consistent with the only previous study analyzing TEG in 25 Fontan patients [25]. The TEG FF results indicated normal clot strength, and the Multiplate results indicated normal platelet aggregation. No significant differences in whole-blood assays were found between patient groups stratified according to antithrombotic therapy (except ASPItest, which, as expected, was suppressed in patients on antiplatelet therapy). Similarly, no significant difference in biomarkers was found between the treatment groups, indicating a similar hemostatic function in Fontan patients regardless of treatment modality. This is in agreement with a recent study in which no significant difference in TE was seen in patients randomized to either acetylsalicylic acid or heparin/warfarin within the first 3 years after the Fontan surgery [21]. We hypothesized that patients with previous TE and patients with high glycocalyx degradation would demonstrate signs of increased thrombogenecity. Surprisingly, the subset of patients with previous TE showed normal platelet function, normal clot strength, and no signs of hypercoagulability in the whole-blood assays. In addition, whole-blood assays and biomarkers were not significantly different between groups with and without TE. However, the results may be explained by the small number of events and potentially many silent TEs. Given the well-documented abnormalities in coagulation factors and high prevalence of TEs in Fontan patients, Raffini et al. [25] speculated that the overall balance between hemostasis and thrombosis are maintained, as reflected by the normal TEG results, and that TEs are related to alterations in circulating coagulations protein concentrations. In our study, blood was sampled during stable clinical conditions, and potentially the results would change if sampled during stress, heart failure, infection, etc. Ideally blood should be sampled immediately after thrombus formation (which in practice would be at detection of TE). In patient groups stratified according to glycocalyx degradation, whole-blood assays showed no signs of hypercoagulability, normal platelet function, and normal clot strength in the group with high syndecan-1 levels; however, in this group, a clear tendency toward higher levels of all biomarkers, except protein C, was found. The vascular endothelium and the glycocalyx are known to play a vital role in maintaining a nonthrombogenic and anticoagulant blood-tissue interface, mainly mediated by anticoagulant proteins. Although endothelial dysfunction is known to be a risk factor for coronary artery disease and stroke [8, 23], less is known about the predictive value of abnormal glycocalyx degradation. Trauma patients with increased syndecan-1 levels are known to have worse outcome [14], and damage to the glycocalyx increases platelet adhesion [28]. Interestingly, we found a strong correlation between syndecan-1 levels and markers of endothelial damage (sTM), fibrinolysis (tPA), and cell damage (hcDNAf) but not platelet activation (sCD40L). Furthermore, we found highly significant correlations between syndecan-1 and sTM, tPA, and hcDNAf in the group with high syndecan-1 levels and no correlations in the group with low syndecan-1 levels. This finding indicates that in a subset of Fontan patients, evidence of increased glycocalyx degradation and endothelial damage/dysfunction is present. Furthermore, the correlation with tPA indicates simultaneous fibrinolysis; however, no correlation with biochemical parameters reflecting thrombus formation (e.g., d-dimer), parameters of whole-blood assays, or anatomical or clinical parameters were found. Thus, although all biomarkers offer different perspectives on hemostatic and thrombotic physiology, it is unclear which biomarker will prove to be the most useful in helping to understand the disease process of increased thrombus formation in Fontan patients.

Optimal follow-up of Fontan patients in terms of diagnosing TE, in particular silent TE, remains challenging. One method could be to measure d-dimer and perform TEE or CT scan of the heart and lungs if it is increased (although being aware of the low specificity of d-dimer). The benefits of prophylactic antithrombotic therapy in Fontan patients still are a matter of debate. A prospective, longitudinal study could potentially add further knowledge to this area. Patients could be randomized to either VKA or antiplatelet therapy and undergo baseline and regular follow-up using imaging modalities (e.g., TEE, CT scan of the heart and lungs, magnetic resonance imaging of the brain) with new TE as the primary end point. Likewise, blood sampled and analyzed longitudinally could potentially add further knowledge to the etiology of TE. In assessment of the etiology of TE, we did not include hemodynamic factors. Because of insufficient correlation between endothelial, glycocalyx, and platelet function, hypercoagulability, and TE, future studies should include hemodynamic factors in the analysis of the TEs experienced by Fontan patients. The clinical implication of high levels of biomarkers on the development of TE remains to be shown.

Limitations

The Fontan cohort was heterogeneous regarding age and antithrombotic therapy, both factors that influence the hemostatic profile. In addition, few patients experienced TE, thereby decreasing the statistical power to show differences between groups. In addition, blood samples were not collected at the time of TE, and the hemostatic profile might change over time. Furthermore, we could not establish the abnormality of the levels of biomarkers due to lack of reference values. In addition, the prevalence of silent TE in our cohort is unknown, which makes comparison between a TE group and a non-TE group uncertain; consequently, the prevalence of TE in our cohort is most likely

underestimated due to the unknown number of silent TEs. Finally, eight patients died during follow-up for unknown reasons, and their TE status is not known.

Conclusion

In conclusion, we found a population-based prevalence of TE of 8.1 % in 210 Fontan patients after a mean follow-up after Fontan completion of 8.4 years. In assessment of the etiology of TE, we found normal global hemostasis, normal platelet aggregation, and normal clot strength in Fontan patients. Furthermore, no significant difference in global hemostasis and separate factors of hemostasis (clot strength, endothelial, glycocalyx, platelet, and fibrinolysis function) were found between patient groups stratified according to age, antithrombotic therapy, previous TE, and glycocalyx degradation. However, all biomarkers, except protein C, correlated with one another, and after stratification of glycocalyx degradation, only syndecan-1 levels $\geq$ median correlated with other biomarkers, thus identifying a potentially more thrombogenic group. However, no correlations between biomarkers and demographic, anatomical, clinical, and biochemical parameters were found.

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Conflict of interest The authors declare that they have no conflict of interest.

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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

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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 μmol/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

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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).

Abbreviations and Acronyms

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

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. Transthoracic 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 ± 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

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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 (≤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.

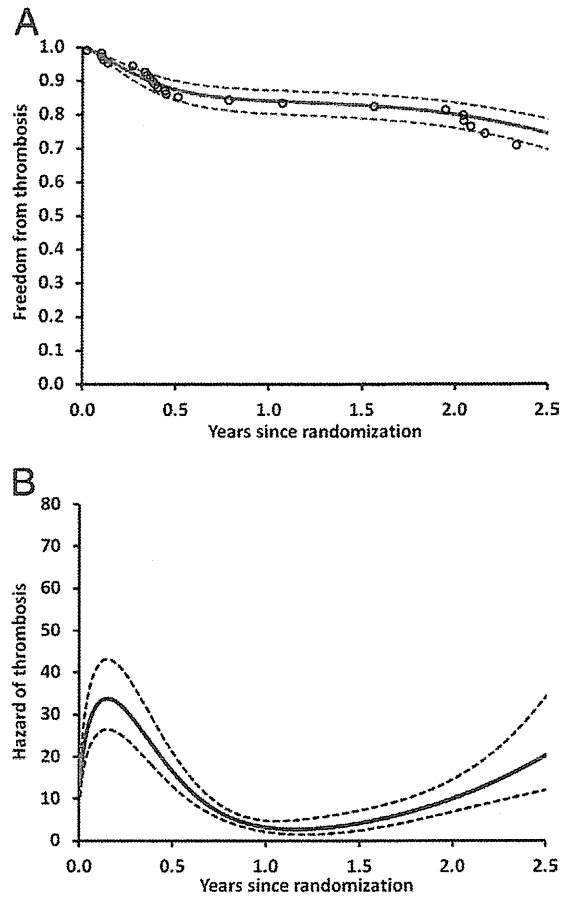

Figure 1 Freedom From and Hazard of Thrombosis Over Time in Patients After Fontan Surgery

Regarding freedom from **(A)** and hazard of **(B)** thrombosis, all patients are included from study randomization up to first thrombotic event, study withdrawal, or end of study, no censoring for drug discontinuation. Dotted lines represent 95% confidence interval. A high early-phase hazard is present followed by a lower, but increasing, hazard of thrombosis in the late phase.

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 μmol/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-

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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 ($\times 10^9$/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 aminotrasnferase; 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

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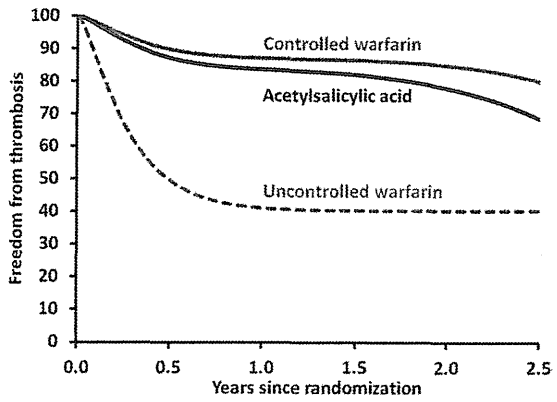

Figure 2 **Freedom From Thrombosis Over Time Stratified by Thromboprophylaxis Choice and Effectiveness**

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 postoperative 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.

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Long-term anticoagulation therapy and thromboembolic complications after the Fontan procedure

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Abstract

Background: The necessity for chronic anticoagulation of Fontan patients remains controversial. We determined the prevalence of thromboembolic complications after the Fontan procedure in relation to different long-term anticoagulation strategies.
Methods: The clinical outcomes, postoperative anticoagulation strategies and occurrence of thromboembolic complications in 102 ethnic Chinese patients who had undergone Fontan procedure between 1980 and 2002 were reviewed.
Results: The early and late surgical mortalities, all unrelated to thromboembolism, were 10.8% (11/102) and 5.8% (6/104), respectively. Of the 85 survivors, 46 (54%) were maintained on long-term warfarin therapy, 8 (9%) on aspirin prophylaxis while 31 (37%) were not on chronic anticoagulation. Four (4.5%) patients, two with and two without warfarin prophylaxis, developed thromboembolic complications at 0.14 to 7.7 years after the Fontan procedure (0.74%/patient-year). Three had a grossly dilated right atrium after atriopulmonary connection, two of whom had atrial fenestrations. The other had atrial tachycardia. Freedom from development of thromboembolic complications (mean±S.E.) at 1, 5 and 10 years after surgery was 97±19%, 96±2.5% and 92±4.2%, respectively. When compared with those on long-term warfarin therapy, patients without chronic anticoagulation were followed-up longer (p=0.001), more likely to have undergone atriopulmonary connection (p<0.001), less likely to have fenestrations (p=0.02) and cardiac arrhythmias (p=0.02) but not predisposed to increased risk of thromboembolism (p=1.00).
Conclusion: The study supports the contention that chronic anticoagulation may not be required for majority of ethnic Chinese Fontan patients. Nonetheless, it may perhaps be considered in those with grossly dilated right atrium, cardiac arrhythmias and residual right-to-left shunts.

Keywords: Fontan procedure; Thromboembolism; Anticoagulation

1. Introduction

Thromboembolic complications occurring after the Fontan procedure are well documented [1–7]. Studies using a thromboembolic event as the primary outcome measure have reported a prevalence of thrombosis and embolism varying from 3% to 16% and from 3% to 19%, retrospectively [1,2,6,8–13]. While imbalance between procoagulant and anticoagulant pathways after the Fontan procedure has been regarded as an important factor predisposing to thrombosis [14–16], the necessity for long-term anticoagulation therapy remains controversial [17,18]. Furthermore, the optimal type and duration of anticoagulation, if indeed indicated, remain to be defined.

The controversies in anticoagulation strategy have led inevitably to differences in clinical practice upon long-term follow-up of Fontan patients. In our institution, depending on the preference of the attending paediatric cardiologist, different strategies, ranging from no anticoagulation to lifelong warfarin prophylaxis, have been used in the past

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two decades. Our heterogeneity in the anticoagulation strategies is, however, not unique, given the limited availability of evidence-based data [18]. Nonetheless, this provides us with an opportunity to determine the relation of different anticoagulation strategies to the occurrence of thromboembolic complications after the Fontan procedure. In this study, we determined the prevalence of thromboembolic complications after the Fontan procedure and its relation to different long-term anticoagulation strategies.

2. Methods

This is a retrospective review of 102 patients who had undergone the Fontan procedure between 1980 and 2002 in our institution. From the clinical records, the following data were collected: demographic data, cardiac diagnoses, the type of modified Fontan procedure, thromboembolic complications, cardiac arrhythmias, long-term use of warfarin or aspirin and early and late mortalities. The cardiac diagnoses of the patients are summarized in Table 1.

The Fontan procedure was performed as an atriopulmonary anastomosis in 64 patients, total cavopulmonary pulmonary connection using the lateral tunnel technique in 21 patients and total cavopulmonary pulmonary connection using an extracardiac polytetrafluoroethylene (IMPRA, Tempe, AZ) conduit in 17 patients. Fenestrations were created in 20 patients.

Serial postoperative echocardiography was performed to assess systemic ventricular function, atrioventricular valve regurgitation, flow pattern within the Fontan circuit and thrombus formation. Transthoracic echocardiography was performed prior to discharge, at 2 and 4 weeks after the operation, and thereafter at 6- to 18-month intervals. In addition, suspicious symptoms or signs thought to be related to thromboembolism were investigated by transthoracic, and transesophageal if necessary, echocardiography and other relevant imaging studies. A thrombus was defined echocardiographically as a localized echogenic mass within the lumen of the Fontan circuit or cardiac chambers and visualized in at least two different planes.

Absolute indications for lifelong warfarin therapy were prosthetic atrioventricular valve replacement and history of documented thromboembolism. In the light of data suggesting an increased thrombotic risk with the use synthetic conduits [1], long-term warfarin was continued indefinitely in our patients with an extracardiac conduit. In the absence of these indications, one of following long-term anticoagulation strategies would be adopted, depending of the preference of the attending paediatric cardiologist: (i) lifelong warfarin therapy, (ii) no or short-term (3 to 12 months) warfarin therapy or (iii) long-term aspirin prophylaxis. For patients on warfarin therapy, the prothrombin time and international normalized ratio (INR) were determined every 3 months and the dose was adjusted to keep the ratio between 1.5 to 2.5 [19]. In addition, bleeding complications in relation to anticoagulation therapy were enquired.

Table 1
Cardiac diagnoses of the 102 patients undergoing the Fontan procedure

Diagnosis	Number (%)
Tricuspid atresia	35 (34.3%)
Univentricular atrioventricular connection	28 (27.5%)
Right atrial isomerism	18 (17.6%)
Mitral atresia	9 (8.8%)
Pulmonary atresia with intact ventricular septum	6 (5.9%)
Left atrial isomerism	3 (2.9%)
Ebstein anomaly	2 (2%)
Discordant atrioventricular connection, crisscrossing of atrioventricular valves, pulmonary stenosis	1 (1%)

Table 2
Current anticoagulation strategies among the 85 survivors

Type of Fontan procedure	Warfarin	Aspirin	None
Atriopulmonary connection	21	4	26
Total cavopulmonary connection (lateral tunnel)	10	4	5
Extracardiac conduit	15	0	0

Data are presented as mean±standard deviation, unless otherwise stated. Comparisons of variables between patients receiving different anticoagulation regimens were performed using unpaired Student's t test and Chi-square test as appropriate. The Kaplan–Meier survival analysis was used to determine the freedom from development of thromboembolic complications after the Fontan procedure. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 10.0 (SPSS, Chicago).

3. Results

One hundred and two ethnic Chinese patients (56 males) underwent Fontan procedure at an age of 6.2±4.8 years. The early surgical mortality, as defined by death within 1 month of operation, was 10.8% (11/102). The causes of death were low cardiac output syndrome in four patients, multiorgan failure in four, bleeding complications in two and failure to wean off cardiopulmonary bypass in one. The late mortality was 5.8% (6/104), being related to cardiac arrhythmia during transcatheter creation of atrial fenestration in a patient with protein-losing enteropathy, infection in one, end-stage heart failure in one and sudden death of unknown aetiology in three patients. None of the latter three patients, however, were found to have venous or intracardiac thrombosis during postmortem examination.

The 85 survivors were followed-up for 6.6±3.8 years. Their current anticoagulation strategies in relation to the different types of Fontan procedure are summarized in Table 2. Forty-six (54%) survivors were maintained on long-term warfarin therapy, 8 (9%) were on daily antiplatelet dose of oral aspirin while 31 (37%) were not on any chronic anticoagulation therapy. Of the latter 31 patients, 24 had not

Table 3
Clinical details of the four patients who developed thromboembolic complications

Patient	Cardiac diagnoses	Type of Fontan procedure	Age at surgery (years)	Time from surgery to thromboembolic complication (years)	Clinical presentation	Echo and other imaging findings	Warfarin at time of thromboembolism	Atrial fenestraton	Other post-Fontan complications
1	TA, VA discordance	APC	2.8	3.3	Right hemiplegia	RA thrombus Cerebral infarct	No	Yes	Nil
2	TA, PA	APC	13.0	7.7	Blurring of right eye version	Cerebral infarct	Yes	No	Atrial tachycardia, PLE
3	TA, DOLV	APC	1.6	0.14	Left third nerve palsy	Normal	No	Yes	Nil
4	DILV, VA discordance PS	ECC	5.2	0.17	Asymptomatic	Thrombus in blind PA stump	Yes	No	Nil

Abbreviations: APC, atriopulmonary connection; DOLV, double-inlet left ventricle; ECC, extracardiac conduit; TA, tricuspid atresia; PA, pulmonary atresia; PLE, protein-losing enteropathy; PS, pulmonary stenosis; RA, right atrial; VA, ventriculoarterial.

been started on any anticoagulation treatment after the Fontan procedure while 7 had been given warfarin for a median duration of 6 months (range: 3 to 12 months). Fifteen survivors had an extracardiac PTFE conduit, for which long-term warfarin was instituted.

Four patients developed thromboembolic complications at 0.14 to 7.7 years after the Fontan procedure. Their clinical data are summarized in Table 3. Three of the four (75%) patients had undergone atriopulmonary connection for tricuspid atresia. One had atrial tachycardia, requiring amiodarone for its control. The overall prevalence of thromboembolism was 4.5% (4/88). At a total follow-up duration of 542 patient-years, the event rate was 0.74% per patient-year. The freedom from development of thromboembolic complications (mean±S.E.) at 1, 5 and 10 years after surgery was 97±19%, 96±2.5 % and 92±4.2 %, respectively (Fig. 1).

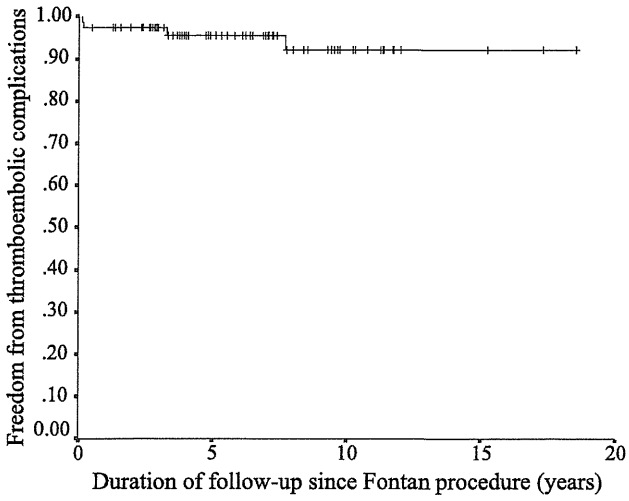

Fig. 1. Kaplan–Meier analysis of the freedom from the development of thromboembolic complications with follow-up duration since the Fontan procedure.

Of the eight patients maintained on aspirin therapy, none developed thromboembolic complications. We then compared the clinical parameters and risk of thromboembolism between patients who were maintained on warfarin therapy and those without chronic anticoagulation, excluding those on aspirin prophylaxis (Table 4). Patients not maintained on long-term anticoagulation were followed-up for a longer duration (p=0.001), more likely to have an atriopulmonary connection (p<0.001) and less likely to have atrial fenestrations (p=0.02) and symptomatic cardiac arrhythmias that required antiarrhythmic medications (p=0.02).

Table 4
Comparisons of demographic and clinical parameters between patients with and those without long-term warfarin therapy

	Patients on long-term warfarin (n=46)	Patients not on long-term anticoagulation (n=31)	p
Age of Fontan procedure (years)	6.7±4.9	6.0±4.4	0.56
Follow-up duration (years)	5.5±3.5	8.6±3.7	0.001[a]
Sex (male/female)	32:14	15:16	0.09
Type of Fontan procedure (APC/TCPC/EC)	21:10:15	25:5:0	<0.001[a]
Atrial fenestrations (yes/no)	13:33	2:29	0.02[a]
Symptomatic cardiac arrhythmias requiring antiarrhythmic medications (yes/no)	8:38	0:31	0.02[a]
Thromboembolic complications (yes/no)	2:42	2:31[b]	1.00

Abbreviations: APC, atriopulmonary anastomosis, EC, extracardiac conduit; TCPC, total cavopulmonary connection.
[a] Statistically significant.
[b] Two patients were not receiving warfarin at the time of developing thromboembolic complications.

Despite the absence of anticoagulation, the prevalence of thromboembolic complication was not significantly different between the two groups. On the other hand, despite warfarin therapy, two patients (patients 2 and 4 in Table 3) developed thromboembolic complications. Their INR at the time of thromboembolic events was 1.69 and 1.97, respectively. However, none of the warfarinized patients developed serious bleeding complications.

4. Discussion

This study is unique in its analysis of the prevalence of thromboembolic complications in relation to different anticoagulation strategies. The controversy of the role of prophylactic anticoagulation therapy after the Fontan procedure is in part related to the paucity of data comparing the outcomes of patients receiving different types of anticoagulation regimen. Despite suggestions of a prothrombotic tendency in Fontan patients [14–16], there were only few reported series in which all or most of the patients receive long-term anticoagulation [18,20]. Indeed, studies comparing the prevalence of thromboembolic events between patients with and without long-term prophylactic warfarin therapy are virtually nonexistent. This study provides evidence that long-term anticoagulation does not confer additional protection against clinically significant thromboembolic complications in ethnic Chinese Fontan patients who had atriopulmonary connection or total cavopulmonary connection using a lateral tunnel.

The 4.5% prevalence of thromboembolism in our patient cohort is in keeping with those reported previously [1,2,6,8–13]. The small number of patients with thromboembolic complications in the present study limits the statistical power to identify predisposing risk factors. Nonetheless, previous studies have implicated cardiac arrhythmia [1], low cardiac output [12], the use of synthetic conduits [1] and residual right-to-left shunting through fenestrations [8,9] as possible risk factors. While the efficacy of total cavopulmonary connection in preventing thromboembolic complications has not been confirmed in previous studies [1,2], it is intriguing that of our four patients who developed the complications, three had undergone atriopulmonary connection, which is known to cause greater distortion of the normal streamlined venous flow [21].

The relatively low prevalence of thromboembolic complications in our cohort may perhaps also be a reflection of the ethnic differences in the risk of venous thrombosis [22,23]. The lower incidence of venous thrombosis in Chinese patients has been attributed in part to ethnic differences in anticoagulant levels and activated protein C resistance [23–25]. Nevertheless, a rising trend in the incidence of venous thromboembolism has been documented in the past decade in this locality due to adoption of more aggressive surgical approaches and westernization of the Chinese diet among other causes [23]. Notwithstanding the possible ethnic differences in coagulation cascade, the use of transthoracic echocardiography for thrombi detection, being a less sensitive imaging modality for detection of silent thrombi [4], and prophylactic warfarinization of high-risk patients may perhaps also account for a low prevalence of thromboembolism in our cohort.

The diversity in anticoagulation strategies in our institution is indeed a reflection of the controversial nature of the issue. Each of the approaches, however, has its proponents. The procoagulant state, the incidence and poor prognosis of thromboembolism after the Fontan procedure have prompted the recommendation of routine prophylactic anticoagulation by a number of authors [2,6,26]. The optimal degree of anticoagulation however remains unknown. In our patients receiving warfarin, we target the international normalized ratio in the range of 1.5 to 2.5, which has been shown to provide adequate protection against thromboembolism in Chinese children after prosthetic valve replacement [19]. On the other hand, Strief et al. [27] suggested a target INR range of 2.0 to 3.0, while Balling et al. [28] suggested an even higher range between 3.0 and 4.5. Regardless of the target INR range, Fontan patients require a lower warfarin dosage as compared to patients after other types of congenital heart surgery for a similar degree of anticoagulation [19,27]. Notwithstanding the perceived benefits of long-term warfarin, the risk of significant bleeding complications has been reported to occur in approximately 1.7% of children warfarinized for indications other than mechanical prosthetic valves [29]. In addition, the need for regular monitoring of INR and the problem of drug compliance, especially in adolescents, are issues of concern. Furthermore, the 7.4% incidence of venous thrombosis despite prophylactic oral anticoagulation, as reported by Jonas [30], casts doubt on the efficacy of routine prophylactic warfarin therapy. It is apparent that factors other than alteration of coagulation contribute to thromboembolism after the Fontan surgery and that the risks attributable to unfavourable surgical or haemodynamic factors cannot possibly be completely eliminated by oral anticoagulation therapy.

Low dose aspirin therapy has recently also been demonstrated to be an alternative, effective strategy by Jacobs et al. [31]. The authors attributed the absence of thromboembolic complications in their 72 patients not only to the use of aspirin alone but also operative and postoperative management designed to minimize the complication. Nevertheless, the lack of a control group in their study casts doubt on the genuine efficacy of prophylactic aspirin therapy. Indeed, the absence of thromboembolic complications was similarly demonstrated in our subgroup of patients, which was under a similar protocol of echocardiographic surveillance, not receiving long-term anticoagulation therapy.

While our findings do not support the need for long-term anticoagulation in all Fontan patients, a number of limitations to this study may deserve comments. In our

institution, it is not a routine to perform regular transesophageal echocardiography for the screening of thrombus formation in Fontan patients. Although the sensitivity of transesophageal echocardiography in the detection of clinically silent thrombus is higher than that of transthoracic echocardiography [4], we concur with Jacobs et al. [31] that in the absence of adverse clinical outcomes secondary to thromboembolic complications, the type of surveillance adopted by us and their group appears efficacious. Second, as all of the patients with an extracardiac synthetic conduit were receiving long-term warfarin therapy, we cannot assess the role of prophylactic anticoagulation in this subgroup. Third, as the follow-up duration of our patients is relatively short, the anticoagulation issues being addressed in the present study are those of the paediatric patient population and may not necessarily apply to the adult cohort.

In conclusion, this study supports the contention that long-term anticoagulation may not be required for majority of ethnic Chinese Fontan patients. Optimization of the venous flow within the Fontan circuit by elimination of stenosis and use of total cavopulmonary connection, elimination of unintended right-to-left shunts and vigorous control of cardiac arrhythmias would probably help to minimize the risk of thromboembolism. Long-term warfarin therapy may perhaps be considered, on an individual basis, in Fontan patients with gross dilation of the right atrium after atriopulmonary connection, poorly controlled cardiac arrhythmias and residual right-to-left shunts. Whether lifelong warfarin is indeed indicated for patients with an extracardiac conduit remains to be clarified.

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EDITORIAL COMMENT

Preventing Thrombosis After the Fontan Procedure

Not There Yet*

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In 2007 (1), a review of the experience with thromboembolism and use of anticoagulation after the Fontan procedure in patients with single-ventricle lesions came to 4 conclusions: 1) thromboembolic events occur both early and late after the Fontan procedure at a frequency higher than any other cardiac surgery in children other than prosthetic valve replacement; 2) these thromboembolic events contribute to the failure of Fontan physiology and their occurrence increases in a "failed Fontan"; 3) these thromboembolic events occur in the presence of absence of standard anticoagulation schemes, including combinations of heparin and warfarin; and 4) the factors predisposing to thromboembolism after the Fontan procedure likely represented a complex interaction of multiple factors. They speculated that it would be unlikely that any single anticoagulation agent would provide a solution to such a complex problem.

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In this issue of the *Journal*, Monagle et al. (2) present the findings of a study that would appear to confirm this opinion. Their study began as an ambitious randomized trial comparing a regimen of acetylsalicylic acid (ASA) with post-operative heparin followed by oral warfarin therapy to prevent thromboembolism in children undergoing the Fontan procedure. In addition to perspective randomization of patients to ASA or heparin/warfarin, the study's primary endpoint was innovative because it included both thrombus that led to clinical events and the presence of asymptomatic or silent thromboemboli that were detected by transesophageal echocardiography (TEE), a relatively invasive procedure not usually in done in the routine clinical management of Fontan patients.

Unfortunately, the execution of the study fell short of its initial intent. The targeted recruitment goal was 242 patients to attain statistical power. Only 111 patients were eventually enrolled. Although 81% of the population underwent at least 1 surveillance TEE, only 48% of the subjects had both surveillance TEEs; thus, the true prevalence of silent thromboemboli was not fully ascertained. The numbers of silent and clinically evident thromboemboli were nearly identical in the ASA and heparin/warfarin groups. However, the sample size is too small to confirm noninferiority of either therapy as the possible differences between ASA and heparin/warfarin therapies range from ASA therapy conferring a 1.6 times greater risk of thromboembolism compared with heparin/warfarin and heparin/warfarin conferring a 3 times greater risk than ASA.

Although this study did not accomplish its initial purpose as a clinical trial, it does offer important data in its final form as 3 large multicenter observational studies rolled into one: 1) a large prospective intention-to-treat study of ASA prophylaxis after the Fontan procedure; 2) a similar intention-to-treat study for heparin/warfarin prophylaxis in Fontan patients; and 3) an assessment of TEE as a means for surveillance for thromboembolism in Fontan patients. The study confirms results from a contemporary Fontan experience (3) demonstrating the rate of clinical events associated with thromboemboli in the first years after the Fontan procedure to be low. In the current study (2), symptoms from a clot in the Fontan connection developed in only 3 of the 111 patients. The rest of the clinically detected thrombi were in the femoral ($n = 3$) and jugular ($n = 1$) veins where previous cardiac catheterization and/or the placement of central intravenous lines may have also influenced thrombus formation. This study also confirms another recent experience (4) demonstrating a low, clinically evident prevalence of thromboemboli using ASA as prophylaxis.

The study clearly illustrates the challenges of using warfarin as prophylactic therapy in children. Nearly one-fifth of the patients started on warfarin stopped the drug before the end of the study. Forty-one percent of international normalized ratio measurements were below the recommended therapeutic range. Poor compliance with warfarin therapy (patients who had <30% of international normalized ratio measurements in the therapeutic range) had a significant greater risk of thrombosis. Thus, even discounting the extra need for performing periodic blood testing with warfarin therapy, "maintenance" of anticoagulation with warfarin was suboptimal and frequently erratic.

This study also confirmed findings from previous experience (5) that surveillance TEE frequently detects emboli without clinical symptoms and/or not seen on standard transthoracic echocardiography. In all cases, the intensity of anticoagulation was increased and no clinical events occurred. However, it appears that routine periodic TEE surveillance was difficult because only one-half of the subjects had 2 TEE studies.

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A recent large, single-center experience (6) of long-term Fontan survivors identified thromboembolism as an important continuing cause of mortality in this patient group and that no anticoagulation therapy confers a substantial risk (hazard ratio: >90) for thromboembolic death. Another study (7) found a higher rate of thromboembolic events in patients not treated with anticoagulation compared with treatment with ASA or warfarin. Thus, it is unlikely that most clinicians would not attempt some form of anticoagulation therapy in patients after the Fontan procedure. Monagle et al. have provided evidence that currently used therapies are not as effective as we would like them to be. However, their experience also suggests that primary prevention antithrombotic strategies using recurrent invasive surveillance must be associated with a high enough benefit/risk and/or inconvenience ratio to gain acceptance by patients and their families.

Optimal strategies to reduce mortality and morbidity with thromboembolism after the Fontan procedure clearly remain to be determined. It is likely that the newer anticoagulants undergoing evaluation in adults with atrial fibrillation (8) will be tested in Fontan patients. Antithrombotic strategies should also not be limited to primary prophylaxis. Screening for hereditary thrombophilia before surgery may be helpful. Care needs to be taken to avoid creation of areas of stagnant flow such as pulmonary artery stumps (9) or ascending aortas in aortic atresia (10) that predispose to arterial thrombi and stroke. Individualization of antithrombotic strategies for patients who demonstrate prothrombotic states such as increased levels of factor VIII (11) may be efficacious. As patients who underwent the Fontan procedure age, and complications develop such as ventricular systolic dysfunction, atrial arrhythmias, and chronic lower extremity venous insufficiency (12) that increase the risk of thromboembolic events, the surveillance and therapy to prevent such events should become more intense and aggressive. Ultimately, tailored antithrombotic therapy for individual Fontan patients as they age will likely be more effective than a "one-size-fits-all" approach.

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EDITORIAL COMMENT

An Aspirin a Day . . .*

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The old adage, "an apple a day keeps the doctor away," when altered to "an aspirin a day keeps the doctor away" appears to be especially appropriate for patients who have had a Fontan operation. The group from the Hospital for Sick Children has in this issue of the *Journal* reported a secondary analysis of an important trial of thromboprophylaxis after the Fontan procedure (1). In this secondary analysis the Toronto group further investigated the unique and important data set accumulated in their previous study, "A Multicenter, Randomized Trial Comparing Heparin/Warfarin and Acetylsalicylic Acid as Primary Thromboprophylaxis for 2 Years After the Fontan Procedure in Children" (2).

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Any surgeon who performs the Fontan procedure has encountered at some point in his or her career a thrombotic post-operative complication. These patients appear to be at risk of thromboembolism for many reasons: a known hypercoagulable state, the use of intracardiac prosthetic materials, atrial arrhythmias, intracardiac shunting (fenestration), low-flow states, and stasis in the venous pathways. The original paper published by the Toronto group randomized patients to receive either aspirin (5 mg/kg/day) or warfarin with a target international normalized ratio of 2.0 to 3.0 (2). A total of 111 eligible patients were randomized in a prospective fashion. The incidence of thrombosis was essentially identical between the 2 groups and major bleeding occurred in only 1 patient in each group. The conclusion of this randomized prospective trial was that there was no significant difference between aspirin therapy and warfarin as primary thromboprophylaxis in the first 2 years following the Fontan procedure. The thrombosis incidence was still high at 19% in both groups, which the authors suggested means there is still room for improvement in the care of these patients.

The current review delves deeper into the potential areas for improvement that might be brought to the forefront from the original study group. This secondary analysis of a unique and important dataset revealed the following important factors. First, the hazard of thrombosis was noted to be highest immediately after the Fontan procedure, but there was also a gradual increase in risk during late follow-up. The higher incidence of thromboembolism in the first several weeks and months following the Fontan procedure has been previously demonstrated and has some logical explanations. The delayed hazard, however, seems somewhat counterintuitive as one would think that after several years there would be less chance of thrombosis formation at suture lines and along prosthetic pathways which presumably would become covered with neointima over a period of time. The inference here is that lifetime anticoagulation of some sort is probably necessary.

The most striking and important new information, though, appears to be the fact that patients who were on a warfarin dose that was subtherapeutic actually had a significantly increased incidence of thrombosis issues compared with patients who were maintained on either carefully controlled warfarin therapy or the aspirin therapy. It is well known to clinicians that the difficulties of managing warfarin therapy in children are not insignificant. Missing doses, changing diets, and intercurrent illnesses all affect the international normalized ratio levels. The ease of aspirin administration by contrast and the attendant higher compliance presumably accounts for the improved outcomes.

There were several other findings with the secondary review regarding the factors associated with a higher risk of thrombosis: 1) the diagnosis of pulmonary atresia with intact ventricular septum; 2) pulmonary artery distortion; 3) higher pre-operative unconjugated bilirubin; 4) the use of central venous lines for >10 days or until hospital discharge; and 5) a lower FiO_2 24 h after the procedure. Pulmonary artery distortion is understandable, as is prolonged central line use. The others are not necessarily intuitive.

Other surgeons have previously suggested that aspirin therapy may be a better strategy after the Fontan procedure than the use of warfarin. Marshall Jacobs published a study in 2002, "Fontan's Operation: Is Aspirin Enough? Is Coumadin Too Much?" (3). He was actually quite prescient in his analysis as many of the points demonstrated by this secondary analysis were noted in his review. His conclusion was that "low dose aspirin can be used safely in young patients with Fontan connections. In the intermediate follow-up the strategy of aspirin therapy was effective in preventing thromboembolic complications. The routine use of more aggressive anticoagulation such as Coumadin may be unwarranted" (3). Those conclusions from a very experienced Fontan surgeon were

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nearly identical to those of the recent randomized prospective study!

It may be that improvements in surgical techniques (i.e., the use of a bidirectional superior cavopulmonary anastomosis and the extracardiac Fontan) will decrease the incidence of thromboembolic events. These operations are associated with more laminar blood flow and less blind cul-de-sacs than the previously described atriopulmonary and lateral tunnel Fontan operations. These operations avoid stasis in the venous pathways and may decrease atrial arrhythmias that are known to contribute to thrombus formation. Other risk factors such as the need for bilateral bidirectional cavopulmonary anastomosis may not be amenable to modification.

I congratulate the Toronto group on enhancing our understanding of the important issue of thrombotic complications after the Fontan operation. Their ability to organize and conduct a randomized trial of thromboprophylaxis is a notable event in pediatric cardiac surgery. The secondary analysis has improved our understanding of how to care for and prevent thrombotic complications in this unique patient population.

An apple a day keeps the doctor away. In Fontan patients an aspirin a day seems to keep the clots away.

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