and young adults.[5,9,23] Because transesophageal echocardiography was not performed on a routine basis in all of our patients, the true incidence of asymptomatic cardiac thrombi may have been underestimated.

The relatively small number of patients with a thromboembolic event during follow-up limits the possibility of identifying a risk factor with statistical significance.

## Conclusion

In all of our patients, thrombus formation was associated with at least 1 additional potential predisposing factor, such as postoperative prolonged immobilization, protein-losing enteropathy, stenosis of the cavopulmonary anastomosis, or atrial arrhythmia, and seems to be highest in the first year after a total cavopulmonary anastomosis. Primary surgery with consequent closure of a patent pulmonary valve, thereby avoiding thrombogenic "blind" pulmonary artery stump, contributed to the low incidence of late thromboembolic events in our cohort. Because our prophylactic anticoagulation strategy proved effective in the prevention of thrombotic complications during long-term follow-up, we do not believe that initial anticoagulation therapy is routinely required in all young children after a total cavopulmonary anastomosis.

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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.

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).

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 |

## 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).

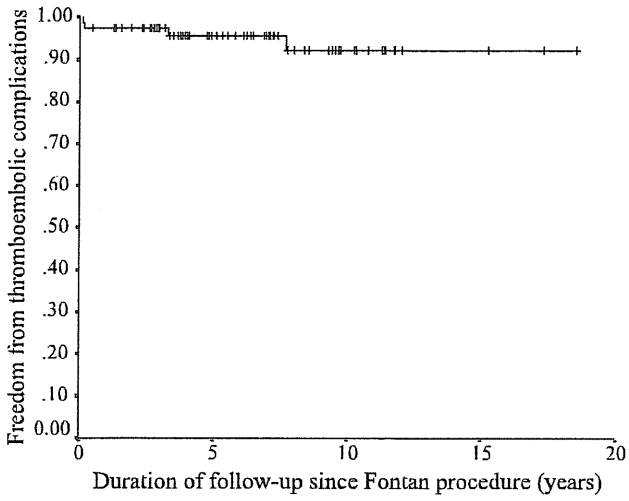


Fig. 1. Kaplan–Meier analysis of the freedom from the development of thromboembolic complications with follow-up duration since the Fontan procedure.

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 post-operative 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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# Thromboembolism and the Role of Anticoagulation in the Fontan Patient

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**Abstract** Among factors contributing to morbidity and failure of the Fontan circulation is the group of events referred to as thromboembolic complications. These events have been variously attributed to low flow states, stasis in the venous pathways, right-to-left shunts, blind cul-de-sacs, prosthetic material, atrial arrhythmias, and hypercoagulable states. Numerous investigations, most retrospective, have been undertaken to characterize thromboembolic events; describe the frequency and circumstances of these occurrences; and relate the risk of these events to patient, surgical, hemodynamic, and hematologic factors. Practices vary widely with respect to strategies of prophylactic anticoagulation in the hopes of minimizing the occurrence and morbidity of thromboembolism after Fontan operations. Review of the literature suggests that the factors associated with thromboembolic events after Fontan operations likely represent a complex field of biologic factors with multiple interactions. It is unlikely that a single agent will represent the solution to this complex problem.

Although the trend in operative mortality for modified Fontan procedures has been one of steady diminution from mortality rates approaching 30% in the earliest series to mortality rates less than 5% in contemporary reports, some factors contributing to morbidity and mortality seem to persist. One of the major factors contributing to morbidity and failure of the Fontan circulation is the group of events referred to as thromboembolic complications.

Thromboembolic complications in Fontan patients fall into two major categories [44]. The first involves thrombosis within the surgically created pathways between the vena cavae and the pulmonary arteries. These pathways are frequently referred to as the Fontan pathway or Fontan circuit. Thrombus formation within these pathways can cause local obstruction to flow with adverse hemodynamic consequences and may also embolize or extend into the pulmonary arteries [2, 20, 25, 34, 47, 57]. Also, in the presence of either intentional (surgically created) or incidental right-to-left intracardiac communications, thrombus in the systemic venous pathway or compartment may embolize through "fenestrations" to the systemic arterial circulation [28, 49, 51]. The second major category of thromboembolic events in Fontan patients involves thrombus originating in the pulmonary venous pathway or compartment (e.g., on the pulmonary venous side of a baffle) or in the systemic ventricle or ligated main pulmonary artery stump [37, 40, 48, 53]. In these cases, morbidity occurs principally in the form of embolism to the central nervous system [42, 62], the coronary circulation [49, 62], or, less commonly, elsewhere in the systemic circulation.

Numerous hypotheses have been invoked to explain the troubling frequency of thromboembolic events in Fontan patients. Thromboembolism after Fontan operations has been variously attributed to low flow states, stasis in the venous pathways, right-to-left shunts, blind cul-de-sacs, prosthetic materials, atrial arrhythmias, and hypercoagulable states. Numerous investigations, most retrospective, have been undertaken to characterize thromboembolic events; describe the frequency and circumstances of these occurrences; and relate the risk of thromboembolic events

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to patient, surgical, hemodynamic, and hematologic factors. A wide variety of practices have evolved with respect to various strategies of prophylactic anticoagulation in the hopes of minimizing the occurrence and morbidity of thromboembolism after Fontan operations. Although numerous authors tout their hypotheses, and the preferred anticoagulation strategies of institutions or individual practitioners, efforts toward evidence-based practice in this area are very limited.

In 2002, Monagle and Karl [45] published an article that included the work product of a comprehensive MEDLINE literature search of the English language literature from 1971 to 2000 using the following key words: Fontan, univentricular heart, children, thrombosis, congenital heart disease, cavopulmonary, and palliation. They identified and analyzed 51 studies and gleaned information concerning incidence, potential morbidity and mortality, risk factors, prophylactic options, and risk/benefit ratio of prophylactic anticoagulation as related to thromboembolic events after Fontan surgery. They concluded that, at the time, there was insufficient data to make clear recommendations about optimal anticoagulant prophylaxis.

Not included among the 51 reports analyzed in Monagle and Karl's review was our cohort study [30], also published in 2002, in which low-dose aspirin prophylaxis (81 mg/day) was used consistently and exclusively as a prophylactic anticoagulation regimen in 72 consecutive patients undergoing Fontan operations during a 5-year period. The patients had been monitored prospectively, with thromboembolism as the primary outcome measure. There were no early or late deaths. Follow-up was complete with 2882 patient-months at a mean of 40 months. There were no documented thromboembolic events: All suspicious events were investigated by transesophageal echocardiography and brain imaging. There were no hemorrhagic events or aspirin-related complications. This study was unique at the time because of the consistent use of a single anticoagulation strategy in a cohort of patients followed prospectively with evaluation for thromboembolic events as a primary end point. With the goal of shedding more light on this complex subject, we updated the literature search originally performed by Monagle and Karl using identical methodology and key words. A survey of the literature from 2000 through 2003 identified 21 additional studies to supplement the original list of 51. These publications included 8 case reports, 1 prospective cohort study that included some details about thromboembolism among other reported outcomes, 1 prospective cohort study (with case controls) in which thromboembolism was the primary outcome measure, 7 retrospective cohort studies that included some details about thromboembolism among the reported outcomes, and 3 retrospective cohort studies in which thromboembolism was the primary outcome measure, in addition to our study, which was the only one to evaluate the consistent use of a single strategy of prophylactic anticoagulation. Herein are summarized the findings of this now current review of the literature.

## Timing and Incidence of Thromboembolic Complications

Monagle and Karl [45] reviewed eight retrospective studies that had thromboembolic events as the primary outcome measure [16, 17, 23, 32, 36, 42, 54, 59]. The number of patients in these eight separate series ranged from 25 to 654 and totaled 1585. The percentage of patients experiencing thromboses ranged from 3 to 16%, and the percentage experiencing stroke or arterial emboli ranged from 3 to 19%. Among reports published subsequent to that review, Coon and associates [12] investigated the frequency of thrombus in patients followed at the Children's Hospital of Philadelphia after a Fontan operation. Between 1987 and 1999, 592 patients underwent echocardiography after Fontan operations, and 52 patients (8.8%) had intracardiac thrombus. Freedom from thrombus was 92, 90, 84, and 82% at 1, 3, 8, and 10 years after the Fontan operation, respectively. There was no difference in frequency of thrombus based on type of operation (atriopulmonary connection vs lateral tunnel) or the presence of fenestrations. Thrombus was detected in the systemic venous atrium in 26 patients (48%), in the pulmonary venous atrium in 22 patients (44%), in both atria in one patient (2%), in the hypoplastic ventricular cavity in 2 patients (8%), and in the ligated pulmonary artery stump in 1 patient (2%). A cerebral vascular accident was documented at approximately the time of thrombus detection on echocardiography in 8 of the 52 patients (15%). Of these 8, 4 were in atrial fibrillation/flutter and 3 had protein-losing enteropathy. Of the 52 patients with thrombus, 24 (46%) were on low-dose aspirin, 6 (12%) were on warfarin, and 1 (2%) was on heparin (for protein-losing enteropathy) at the time of detection of thrombus. The detection of thrombus on echocardiography was within the first year after Fontan operation in 34 of the 52 cases (65%). The median time interval between Fontan operation and detection of thrombus was 2.3 months (range, 1 day to 163 months). The curve describing the frequency of thrombus occurrence over time closely resembled previously published curves for the development of arrhythmia and protein-losing enteropathy, leading the authors to suggest a lifelong risk of thrombus formation in Fontan patients and the possibility of a codependent relationship between these late complications.

In 2002, Seipelt and associates [56] reported a retrospective series of 101 Fontan operations between 1986 and

1998 with analysis of thromboembolic events as the primary outcome measure. Of 85 survivors available for evaluation, 13 patients (15.3%) experienced thromboembolic events. Type of operation had no influence on the rate of thromboembolism. Patients were further analyzed by medical regimen within three groups: no anticoagulation, aspirin therapy, and Coumadin. There were complex interactions between date of operation, type of operation (modified Fontan vs total cavopulmonary connection), and prophylactic anticoagulant medical regimen (virtually none of the earlier Fontan patients received Coumadin, whereas half of the more recent total cavopulmonary connection patients did). Thromboembolic events occurred in patients within each of the three anticoagulant regimens, but there was a lower incidence in the more recent cohort managed with Coumadin.

Chun and associates [11] reported the incidence of stroke after Fontan procedures in 139 patients as 3.6% (seven strokes in 5 patients). Events occurred between 2 weeks and 9 years postoperatively. Two strokes occurred while on aspirin and Warfarin, two while on aspirin alone, and three while on no anticoagulant medications. Of the 5 patients, 3 had unfenestrated Fontans and 2 had fenestrated Fontans. Curiously, no intracardiac thrombus was detected by transthoracic echo at the time of the strokes. Transesophageal echos were done within a few days of stroke in 2 patients and did not demonstrate intracardiac thrombus. To our knowledge, this is the only study to have identified previous pulmonary artery banding as a risk factor for stroke. The authors invoked a potential mechanism similar to that in patients with a ligated main pulmonary artery stump.

An interesting cross-sectional study evaluating the prevalence of clinically silent pulmonary emboli in adults after Fontan operations was reported in 2003 by Varma et al. [61]. All consecutive adult Fontan patients attending the clinic at the University of Toronto Congenital Cardiac Center for Adults underwent ventilation–perfusion scanning and blood testing for thrombophilic tendency. Five adult patients (17%) had an intermediate or high probability for pulmonary embolism on ventilation perfusion scan, all of which were confirmed by computed tomography (CT) pulmonary angiography. No patient had a thrombophilic tendency (deficiency of protein C, protein S, antithrombin III, or antiphospholipid syndrome), although complete hematologic surveys were not done on patients receiving warfarin. Thirty percent of the patients were taking warfarin because of atrial flutter or atrial fibrillation, either chronic or paroxysmal. None of them had pulmonary emboli. Later age at the time of Fontan operation was associated with increased risk of silent pulmonary embolism, as was the type of Fontan anatomy (lateral tunnel > right atrium–right ventricle connection > atrial pulmonary connection). Not associated with silent pulmonary embolism were atrial arrhythmias, right atrial thrombus, or previous systemic thromboembolic events.

Three studies have compared transthoracic echocardiography (TTE) with transesophageal echocardiography (TEE) in the diagnosis of thromboembolic events after Fontan surgery. Stumper et al. [60], in a cross-sectional survey of 18 patients, found three intracardiac thrombi using TEE, only one of which was detected by TTE. The three positive cases were confirmed by angiography. Fyfe et al. [27] found six thrombi in 4 patients by TEE, only one of which was detected by TTE. The cases defined as positive by TEE were confirmed by angiography, surgery, or resolution of findings after treatment. Balling et al. [7] performed a cross-sectional study of 52 patients after Fontan operations. Seventeen patients (33%) had thrombus seen on TEE, only one of which was identified on TTE. Frequency of thromboembolic events reported is increased in recent studies compared with earlier studies, and the significant incidence of clinically silent thromboembolic events is noteworthy. Improved survival rates, longer duration of follow-up, improved diagnostic studies, and increased awareness of the potential for thromboembolic events must all contribute to the apparent increase in prevalence.

## Mortality Associated with Thromboembolic Complications

In general, information on the management and outcome of thromboembolic events in Fontan patients is scarce and poorly documented. Monagle and Karl [45] summarized the management approaches described in the literature and subsequent outcomes (Table 1).

Complete resolution of thrombosis was obtained in 48% of cases and death occurred in that compendium 25% of cases. Follow-up ranged from 1 month to 5 years [6, 8, 15, 17, 20, 21, 23, 25–27, 29, 32, 35, 36, 38, 39, 41, 50, 54, 58, 60, 62].

## Risk Factors for Thromboembolic Complications

The influence of patient age at operation on subsequent risk of thromboembolic events is uncertain. Whereas at least one cohort study identified older age at Fontan operation as a risk factor [61], other studies showed no correlation between age at surgery and risk of thromboembolic events. In retrospective cohort studies, type of Fontan operation performed, type of material used for the conduit, and the use of valved versus nonvalved conduits did not influence the incidence of venous thrombosis [32, 54]. Potentially

Table 1 Outcomes of thromboembolic events after Fontan procedures according to antithrombotic treatment[a]

| Treatment | No. treated | Complete resolution | Death | Subsequent embolization, extension, or incomplete resolution | Subsequent takedown of Fontan |
|---|---|---|---|---|---|
| Surgery | 5 | 2 | 2 | 1 | — |
| Surgery + anticoagulation | 14 | 7 | 6 | — | 1 |
| Thrombolysis | 6 | 3 | 1 | 3 | — |
| Thrombolysis + anticoagulation | 12 | 4 | 4 | 8 | — |
| Heparin | 5 | 3 | 1 | 1 | — |
| Coumadin | 23 | 14 | 2 | 7 | 1 |
| Aspirin | 2 | — | — | 2 | — |
| Total | 67 | 33 | 16 | 22 | 2 |

[a] Reproduced from: Monagle and Karl [45]

important exceptions to these general observations are highlighted in a report by Schoof et al. [55] of thrombus development in all three of their patients who underwent extracardiac total cavopulmonary connection using bovine jugular vein (Contegra, Medtronic, Minneapolis, MN, USA) as the extracardiac connection between the inferior vena cava and the pulmonary artery. Although the incidence of thromboembolic events appears to be independent of the individual type of Fontan pathway connections, Konstantinov and associates [47] from the Mayo Clinic have described thrombosis of both intracardiac and extracardiac conduits after modified Fontan operations in patients with azygous continuation of the inferior vena cava. The inference is that conduits carrying only hepatic venous blood may have a higher incidence of thrombosis.

Among potential hemodynamic risk factors for thromboembolic phenomena, low cardiac output, polycythemia, arrhythmias, and right-to-left shunts have all been discussed more completely than they have been analyzed. Although there is a general consensus that right-to-left shunts in congenital heart disease are associated with an increased risk of cerebral vascular embolization and stroke, du Plessis et al. [23] and Day et al. [17] assessed the role of fenestration in causing strokes and neither group found a significantly increased incidence of stroke in patients with fenestrations.

Danielson [16] reported that 16 of 18 patients who had strokes after Fontan operations at the Mayo Clinic had low cardiac output. The number of patients considered to have low cardiac output who did not experience strokes or thromboembolic events is unknown. du Plessis et al. [23] reported that polycythemia had no relationship to the risk of stroke in Fontan patients at Children's Hospital Boston. Rosenthal et al. [54] found arrhythmias in 71% of patients who subsequently developed thrombosis compared to 43% of those who did not. However, 70% of patients diagnosed with thromboembolic events were in sinus rhythm. Already noted was the study by Varma et al. [61], in which patients who received warfarin because of atrial arrhythmias had a zero incidence of clinically silent pulmonary embolism. du Plessis et al. found no relationship between arrhythmia and stroke after Fontan operation. Day et al. [17], in assessing potential risk factors for stroke after the Fontan procedure, reported the presence of residual right-to-left shunts (non-surgical fenestrations) in 6 of 7 patients with neurologic symptoms and in only 3 of 21 asymptomatic patients who also underwent post-Fontan catheterization. However, the denominator of asymptomatic patients with residual shunts is unknown.

In 1997, Kaulitz et al. [36] from Hannover, Germany, analyzed sequelae of the Fontan operation in the 80 survivors among 90 patients who underwent modified Fontan procedures between 1986 and 1994. Of 5 patients (6.2%) in whom intra-atrial thrombus was detected by transthoracic echocardiography, 3 had early postoperative thrombus formation despite heparin therapy. Each was believed to have mild obstruction of the cavopulmonary connection and preoperatively had raised pulmonary arteriolar resistance. Late postoperative atrial thrombosis was diagnosed on routine echocardiogram in 2 patients; both had previously developed signs of protein-losing enteropathy.

## Hematologic Factors in Fontan Patients

Cromme-Dijkhuis et al. [13] were among the first to measure coagulation factors and describe quantitative abnormalities involving both procoagulant and anticoagulant proteins in patients following Fontan operations. In their first study of 37 patients [13], they described 63 coagulation abnormalities in 24 patients. These included subnormal levels of protein C, antithrombin III, and factors II and X. In their second study [14], which evaluated an additional 66 patients, 62% were reported to have protein C deficiency. Deficiencies of protein S (6%), antithrombin III (4%), factor II (36%), factors VII and IX (43%), factor X

(36%), and plasminogen (15%) were also detected. Although these findings have been questioned because the authors did not use age-appropriate reference ranges for normal values [43], they show alterations that suggest the possibility of a procoagulant state after Fontan operations.

Jahangiri et al. [33], in a cross-sectional study of 20 children who had undergone modified Fontan procedures, reported similar coagulation factor abnormalities. However, their findings also included levels of factor VII that were significantly less than the normal range. Factor VII deficiency, if moderate in degree, should predispose to bleeding, not coagulation. This, together with the fact that protein C is a natural anticoagulant synthesized in the liver as a vitamin K-dependent protein, suggests a complex interaction between procoagulant factors and anticoagulant factors in Fontan patients. Furthermore, Jahangiri and other investigators [31] ruled out localized differences in coagulation abnormalities within the heart in patients late after the Fontan operation. Thus, the available information concerning the state of the coagulation system in Fontan patients suggests a complex field of physiologic variables, some potentially predisposing to thrombotic events and some potentially predisposing to a hypocoagulable state. Until recently, no authors had demonstrated any clear relation between the presence of coagulation factor abnormalities and the clinical and hemodynamic condition of the patients. To shed further light on this question, Odegard and colleagues [46] at Harvard designed a prospective case–control study to evaluate coagulation factor abnormalities and hemodynamic variables in children undergoing the Fontan operation. Coagulation factors were assayed in 20 children (age, 6.4 ± 2.9 years) at a mean of 3.7 ± 2.3 years after the Fontan procedure and in 24 age-matched healthy control subjects. Normal reference intervals were based on the control group. Concentrations of protein C, factors II, V, VII, and X, plasminogen, and antithrombin III were significantly lower in Fontan patients compared with age-matched controls. Factor VIII was significantly elevated in 6 patients (35%), 2 of whom had protein-losing enteropathy and thromboembolic events. A higher superior vena cava pressure was predictive of an elevated factor VIII level ($p = 0.003$). No other significant hemodynamic variables were predictive of a procoagulant or anticoagulant abnormality.

Whereas considerable emphasis has been placed on quantitation of coagulation factor proteins in post-Fontan patients, less attention has been focused on the issue of platelet reactivity. Ravn et al. [52] investigated platelet reactivity and quantified coagulation markers in a cross-sectional survey of 24 patients (median age, 11 years) at 2 years (range, 0.5–6) after a total cavopulmonary connection ($n = 14$) or a bidirectional Glenn anastomosis ($n = 10$). The reduction in serum proteins and clotting factors was generally similar to that described by other authors. None of the patients had clinically apparent thromboembolic events. However, increased platelet reactivity was observed *ex vivo* both after collagen-induced platelet aggregation [median, 73% (range, 61–84) in patients vs 61% (range, 47–69) in controls; $p < 0.01$] and after ADP-induced platelet aggregation [median, 69% (range, 52–77) in patients vs 56% (range, 40–66) in controls; $p < 0.05$). Among the many investigators who have examined the influence of connection geometry on the hemodynamic efficiency of various types of Fontan pathways, Monagle and Karl [45] evaluated the role of shear stress, among other major flow parameters, and hypothesized that changes in local flow structure produced changes in maximum shear stress values that may have consequences for platelet activation and thrombus formation in the clinical situation.

## Discussion

Ultimate reduction of the morbidity and mortality associated with Fontan's operation requires a strategy to minimize thromboembolic events. Three decades after the popular acceptance of the modified Fontan procedure as primary therapy, first for tricuspid atresia and later for a wide variety of malformations, there remain more controversies than hard facts concerning the causes and nature of these complications [1, 3, 4, 5, 9, 10, 18, 19, 22, 24]. Although there is general agreement that ligation of the main pulmonary artery, leaving a blind pouch or cul-de-sac distal to the pulmonary valve, is a worrisome substrate for the occurrence of thromboembolism [37, 40, 48, 53], almost any other assertion with respect to thromboembolic events after Fontan operations is the subject of controversy. The extent to which surgical factors and patient factors contribute to the overall risk remains poorly defined. Importantly, there is little agreement regarding the efficacy of various forms of prophylactic anticoagulant therapy in reducing the morbidity and mortality from thromboembolic events after Fontan operations.

What do we know? We know that (1) thromboembolic events occur more frequently, both early and late after modified Fontan operations, than they do after any other form of cardiac reconstruction other than prosthetic valve replacement; (2) thromboembolic events contribute to failure of the Fontan circulation and may occur with increased frequency in the "failing" Fontan circulation; (3) thromboembolic events occur in patients receiving heparin, aspirin, or Coumadin, as well as combinations or none of these; and (4) the factors predisposing to thromboembolic events after Fontan operations likely represent a complex field of biologic factors with multiple interactions. As such, it is very unlikely that a single agent will represent the

solution to this complex problem. In our institution, we completely avoid direct caval cannulation and the use of central venous lines. Single atrial cannulation and a very brief period of hypothermic circulatory arrest to create either a lateral atrial tunnel or extracardiac inferior vena cava-to-pulmonary artery connection avoids dissection around the cavae with the attendant risks of bleeding, caval injury or distortion, and phrenic nerve dysfunction. Obviating the need for repairs at caval cannulation sites, and avoiding the use of central venous lines, minimizes the likelihood of developing a nidus of thrombus within the venous pathway in the perioperative period. The use of only transthoracic atrial lines allows continuous monitoring of cardiac filling pressures during the early postoperative period, without the additional presence of foreign bodies in the cavopulmonary pathway. Inotropic support is routinely administered for 48–72 hours postoperatively, even in patients with ideal hemodynamics. We believe that maximizing cardiac output without significant elevation of venous pressure may contribute to the reduction of early postoperative thromboembolic events.

In our practice, we are encouraged with the results of our initial 5-year trial [30] and subsequent experience over 3 additional years with the use of aspirin (81 mg/day) beginning on the first postoperative day and continuing indefinitely during long-term follow-up. Despite routine surveillance, in addition to focused investigation of all clinically suspicious events, we have detected no thromboembolic events in our patient group. We are aware of the multiple reports of thromboembolic events occurring in Fontan patients while on aspirin, but we have so far not experienced this morbidity in our series.

We emphasize the importance of careful ongoing evaluation of post-Fontan patients for thromboembolic events. Clinically suspicious occurrences must be investigated in a timely fashion. This includes transesophageal echocardiography in circumstances in which there is an alteration from baseline hemodynamics and also transesophageal echocardiography and brain imaging (CT scan and/or magnetic resonance imaging) when there is suspicion of a cerebrovascular event. Investigations described previously have highlighted the occurrence of clinically silent thromboembolic events in patients in other series. Our routine follow-up includes clinical evaluation with transthoracic echocardiography at 6-month intervals and cardiac catheterization with angiography 1 year after the Fontan procedure. A transesophageal echocardiogram is performed in patients who demonstrate new onset of atrial arrhythmias, and both transthoracic echocardiography and cardiac catheterization with angiography are undertaken to investigate any hemodynamic deterioration. Although subclinical thrombi may have been missed in our patients, they have not progressed to clinically relevant events. In addition, although we remain satisfied with the results of this regimen, we concur with those who recommend Coumadin in the setting of poor hemodynamics and chronic venous hypertension and for patients with uncontrolled atrial tachyarrhythmias. We also concur with the use of Coumadin in adult patients who undergo Fontan revisions or conversions for failure of an initial form of Fontan connection.

The problem of reducing thromboembolic complications in Fontan patients is, of course, not as simple as finding a single optimal regimen of anticoagulant therapy. In patients with chronic effusions or protein-losing enteropathy, it is important to measure procoagulant and anticoagulant factor levels. In replacing the protein losses associated with these pathologic conditions, it is important to periodically administer fresh frozen plasma in addition to albumin in order to replete stores of protein C, protein S, and antithrombin III and to avoid a prothrombotic state.

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ORIGINAL ARTICLE

# Antiplatelet Versus Anticoagulation Therapy After Extracardiac Conduit Fontan: A Systematic Review and Meta-Analysis

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**Abstract** The benefits of prophylactic anticoagulation or antiplatelet therapy for patients undergoing extracardiac conduit (ECC) Fontan procedure still are a matter of debate. Through a systematic review and meta-analysis, this study aimed to determine the incidence of thromboembolism among patients undergoing ECC Fontan who received anticoagulation or antiplatelet therapy. Until February 2010, MEDLINE studies describing the incidence of thromboembolic events after ECC Fontan were reviewed. Information on type of drugs and clinical outcome was extracted. The 20 studies analyzed involved 1,075 patients: 220 (20.4%) in the antiplatelet group and 855 (79.5%) in the anticoagulation group. The mean follow-up period ranged from 2 to 144 months. The overall thromboembolism rate was 5.2% (95% confidence interval [CI], 3.8–7%; $I^2 = 0\%$; $p_{het} = 0.32$). The effect of different therapeutic strategies on the occurrence of thromboembolic and bleeding events was analyzed. Interestingly, the anticoagulation therapy compared with the antiplatelet therapy was not associated with a significant reduction in the incidence of overall thromboembolic complications (5% vs 4.5%, respectively; $I^2 = 0\%$; $p_{het} = 0.80$). Only two cases of bleeding were observed among patients receiving anticoagulant therapy at the time of the event. For patients undergoing ECC Fontan, the rate of thromboembolic and bleeding events associated with antiplatelet therapy is similar to that associated with anticoagulation therapy.

**Keywords** Anticoagulation · Antiplatelet · Fontan procedure · Stroke · Thromboembolism

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The Fontan procedure is the last staged operation for all children born with congenital heart disease for whom a two-ventricle repair cannot be offered. Since its original description, the procedure has undergone two major technical modifications aimed to improve streaming of the systemic venous blood flow to the lungs: the lateral tunnel technique (LT) and the extracardiac conduit (ECC).

Several studies have shown that the ECC procedure has excellent early and midterm outcomes and a lower incidence of postoperative complications compared with the LT procedure [6, 20, 24]. Thromboembolic events occurring after the Fontan procedure are a well-recognized source of morbidity [26]. Multiple clotting factor abnormalities have been reported including decreased levels of protein C, protein S, and antithrombin III [31]. Increased platelet reactivity also has been described [25]. However, the necessity for prophylactic antiplatelet or anticoagulant therapy remains controversial, with some retrospective reviews supporting antiplatelet therapy, with others suggesting that anticoagulants are more effective, and with still others discouraging routine anticoagulation [16, 27].

Therefore, this study aimed to perform a systematic review and meta-analysis to establish the rate of thromboembolic complications for patients undergoing the ECC Fontan procedure by comparing antiplatelet and anticoagulant prophylactic therapies.

## Methods

### Search Strategy and Selection Criteria

We performed a MEDLINE search of all articles until February 2010 and scientific session abstracts in the following journals: *Circulation, Journal of the American College of Cardiology, European Heart Journal,* and *The American Journal of Cardiology.* We also searched relevant websites including www.acc.org, www.americanheart.org, www.escardio.org, and www.clinicaltrialresults.org for the same information. No language, publication date, or publication status restrictions were imposed. We used the search terms "extracardiac conduit Fontan," "thromboembolism," "stroke," "antiplatelet," "anticoagulation," "thrombus," "Fontan outcome," and "extracardiac total cavopulmonary connection." The full search strategy is available on request from the authors.

We identified additional references through a manual search of the bibliographies in retrieved articles. We obtained results from all articles on extracardiac Fontan procedure and included only articles that described primary ECC Fontan procedure, clearly reported patient selection, clearly reported anticoagulation/antiplatelet therapy, enrolled al least five patients, and described a mean follow-up period of 2 months or longer. The exclusion criteria specified ongoing studies, irretrievable data, letters to the editor, editorials, reviews, case reports, and comment articles.

### Data Extraction and Quality Assessment

Two investigators (C.M. and G.G.) independently reviewed reports for eligibility at the title and abstract levels, resolving divergences by consensus. Studies that met the inclusion criteria were selected for further analysis. Study quality was assessed by the following items: type of study (retrospective or prospective), patient enrollment, outcome assessment (both imaging and clinical evaluation or clinical examination alone), total number of patients lost to follow-up evaluation (less than 5%, more than 10%, or between 5 and 10%). However, we did not use a quality score because this practice remains controversial for observational studies [11].

### Data Synthesis and Statistical Analysis

We analyzed the incidence of thromboembolic events, defined as stroke, pulmonary embolism, intracardiac or deep vein thrombosis, and reversible ischemic neurologic deficit occurring early or late after the ECC Fontan procedure. Early outcome was defined as outcome within the hospital or during the first 30 postoperative days. The $\kappa$ statistic was used to assess agreement between reviewers for study selection. We evaluated the incidence of thromboembolic and bleeding events, with 95% confidence intervals (95% CI), among patients undergoing the ECC Fontan procedure who received either antiplatelet therapy or anticoagulant regimen with or without antiplatelet agents.

Summary event rates per group were calculated with a random-effect meta-analysis using the DerSimonian and Laird method. A $z$ score was used to calculate the statistical significance of differences in thromboembolic rate according to the use of antiplatelet or anticoagulant agents. The Breslow-Day chi-square test was calculated to test the statistical evidence of heterogeneity across the studies ($p < 0.1$). In addition, we used the $I^2$ statistic, which describes the percentage variation across studies due to heterogeneity rather than chance. As a guide, $I^2$ values less than 25% indicated low, values 25% to 50% indicated moderate, and values exceeding 50% indicated high heterogeneity.

We assessed the possibility of small study effects by visual inspection of funnel plot asymmetry. Statistical analysis was performed with the Meta-Analyst beta 3.0 software program (Tufts Medical Center, Boston, US, https://research.tufts-nemc.org/metaanalyst). The study was conducted in compliance with the Observational Studies in Epidemiology (MOOSE) group [28].

## Results

### Description of Included Studies

We identified 981 potentially eligible studies. After screening titles and abstracts, we deemed 844 publications ineligible because they did not describe extracardiac Fontan procedure or did not meet the established inclusion criteria. We also excluded 24 duplicate references and 43 letters to the editor, editorials, case reports, reviews, and comment articles. We retrieved and reviewed the remaining 70 studies for possible data extraction. Figure 1 shows the flow of articles.

Of the 70 studies, 20 provided complete data on the thromboembolism rate after ECC Fontan procedures [1–10, 14–16, 20–24, 29, 34]. A total of 1,075 patients undergoing the ECC Fontan procedure were included in the meta-analysis. Study design, patient population, surgical technique, and thromboembolic rate are summarized in Fig. 2. All the included articles except one had a retrospective study design [29]. The sample sizes ranged from 6 to 282 patients. Of the 20 studies, 17 enrolled consecutive patients without potential bias of selection, whereas 3 included selected patients [3, 23, 29].

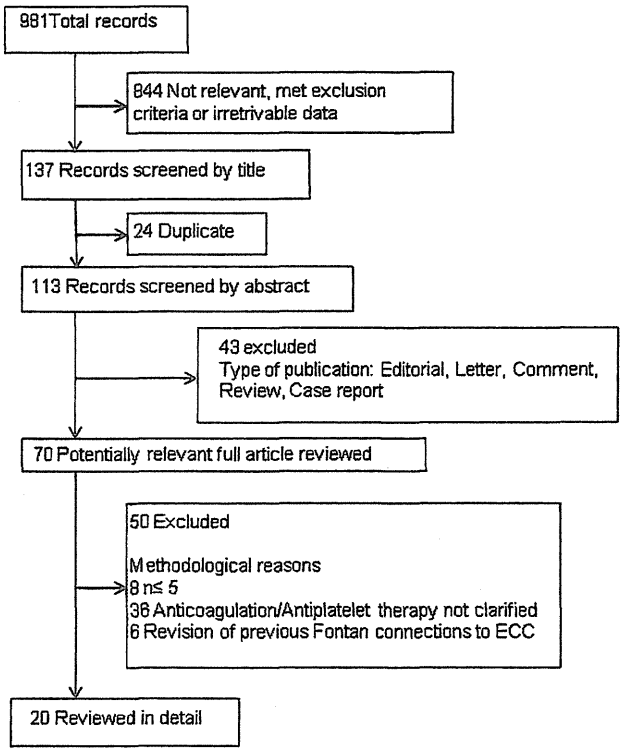


**Fig. 1** Results of the literature search

All the studies except two used imaging and clinical examination for outcome assessment [5, 9]. In particular, throughout the included studies, detection of thromboembolism had been performed by an imaging test such as echocardiography or magnetic resonance imaging (MRI). The patients lost to follow-up evaluation were less than 5% in 15 studies [1, 3, 5, 7–10, 14–16, 20–23, 29], more than 10% in 1 study [6], and between 5% and 10% in 4 studies [2, 4, 24, 34].

With regard to therapeutic strategy, 7 studies included patients receiving antiplatelet therapy, 3 evaluated patients receiving anticoagulation therapy, and 10 evaluated patients receiving both therapeutic strategies. In seven studies, the patients received both antiplatelet and anticoagulation therapy for 3 to 12 months and then continued with antiplatelet therapy alone [3, 5, 6, 14, 22–24], whereas one study evaluated patients who received lifelong antiplatelet and anticoagulation therapy [20]. For all the patients receiving warfarin therapy, the dose was adjusted to keep the international normalized ratio (INR) between 1.5 and 2.5, except for 57 patients for whom INR was kept up to 3.5 [5, 16]. Five studies involving 502 patients did not specify INR [4, 6, 7, 14, 24].

All the patients receiving antiplatelet therapy took aspirin 1 to 10 mg/kg/day except for 23 patients who received aspirin 81 mg/day [9, 10]. In five studies involving 505 patients, the dose was not specified [1, 6, 7, 14, 24], whereas two studies included 84 patients receiving ticlopidine 5 mg/kg/day [8, 21].

### Primary End Point

A total of 35 thromboembolic events, 16 early (46%) and 19 late (54%), occurred among 1,075 patients undergoing the ECC Fontan procedure, yielding a summary thromboembolism rate of 5.2% (95% CI, 3.8–7%) by meta-analysis, as shown in Table 1. Thromboembolism among individual studies varied from 0% to 16.7% and was not statistically heterogeneous across studies ($I^2 = 0\%$; $p_{het} = 0.32$). As shown in Table 1, the total incidence of thromboembolic events was similar between the patients who received antiplatelet therapy and those who received anticoagulation therapy with or without the use of antiplatelet agents (4.5% vs 5%; 95% CI, 2.3–8.8% vs 3.1–8.1%). Moreover, anticoagulation, alone or as adjunctive to antiplatelet therapy, was not associated with a significant reduction in the thromboembolism rate compared with antiplatelet therapy alone in all the reports combined ($I^2 = 0\%$; $p_{het} = 0.8$).

To analyze the effect of therapy further, we performed a dedicated statistical analysis evaluating the incidence of early events. Consistent with previous findings, the incidence of thromboembolic events within the first month after the index surgery did not differ significantly between the patients treated by warfarin (3%; 95% CI, 3.8–7%) and those who received antiplatelet therapy alone (3.7; 95% CI, 1.8–7.6%) ($I^2 = 0\%$; $p_{het} = 0.6$).

### Safety End Point

Two cases of bleeding events occurred in the eight studies that evaluated the safety end point [2, 3, 6, 9, 10, 16, 20, 34]. Notably, both cases involved patients receiving anticoagulant therapy at the time of the event.

## Discussion

Thromboembolic events account for significant morbidity and mortality, and the risk of death increases 15 years after Fontan surgery [13, 19]. The incidence ranges from 3% to 20% based on the surgical technique, the population of patients considered, and the accuracy of the diagnostic methods used [19, 27].

Early analyses demonstrated a low risk of thromboembolism associated with extracardiac Fontan using homografts or pericardial conduits [26]. However, other risk factors related to surgery have been proposed such as persistent right-to-left shunts, presence of fenestration, type of conduit material, use of a valved or nonvalved conduit, presence of a conduit diverting hepatic venous drainage in

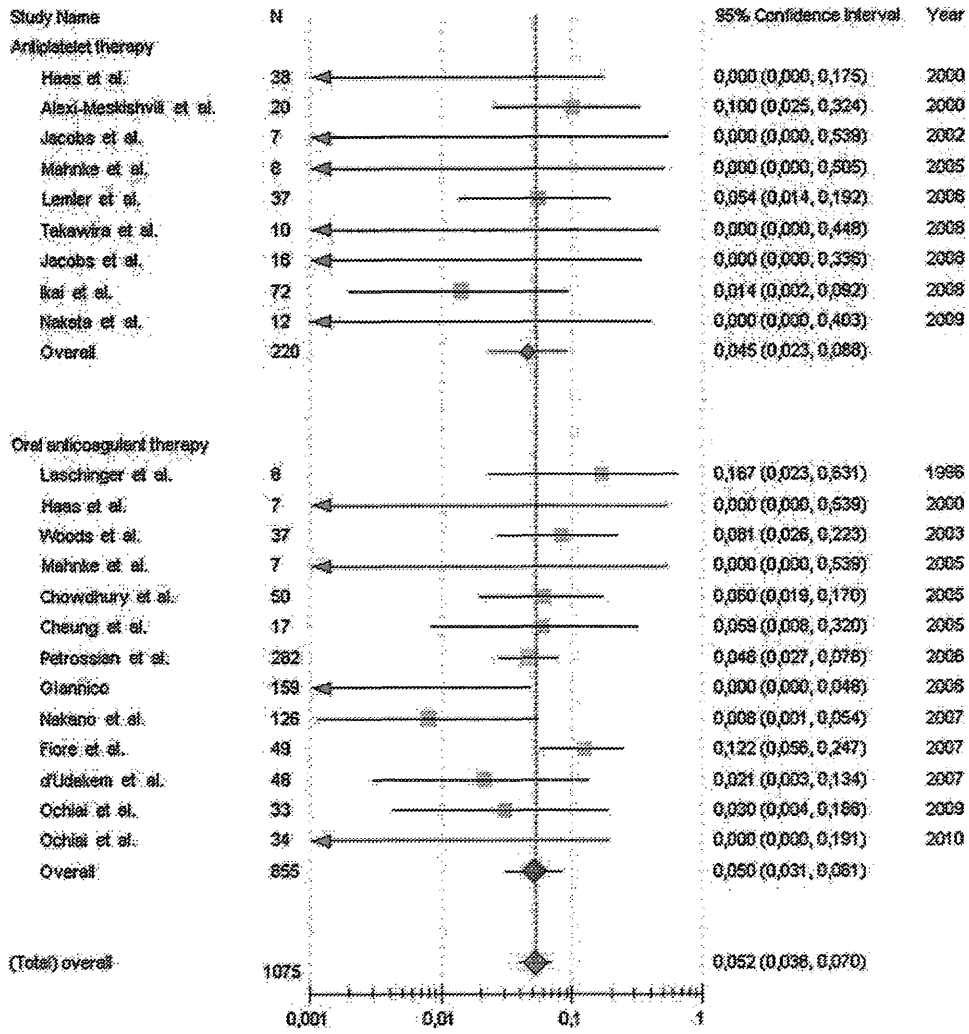


**Fig. 2** Forest plot of thromboembolic rates after ECC Fontan. The *x*-axis is drawn on a log scale. Studies are organized by therapeutic strategies and then by year of publication. Squares indicate the proportion of thromboembolic events after ECC Fontan in each study. The *horizontal lines* show the 95% confidence interval. The *diamonds* at the bottom of the each subgroup and the overall total at the bottom of the figure show the pooled estimates (with 95% confidence intervals) from the random-effects models. All studies were included in the overall total analysis

azygos continuation of the inferior vena cava, and history of pulmonary artery banding [26, 33].

Several studies reported a very poor survival after thromboembolic complications, with mortality rates as high as 25% in pediatric series and up to 38% in adult series [19, 33]. The poor prognosis is further compounded by controversy surrounding the management of acute thromboembolic events in these patients. As a result, aspirin (1–5 mg/kg/d) or therapeutic unfractionated heparin followed by vitamin K antagonists to achieve a target INR of 2.5 (range, 2–3) is recommended for all patients after the Fontan procedure [18]. However, the association of antiplatelet and anticoagulation therapy for 6 to 12 months followed by lifelong antiplatelet therapy is the most common therapeutic strategy used after ECC Fontan [3, 5, 6, 14, 20, 22–24].

To date, no consensus exists in the literature or in routine clinical practice as to the optimal type or duration of antithrombotic therapy for prevention of thromboembolic events after Fontan surgery [18]. Therefore, the prophylactic strategy depends on the experiences of the single center. The current study aimed to perform a comprehensive meta-analysis of all trials describing thromboembolic complications experienced by patients undergoing the ECC Fontan procedure who received antiplatelet therapy, anticoagulation prophylactic therapy, or both.

## Thromboembolism Rate

We found an overall 5.2% incidence of thromboembolic events after the ECC Fontan procedure. As reported earlier, this is consistent with the data reported in literature for patients undergoing Fontan [19]. Notably, we did not find any adjunctive protective effect associated with antiplatelet or anticoagulation therapy compared with different therapeutic approaches for either early or late events. Indeed, the overall incidence of thromboembolic events according to meta-analysis was 4.5% in the antiplatelet group and 5% in the anticoagulation group. Moreover, we did not find any adjunctive benefit from anticoagulation therapy in terms of

**Table 1** Trial

| | Trial period | No. of subjects | Mean follow-up (months) | Median age at time of Fontan (years) | Study drug | Total events | Early | Late | Material conduit | No. fenestrated |
|---|---|---|---|---|---|---|---|---|---|---|
| Haas et al. [7] | 1990–1997 | 45 | 64[a] | 4 | Asp ($n = 38$), W ($n = 7$) | 0 | 0 | 0 | PTFE | 18 |
| Alexi-Meskishvili et al. [1] | NR | 20 | 8[a] | 3 | Asp | 2 | 1 | 1 | PTFE | 12 |
| Jacobs et al. [10] | 1996–2000 | 7 | 40 | 2.1 | Asp 81 mg/day | 0 | 0 | 0 | PTFE | 4 |
| Mahnke et al. [16] | 1976–2001 | 15 | 18[a] | 13.2 | Asp 81–325 mg/day ($n = 8$), W ($n = 7$, INR 2.0–3.0) | 0 | 0 | 0 | NR | nr |
| Lemler et al. [15] | 1997–2002 | 37 | 2 | 3.4 | Asp 5 mg/kg/day | 2 | 2 | 0 | PTFE; aortic homograft | 14 |
| Takawira et al. [29] | 1997–2002 | 10 | 63 | 4.7 | Asp 3–5 mg/kg/day | 0 | 0 | 0 | NR | 3 |
| Jacobs et al. [9] | 1996–2006 | 16 | 14–139[b] | 2.1 | Asp 81 mg/day | 0 | 0 | 0 | PTFE | nr |
| Ikai et al. [8] | 1997–2006 | 72 | 29.2/42.1[a,c] | 1.5/3.5[c] | Ticlopidine 5 mg/kg/day | 1 | 1 | 0 | PTFE | 5 |
| Nakata et al. [21] | 1998–2008 | 12 | 66 | 2.1 | Ticlopidine 5 mg/kg/day | 0 | 0 | 0 | PTFE | nr |
| Woods et al. [34] | 1995–2001 | 37 | 23 | 3.3 | W (INR 1.5–2.0) | 3 | 3 | 0 | PTFE ($n = 33$); aortic allograft ($n = 4$) | 32 |
| Cheung et al. [2] | 1980–2002 | 17 | 79.2 | 6.2[d] | W (INR 1.5–2.5) | 1 | 0 | 1 | PTFE | nr |
| D'Udekem et al. [4] | 1998–2000 | 48 | 120 | 5.4 | W | 1 | 0 | 1 | PTFE ($n = 42$); aortic homograft ($n = 6$) | 12 |
| Laschinger et al. [14] | 1991–1995 | 6 | 13.5 | 5 | W+Asp | 1 | 1 | 0 | PTFE($n = 4$); homograft ($n = 2$) | 2 |
| Chowdhury et al. [3] | 1998–2003 | 50 | 77 | 7 | W (INR 2.5–3;) +Asp (5 mg/kg/day) | 3 | 3 | 0 | PTFE | nr |
| Petrossian et al. [24] | 1992–2005 | 282 | 44.4 | 4.5 | W+Asp | 13 | 5 | 8 | Homograft ($n = 12$); PTFE ($n = 270$) | 49 |
| Giannico et al. [6] | 1988–2003 | 159 | 63 | 6[d] | W+Asp | 0 | 0 | 0 | Dacron ($n = 43$); aortic homograft ($n = 3$); PTFE ($n = 113$) | 52 |
| Fiore et al. [5] | 1990–2004 | 49 | 36 | 5.6[d] | W (INR 1.5–2.0) +Asp (1 mg/kg/day) | 6 | 0 | 6 | PTFE | 16 |
| Ochiai et al. [22] | 1993–2008 | 34 | 112.8 | 3.8[d] | W (INR 1.5–2.0) +Asp (5 mg/kg/day) | 0 | 0 | 0 | PTFE | 0 |
| Ochiai et al. [23] | 1997–2007 | 33 | 105.6[a] | 4.1[d] | W (INR 1.5–2.0) +Asp (5 mg/kg/day) | 1 | 0 | 1 | PTFE | 0 |
| Nakano et al. [20] | Since 1994 | 126 | 96.4 | 4.3 | W (INR 1.5–2.0) +Asp (10 mg/kg/day) | 1 | 0 | 1 | PTFE | 2 |

*Asp* aspirin, *PTFE* polytetrafluoroethylene, *W* warfarin, *NR* data not reported, *INR* international normalized ratio, *W+Asp* warfarin plus aspirin

[a] Median follow-up period (months)

[b] Range of values in the follow-up period

[c] Value for each group of patients

[d] Mean age at time of Fontan (years)

the in-hospital outcome or the outcome within the first month after the index procedure. Therefore, anticoagulation therapy, alone or as adjunctive to antiplatelet therapy, is not associated with a significant reduction in the thromboembolism rate after ECC Fontan compared with antiplatelet therapy alone.

It must be considered that although the actual Evidence-Based Guidelines on Antithrombotic Therapy in Children suggest a specific therapy with aspirin or vitamin K antagonists as the primary prophylaxis for Fontan surgery in children, the optimal dose of aspirin and the INR target for the Fontan population still are unproved. Therefore, this meta-analysis included papers describing drugs doses different from those suggested by the Guidelines [18].

The benefits of antiplatelet therapy after the ECC Fontan procedure may be related to the fact that it is possible to minimize progression of peel-thickening of the conduit. In particular, it is well known through histologic studies conducted in experimental models on Gore-Tex graft that the internal surface of the Gore-Tex graft is completely covered with a thin and smooth neo-intima in the middle of the graft 1 year after the initial Fontan operation and that this mechanism includes deposition of platelet-fibrin aggregates and thrombi between the peel itself and the conduit wall [23]. Also, Kajimoto et al. [12] demonstrated that the expression of P-selectin, an important adhesion molecule playing a pivotal role in platelet aggregation, is elevated in patients after the direct right atrium–pulmonary artery connection, suggesting platelet activation in these patients [17]. Interestingly, anticoagulation therapy did not significantly reduce the platelet P-selectin levels [12]. Taken together, these data pointing out the important role of platelets in the formation of thrombus in the conduit can explain the protective effects of antiplatelet therapy in preventing early and late thromboembolic events after the Fontan procedure.

### Bleeding Rate

It must be considered that multiple clotting factor abnormalities in Fontan patients, with a complex interaction between pro- and anticoagulant factors, have been reported. Decreased levels of protein C, protein S, and antithrombin III as well as increased levels of factor VIII are well described [1, 15]. Also, reports have described a relative decrease in levels of factor VII, which should predispose Fontan patients to bleeding [15]. The risk of bleeding in these patients is estimated to be 3.9 events per 100 patient years [26].

Also, it must be considered that the real compliance problems related to anticoagulation therapy are associated with a largely adolescent and young adult population. In this regard, we did not find a significant incidence of bleedings with either therapeutic strategy. Moreover, all the events that we found in the overall population occurred with patients taking anticoagulation therapy, suggesting an additional protective role of antiplatelet therapy in preventing adverse events during the follow-up period.

### Study Limitation

Because this was a meta-analysis of nonrandomized studies, we cannot exclude unpredictable biases that led to both over- and underestimates of treatment efficacy in individual studies. Moreover, publication bias is a frequent concern with meta-analysis, although there is no consensus as to what methods (e.g., funnel plots) are reliable for measuring the bias [30]. Nevertheless, the absence of heterogeneity between the included studies, as demonstrated by the $I^2$ statistic, validate our results. It is important to note that the vigilance of detection (i.e., aggressive use of transesophageal echocardiography) will determine the incidence of events. Thus, the reported event rate in this meta-analysis could have been increased by the use of more sensitive diagnostic testing.

In addition, few studies reported complete data on important risk factors such as patient age at operation, presence of fenestration, polycytemia, arrhythmias, low cardiac output, type of conduit material, and use of valved or nonvalved conduit, leading to uncertainty about the true effect of these variables [26, 32]. It is possible that some of these factors would be associated with a higher incidence of thromboembolism, independent of the anticoagulation/antiplatelet prophylactic therapy, if more studies directly compared the tromboembolism rate in patients undergoing the ECC Fontan with or without these putative variables. Finally, despite these limitations, to date, this is the first meta-analysis including a large number of studies that allows an estimate of the thromboembolism rate after ECC Fontan with different therapeutic approaches.

## Conclusions

Although the pathogenesis of thrombus in patients after extracardiac Fontan procedure remains undetermined and the process is most likely multifactorial, this meta-analysis demonstrates the safety and efficacy of a therapeutic strategy based only on antiplatelet therapy. Indeed, our study demonstrated that for patients undergoing ECC Fontan, antiplatelet therapy alone is associated with a rate of early or late thromboembolic events and bleedings similar to that for anticoagulation therapy alone or in association with antiplatelet drugs. Our analyses should be considered as hypothesis-generating. Thus, future research should confirm our findings and clarify which factors are