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Assessment of Late Thromboembolic Complications Post–Fontan Procedure in Relation to Different Antithrombotic Regimens: 30-Years' Follow-up Experience

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Abstract

Background: The current CHEST guidelines recommend the use of antithrombotic therapy, either aspirin or warfarin, as a primary thromboembolic complications (TECs) prophylaxis in patients who undergo Fontan procedure, without specification on drug selection or duration of therapy. **Objective:** To investigate the incidence rate of late TECs, occurring after 1-year post–Fontan procedure and to assess the difference in rate of late TECs between warfarin and aspirin. **Methods:** A retrospective cohort study included patients who had Fontan procedures between 1985-2010 at our institution. Patients were stratified according to the antithrombotic regimen—warfarin, aspirin, or no therapy—at the time of TECs. **Results:** We screened 499 patients who underwent Fontan procedures; 431 procedures met the inclusion criteria. Over a median follow-up of 13.6 years (IQR= 8.7), freedom from late TECs at 5, 10, 15, and 20 years was 97.54%, 96.90%, 90.78%, and 88.07%, respectively. There was no difference in late TEC incidence rates per 1000 patient-years between warfarin and aspirin: 7.82 and 5.83 events, respectively; rate ratio= 1.34 (95% CI= 0.68-2.60). Warfarin was associated with a higher major bleeding incidence rate per 1000 patient-years: 3.70 versus 2.91 events with aspirin; rate ratio= 1.27 (95% CI= 0.49 to 3.29). Conclusion and Relevance: The incidence rate of late clinical TECs post–Fontan procedure in our population is low. Warfarin was not superior to aspirin for prevention of late TECs. Yet warfarin was associated with a higher rate of bleeding. This finding suggests a simpler antithrombotic regimen for prevention of TEC after 1-year post-Fontan procedure.

Keywords

thromboembolism, antithrombotic therapy, congenital heart anomalies, Fontan procedure

Introduction

Thromboembolic complications (TECs) are a known concern after the Fontan procedure since the beginning.[1-3] The true frequency of TECs after the Fontan procedure remains unknown. Freedom from TECs is estimated to be 92% at 1 year, 90% at 3 years, and 82% at 10 years after Fontan operation.[4] There are multiple risk factors associated with thrombus formation, such as atrial arrhythmia, right-to-left shunt, venous stasis, prosthetic material, fenestration, hepatic dysfunction, and hypercoagulable states.[5,6] The current CHEST guidelines recommend the use of antithrombotic therapy, either aspirin or warfarin, as a primary prophylaxis in Fontan patients. However, there is no recommendation, neither on the preferred agent nor the optimal duration of therapy, particularly in light of recent modifications of the Fontan procedure.[7] This can be attributed to insufficient long-term follow-up data[8,9] as well as the fact that TECs may occur any time after the Fontan procedure, so that the need for antithrombotic therapy could be extended to years. Hence, selecting the agent and duration of therapy remain controversial among practitioners.

We hypothesized that longer duration of antithrombotic therapy is associated with fewer late TECs, and there might be a variance in response and safety between different antithrombotic regimens. The aim of our study is to investigate

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the incidence rate of late TECs, occurring 1 year post–Fontan procedure and to assess the difference in rate of late TECs between different antithrombotic approaches as well as the therapy duration.

Methods

This is a retrospective cohort study that identified patients who underwent Fontan procedures from the Congenital Heart Defects Registry of the King Faisal Specialist Hospital and Research Centre. We included all patients who underwent Fontan procedures that took place at King Faisal Specialist Hospital and Research Centre, Riyadh, between 1985 and 2010, to allow a minimum of 6 years of follow-up for the last patient recruited. We excluded patients who died, were lost to follow-up, or had a Fontan redo within 1 year of the first Fontan procedure because they did not serve the purpose of the study. The primary objective is to determine the level of freedom from late TECs after the Fontan procedure. Late was defined as any TECs that occurred at least 1 year following the Fontan procedure. Secondary objectives included the following: (1) comparison between warfarin and aspirin with regard to the rate of late TECs; (2) freedom from late TECs based on the duration of antithrombotic therapy; (3) freedom from late TECs based on the presence of risk factors for late TECs (type of Fontan procedure, fenestration, and arrhythmia); (4) rate of late major, clinically relevant nonmajor, and minor bleeding that occurred after 1 year following the Fontan procedure[10]; and (5) comparison between warfarin and aspirin with regard to the rate of major bleeding and rate of major and clinically relevant nonmajor bleeding combined. To assess the freedom from late TECs based on the duration of antithrombotic therapy and based on our knowledge of practice, we anticipated switching among different antithrombotic therapies during the follow-up time period; so the duration was calculated, for the sake of analysis, based on 2 different approaches. First, the duration of the antithrombotic regimen started from time of discharge until time of first switch. Second, the duration of the antithrombotic regimen started at 1 year after the Fontan procedure until the time of antithrombotic therapy switch.

Data Collection

The study investigator collected data utilizing electronic medical records and patients' charts, as deemed necessary. Complete volumes of patients' charts were requested from the medical records department. Information collected was directly entered to REDCap, a secured web application for building and managing online surveys and databases. Because some patients could have undergone more than 1 Fontan procedure, we counted the second Fontan procedure as a new encounter. For this reason, we report the number of procedures rather than the number of patients. The study was approved by King Faisal Specialist Hospital and Research Centre's Institutional Review Board (IRB; Research Advisory Council Number 2161032). Informed consent waiver was approved by the IRB considering the study's retrospective nature and no risk.

Echocardiography

According to our institutional practice, Fontan patients have an echocardiography on an annual basis with each follow-up visit and if clinically indicated.

Statistical Analysis

The statistical methods used to evaluate the level of freedom from late TECs after the Fontan procedure were of a "time-to-event" nature. These included Kaplan-Meier actuarial analyses and comparisons between treatment groups evaluated using the log-rank test. Furthermore, the relationships of various risk factors on the time to the first late TEC were also analyzed with such analyses, including the use of the proportional hazards model. Patients who were observed to have switched therapy before a first late TEC were censored as of the date of the therapy switch. There was no attempt to analyze for multiple TEC events within each patient (to be reported in a separate study). If a patient developed more than 1 late TEC, then only the first such TEC was used and further follow-up for the patient beyond the first such TEC was not analyzed.

For analyzing the relationship between warfarin and aspirin on the time to the first late TEC, a Poisson model was used to express the incidence of late TECs and bleeding events over the duration of antithrombotic therapy in order to compare different regimens with regard to the event rates. Discrete data are expressed as percentages and cross-tabulations. Continuous data are expressed as means $\pm$ SDs or medians and interquartile ranges (IQR). A value of $P < 0.05$ was considered to be statistically significant. All analyses were performed using SAS/JMP version 14.0.

Results

We identified 499 patients who had undergone Fontan procedures, and they were screened for eligibility. Overall, 423 patients met the inclusion criteria and were included in the analysis, which accounts for 431 procedures; 419/431were first Fontan and 12/431 were second Fontan procedures (Figure 1).

The majority of the population were male: 58.46% (252/431). At the time of data collection, 70.77% (305/431) of patients were alive, 24.14% (104/431) were lost to follow-up, and 5.10% (22/431) were deceased. The most common documented causes of mortality were heart failure

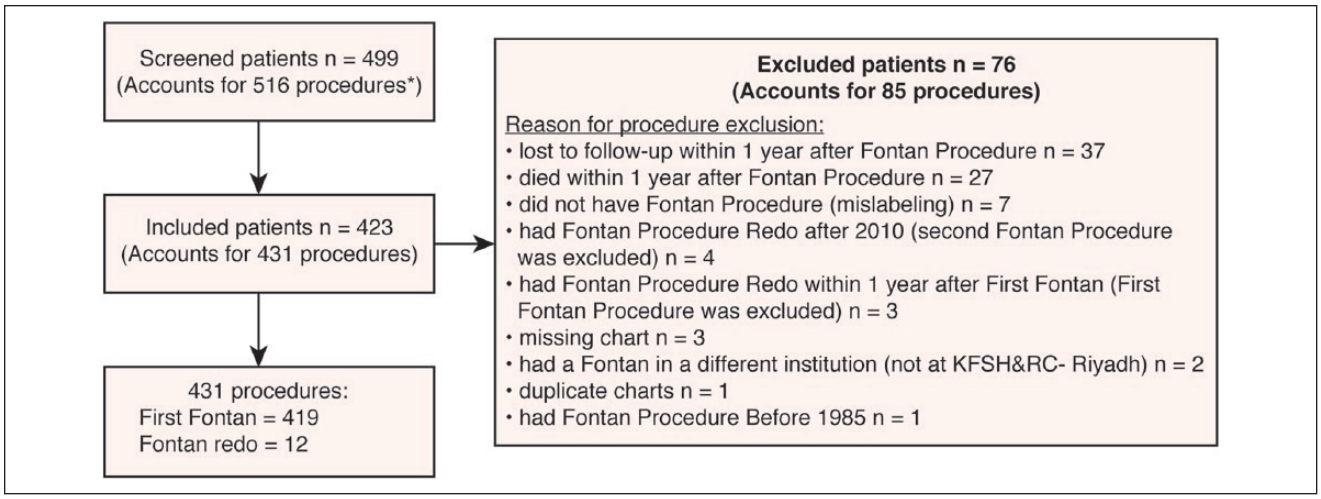

Figure 1. Patient screening and enrolment.
Abbreviation: KFSH&RC, King Faisal Specialist Hospital and Research Centre.
*Some patients might have had a Fontan redo.

72.72% (16/22), sepsis 13.63% (3/22), and others (sudden cardiac death, end-stage protein losing enteropathy and/or plastic bronchitis) 13.63% (3/22). The most commonly prescribed antithrombotic regimen at discharge post–Fontan procedure was warfarin (89.33%, 385/431), followed by aspirin (5.10%, 22/431), whereas 5.57% (24/431) were discharged without antithrombotic therapy. The majority of the patients were switched from one regimen to another during the follow-up period. Other complications were commonly reported after the Fontan procedure: supraventricular arrhythmia (28.47%, 123/431), exercise intolerance (12.76, 55/431), protein-losing enteropathy (12.30%, 53/431), hepatic complications (7.42%, 32/431), and ventricular dysfunction (7.42%, 32/431). Patients' baseline characteristics are outlined in Table 1.

Thromboembolic Complications

Throughout the study period, TECs were reported to have occurred after the Fontan procedure in 9.97% (43/431), of which 86.04% (37/43) were described as late TECs, with 13.95% (6/43) being a recurrent late TECs (Table 2). The fitted Kaplan-Meier curve showed that freedom from late TECs at 5, 10, 15, and 20 years were 97.54%, 96.90%, 90.78%, and 88.07%, respectively (Figure 2).

At a median follow-up of 13.6 years (IQR = 8.7), the incidence rate of late TECs was 16.99 events per 1000 patient-years. The incidence rates per 1000 patient-years specific to warfarin and aspirin were 7.81 and 5.83 events, respectively. There was no difference in the late TEC rate ratio between warfarin and aspirin: 1.34 (95% CI = 0.68 to 2.60).

We narrowed the follow-up duration to capture late TECs that occurred within the window of discharge after

Table 1. Baseline Characteristics.

Characteristic	n (%), Or mean ± SD, or median IQR
Age at diagnosis, months	2.4, IQR 8.4
Most common underlying anomaly, some patients might have associated cardiac anomalies	
Tricuspid atresia	121 (28.07)
Double inlet ventricle	104 (24.13)
Pulmonary atresia with intact ventricular septum	92 (21.35)
Unbalanced atrioventricular defect	76 (17.63)
Hypoplastic left heart syndrome	53 (12.30)
Straddling atrioventricular valve	16 (3.71)
Age at Fontan procedure, years	3.0, IQR 2.0
Weight at Fontan procedure, kg	14.4 ± 6.9
Type of procedure	
Lateral tunnel	307 (71.23)
Extracardiac conduit	107 (24.83)
Percutaneous Fontan	10 (2.32)
Atriopulmonary connection	7 (1.62)
Type of extracardiac conduit (n = 107)	
GORE-TEX	94 (87.85)
Gelseal Vascutek graft	6 (5.60)
Other	4 (3.73)
Size of the conduit, mm	19.40 ± 3.3
Fenestration	92 (21.35)
Size of fenestration, mm	4.30 ± 1.0
Potential risks for TECs	
Arrhythmia	123 (28.53)
Supraventricular tachycardia	109 (88.61)

Abbreviations: IQR, interquartile range; TEC, thromboembolic complication.

Table 2. Thromboembolic Complications (TECs) Post–Fontan Procedure.

Outcomes	n (%)
TECs over the study follow-up	43 (9.97)
Early TECs (within 1 year after the Fontan procedure)	6 (13.95)
Late TECs (1 year after the Fontan procedure)	37 (86.04)
First late TECs	31 (72.09)
Antithrombotic regimen at first late TECs (n = 31)	
Warfarin	15 (48.38)
INR at time of TECs (Mean ± SD)	1.3 ± 0.9
Aspirin	14 (45.16)
No anticoagulation	2 (6.45)
Recurrent late TECs	6 (13.95)
Antithrombotic regimen at recurrent late TECs (n = 6)	
Warfarin	4 (66.66)
INR at time of TECs (Mean ± SD)	1.8 ± 1.2
Aspirin	2 (33.33)
Anatomical location of late TECs	
Fontan conduit/right atrial thrombus	17 (45.94)
Stroke	7 (18.91)
Venous thromboembolism	5 (13.51)
Other (eg, jugular vein, radial artery, popliteal artery)	4 (10.81)
Mode of diagnosis of late TECs	
Transesophageal echocardiography	8 (21.62)
Transthoracic echocardiography	7 (18.91)
CT scan	5 (13.51)
Duplex ultrasound	4 (10.81)
Angiography	4 (10.81)
Clinical	3 (8.10)
MRI	3 (8.10)
Other (eg, pathological report)	2 (5.40)
Risk factors for TEC	
Supraventricular tachycardia	28 (75.67)
Fenestration	8 (21.62)

Abbreviations: CT, computed tomography; INR, international normalized ratio; MRI, magnetic resonance imaging.

the Fontan procedure until switching to different agent or development of TECs, where the other model was narrowed to capture late TECs that occurred within the window starting from 1 year post–Fontan procedure until switching to a different agent or development of TECs. There was no significant difference in either the first or second models, comparing warfarin with aspirin (Figures 3 and 4). There was no relationship between the time to late TECs and whether the Fontan was a lateral or an extracardiac conduit (hazard ratio [HR] = 0.57; $P = 0.298$). Fenestration was not significantly associated with time to late TECs (HR = 0.84; $P = 0.572$) (Supplemental figure 1); (Supplemental figure 2) yet the presence of fenestration was significantly associated with higher number of strokes (odd ratio = 9.68; $P = 0.0059$). The occurrence of supraventricular arrhythmia was significantly associated with a shorter time to late TECs (HR = 5.43; $P < 0.0001$). Overall, the time in therapeutic range over follow-up time for patients on warfarin was 41.42% (Supplemental figure 3). However, time in therapeutic range (INR = 2.0-3.0) for patients on warfarin at the time of late TECs was 73.68% (14/19).

Major bleeding after 1 year from the Fontan was reported in 50% (9/18) and 44.44% (8/18) of patients when they were receiving warfarin and aspirin, respectively. Warfarin was associated with a higher major bleeding incidence rate per 1000 patient-years: 3.70 events compared with 2.91 events with aspirin. The rate ratio was 1.27 (95% CI = 0.49 to 3.29) when warfarin was compared with aspirin. Clinically relevant nonmajor bleeding occurred in 68.75% (11/16) and 31.25% (5/16) of patients while they were on warfarin and aspirin, respectively, with incidence rate per 1000 patient-years of 4.52 events compared with 1.82 events. Minor bleeding was reported in 62.12% (41/66) and in 37.87% (25/66) of patients while they were on warfarin and aspirin, respectively, with incidence rate per 1000 patient-years of 16.8 events compared with 9.11 events. The rate ratio of major and clinically relevant nonmajor bleeding combined was 2.34 (95% CI = 1.16 to 4.72) when warfarin was compared with aspirin.

Discussion

Our study is particularly focused on late TECs, so we targeted long-term TECs that occurred after 1 year post–Fontan procedure. There is inconsistency in the literature regarding the actual prevalence of late TECs after a Fontan procedure. The freedom from development of late TECs at 1, 5, and 10 years after the Fontan procedure was reported as 97% ± 19%, 96% ± 2.5% and 92% ± 4.2%, respectively.[8] In 265 patients who had their Fontan procedure at the Mayo Clinic with mean follow-up of 18 ± 4 years, the overall freedom from TECs was 96%, 87%, and 63% at 10, 15, and 20 years, respectively.[5] Our cohort showed improvement when compared to those from the literature in terms of freedom from late TECs over a median follow-up of 13.6 years. However, this sizeable improvement in freedom from TECs in our study may be attributed to the fact that we eliminated TECs that occurred within 1 year of the Fontan procedure.

The most commonly prescribed antithrombotic regimen at discharge was warfarin, followed by aspirin; 5.57% were discharged without antithrombotic therapy, despite the fact that it was the standard of practice at our center. However, prescribing aspirin, warfarin, or no antithrombotic therapy on discharge is left to the prescriber's discretion based on the patient's risk of bleeding. Only 5.57% (24/431) of the patients were discharged without any kind of antithrombotic therapy. Most likely because they have an elevated INR already, secondary to liver congestion post-Fontan. The

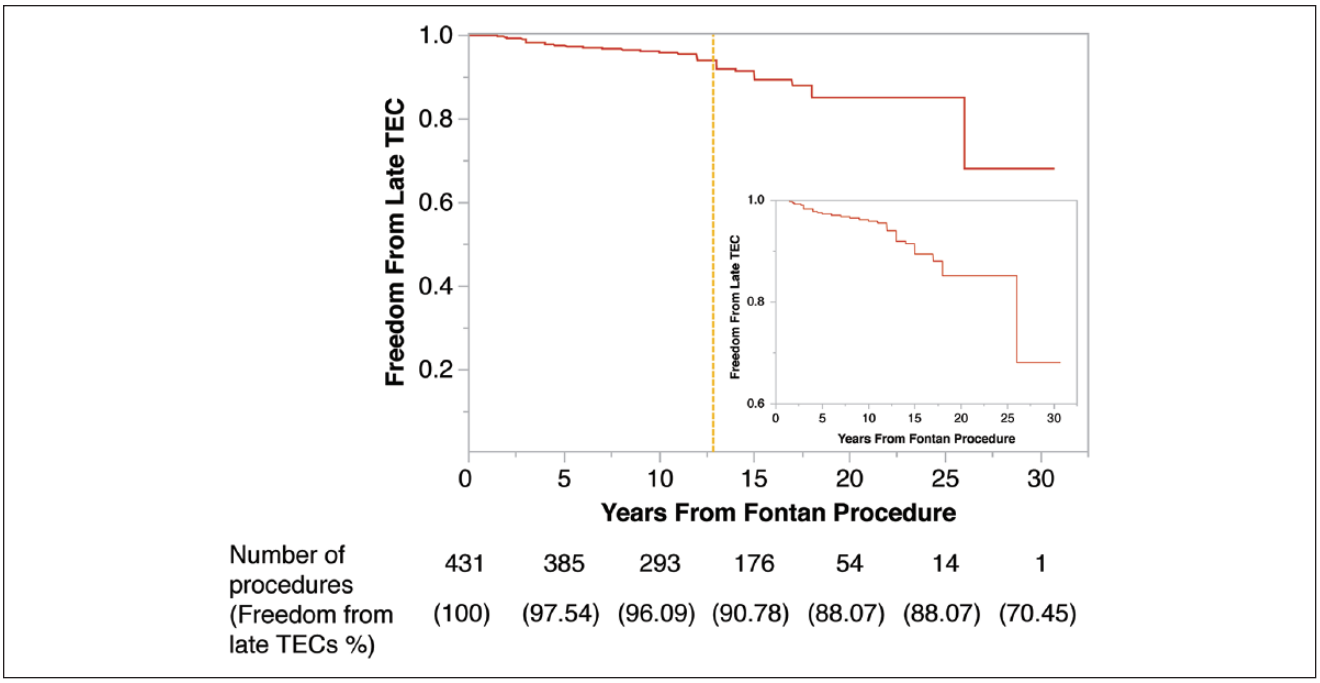

Figure 2. Freedom from late thromboembolic complications (TECs) post–Fontan procedure. The fitted Kaplan-Meier curve showed that freedom from late TECs at 5, 10, 15, 20, and 25 years were 97.54%, 96.90%, 90.78%, 88.07% and 88.07%, respectively. At median follow-up (13.6 years, IQR = 8.7), freedom form late TECs was 92.83%.
Abbreviations: IQR, interquartile range; TECs, thromboembolic complications.

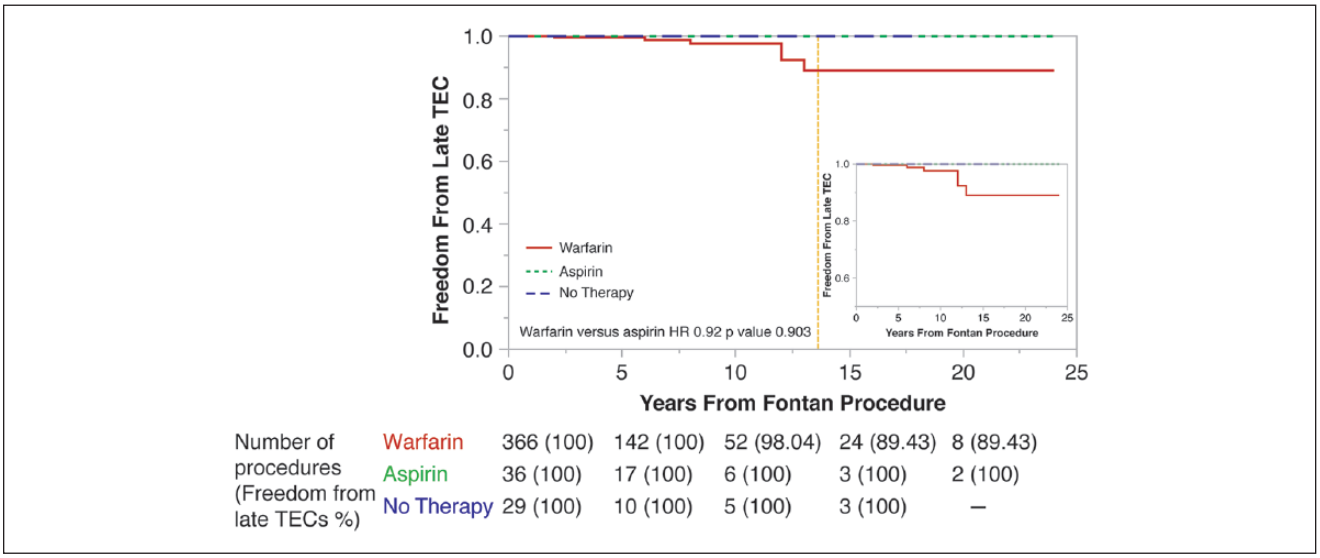

Figure 3. Freedom from late thromboembolic complications (TECs) post–Fontan procedure based on antithrombotic regimen duration at discharge until switching to different agent or development of late TECs. The fitted Kaplan-Meier method examined the freedom from late TECs based on the antithrombotic agents' duration of therapy. We narrowed the follow-up duration to capture late TECs that occurred within the window starting from discharge after the Fontan procedure until switching to different agent or development of late TECs. There was no significant difference comparing warfarin with aspirin. Median follow-up = 13.6 years (IQR 8.7).
Abbreviations: HR, hazard ratio; IQR, interquartile range.

usual practice is to have follow-up visit and get started on an antithrombotic agent. For this reason, we analyzed late TEC based on the discharge regimen and the regimen that they were on at 1 year, reflected in Figures 3 and 4, respectively. At 1 year post–Fontan procedure, there were 80.06% (253/316) on warfarin, 11.39% (36/316) on aspirin, and

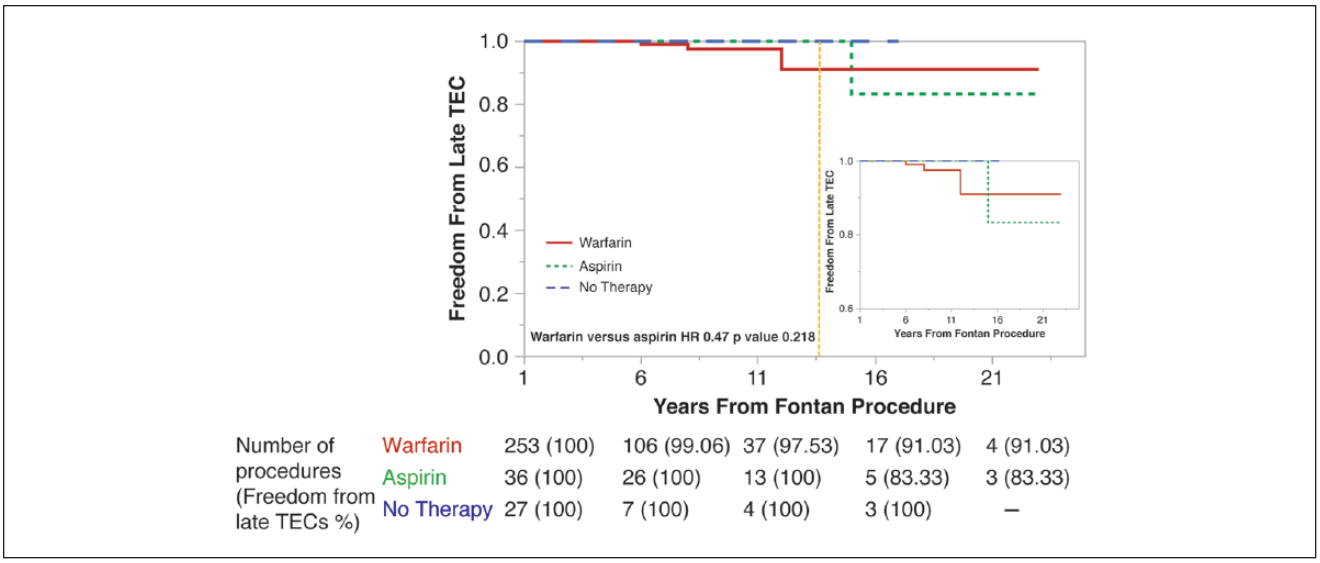

Figure 4. Freedom from late thromboembolic complications (TECs) post–Fontan procedure based on antithrombotic regimen duration at 1-year post–Fontan procedure until switching to different agent or development of late TECs. We used the Kaplan-Meier method to examine the freedom from late TECs based on the antithrombotic agents' duration of therapy. We narrowed the follow-up duration to capture late TECs that occurred within the window starting from 1-year post–Fontan until switching to a different agent or development of late TECs. There was no significant difference comparing warfarin with aspirin. Median follow-up = 13.6 years (IQR = 8.7).
Abbreviations: HR, hazard ratio; IQR, interquartile range.

8.54% (27/316) on no therapy (Figure 4). Some practitioners initiate warfarin in the first 6 months post–Fontan followed by aspirin because the risk of thrombosis is claimed to be higher within the early months.[11] Our study did not detect difference between warfarin and aspirin with regard to late TECs. This finding stresses on the fact that the preferred antithrombotic therapy remains debatable. A meta-analysis among 1200 patients with an avarage follow-up time of 7.1 years, compared with warfarin, aspirin, or no therapy and revealed significant reduction in TECs between warfarin or aspirin prophylaxis versus no therapy. However, there was no significant difference between aspirin or warfarin (odds ratio = 0.776; 95% CI = 0.249-2.42).[11]

A retrospective study assessed the relation of antithrombotic therapy duration and TECs in 85 Chinese patients who had undergone the Fontan procedure. The treatment regimens used were lifelong warfarin therapy, short-term (3 to 12 months) warfarin therapy then no therapy, and long-term aspirin prophylaxis, with a mean follow-up 6.6 ± 3.8 years. The freedom from development of TECs at 1, 5, and 10 years was 97% ± 19.0%, 96% ± 2.5%, and 92% ± 4.2%, respectively. The prevalence of TECs was not significantly different between the studied groups.[8] Correspondingly, our findings could not detect differences in the freedom from late TECs between warfarin and aspirin, regardless of the duration of therapy in the 2 models we used.

Several risk factors have been associated with increased risk of TECs, including arrhythmia, fenestration, subtherapeutic INR, and type of Fontan procedure.[5] In our study, the overall prevalence of supraventricular tachycardia at baseline was 89.61% (109/123). Most of the patients who developed late TECs were diagnosed with arrhythmia (75.67%), and it was significantly associated with higher rate of late TECs, which is not surprising. The most common type of arrhythmia was atrial fibrillation, and patients were initiated on warfarin once diagnosis was confirmed (Supplemental figure 3). It was reported in a recent study of 278 patients diagnosed with arrhythmia, with a mean follow-up 7.33 ± 1.16 years, that the overall TEC prevalence was 29%, with an event rate of 6.5 TECs per 100 patient-years,[12] which further supports that arrhythmia is a strong risk factor for the development of TECs.

Fenestration, on the other hand, is a theoretical risk factor for the development of TECs because of the potential for systemic embolization combined with the venous stasis and hypercoagulability.[13] Despite the fact multiple reports failed to show increased risk of thrombus formation with fenestration,[4,13] one study recommended anticoagulation instead of antiplatelet therapy for patients with fenestrated Fontan.[3] Our study showed that 21.62% of patients with late TECs were having fenestrated Fontan circulation, which was associated numerically with a higher rate of late TECs. Yet the presence of fenestration was significantly associated with a higher number of strokes (Supplemental figure 2).

It has been discussed in the literature that the Fontan procedure evolved through the years with the aim of reducing surgical complications and improving survival and outcomes. Lateral tunnel Fontan replaced the

atriopulmonary Fontan and, thus, overcame the right atrial dilation and arrhythmia resulting from an overstretched atrium. Later on, extracardiac Fontan was introduced to the practice, with the aim of minimizing occurrence of arrhythmia.[14] There was an interest in the literature to explore the influence of type of Fontan procedure on the development of TEC for many reasons. There was a theoretical concern that the use of synthetic material may increase the risk of thrombosis. Also, studies aimed to assess the improvement in Fontan procedure technique and its impact on decreasing the rate of TECs, as with the introduction of lateral tunnel Fontan in order to overcome the turbulent blood flow with atriopulmonary Fontan and to deliver a streamlined venous flow into the pulmonary arteries and the introduction of extracardiac Fontan, with the goal of reduction in atrial fibrillation postoperatively.[15,16] Interestingly enough, one study of 142 patients (14.7% had extracardiac Fontan) with a mean follow-up of 7.59 ± 3.65 years indicated that extracardiac conduit is a risk factor for the development of TECs.[17] On the other hand, in a relatively large study that compared thromboembolic outcomes between lateral tunnel Fontan and extracardiac Fontan, there was no significant difference between the 2 approaches.[18] In contrast, our study showed that patients with lateral tunnel Fontan tended to develop, numerically, a higher rate of late TECs compared with extracardiac conduit, which is an interesting finding, given that the literature has failed to find a significant influence of the surgical technique on the rate of TECs. Our study's long duration and large number of patients can explain this unique association (Supplemental figure 1).

Our findings showed that the overall time in therapeutic range (INR = 2.0-3.0) for patients on warfarin over the follow-up period was only 41.42%, which is low, but might be expected considering the long duration of follow-up. Among patients who were not in therapeutic range, late TECs were reported in 26.32% (5/19). There is consensus among most previous literature for the preferred INR target of 2.0 to 3.0, although some studies adjusted warfarin dose to attain INR between 1.5 and 2.5.[11,17] Another study suggested a significant association between subtherapeutic INR (<30% of INR measurements being greater than 2.0) and the risk of development of TECs for patients who were on warfarin at the time of TECs.[9]

Bleeding generally is a common complication associated with an antithrombotic regimen. Major bleeding is a specific concern that compromises patient outcomes.[19] Our study could not demonstrate a significant difference between warfarin and aspirin in the risk of development of major bleeding, which was not different from previous studies.[12,17,20] However, when combining major bleeding with clinically relevant nonmajor bleeding, warfarin was associated with significantly high rates of bleeding compared with aspirin.

Our study has several shortcomings; it is a single-center study with retrospective design. The fact that our hospital is a tertiary care institution led to a high rate of loss to follow-up over the study duration. Frequent switches between antithrombotic regimens, although it mimics real-life practice, made it challenging to assess the correlation between the duration of antithrombotic regimens and the development of late TECs. The selection of antithrombotic therapy, whether it is warfarin or aspirin, was based on the discretion of the surgeon and patient factors. Liver function was not assessed in this study because a complete hepatic profile was not available for all patients at similar intervals of follow-up.

On the other hand, our study is considered the largest retrospective single-center cohort that focused on late TECs post–Fontan procedure; with its long follow-up duration and the inclusion of different generations of the Fontan procedure, it further adds to the literature with real-world incidence rates of late TECs. We believe that our findings may suggest the role of a simpler antithrombotic regimen: for instance, starting with warfarin post–Fontan procedure for the first 3 to 6 months then switching to a regimen that does not require therapeutic drug monitoring, such as aspirin, especially when compliance with therapy becomes a challenge, unless a compelling indication to continue warfarin therapy exists. As for the optimal duration of antithrombotic therapy and the development of late TECs, it is still difficult to answer the question, "When to stop antithrombotic therapy post–Fontan?" especially because we encountered frequent switching between antithrombotic regimens throughout the study follow-up for most of the patients. Our study urges the need for development of a risk stratification tool to guide the decision of antithrombotic therapy. Also, a future controlled prospective study comparing the different treatment approaches—warfarin, aspirin, or no therapy—in addition to investigating the role of new oral anticoagulants is most needed.

Conclusion and Relevance

The incidence rate of late clinical TECs post–Fontan procedure in our population is low. The use of warfarin as compared with aspirin did not yield better outcomes for the prevention of late TECs; yet warfarin was significantly associated with higher combined rate of major and clinically relevant nonmajor bleeding. We believe that our findings suggest a simpler antithrombotic regimen: for instance, starting with warfarin in the first 3 to 6 months, then switching to aspirin, unless a compelling indication for warfarin exists.

Authors' Note

Presentation of the work: Our research scientific abstract won the third highest-ranking abstract submitted from participating Middle East countries and accepted for presentation at the ACC annual

scientific session in Orlando, Florida, in March 2018. Also, it earned the highest-ranking abstract submitted from Saudi Arabia and accepted for presentation at the ACC annual scientific session in Orlando, Florida, March 2018.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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