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Effect of Aspirin and warfarin therapy on thromboembolic events in patients with univentricular hearts and Fontan palliation

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ABSTRACT

Background: Patients with univentricular hearts and Fontan palliation are at risk for thromboembolic complications. While aspirin and warfarin therapies are currently the mainstay of prophylaxis, controversy exists as to the optimal prevention strategy.
Methods: A cohort study was conducted on the New England registry of patients born in 1985 or earlier with Fontan surgery at Boston Children's Hospital, in order to assess and compare the effect of prophylactic aspirin and warfarin on incident thromboembolic events.
Results: A total of 210 qualifying patients (49% male) underwent Fontan surgery at a median age of 8.5 years: 48.6% had a right atrium to pulmonary artery anastomosis, 11% a right atrium to right ventricle conduit, 38.6% a lateral tunnel, and 1.9% an extracardiac conduit. No thromboembolic prophylaxis was prescribed to 50.0%, whereas 24.3% received aspirin, and 25.7% warfarin. In multivariate analyses, lack of aspirin or warfarin was associated with a significantly higher thromboembolic event rate when compared to therapy with either [hazard ratio 8.5, 95% confidence interval (3.6–19.9), $P < 0.001$], with no difference between the two treatment strategies ($P = 0.768$). Twenty-year freedom from thromboemboli was 86% versus 52% in patients with and without thromboprophylaxis, respectively. Other factors independently associated with thromboemboli were a low post-operative cardiac index [hazard ratio 2.6, 95% confidence interval (1.2, 5.9)] and atrial fibrillation or flutter [hazard ratio 3.1, 95% confidence interval (1.2, 8.0)].
Conclusions: Prophylaxis with either aspirin or warfarin was associated with a significantly lower rate of incident thromboembolic events following Fontan palliation, with no difference between the two therapies.

1. Introduction

The Fontan procedure encompasses a family of related operations [1–7] with the common goal of palliating the "univentricular heart" [6] by rerouting systemic venous return directly to the pulmonary arterial circulation. Outcomes have improved considerably over the last 25 years such that patients are now increasingly surviving into adulthood, exposing them to various longer-term complications, including heart failure, arrhythmias, and thrombosis [4–6,8–12]. Thromboembolic complications are a well-recognized source of morbidity [13–15] and mortality [9] in patients with Fontan physiology. Thromboembolic death may occur suddenly or be preceded by other thromboembolic events, which may or may not be symptomatic [16–18]. As many as 25% of clinical thromboembolic events in patients with Fontan surgery are fatal [16,18]. While the prevention of thromboembolic events is a desirable clinical goal, controversy exists as to the optimal prophylaxis strategy [16,18–25]. Given the paucity of evidence regarding prophylactic therapy with newer antithrombotic regimens in this patient population [24], aspirin (ASA) or warfarin remain the mainstay of antiplatelet or anticoagulant therapy. We, therefore, sought to evaluate and compare the effect of prophylactic ASA and warfarin on incident thromboembolic events in a cohort of patients with Fontan palliation.

2. Methods

2.1. Study cohort

The New England Fontan registry included all patients who lived in the New England area, were born before 1985, and had Fontan surgery between April 1973 and July 1991 at Boston Children's Hospital. Details of this cohort have been previously described [9,10]. Patients with surgery limited to cavopulmonary shunts were ineligible, including those with an interrupted inferior vena cava and azygos extension to a superior vena cava who underwent a bidirectional cavopulmonary shunt. For the current analysis, patients with early post-operative death (<30 days) or a thromboembolic event within the first 14 days of Fontan surgery were excluded [26,27]. The study

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protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

2.2. Definitions

Systemic ventricular morphology (left, right, or both) and atrioventricular valve anatomy were categorized in accordance with previously defined nomenclature [28] on the basis of preoperative studies and surgical observations. The type of Fontan procedure was classified as right atrial (RA) to pulmonary artery (PA) anastomosis, RA to right ventricle (RV) connection, intracardiac lateral tunnel (LT), or extracardiac conduit (ECC). In all cases, surgery involved separating systemic from pulmonary venous return by excluding the systemic venous return from the systemic ventricle, with or without a residual atrial communication or baffle fenestration. Fontan fenestration, surgical arrhythmia ablation, and concomitant surgery for associated anomalies were recorded as separate variables.

The "era" of the Fontan procedure was classified as "early" if surgery was performed prior to 1985 and "late" if in 1985 or after. "Revision" was defined as a repeat operation that sought to correct a defect in the original Fontan palliation. A surgery that sought to transform an earlier Fontan into another type of Fontan was termed a "conversion". Atrial fibrillation was defined as the absence of consistent P waves on electrocardiography, with rapid oscillations or fibrillatory waves typically associated with an irregular ventricular response. Intra-atrial re-entry/atrial flutter was defined as a regular atrial rhythm with a constant atrial rate ≥200 bpm.

2.3. Outcomes

The primary outcome was the occurrence of a fatal or non-fatal thromboembolic event, whether within the systemic or pulmonary circulation. All clinical thromboembolic events required documentation by non-invasive imaging, angiography or post-mortem evaluation. Death was considered thromboembolic if deemed secondary to thrombus identified either clinically or posthumously. The site of thromboembolism was further classified in one or more of the following locations: right atrium/Fontan, superior vena cava, inferior vena cava, systemic venous atrium, pulmonary artery, or other.

2.4. Statistical Analyses

Continuous variables are summarized by median values and interquartile ranges (IQR; 25th, 75th percentile). Categorical variables are presented as frequencies and percentages. Baseline comparisons between patients with no thromboembolic prophylaxis, ASA, and warfarin therapy were performed by Kruskal-Wallis, chi-squared, or Fisher Exact tests when appropriate. Survival free from a first thromboembolic event according to the type of thromboembolic prophylaxis was plotted using the Kaplan–Meier method and compared by the log-rank statistic. Time 0 was defined as time of Fontan surgery, after which patient-years were accrued until occurrence of the primary outcome or upon censoring. Censoring occurred at the last follow-up visit, upon takedown of the Fontan circulation, or at the time of Fontan conversion, cardiac transplantation, or non-thromboembolic death.

Predictors of thromboembolic events were explored in univariate and multivariate Cox regression analyses, from which hazard ratios and 95% confidence intervals (CI) were generated. For multivariate analyses, an automated stepwise algorithm was used, with levels of significance for entry and staying in the model of 0.25. The type of prophylactic therapy and presence of atrial fibrillation or flutter were forced into the model as covariates. In order to test the robustness of the primary analysis, several sensitivity analyses were performed including 1) omitting reoperation (revision or conversion surgery) from the censoring definition, 2) varying the exclusion period for early thromboembolic events from 14 to 30 days, and 3) varying the early death exclusion criterion from 30 to 14 days.

Two-tailed values of P-values <0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

3. Results

3.1. Baseline characteristics

A total of 210 patients, 49.0% of whom were male, underwent a first Fontan surgery at a median age of 8.5 (IQR 4.8, 15.2) years. Seventy-two (34.3%) patients had tricuspid atresia, 51 (24.3%) a double-inlet left ventricle, and 4 (1.9%) hypoplastic left heart syndrome. The single ventricle was morphologically left in 70.5%. The type of first Fontan procedure was a RA to PA connection in 102 (48.6%) patients, RA to RV conduit in 23 (11.0%), lateral tunnel in 81 (38.6%), and extracardiac tunnel in 4 (1.9%). No thromboembolic prophylaxis was prescribed in 50.0%, 24.3% received ASA, and 25.7% warfarin-based therapy. Patient characteristics and clinical events during follow-up according to the prophylaxis strategy are presented in Table 1.

3.2. Clinical Events

Over a median follow-up of 14.5 years (IQR 8.7–18.4 years), 25 (9.5%) patients had an eventual surgical conversion, 5 (2.4%) had at least one surgical revision, 23 (11%) were transplanted, and 34 (16%) died. Overall, a total of 40 (19.%) patients experienced a thromboembolic event, 5 (12.5%) of which were fatal. The thromboembolic

Table 1
Patient characteristics.

	All Patients N = 210	No Prophylaxis N = 105	ASA N = 51	Warfarin N = 54	P-value[†]
Age at Fontan, years[*]	8.5 (4.8, 15.2)	7.0 (4.3, 13.1)	6.8 (4.5, 15.9)	11.3 (8.0, 17.6)	0.0006
Male, N (%)	103 (49)	49 (47)	26 (51)	28 (52)	0.7889
Type of congenital heart disease, N (%)					0.4715
Tricuspid atresia	72 (34)	36 (34)	13 (25)	23 (43)	
Double-inlet left ventricle	51 (24)	26 (25)	14 (27)	11 (20)	
Hypoplastic left heart syndrome	4 (2)	1 (1)	1 (2)	2 (4)	
Other	83 (40)	42 (40)	23 (45)	18 (33)	
Systemic right ventricle, N (%)	55 (26)	26 (25)	14 (27)	15 (28)	0.8773
Type of Fontan, N (%)					0.0008
Lateral tunnel	81 (39)	35 (33)	28 (55)	18 (33)	
RA-PA anastomosis	102 (49)	58 (55)	22 (43)	22 (41)	
RA-RV connection	23 (11)	11 (10)	0 (0)	12 (22)	
Extracardiac conduit	4 (2)	1 (1)	1 (2)	2 (4)	
Early surgical era (pre-1985), N (%)	69 (33)	36 (34)	7 (14)	26 (48)	0.0006
Low cardiac index (<2.35 mL/min/m^2), N (%)	80 (38)	35 (33)	20 (39)	25 (46)	0.2771
Atrial fibrillation or flutter, N (%)	95 (45)	33 (31)	24 (47)	38 (70)	<0.0001
Ablation procedure, N (%)	49 (23)	17 (16)	10 (19)	22 (41)	0.0032
Follow-up, years[*]	14.5 (8.6, 18.1)	12.0 (4.8, 16.4)	15.8 (13.5, 18.7)	17.1 (10.9, 20.1)	<0.0001
Redo-surgery, N (%)					
Fontan revision	5 (2)	1 (1)	1 (2)	3 (6)	0.1902
Fontan conversion	20 (10)	8 (8)	5 (10)	7 (13)	0.5594
Transplantation	23 (11)	8 (8)	6 (12)	9 (17)	0.1962
Thromboembolic event, N (%)	40 (19)	28 (27)	5 (10)	7 (13)	0.0207

ASA denotes aspirin; RA, right atrium; PA, pulmonary artery; RV, right ventricle.
[*] Continuous variables are summarized by median and interquartile range (25th, 75th percentile).
[†] Comparison between the three prophylaxis groups.

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events consisted of thrombus within the RA/Fontan in 25 patients (62.5%), limited to the PA in 3 (7.5%), the superior vena cava in 2 (5%), and the pulmonary venous atrium in 3 (7.5%). No clots were identified within the inferior vena cava and precise location information was missing for the remaining 7 (17.5%) cases. In one patient with a fatal thromboembolic event, thrombolysis with recombinant tissue plasminogen activator was unsuccessful, and a second patient died despite an attempted thrombectomy.

3.3. Prophylactic strategy and thromboembolic events

Overall, 28 (26.7%) thromboembolic events occurred among 105 patients without any prophylaxis (median follow-up 12.0 years), 5 occurred among the 51 (9.8%) patients on ASA therapy (median follow-up 15.8 years), and 7 occurred among 54 (13.0%) patients on warfarin-based therapy (median follow-up 17.1 years). In the 7 patients receiving warfarin, the international normalized ratio (INR) was therapeutic (≥2.0) in 1, subtherapeutic in 2, and unknown in 4 at the time of the thromboembolic event.

Univariate and multivariate predictors of incident thromboembolic events are summarized in Table 2. In univariate analyses, warfarin was associated with a significantly lower thromboembolic event rate [hazard ratio 0.39, 95% CI (0.16, 0.96), P = 0.040]. Aspirin was associated with a numerically similar albeit non-significant reduction in the thromboembolic event rate [hazard ratio 0.37, 95% CI (0.13, 1.06), P = 0.063]. In multivariate analyses, there was no significant advantage of warfarin compared to ASA therapy (P = 0.768). The lack of ASA or warfarin was associated with a highly significant 8.5-fold increase in the thromboembolic event rate when compared to therapy with either [adjusted hazard ratio 8.49, 95% CI (3.64–19.86), P < 0.0001]. The Kaplan-Meyer plot depicting freedom from a first thromboembolic event is shown in Fig. 1. In patients without aspirin or warfarin therapy, freedom from a thromboembolic event was 92% at 10 years and 52% at 20 years. For those receiving aspirin or warfarin prophylaxis, corresponding 10 and 20-year event-free survival rates were 94% and 86%, respectively.

Other factors independently associated with a higher thromboembolic event rate in multivariate analyses were a low post-operative cardiac index [adjusted hazard ratio 2.63, 95% CI (1.17, 5.93), P = 0.0199] and a diagnosis of atrial fibrillation or flutter [adjusted hazard ratio 3.10, 95% CI (1.20, 7.96), P = 0.0190]. Prespecified sensitivity analyses with alternate group assignment algorithms and exclusion criteria did not alter the results appreciably.

4. Discussion

The key findings of this analysis from the New England Fontan registry are that 1) prophylaxis with either aspirin or warfarin is associated with a significantly lower incident thromboembolic event rate; 2) no signal favored one therapy over the other; 3) the residual risk of thromboemboli remains substantial despite ASA or warfarin therapy;

Table 2
Factors associated with incident thromboembolic events.

Characteristic	Hazard ratio	95% CI	P-value
Univariate			
ASA therapy	0.37	0.13, 1.06	0.0633
Warfarin therapy	0.39	0.16, 0.96	0.0400
ASA or warfarin therapy	0.25	1.88, 8.46	0.0003
Low cardiac index (<2.35 mL/min/m^2)	2.33	1.16, 4.68	0.0172
Atrial fibrillation or flutter	2.44	1.10, 5.43	0.0290
Multivariate			
Lack of ASA or warfarin therapy	8.49	3.63, 19.86	<0.0001
Low cardiac index (<2.35 mL/min/m^2)	2.63	1.17, 5.93	0.0199
Atrial fibrillation or flutter	3.10	1.20, 7.96	0.0190

CI denotes confidence interval; ASA, aspirin.

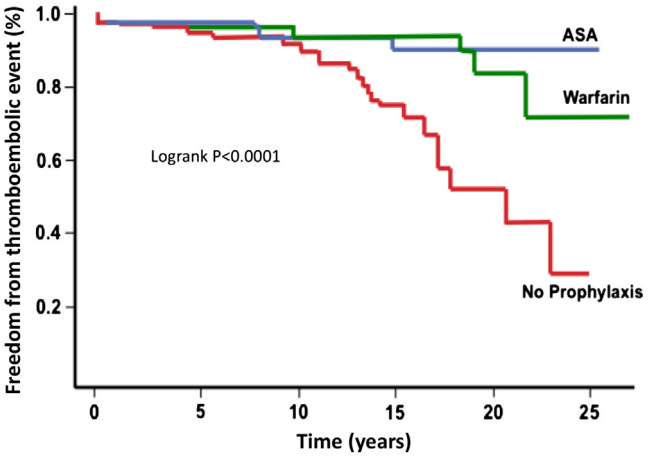

Fig. 1. Freedom from thromboemboli according to the type of prophylactic therapy. The Kaplan–Meier curves depict freedom from an incident thromboembolic event according to whether patients received thromboprophylaxis with aspirin (ASA), warfarin, or neither.

and 4) other factors associated with a higher risk of thromboembolic events include a low post-operative cardiac index and a history of atrial fibrillation or flutter.

The high incidence and the type of thromboembolic events observed in our patient population (i.e., 48% at 20 years in patients without prophylactic therapy) are consistent with previous reports [9,13,15,16,18,25–27]. During the study period, no formal departmental policy was implemented for anticoagulation therapy, although standard indications (e.g., atrial tachyarrhythmias) were generally respected. The major reduction in the thromboembolic event rate with ASA or warfarin therapy (i.e., 14% at 20 years in patients without prophylactic therapy, representing a 71% unadjusted relative risk reduction) would suggest that some form of prophylaxis should be considered as the mainstay treatment for patients with Fontan palliation, barring contraindication.

The optimal thromboprophylaxis strategy remains a source of controversy [16,19,22]. The observed lack of superiority of one strategy over the other is consistent with a recent clinical trial that compared ASA to heparin/warfarin therapy in children during the first two years after Fontan surgery [16]. Our study extends these findings to an older population with over 14 years of follow-up. Reasons as to why warfarin therapy does not outperform ASA in this patient population remain speculative and may reflect the multifactorial mechanisms of thrombus formation in Fontan patients, including decreased cardiac output, abnormal venous flow, prosthetic material, blind cavities, lack of atrioventricular synchrony, coagulation defects, and platelet abnormalities [16,18,29–31].

Alternatively, the lack of superiority of prophylactic anticoagulation versus antiplatelet therapy may be due, in part, to difficulties achieving and maintaining therapeutic INR levels [16,18,32,33]. In an exploratory analysis of the pediatric Fontan study, patients on warfarin who often failed to meet targeted INR levels experienced a significantly higher rate of thromboemboli than those who consistently achieved targeted INR levels or received ASA therapy [18]. Our results and others suggest that alternate thromboprophylaxis strategies should be explored in light of the high prevalence of thromboembolic events in this patient population, difficulties achieving consistent protection with warfarin therapy, and the considerable residual risk that remains in patients treated with warfarin or ASA.

4.1. Study limitations

The study is observational in nature and subject to the limitations inherent to retrospective designs, particularly with regards to unmeasured

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potential confounders. INR values were not routinely collected during the >14-year follow-up, precluding exploratory analyses regarding the prevalence of subtherapeutic anticoagulation and its potential impact. In addition, study power was limited by the 40 thromboembolic events. The final Cox regression model contained 4 covariates in addition to the presence or absence of prophylactic therapy and history of atrial tachyarrhythmias, resulting in 6 degrees of freedom. Such a model may be at risk of "over-fitting", since fewer than 10 outcome events occurred per predictor variable. However, this approach was deemed justified given the potential for important confounding in this cohort and our impression that a model that did not adequately control for such would have limited utility. Moreover, simulation studies suggest that problems are seldom encountered with 5–9 events per predictor variable [34].

5. Conclusion

A high rate of incident thromboembolic events was observed in the New England cohort of Fontan patients followed for over 14 years. Prophylactic therapy with ASA or warfarin was associated with a significant reduction in the thromboembolic event rate, with the two treatment strategies yielding similar outcomes. Despite protective therapy, patients remained at substantial residual risk for thromboembolic events. Adequately powered prospective trials comparing these and other prophylactic antithrombotic regimens in this high-risk population are warranted. In the interim, in light of these results, it would appear reasonable to favor some form of routine thromboprophylaxis.

Statement of authorship

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflict of interest disclosures

Dr. Khairy has received research support for an investigator-initiated grant from Boehringer Ingelheim.

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