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A Multicenter, Randomized Trial Comparing Heparin/Warfarin and Acetylsalicylic Acid as Primary Thromboprophylaxis for 2 Years After the Fontan Procedure in Children

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Objectives The purpose of this study was to compare the safety and efficacy of acetylsalicylic acid (ASA) and warfarin for thromboprophylaxis after the Fontan procedure.

Background Fontan surgery is the definitive palliation for children with single-ventricle physiology. Thrombosis is an important complication; the optimal thromboprophylaxis strategy has not been determined.

Methods We performed a multicenter international randomized trial of primary prophylactic anticoagulation after Fontan surgery. Patients were randomized to receive for 2 years either ASA (5 mg/kg/day, no heparin phase) or warfarin (started within 24 h of heparin lead-in; target international normalized ratio: 2.0 to 3.0). Primary endpoint (intention to treat) was thrombosis, intracardiac or embolic (all events adjudicated). At 3 months and 2 years after the Fontan procedure, transthoracic and transesophageal echocardiograms were obtained as routine surveillance. Major bleeding and death were primary adverse outcomes.

Results A total of 111 eligible patients were randomized (57 to ASA, 54 to heparin/warfarin). Baseline characteristics for each group were similar. There were 2 deaths unrelated to thrombosis or bleeding. There were 13 thromboses in the heparin/warfarin group (3 clinical, 10 routine echo) and 12 thromboses in the ASA group (4 clinical, 8 routine echo). Overall freedom from thrombosis 2 years after Fontan surgery was 19%, despite thrombosis prophylaxis. Cumulative risk of thrombosis was persistent but varying and similar for both groups ($p = 0.45$). Major bleeding occurred in 1 patient in each group.

Conclusions There was no significant difference between ASA and heparin/warfarin as primary thromboprophylaxis in the first 2 years after Fontan surgery. The thrombosis rate was suboptimal for both regimens, suggesting alternative approaches should be considered. (International Multi Centre Randomized Clinical Trial Of Anticoagulation In Children Following Fontan Procedures; NCT00182104) (J Am Coll Cardiol 2011;58:645–51) © 2011 by the American College of Cardiology Foundation

Fontan surgery, first performed for tricuspid atresia in the late 1960s, has evolved as the definitive palliative surgery for all children with univentricular cardiac physiology, irrespective of whether they have a functioning right, left, or indeterminate ventricle. The Fontan principle is diversion of systemic venous return directly to the pulmonary arteries, and the use of the single ventricle as a functioning systemic ventricle (1). In subsequent years, many modifications of the original procedure have been described, although the

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basic principle remains the same (2–4). Improvements in surgical techniques and supportive care have significantly im-

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Abbreviations and Acronyms

ASA = acetylsalicylic acid
INR = international normalized ratio
TEE = transesophageal echocardiography

proved long-term survival for children after Fontan surgery; hence, the frequency of Fontan surgery continues to increase (5–7).

Thrombosis remains a major complication after Fontan surgery, presenting as intracardiac or intravascular thrombosis, cerebrovascular thromboembolism, or other embolic phenomena. The true frequency of thrombembolism post-Fontan surgery remains unknown (1,8). Cross-sectional surveys using transesophageal echocardiography (TEE) reported a prevalence of intracardiac thrombosis of 17% to 33% (9–11). Cohort studies that had venous thrombosis or arterial emboli (or both) as a primary outcome measure reported incidences of venous thrombosis ranging from 3% to 19% and the incidence of stroke ranging from 3% to 19%, depending on the nature of the cohort and the duration and nature of follow-up. The reported mortality from post-Fontan surgery thromboembolism is 25% (1). In this context, a multitude of primary thromboprophylaxis strategies have been suggested. However, there have been no prospective data on which to base any prophylactic protocols (12,13).

We performed a multicenter, randomized, controlled trial of primary prophylactic anticoagulation after Fontan surgery, comparing 2 commonly used strategies, to determine their efficacy and safety in the first 2 years after Fontan surgery.

Methods

Study subjects. All patients scheduled for a Fontan procedure were eligible for inclusion. Exclusion criteria included the presence of a recognized indication for long-term anticoagulation; characteristics associated with an increased risk of bleeding; known medical contraindication to heparin, warfarin, or acetylsalicylic acid (ASA); inability to supervise therapy due to social or geographic reasons; and pregnancy or potential pregnancy during the study period.

Randomization. Randomization was performed centrally immediately after completion of the Fontan procedure. Randomization was stratified by center.

Study intervention. The study interventions were delivered in accordance with standard protocols for a 2-year period. Subjects randomized to warfarin received heparin initially at a dose of 10 to 20 U/kg/h. Usually within 24 h of starting heparin and when the patient was first able to tolerate oral medication, a loading dose of warfarin of 0.1 mg/kg was given. The dose was then titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and heparin was discontinued when the INR first reached 2.0. Adjustment of the maintenance dose of warfarin was dependent on INR monitoring as follows: INR of 2.0 to 3.0, no change in dose; INR of 1.1 to 1.4, increase dose by 20%; INR of 1.5 to 1.9, increase dose by 10%; INR of 3.1 to 3.5, decrease dose by 10%; and INR of >3.5, hold warfarin until INR was <3.5, then decrease dose by 20% when restarted. Patients randomized to ASA were started when they were tolerating any oral intake (ASA, 5 mg/kg/day, no heparin phase, no monitoring). Because Fontan patients are well documented to be at an important risk of thrombotic complications, there was believed to be insufficient clinical equipoise to include a nonintervention group.

Measurements. Study measurements included a baseline medical record review to abstract data regarding demographics, underlying cardiac anatomy, previous interventions and complications, and previous and current medical therapy. Data regarding the Fontan procedure and postoperative complications were collected. Clinical monitoring was performed at 3, 6, 12, 18, and 24 months after randomization and whenever it was clinically indicated. INR monitoring and dose adjustments for warfarin to maintain the patient within the therapeutic range were the responsibility of the treating center and were dependent on the clinical status of the child. 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. Routine transthoracic echocardiography and TEE was performed at 3 and 24 months post-Fontan surgery. All patients were requested to attend all study visits regardless of whether they were still taking their assigned study medication and/or had reached a study outcome. Thrombosis with clinical presentation, severe bleeding complications, Fontan takedown, death, and all other serious adverse events were captured for all patients.

Blinding. All medication use was open label. Local echocardiographic assessments were performed by sonographers and echocardiographers in a blinded manner. There was an independent central adjudication of clinically driven and routine echocardiograms. All thrombosis and major adverse clinical events were adjudicated by an expert panel.

Study endpoints. The primary endpoint was any thrombotic event (venous or arterial). This was defined as the ultrasound appearance of a space-occupying lesion 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 (cardioembolic stroke, pulmonary embolism). Additional endpoints included Fontan takedown, death, and study drug discontinuation or crossover.

Statistics. Data are described as mean ± SD, median (minimum, maximum values), or frequencies as appropriate. Differences between groups were assessed using the Student *t* test with Satterthwaite correction for variance estimation and the Fisher exact chi-square test. Timed-event analysis of thrombosis after randomization was modeled using nonparametric Kaplan-Meier estimates with a log-rank test for group comparison. Timed-event analyses were performed twice, once with patients being censored at the time drug discontinuation and once with censoring only at study termination. All analyses were based on an intention-to-

treat principle and performed using SAS statistical software version 9.1 (SAS Institute, Cary, North Carolina).

Results

Enrollment and patient population. Patients were recruited from 6 institutions from 1998 through 2003. During that time, 242 patients were scheduled for Fontan surgery, of whom 111 were eventually enrolled and randomized, 57 to ASA and 54 to warfarin. All randomized patients were included in the final analysis (Fig. 1).

Patient baseline characteristics. Baseline characteristics were similar between groups regarding demographics and underlying cardiac diagnoses. Previous thrombosis before Fontan surgery was equally prevalent in both groups. There were no differences in pre-operative characteristics or hemodynamics. The groups were similar regarding age at Fontan surgery, with the majority having extracardiac conduits and being fenestrated. There were no differences in perioperative or post-operative variables, including length of hospital stay and laboratory values (Table 1).

Compliance with study intervention and assessments. Patients taking ASA completed 92% of days on the study drug, and patients taking warfarin completed 84% of days ($p = 0.02$). Early discontinuations of the study drug were more frequent in the warfarin group (19% vs. 9%). Compliance with undergoing TEE was good, with 81% of patients undergoing TEE at least once (69% undergoing 3-month TEE, 61% undergoing 24-month TEE) and 48% undergoing both TEE protocols. A total of 3 patients prematurely withdrew from the study (2 receiving warfarin, 1 receiving ASA). One patient died due to massive cerebral hemorrhage secondary to low cardiac output syndrome early in the study. This patient was assigned to but had not yet received ASA at the time of death (Table 2). Overall, 95% of patients attended all 5 study assessments, and complete accrual of clinical events was obtained.

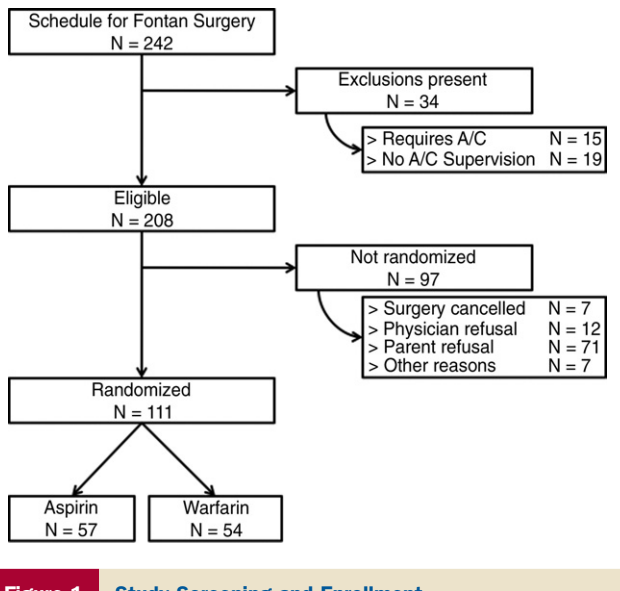

Figure 1 Study Screening and Enrollment

Of 242 patients screened, 208 were eligible for the trial of whom 111 were eventually randomized. Of the 111 patients randomized, 54 (49%) were randomized to warfarin and 57 (51%) were randomized to acetylsalicylic acid. A/C = anticoagulation.

Table 1 Patient Characteristics

	ASA (n = 57)	Warfarin (n = 54)
Demographics		
Male	34 (60%)	37 (69%)
Age at Fontan surgery, yrs	4.6 ± 2.3	5.1 ± 3.4
Weight at date of surgery, kg	16.5 ± 4.4	18.1 ± 9.3
Major cardiac defect		
Tricuspid atresia	11 (19%)	10 (19%)
Double inlet left ventricle	13 (23%)	8 (15%)
Double outlet right ventricle	4 (7%)	8 (15%)
Pulmonary atresia and intact ventricular septum	1 (2%)	5 (9%)
Unbalanced atrioventricular septal defect	4 (7%)	6 (11%)
Hypoplastic left heart	8 (14%)	9 (17%)
Ebstein's anomaly	1 (2%)	1 (2%)
Other/multiple anomalies	15 (26%)	7 (13%)
Previous cardiac surgical procedures (not mutually exclusive)		
Cardiac catheter/interventional procedures	32 (56%)	31 (57%)
Norwood operation	11 (19%)	13 (24%)
Damus-Kaye-Stansell procedure (for subaortic stenosis)	8 (14%)	8 (15%)
Bidirectional cavopulmonary shunt	40 (70%)	40 (74%)
Bilateral cavopulmonary shunt	7 (12%)	8 (15%)
Aortic coarctation repair	5 (9%)	3 (6%)
Other cardiac surgical procedures	21 (37%)	24 (44%)
Thrombosis history		
Patient has a previous thrombotic event	10 (18%)	5 (9%)
Years (range) since last event	2.4 (0.3–4.3)	2.2 (1.2–2.9)
On anticoagulation within 7 days of randomization	6 (11%)	2 (4%)
Fontan procedure		
Type of Fontan procedure: extracardiac conduit vs. lateral tunnel	49 (86%)	46 (85%)
Type of baffle or conduit used: GORE-TEX vs. homograft	43 (75%)	38 (70%)
Size of baffle or conduit used, mm	[54] 19 ± 3	[47] 19 ± 4
Fenestration	37 (65%)	32 (59%)
Size of fenestration used, mm	[35] 4.8 ± 2.0	[32] 4.3 ± 1.3
Concurrent procedures	25 (44%)	29 (54%)
Perioperative characteristics		
Cardiopulmonary bypass time, min (range)	96 (29–307)	104 (11–313)
Aortic cross-clamping used	19 (33%)	22 (41%)
Circulatory arrest used	2 (4%)	2 (4%)
Reoperation		
Bleeding	1 (2%)	1 (2%)
Delayed sternal closure	1 (2%)	2 (4%)
Open/close fenestration	2 (4%)	1 (2%)
Revise Fontan connections	3 (5%)	1 (2%)
Thrombosis	0 (0%)	1 (2%)

Values are n (%), mean ± SD, or median (minimum–maximum). Numbers in square brackets represent available sample size if there are any missing values.
ASA = acetylsalicylic acid.

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Table 2 Frequency of Patient Withdrawal and Early Drug Discontinuation

	ASA (n = 57)	Warfarin (n = 54)	p Value
Patient withdrew	0 (0%)	2 (4%)	0.23
Death	1 (2%)	0 (0%)	1.00
Patient stopped study drug	2 (4%)	3 (6%)	0.68
Physician stopped study drug	3 (5%)	6 (11%)	0.49
Study drug stopped after adverse event	0 (0%)	1 (2%)	1.00
Early discontinuation for any reason	6 (11%)	12 (22%)	0.13

ASA = acetylsalicylic acid.

Primary endpoint: thrombosis. Thrombosis occurred in 21% of patients receiving ASA and 24% of those receiving warfarin during the full duration of the study (Fig. 2). On Kaplan-Meier analysis, the estimate of the proportion of patients who had a thrombosis event at 2 years (including all patients, intention to treat) was 19% overall, with no significant differences between warfarin and ASA (24% vs. 14%, p = 0.45) (Fig. 3). The magnitude of the difference was further reduced with inclusion of delayed follow-up of some patients beyond 2 years. Kaplan-Meier analysis further showed that results were similar when patients were additionally censored at the time of study drug discontinuation, with a 2-year incidence of 20%, with no significant difference between warfarin and ASA (26% vs. 15%, p = 0.36). When the analysis was restricted to those thromboses associated with a clinical presentation, the overall incidence at 2 years was 7%, with no significant difference between warfarin and ASA (6% vs. 8%, p = 0.80). A post hoc analysis, which was not pre-specified, of the warfarin group only showed that patients with a high prevalence of subtherapeutic INR measurements (<30% of INR measurements >2) had a significantly greater risk of thrombosis (hazard ratio: 5.95; 95% confidence interval: 2.01 to 31.9; p = 0.003) than those patients well maintained in the therapeutic range (≥30% of INR measurements >2).

Of the 25 initial thromboses, all were venous, with 18 (72%) detected on routine assessments, and 7 (28%) associated with a clinical presentation with signs and symptoms (1 with swelling/edema associated with thrombosis in the jugular vein, 2 with swelling/edema associated with thrombosis in the femoral veins, 3 with dyspnea/respiratory insufficiency associated with thrombosis in the Fontan connection, and 1 patient with a cold/hypotensive limb associated with thrombosis in the femoral veins). Of those 25 patients with thromboses (7 of whom had thromboses identified in multiple locations), 20 had thromboses within the Fontan connection, 4 within the pulmonary arteries, and 7 within other venous sites. The mean INR at the time of detection for those receiving warfarin was 2.2. Thromboses were noted with transthoracic echocardiography for 52% of patients and with TEE for 84% of patients, with 20% of intracardiac thromboses detected with TEE but not transthoracic echocardiography.

Almost all detected thromboses in the 25 patients were treated with an increase in anticoagulation; 9 were initially treated with heparin followed by a return to their assigned study treatment, 6 ASA patients received heparin initially and were then crossed over to warfarin, 2 ASA patients were directly switched to warfarin, 4 warfarin patients had their dose increased (1 of whom also initially received heparin), and 1 patient required thrombolytic agents. Only 3 patients had no change in management related to the detected thrombosis.

Recurrent thrombosis. Thrombosis recurred in 7 patients (28%), despite some increase in anticoagulation therapy after the initial thrombosis. Acute treatment after the initial episode was unfractionated heparin for 4 patients and unfractionated heparin with thrombolytic agents for 1 patient with a clinical presentation (this patient later died of multiorgan failure unrelated to the thrombosis or thrombolytic agent). Subsequent maintenance therapy for patients originally receiving ASA was warfarin for 2 patients, 1 patient remained on ASA only, and 1 patient was changed from ASA to low molecular weight heparin. All 3 patients on warfarin at the time of the initial thrombus subsequently had their target INR range increased from 2.5 to 3.5. All had a thrombus located within the Fontan connection, with 3 within additional venous sites. Recurrent thromboses were asymptomatic in 6 patients.

Adverse events. One late death occurred in a patient assigned to ASA who had a recurrent thrombosis and went on to have a complicated surgery for Fontan revision, and multiorgan failure subsequently developed. One patient assigned to warfarin required Fontan takedown after an initial thrombosis, and pulmonary hypertension and collaterals vessels subsequently developed.

There were 2 major bleeding events, with 1 patient having massive cerebral hemorrhage as previously described occurring before study drug had been started. The second patient was assigned to warfarin and presented with gastrointestinal bleeding and bruising and was noted to have an INR of 11.9; the patient was treated with vitamin K and required multiple blood transfusions. Minor bleeding was more prevalent for those taking warfarin versus ASA for all locations, with 33% of those taking warfarin and 14% taking ASA having at least 1 minor bleeding episode (p = 0.03) (Table 3). For those taking warfarin, the median INR at assessments was 2.1 to 2.3, with 45% of readings within the recommended therapeutic range of 2 to 3, 41% below target, and 14% above target. One third of the patients had <30% of warfarin levels above 2. Extreme increases in the INR were noted, but were infrequent (Table 3).

Discussion

Fontan surgery is the definitive palliative procedure for univentricular hearts and is being performed with increasing frequency (14). Fontan surgery provides stable cardiovascular hemodynamics that has been shown to be compatible with

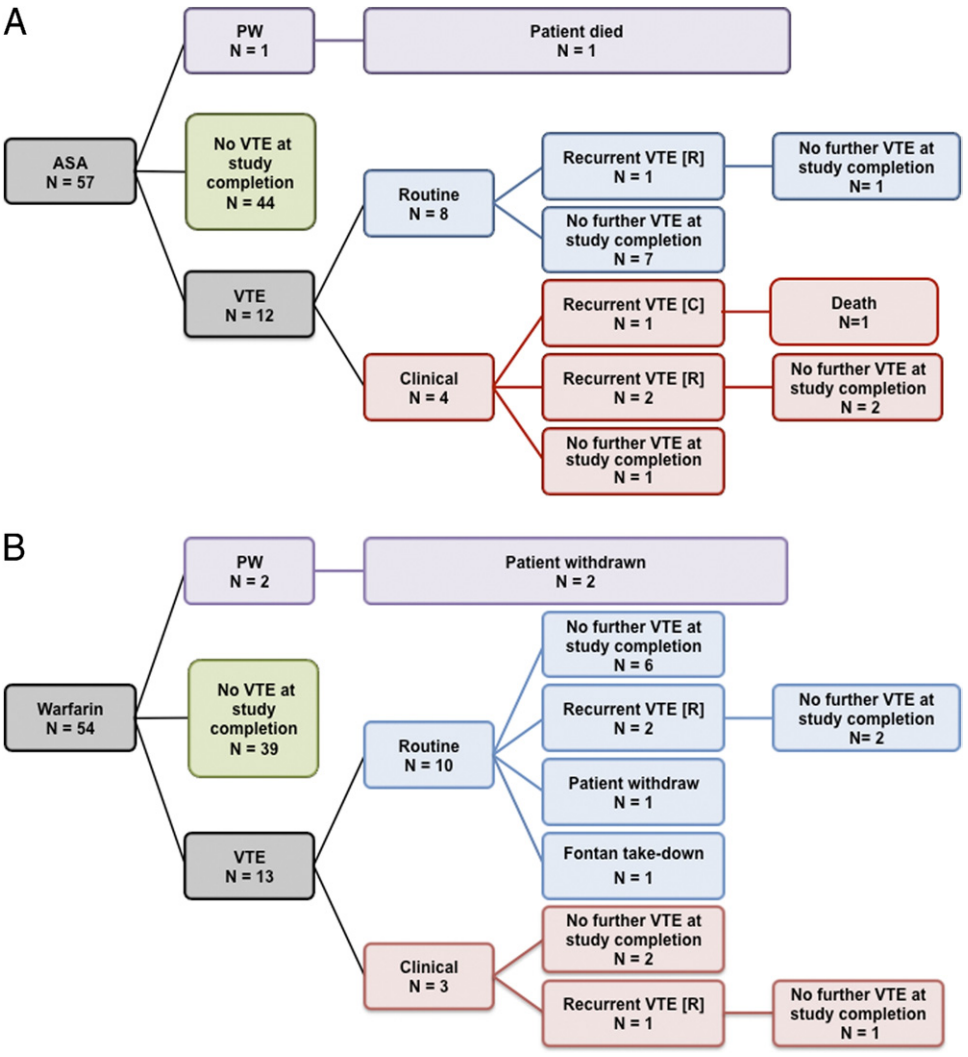

Figure 2 **Flow Chart of Patient Withdrawal and Events for Patients Randomized to ASA and Warfarin**

(A) Of 57 patients randomized to acetylsalicylic acid (ASA), 1 patient prematurely withdrew from the study, 44 (77%) completed the study without venous thrombotic events, 8 (14%) experienced venous thrombotic events (1 clinical/7 routine) without recurrence, and 4 (7%) (3 clinical/1 routine) with recurrence. **(B)** Of 54 patients randomized to warfarin, 2 patients prematurely withdrew from the study, 39 (72%) completed the study without venous thrombotic events, 10 (19%) experienced venous thrombotic events (2 clinical/8 routine) without recurrence, and 3 (6%) (1 clinical/2 routine) with recurrence. PW = premature withdrawal; recurrent VTE [R] = routine recurrent venous thrombotic event; recurrent VTE [C] = clinical recurrent venous thrombotic event; VTE = venous thrombotic event.

good-quality long-term survival (5–7,15). However, thrombosis remains a major complication both early and late after Fontan surgery (5,8,12). Currently, most pediatric cardiac surgical units prescribe primary thromboprophylaxis with either warfarin or ASA for varying durations after Fontan surgery; however, the relative efficacy of these approaches has never been compared prospectively (12). This study is a prospective, multicenter, randomized, controlled trial comparing warfarin with ASA as primary thromboprophylaxis after Fontan surgery. The cumulative thrombosis rate was 23% in the first 2 years post-surgery. Despite the finding that there was no difference between warfarin and ASA, the event rate was not trivial and as such supports our decision not to include a nontreatment group in this study. Novel approaches are required to reduce the frequency of thrombosis after Fontan surgery to further enhance the survival and quality of life of this group of patients.

Importantly, this study confirms that thrombosis remains a major complication after Fontan surgery, despite the improvements in surgical and supportive techniques over the past decade. The clinical thrombosis event rate in this study was 8%. Interestingly, there were no recorded central nervous system thromboembolic events in this study, despite studies previously reporting stroke rates as high as 19% after Fontan surgery (8). Children in our study did not undergo routine central nervous system imaging, so whether clinically silent events occurred is unknown. The use of routine echocardiography in our study, particularly TEE, increased

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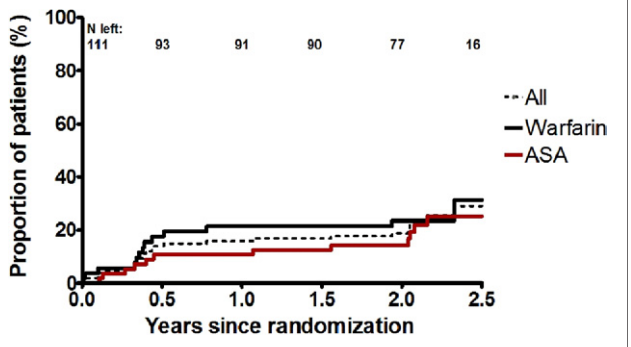

Figure 3 Thrombosis After Randomization

Patients classified by randomization, no censoring for drug discontinuation. Kaplan-Meier estimate for the proportion of patients with thrombosis 2 years after randomization was 19% (24% in patients randomized to warfarin vs. 14% in patients randomized to aspirin). Hazard ratio for thrombosis for patients randomized to warfarin vs. acetylsalicylic acid (ASA) was 1.35 (95% confidence interval: 0.62 to 3.00), p = 0.45.

the detected thrombosis rate significantly. The clinical relevance of asymptomatic intracardiac (Fontan circuit) thrombosis is likely high. First, given that the cumulative event rate was constant, thromboses that are currently clinically silent may have progressed if untreated and caused later clinical events. Second, the risk of embolization of small thromboses to the central nervous system, especially in children with open fenestrations, is likely important in children with untreated intracardiac thrombosis (16). Third, the Fontan circuit is dependent on low pulmonary vascular resistance because venous return is the sole driver of pulmonary blood flow (5). Recurrent small thromboses in the Fontan circuit, with or without embolization to the lungs may increase the pulmonary resistance and contribute to late failure of the Fontan circuit. Of note, all clinicians treated the asymptomatic thromboses when they were detected on routine echocardiography, and this seems consistent with current clinical practice.

The initial study design was for more patients (n = 113 per group, 226 total for 80% power to detect a 15% difference in event rate); however, slower than anticipated recruitment (possibly due to the requirement of TEE, which caused many families to decline) over a 5-year period forced the study to stop with fewer participants. Nonetheless, with 111 patients enrolled in the study, this is the largest prospective study of anticoagulation in Fontan patients ever performed, and the 95% confidence interval for the hazard ratio suggests that, at worst, the thrombotic risk with ASA is 1.6 times that seen with warfarin, or, alternatively, the risk with warfarin is 3 times that seen with ASA. Given the burden of warfarin therapy, as discussed subsequently, clinicians may argue that based on this hazard risk, in terms of prevention of major thrombosis as a sole outcome, ASA may potentially be preferable to warfarin therapy. One consideration for the lack of treatment difference is whether patients receiving warfarin were adequately anticoagulated. Of note, the mean INR at the time of thrombosis detection for those patients taking warfarin was 2.2. Although 41% of all warfarin measurements were below the target range, this is not uncommon in children taking warfarin (17,18). Whether increasing the target range for warfarin therapy (e.g., to an INR of 2.5 to 3.5) would further reduce the risk of thrombosis is unknown. The possibility of ASA resistance may have contributed to treatment failure and was not assessed in this study (19).

This study confirmed the findings of previous cross-sectional studies that TEE is more sensitive than transthoracic echocardiography for detecting thrombosis within the Fontan circuit (9–11). This difference in sensitivity was operator independent, in that it occurred across multiple centers and was confirmed by independent adjudication of all echocardiograms. Newer imaging modalities, such as magnetic resonance imaging, are in almost routine use and may supersede TEE for thrombosis detection, thus, facilitating recruitment in future trials by removing the requirement of invasive imaging modalities. One of the key considerations in comparing long-term ASA therapy with warfarin therapy is the risk of bleeding. There was no difference in major bleeding between the treatment regimens of this study. However, there was a marked difference in minor bleeding, which was increased for patients on warfarin therapy. This contributes to the assumption that warfarin therapy imposes a considerable burden on children, including the need for regular blood tests and potentially lifestyle restrictions (for example, limitations on sporting activities) to minimize the risk of trauma-induced bleeding. Assessing quality of life of patients randomized to warfarin compared with ASA was beyond the scope of this study, but such data would be most useful given the lack of difference in thrombosis prevention between the 2 treatment regimens.

Conclusions

In summary, this study is a large multicenter, randomized trial of thromboprophylaxis in children after Fontan surgery

Table 3 Adverse Events and Monitoring

	ASA (n = 57)	Warfarin (n = 54)	p Value
Bleeding events			
Nose	8 (14%)	12 (26%)	0.33
Oral	1 (2%)	5 (9%)	0.11
Gastrointestinal	3 (5%)	4 (7%)	0.72
Genitourinary	2 (4%)	4 (8%)	0.43
Skin	4 (7%)	9 (17%)	0.15
Other	5 (9%)	9 (17%)	0.26
Any minor bleeding	8 (14%)	18 (33%)	0.03
Major bleed event	1 (2%)	1 (2%)	1.00
Abnormal warfarin monitoring (n = 2,143)			
INR >5 to <7	—	30 (1.4%)	—
INR ≥7 to <9	—	10 (0.5%)	—
INR ≥9	—	7 (0.3%)	—

ASA = acetylsalicylic acid; INR = international normalized ratio.

for univentricular congenital cardiac disease. The study demonstrated that thrombosis is a frequent problem after Fontan surgery, despite thromboprophylaxis with either warfarin or ASA. The cumulative risk of thrombosis is persistent, suggesting prophylaxis should not be time limited after Fontan surgery. However, whether novel agents, such as oral factor Xa inhibitors, or combination therapy with both warfarin and ASA, or increased intensity antiplatelet therapy will be more effective in reducing the thrombosis risk will need to be the subject of future studies. Further studies that include long-term follow-up, studies that elucidate the mechanism of late Fontan circuit failure, and studies that determine the long-term neurological outcome will be important to help justify the duration and intensity of primary thromboprophylaxis. The potential long-term damage due to microvascular thromboemboli to either the pulmonary or systemic circulation remains unclear. Whether regular routine TEE (or other imaging modalities) should be performed is also a question requiring further study; however, it is reasonable to conclude that all available evidence now supports TEE as being more sensitive than transthoracic echocardiography for Fontan circuit thrombosis detection. Our study demonstrates the feasibility of undertaking multicenter, prospective studies of medical therapy in children with uncommon and heterogeneous cardiac malformations. This should be the first of many such studies that will be required to optimize the medical management of children with univentricular physiology because survival into adulthood for these children is now expected. The challenge is to maximize their life potential.

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APPENDIX

Fontan Anticoagulation Study Group

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Operations Group: Paul Monagle, Maureen Andrew, Robin Roberts, Barbara Szechtman

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