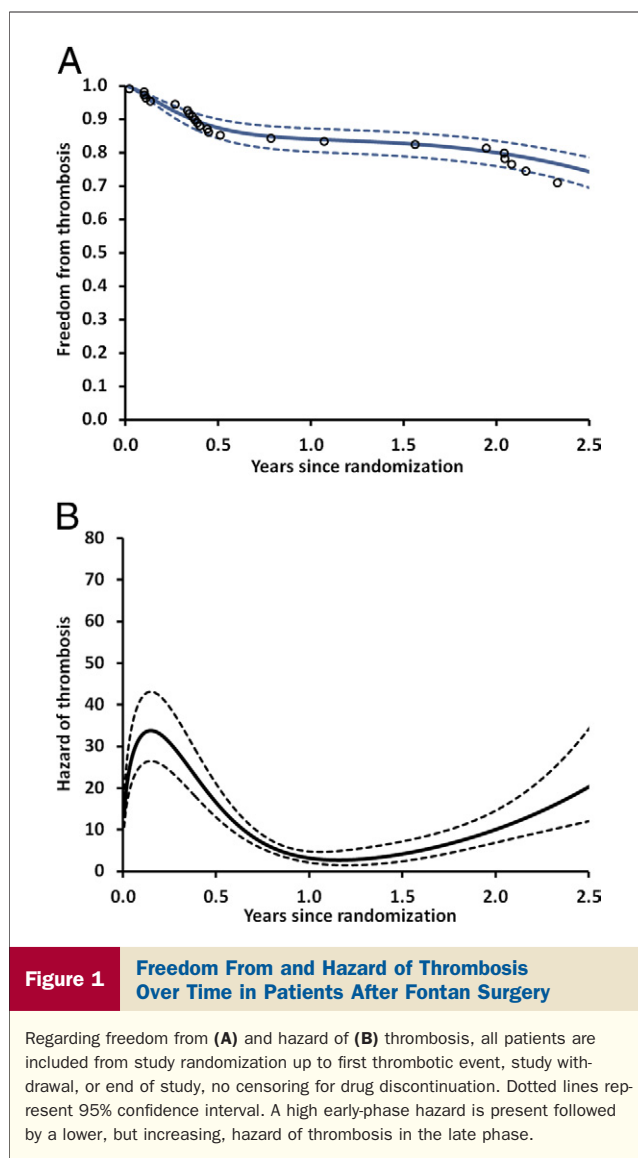
Study population. A total of 111 patients (64% male, average age at Fontan 4.8 ± 2.8 years) were enrolled. Primary diagnoses were tricuspid atresia ($n = 21$, 19%), double inlet left ventricle ($n = 21$, 19%), double outlet right ventricle ($n = 12$, 11%), pulmonary atresia with intact ventricular septum ($n = 6$, 5%), unbalanced atrioventricular septal defect ($n = 10$, 9%), hypoplastic left heart ($n = 17$, 15%), and other/multiple anomalies ($n = 24$, 22%). The majority of patients had previous cardiac catheterization ($n = 63$, 56%), and 24 (22%) had a previous Norwood operation. A total of 72% of patients had a previous bidirectional cavopulmonary shunt, 14% had a bilateral cavopulmonary shunt, and 14% had undergone the Damus-Kaye-Stansel procedure. The majority of patients had a Fontan procedure utilizing an extracardiac conduit ($n = 95$, 85%) with GORE-TEX baffle ($n = 81$, 73%) and fenestration ($n = 69$, 62%).

Original trial results. The original trial found no difference in risk of thrombosis between patients randomized to warfarin ($n = 54$) versus those randomized to ASA ($n = 57$); hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 0.62 to 3.00, $p = 0.45$) at the 2 years study endpoint (24). Patient characteristics and compliance with study procedures and measurements were similar between both experimental groups (24). Because of the lack of differences, all analyses presented in this study combined both groups.

Study follow-up and compliance with study procedures. Of the 111 patients enrolled in this study, 3 patients died or were withdrawn from the study prior to study end or reaching primary outcomes. A further 3 patients died or were withdrawn from the study after reaching the study primary outcome. All other patients attended the final study visit within 30 months of enrollment. Complete accrual of clinical events was obtained, 81% of patients underwent at least 1 TEE (69% having the 3-month TEE, 61% having the 24-month TEE) and 48% having both protocol TEEs.

Prevalence of thrombosis. At 2.5 years after randomization, time-related freedom from thrombosis was 69% (all venous, no arterial events), with 28% of thrombosis presenting with clinical signs or events. Time-related risk of thrombosis was divided in 2 distinct phases—an early phase of risk spanning the first 6 months after the Fontan procedure, followed by late phase spanning the subsequent 2 years (Fig. 1). The risk of thrombosis associated with a clinical presentation was highest immediately following Fontan surgery, but persisted with a gradual increase throughout the study period.

Compliance with study drug assignment and protocol. Early discontinuations of study drug were more frequent in the warfarin group (19% vs. 9%), with patients assigned to ASA therapy spending 92% of expected study days on the



study drug compared to 84% for patients assigned to warfarin ($p = 0.02$). A total of 2,166 INR monitoring values were available in 45 patients (INR monitoring results were not available for 9 patients), of which 41% were below target range (<2), 44% were within target range, and 15% were above target range (>3). According to our classification 30/45 patients (66%) assigned to warfarin had controlled INR ($>30\%$ of INR values within target) and 15 of 45 patients (33%) had uncontrolled INR ($\leq 30\%$ within of INR values within target). None of the factors evaluated in this study was found to be associated with increased risk of poorly controlled warfarin therapy.

Factors associated with increased risk of thrombosis. Patient characteristics at the time of randomization are presented in Table 1, stratified according whether they developed thrombosis during follow-up. Because of the limited number of events, risk factor analysis was performed by combining the early and the late phase into a single phase of risk. Factors associated with thrombosis in multivariable

parametric regression models are listed in Table 2. In multivariable models, factors associated with higher risk of thrombosis included pulmonary atresia with intact ventricular septum (HR: 3.64, 95% CI: 1.04 to 12.70, $p = 0.04$), pulmonary artery distortion before Fontan procedure (HR: 2.35, 95% CI: 0.96 to 5.73, $p = 0.06$), lower pre-operative unconjugated bilirubin (HR: 0.84 $\mu\text{mol/l}$, 95% CI: 0.72 to 0.99, $p = 0.04$), post-operative use of central venous lines for >10 days or until discharge (HR: 17.8, 95% CI: 3.97 to 79.30, $p < 0.001$), and lower FiO_2 at 24 h post-surgery (HR: 0.67, 95% CI: 0.45 to 1.00, $p = 0.06$). Patients on warfarin who achieved target INR levels >30% of time or those on acetylsalicylic acid had a 3.5-fold decrease in risk of thrombosis compared patients who often failed to meet target INR level (HR: 3.53, 95% CI: 1.35 to 9.20, $p = 0.01$) (Fig. 2). The difference in risk between controlled warfarin and ASA was not statistically significant (HR: 0.34, 95% CI: 0.10 to 1.13, $p = 0.08$). There was no association between presence of pulmonary atresia or pulmonary artery distortion and location of thrombosis. Year of enrolment, age at Fontan surgery, interventions prior to Fontan, previous thromboembolic complications, pre-operative hematological laboratory values, or hemodynamics and type of Fontan connection were not associated with risk of thrombosis.

Discussion

The current study found that there is a substantial immediate risk of thrombosis which diminishes but persists over the first 2.5 years after Fontan procedure. Overall time-related risk of thrombosis as found in this study was somewhat different from that reported before in population-based observational studies (3,11,17), which have showed a ~10% surgery-related thrombosis prevalence and then an ongoing risk over time. Prevalence of surgery-related thrombosis has previously been reported (10) at approximately ~10% for low-risk surgeries such as the Fontan procedure. Because patients with surgery-related thrombosis are often required to be on anticoagulation for an extended period of time, these patients would not have been eligible for this study. Our rate of thrombosis after the immediate high-risk surgical period in enrolled patients is consistent with previously reported studies (11). Of note, all thromboses were found in the venous system. This is consistent with previous reports where thrombosis is typically located within both pulmonary and systemic venous systems (2,25). However, no thromboembolic event, such as central nervous system (CNS) or pulmonary or coronary artery embolism, were noted in our subjects. There was no routine CNS surveillance, so clinically silent events may have been missed. Previous studies have reported the incidence of stroke to be as high as 19% post-Fontan (2,7,26–28).

Factors associated with thrombosis in this population included anatomical characteristics, pre-operative clinical

status and post-operative outcomes, and anticoagulation management. Anatomical factors disturbing laminar blood flow are known to increase the risk of thrombosis in children with congenital heart disease by creating physiological dead ends and areas of sluggish flow promoting thrombus formation (2,16). Other identified risk factors have been associated with increased propensity to clot, either by promoting platelet activation through inflammation (low oxygen saturation), impaired metabolism of coagulation proteins secondary to liver dysfunction (low bilirubin) (29–31), and/or damage to vascular walls (central venous lines). Most of these risk factors have been reported previously, both in the Fontan population and in other populations with congenital heart disease (10). Of particular importance is the increased risk of thrombosis associated with prolonged use of central venous lines (10). Aggressive strategies for early line removal and interventions aimed at reducing the prevalence of line-related thrombosis might have an important impact on the occurrence of early thrombosis in this population.

The most important finding of this study is the decreased risk of thrombosis associated with properly controlled warfarin therapy or ASA compared with warfarin therapy with <30% of INR monitoring within the target range. Difficulties in controlling warfarin therapy are well documented in pediatric patients (32,33). Individual response to warfarin varies between patients on the basis of physiological and genetic factors. Furthermore, warfarin dosing is known to be affected by a multitude of drug and food interactions. Previous studies have shown minimal anticoagulation activity with INR <2, and almost nonexistent anticoagulation activity when INR falls below 1.5 (34).

Our study showed an increased risk of thrombosis for patients with poorly controlled warfarin therapy. Clinically, this finding has multiple implications; it may provide an explanation why previous studies have found inconsistent results regarding the efficacy of strategies for thromboprophylaxis in Fontan patients. The earliest nonrandomized comparison reported better event-free survival for patients receiving warfarin versus no anticoagulation (3). Three small case series with few events (2 studies, $n = 4$; 1 study, $n = 10$) concluded that there was no influence of anticoagulation (6,28,35). The trial on which this study is based found no differences between ASA and warfarin (24). Finally, a recent single-center observational study of thromboprophylaxis in single ventricle patients, in which warfarin was favored for the majority of patients, found that warfarin-based thromboprophylaxis was associated with a significant reduction of thrombosis risk compared with no thromboprophylaxis and to ASA-based thromboprophylaxis (11).

The other important clinical consideration raised by these results regards the risk-benefit ratio for these patients. Since risk reduction for thrombosis is minimal in patients with poorly controlled warfarin therapy, the risk of anticoagulation becomes unwarranted. Future studies should try to determine patient characteristics are associated with diffi-

Table 1 Factors Associated With Thrombosis

	n	No Thrombosis	n	Thrombosis	Univariable HR (95% CI)	p Value
Treatment and randomization						
Treated with aspirin	86	45 (52%)	25	12 (48%)	0.74 (0.33–1.09)	0.45
Controlled warfarin	86	27 (31%)	25	3 (12%)	0.34 (0.10–1.13)	0.08
Uncontrolled warfarin	86	8 (9%)	25	7 (28%)	3.70 (2.81–4.58)	0.004
Warfarin monitoring, no data	86	6 (7%)	25	3 (12%)	2.17 (0.64–7.33)	0.21
Demographics						
Gender (female)	86	27 (31%)	25	13 (52%)	0.50 (0.23–1.10)	0.09
Older age at surgery, yrs	86	4.7 ± 2.6	25	4.7 ± 3.9	1.05 (0.93–1.19)	0.45
Greater weight (kg) at surgery	86	17.0 ± 6.8	25	18.1 ± 8.8	1.01 (0.96–1.06)	0.86
Primary diagnosis						
Tricuspid atresia	86	16 (19%)	25	5 (20%)	1.03 (0.39–2.76)	0.95
Double inlet ventricle	86	17 (20%)	25	4 (16%)	0.80 (0.27–2.36)	0.69
Double outlet right ventricle	86	8 (9%)	25	4 (16%)	1.60 (0.54–4.72)	0.39
Pulmonary atresia with intact ventricular septum	86	3 (3%)	25	3 (12%)	3.31 (0.98–11.18)	0.05
Unbalanced atrioventricular septal defect	86	8 (9%)	25	2 (8%)	0.86 (0.20–3.65)	0.83
Hypoplastic left heart syndrome	86	14 (16%)	25	3 (12%)	0.95 (0.28–3.20)	0.93
Previous cardiac surgical procedures						
Cardiac catheter/interventional procedures	86	48 (56%)	25	15 (60%)	1.10 (0.49–2.46)	0.81
Pulmonary artery banding	86	15 (17%)	25	5 (20%)	1.09 (0.41–2.91)	0.86
Patent ductus arteriosus ligation or clipping	86	16 (19%)	25	3 (12%)	0.76 (0.23–2.57)	0.66
Systemic-pulmonary shunt	86	49 (57%)	25	16 (64%)	1.25 (0.55–2.83)	0.60
Atrial septostomy	86	28 (33%)	25	7 (28%)	0.87 (0.36–2.09)	0.75
Norwood operation	86	18 (21%)	25	6 (24%)	1.52 (0.60–3.85)	0.38
DKS procedure for subaortic stenosis	86	13 (15%)	25	3 (12%)	0.96 (0.28–3.22)	0.94
Bidirectional cavopulmonary shunt	86	61 (71%)	25	19 (76%)	1.30 (0.52–3.28)	0.57
Bilateral cavopulmonary shunt	86	12 (14%)	25	3 (12%)	0.83 (0.25–2.77)	0.76
Classic Glenn shunt	86	7 (8%)	25	2 (8%)	1.03 (0.24–4.42)	0.96
Coarctation repair	86	6 (7%)	25	2 (8%)	1.37 (0.32–5.88)	0.67
Branch pulmonary artery repair	86	12 (14%)	25	3 (12%)	0.78 (0.23–2.61)	0.69
Previous thromboembolic event	86	13 (15%)	25	2 (8%)	0.57 (0.13–2.44)	0.45
Pre-operative assessment (bloodwork)						
Hemoglobin (×10 g/l)	86	166 ± 20	25	167 ± 20	1.00 (0.98–1.02)	0.75
Platelet count (×10 ⁹ /l)	86	280 ± 79	25	292 ± 82	1.00 (1.00–1.01)	0.64
Activated partial thromboplastin time, s	79	36.3 ± 17.9	21	32.4 ± 3.6	0.97 (0.91–1.04)	0.38
International normalized ratio (×0.1)	75	1.18 ± 0.51	18	1.05 ± 0.11	0.82 (0.57–1.18)	0.29
Prothrombin time, s	41	12.5 ± 4.5	13	13.4 ± 1.4	1.03 (0.88–1.20)	0.74
Albumin, g/l	33	39.8 ± 6.4	17	42.3 ± 3.1	1.05 (0.96–1.16)	0.30
AST, U/l	20	37 (26–163)	8	30 (18–45)	0.88 (0.79–0.99)	0.03
ALT, U/l	31	20 (9–33)	17	20 (11–33)	1.02 (0.95–1.11)	0.56
Bilirubin (conjugated), μmol/l	29	0 (0–3)	16	0 (0–11)	1.14 (0.92–1.41)	0.23
Bilirubin (unconjugated), μmol/l	31	10 (5–24)	17	9 (0–19)	0.90 (0.79–1.01)	0.07
Pre-operative assessment (cardiac catheterization)						
Mean pulmonary artery pressure, mm Hg	84	11 ± 3	25	11 ± 2	0.96 (0.81–1.13)	0.62
Mean left atrial pressure, mm Hg	64	6 ± 2	23	7 ± 2	1.10 (0.93–1.29)	0.26
Right atrial pressure, mm Hg	66	6 ± 2	22	6 ± 3	1.03 (0.87–1.23)	0.70
Systolic aortic pressure, mm Hg	83	84 ± 12	24	81 ± 12	0.98 (0.94–1.02)	0.27
Mean aortic pressure, mm Hg	81	59 ± 13	22	59 ± 9	1.01 (0.97–1.04)	0.72
SVC oxygen saturation, %	77	69 ± 10	22	69 ± 9	0.99 (0.96–1.03)	0.78
Pulmonary artery oxygen saturation, %	72	70 ± 8	22	70 ± 7	0.99 (0.94–1.04)	0.62
Left atrium oxygen saturation, %	51	86 ± 19	19	91 ± 9	1.03 (0.98–1.08)	0.25
Aorta oxygen saturation, %	79	87 ± 5	22	86 ± 6	0.98 (0.90–1.07)	0.69
Oxygen saturation in room air, %	81	81 ± 8	25	78 ± 9	0.98 (0.95–1.02)	0.39
Sinus rhythm	86	77 (90%)	25	23 (92%)	1.33 (0.31–5.67)	0.70
Current atrioventricular valve regurgitation	86	12 (14%)	25	4 (16%)	0.64 (0.24–1.70)	0.36
Current pulmonary artery distortion	86	15 (17%)	25	8 (32%)	2.25 (0.96–5.28)	0.06

Continued on the next page

Table 1 Continued

	n	No Thrombosis	n	Thrombosis	Univariable HR (95% CI)	p Value
Fontan procedure						
Type of Fontan procedure	86		25		0.27 (0.04–1.98)	0.20
Lateral tunnel/total cavopulmonary connection		15 (17%)		1 (4%)		
Extracardiac conduit		71 (83%)		24 (96%)		
Type of baffle or conduit used	86		25		0.67 (0.29–1.57)	0.36
GORE-TEX		64 (74%)		17 (68%)		
Homograft		22 (26%)		8 (32%)		
Size of baffle or conduit used, mm	79	19.0 ± 3.0	22	19.4 ± 2.5	1.02 (0.88–1.18)	0.80
Fenestration	86	55 (64%)	25	14 (56%)	0.90 (0.40–1.99)	0.79
Size of fenestration, mm	55	4.5 ± 1.8	14	3.8 ± 1.8	0.92 (0.78–1.09)	0.34
Patch repair of pulmonary artery stenosis	86	5 (6%)	25	3 (12%)	1.86 (0.55–6.27)	0.31
Atrial septostomy	86	7 (8%)	25	2 (8%)	0.99 (0.23–4.20)	0.99
Division of main pulmonary artery	86	6 (7%)	25	4 (16%)	1.81 (0.62–5.30)	0.28
Perioperative assessment						
Cardiopulmonary bypass time (×10 min)	86	106 ± 55	25	102 ± 42	0.99 (0.91–1.07)	0.78
Aortic cross-clamp time (×10 min)	86	0 (0–78)	25	0 (0–48)	0.85 (0.69–1.06)	0.14
Minimum temperature on bypass, °C	81	30.6 ± 4.2	23	31.3 ± 3.7	1.04 (0.92–1.17)	0.55
Inotropes support duration (×10 h)	86	22 (0–165)	25	24 (0–95)	0.99 (0.92–1.08)	0.88
Vasodilators support duration (×10 h)	86	12 (0–60)	25	11 (0–70)	1.14 (0.97–1.34)	0.11
Central venous line >10 days or at CCU discharge	86	4 (5%)	25	3 (12%)	3.06 (0.91–10.29)	0.07
Mean blood pressure, mm Hg	86	69 ± 11	25	71 ± 9	1.02 (0.98–1.05)	0.42
Central venous/pulmonary artery pressure, mm Hg	83	14 ± 5	24	14 ± 5	1.02 (0.93–1.11)	0.67
Left atrial pressure, mm Hg	58	8 ± 3	19	7 ± 2	0.96 (0.83–1.12)	0.64
Arterial oxygen saturation, %	82	91 ± 9	24	92 ± 6	1.02 (0.96–1.08)	0.57
Inspired oxygen (FIO ₂) (×10%)	64	41 ± 18	24	34 ± 11	0.82 (0.59–1.14)	0.24
Post-operative assessment						
Persistent effusion	86	39 (45%)	25	15 (60%)	1.79 (0.80–3.99)	0.16
Persistent chylothorax	86	16 (19%)	25	5 (20%)	1.18 (0.44–3.15)	0.75
Total parenteral nutrition	86	5 (6%)	25	3 (12%)	2.98 (0.89–10.03)	0.08
Creatinine (×10 μmol/l)	84	40 (28–105)	25	44 (25–80)	0.97 (0.82–1.13)	0.67
AST (×20 U/l)	38	59 (16–2,658)	15	51 (29–2,617)	1.03 (0.90–1.16)	0.70
ALT (×20 U/l)	50	26 (11–1,142)	21	36 (16–540)	1.01 (0.99–1.03)	0.18
Duration of ventilation (×10 h)	86	10 (3–190)	25	11 (3–143)	1.00 (0.94–1.08)	0.89
Duration of intensive care unit stay, days	84	2 (1–7)	25	2 (1–7)	0.98 (0.82–1.16)	0.81
Central venous lines >10 days	86	4 (5%)	25	3 (12%)	2.97 (0.45–16.42)	0.19

Values are n (%), mean ± SD, or median (5th, 95th percentile).

ALT = alanine aminotransferase; AST = aspartate transaminase; CCU = critical care unit; CI = confidence interval; DKS = Damus-Kaye-Stansel; HR = hazard ratio; SVC = superior vena cava.

culties achieving consistent anticoagulation with warfarin. The thromboprophylaxis strategy in these patients should be carefully selected taking this information into account.

Table 2 Factors Associated With Thrombosis in Multivariable Regression Model

Variables	Multivariable HR (95% CI)	p Value
Pulmonary atresia with intact ventricular septum	3.64 (1.04–12.7)	0.04
Pulmonary artery distortion	2.35 (0.96–5.73)	0.06
Lower preoperative bilirubin (unconjugated), μmol/l	0.84 (0.72–0.99)	0.04
Central venous line >10 days or at CCU discharge	17.8 (3.97–79.3)	<0.001
Lower inspired oxygen (FIO ₂) at 24 h after surgery (×10%)	0.67 (0.45–1.00)	0.06
Uncontrolled warfarin thromboprophylaxis	3.53 (1.35–9.20)	0.01

Abbreviations as in Table 1.

Patients who have started warfarin-based thromboprophylaxis but who are unable to maintain adequate INR levels may be better off receiving ASA therapy alone. New oral anticoagulants, which have been shown in adult trials to be noninferior regarding efficacy while being more stable, easier to dose, and overall safer than warfarin (36–39), might be a solution for this population, however, as their safety in children is undetermined, future comparative trials would be required (40).

Study limitations. This study must be viewed in light of some limitations. Children in our study did not undergo CNS imaging, and clinically silent events may have been missed. Not all patients had both TEEs as stipulated in the protocol. Therefore, some asymptomatic thrombi might not have been identified. Because of the limited number of events available for analysis we had to collapse the 2 identified phases of risk (early and late) into 1 and perform

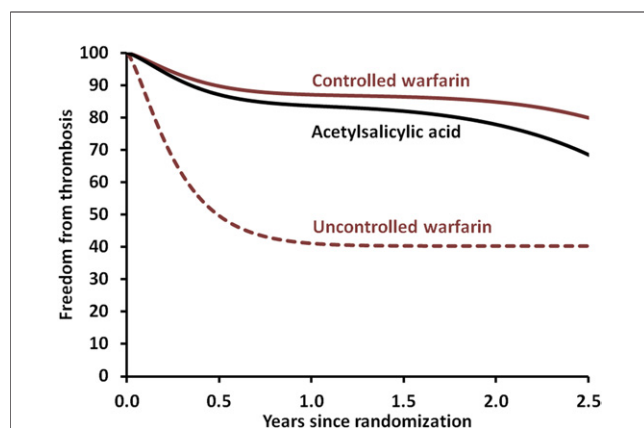


Figure 2 Freedom From Thrombosis Over Time Stratified by Thromboprophylaxis Choice and Effectiveness

All patients included from study randomization up to first thrombotic event, study withdrawal, or end of study, no censoring for drug discontinuation. Controlled warfarin was defined as >30% of international normalized ratio (INR) within target over the study period. Patients on warfarin who consistently achieved target INR levels >30% of the time or those on acetylsalicylic acid had a 3.5-fold decrease in risk of thrombosis compared patients who often failed to meet target INR level (hazard ratio: 3.53, 95% confidence interval: 1.35 to 9.20, $p = 0.01$), and difference in risk between controlled warfarin and ASA was not statistically significant (hazard ratio: 0.34, 95% confidence interval: 0.10 to 1.13, $p = 0.08$).

a classic single-phase risk factor analysis that might not be optimal. Additionally, details of INR monitoring were not available for all patients included in the warfarin group; therefore, our classification of controlled vs. uncontrolled warfarin applied only to a subset of patients. Finally, although our study outlines the importance of achieving target levels of anticoagulation with warfarin, the determination of whether a given patient is likely to have warfarin dosing difficulties requires a lengthy exposure to warfarin and consequently a lengthy increased-risk period for thrombosis. The results of this post hoc secondary analysis must be viewed as hypothesis generating, although they also suggest superiority of well-controlled warfarin over ASA, which is in contrast to the primary intention to treat analysis reported for the clinical trial (24). Considering the fact that we could not identify factors associated with poorly controlled warfarin therapy in these patients, ASA might be the best current strategy to prevent thrombosis for the overall population. Future studies, including both laboratory assessments and genetic evaluations, may be helpful to determine which patients are at increased likelihood of having problems with warfarin dosing.

Conclusions

This study demonstrated that patients with Fontan physiology have a high and ongoing risk of thrombosis, which is highest in the immediate perioperative period, followed by a lower chronic risk that may gradually increase with longer-term follow-up. Underlying physiology and post-operative clinical status were associated with increased risk

of thrombosis. This study also outlined the importance of achieving minimum therapeutic targets when using warfarin for thromboprophylaxis. Future studies should focus on identifying factors associated with failure of warfarin therapy and evaluating the effectiveness and safety of new oral anticoagulants.

Reprint requests and correspondence: Dr. Brian W. McCrindle, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. E-mail: brian.mccrindle@sickkids.ca.

REFERENCES

- Kim SJ, Kim WH, Lim HG, Lee JY. Outcome of 200 patients after an extracardiac Fontan procedure. *J Thorac Cardiovasc Surg* 2008;136:108–16.
- Monagle P, Karl TR. Thromboembolic problems after the Fontan operation. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2002;5:36–47.
- Seipelt RG, Franke A, Vazquez-Jimenez JF, et al. Thromboembolic complications after Fontan procedures: comparison of different therapeutic approaches. *Ann Thorac Surg* 2002;74:556–62.
- Balling G, Vogt M, Kaemmerer H, Eicken A, Meisner H, Hess J. Intracardiac thrombus formation after the Fontan operation. *J Thorac Cardiovasc Surg* 2000;119:745–52.
- Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. *Circulation* 1992;85:469–96.
- Kaulitz R, Ziemer G, Rauch R, et al. Prophylaxis of thromboembolic complications after the Fontan operation (total cavopulmonary anastomosis). *J Thorac Cardiovasc Surg* 2005;129:569–75.
- Monagle P, Cochrane A, McCrindle B, Benson L, Williams W, Andrew M. Thromboembolic complications after fontan procedures—the role of prophylactic anticoagulation. *J Thorac Cardiovasc Surg* 1998;115:493–8.
- Tweddell JS, Nersesian M, Mussatto KA, et al. Fontan palliation in the modern era: factors impacting mortality and morbidity. *Ann Thorac Surg* 2009;88:1291–9.
- Fyfe DA, Kline CH, Sade RM, Gillette PC. Transesophageal echocardiography detects thrombus formation not identified by transthoracic echocardiography after the Fontan operation. *J Am Coll Cardiol* 1991;18:1733–7.
- Manlhiot C, Menjak IB, Brandao LR, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. *Circulation* 2011;124:1511–9.
- Manlhiot C, Brandao LR, Kwok J, et al. Thrombotic complications and thromboprophylaxis across all 3 stages of single ventricle heart palliation. *J Pediatr* 2012;161:513–9.
- Khairy P, Fernandes SM, Mayer JE Jr., et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 2008;117:85–92.
- Varma C, Warr MR, Hendler AL, Paul NS, Webb GD, Therrien J. Prevalence of “silent” pulmonary emboli in adults after the Fontan operation. *J Am Coll Cardiol* 2003;41:2252–8.
- Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008;133:887S–968S.
- Anderson PA, Breitbart RE, McCrindle BW, et al. The Fontan patient: inconsistencies in medication therapy across seven pediatric heart network centers. *Pediatr Cardiol* 2010;31:1219–28.
- Madan N, Robinson BW, Jacobs ML. Thrombosis in the proximal pulmonary artery stump in a Fontan patient. *Heart* 2002;88:396.
- Rosenthal DN, Friedman AH, Kleinman CS, Kopf GS, Rosenfeld LE, Hellenbrand WE. Thromboembolic complications after Fontan operations. *Circulation* 1995;92:287–93.
- Cromme-Dijkhuis AH, Henkens CM, Bijleveld CM, Hillege HL, Bom VJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. *Lancet* 1990;336:1087–90.

19. Cromme-Dijkhuis AH, Hess J, Hahlen K, et al. Specific sequelae after Fontan operation at mid- and long-term follow-up. Arrhythmia, liver dysfunction, and coagulation disorders. *J Thorac Cardiovasc Surg* 1993;106:1126–32.
20. Jahangiri M, Kreutzer J, Zurakowski D, Bacha E, Jonas RA. Evaluation of hemostatic and coagulation factor abnormalities in patients undergoing the Fontan operation. *J Thorac Cardiovasc Surg* 2000;120:778–82.
21. Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E. Coagulation factor abnormalities after the Fontan procedure and its modifications. *J Thorac Cardiovasc Surg* 1997;113:989–92.
22. Odegard KC, Zurakowski D, DiNardo JA, et al. Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion. *J Thorac Cardiovasc Surg* 2009;137:934–41.
23. Ravn HB, Hjortdal VE, Stenbog EV, et al. Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection. *Heart* 2001;85:61–5.
24. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol* 2011;58:645–51.
25. Coon PD, Rychik J, Novello RT, Ro PS, Gaynor JW, Spray TL. Thrombus formation after the Fontan operation. *Ann Thorac Surg* 2001;71:1990–4.
26. Chun DS, Schamberger MS, Flaspohler T, et al. Incidence, outcome, and risk factors for stroke after the Fontan procedure. *Am J Cardiol* 2004;93:117–9.
27. Day RW, Boyer RS, Tait VF, Ruttenberg HD. Factors associated with stroke following the Fontan procedure. *Pediatr Cardiol* 1995;16:270–5.
28. Mahnke CB, Boyle GJ, Janosky JE, Siewers RD, Pigula FA. Anticoagulation and incidence of late cerebrovascular accidents following the Fontan procedure. *Pediatr Cardiol* 2005;26:56–61.
29. Cheung EW, Chay GW, Ma ES, Cheung YF. Systemic oxygen saturation and coagulation factor abnormalities before and after the fontan procedure. *Am J Cardiol* 2005;96:1571–5.
30. Procelewska M, Kolcz J, Januszewska K, Mroczek T, Malec E. Coagulation abnormalities and liver function after hemi-Fontan and Fontan procedures - the importance of hemodynamics in the early postoperative period. *Eur J Cardiothorac Surg* 2007;31:866–72.
31. Tomita H, Yamada O, Ohuchi H, et al. Coagulation profile, hepatic function, and hemodynamics following Fontan-type operations. *Cardiol Young* 2001;11:62–6.
32. Newall F, Savoia H, Campbell J, Monagle P. Anticoagulation clinics for children achieve improved warfarin management. *Thromb Res* 2004;114:5–9.
33. Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999;94:3007–14.
34. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S–21S.
35. Cheung YF, Chay GW, Chiu CS, Cheng LC. Long-term anticoagulation therapy and thromboembolic complications after the Fontan procedure. *Int J Cardiol* 2005;102:509–13.
36. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
37. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363–72.
38. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
39. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376:975–83.
40. Chan VH, Monagle P, Massicotte P, Chan AK. Novel paediatric anticoagulants: a review of the current literature. *Blood Coagul Fibrinolysis* 2010;21:144–51.

Key Words: congenital ■ heart defects ■ morbidity ■ pediatrics ■ surgery.