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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

See page 354

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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