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EDITORIAL: THROMBOEMBOLIC COMPLICATIONS AFTER FONTAN PROCEDURES—THE ROLE OF PROPHYLACTIC ANTICOAGULATION

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The Fontan procedure was initially described by Francis Fontan for the surgical management of tricuspid atresia in 1971. The principle is diversion of systemic venous return directly to the pulmonary arteries in the setting of single ventricle physiology.¹ Over subsequent years, many modifications of the original procedure have been described, although

the basic principle remains the same.²⁻⁵ The Fontan procedure has evolved as the definitive palliative surgical treatment for most heart lesions when a biventricular circulation is not feasible.⁶

Central venous and intracardiac thrombosis are a major cause of morbidity and mortality after Fontan procedures. Arterial embolization to the central nervous system resulting in persistent neurologic deficits is also a significant complication of Fontan procedures. Shirai and colleagues in this issue of the Journal describe a retrospective series of 16 patients undergoing extracardiac Fontan procedures. The median follow-up is 13 months, and the incidence of intracardiac thrombosis is 19%. On the basis of these findings, the authors have begun routine anti-thrombotic prophylaxis with aspirin for 6 months after all Fontan procedures. The usefulness of such a protocol, as the authors point out, remains to be proven.

Prophylactic anticoagulation with warfarin or antiplatelet agents after Fontan procedures is frequently recommended.⁷⁻⁹ However, no consensus is found in the literature or in routine clinical practice

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Table I. Cross-sectional studies using transesophageal echocardiography to assess point prevalence of thromboembolic events after Fontan procedures

Author et al.	Patients in series	No. (%) of thromboses
Stumper ¹⁸	18	3 (17)
Fyfe ¹⁷	30	6 (20)

Table II. Studies that had thromboembolic events as the primary outcome measure

Author et al.	Patients in series (survivors)	No. (%) of thromboses	Stroke or arterial emboli: N (%)
Rosenthal ⁶	70	11 (16)	3 (4)
Jahangiri ⁷	64 (57)	8 (14)	3 (5)
du Plessis ¹⁹	645	NA	17 (3)
Day ²⁰	68	NA	6 (9)
Matthews ²¹	25 (16)	NA	3 (19)
Fletcher ²²	64	6 (9)	NA
Dobell ²³	128	4 (3)	NA
Danielson ²⁴	449	18 (4)	NA
Kaulitz ²⁵	72	5 (6)	NA

NA, Not assessed.

as to the optimal type or duration of anticoagulation. Consequently, a wide variety of prophylactic anticoagulant regimens are currently used.¹⁰

How does one decide on the most appropriate therapy? Any decision about instituting preventive anticoagulation involves a trade-off between benefits (reduced thromboembolism) and toxicity and cost. Clinical recommendations and treatment guidelines should be based on the best available evidence. This is the founding principle of evidence-based medicine.¹¹ Such an approach begins with a systematic overview followed by a critical assessment of the existing evidence.¹² Assessment of the literature involves analyzing the strength of study designs, the validity of the results obtained within those designs, and the relevance of those results to the wider patient population.^{11, 13, 14} Useful measures of a treatment's value, such as relative risk reduction and the number needed to treat (to avoid one episode of thromboembolism) can then be used to determine clinical recommendations.¹² In other words, one must assess the strength of the evidence, the necessary impact of treatment to warrant its use, and how well the proposed treatment works.¹²

A comprehensive review of the literature pertaining to thromboembolism after Fontan procedures

Table III. Studies in which thromboembolic events were not the primary outcome measure, but that gave some details of thromboembolic events

Author et al.	Patients in series (N)	No. (%) of thromboses	Stroke or arterial emboli: N (%)
Driscoll ¹	352	3 (1)	4 (1)
Fontan ²⁶	100	3 (3)	NA
Prenger ³	22	2 (7)	NA
Laks ²⁷	45	1 (2)	NA
Annechino ²⁸	38	1 (3)	NA
Myers ²⁹	34	1 (3)	NA
Mair ³⁰	65	1 (2)	NA
Cromme-Dijkhuis ³¹	37	2 (5)	NA
Cromme-Dijkhuis ⁴⁵	66	3 (5)	NA

NA, Not assessed.

reveals no prospective studies or randomized trials. The current literature consists of cross-sectional point surveys ($n = 4$, however only two directly assessed thromboembolism), retrospective series in which thromboembolism was either the primary outcome measure ($n = 9$) or one of multiple outcomes ($n = 7$), and case reports ($n = 15$). The potential for bias in such observational studies, especially the latter types (multiple outcomes, case reports), is increased.¹²⁻¹⁵ Any treatment recommendations based on these studies would be very weak compared with those obtained from prospective randomized trials.^{12, 16}

The incidence of thromboembolism after Fontan procedures is crucial to the appropriateness of prophylactic anticoagulation. Point prevalences for intracardiac thrombosis ranged from 17% to 20% in the cross-sectional surveys^{17, 18} (Table I). Reported incidences of venous thromboembolism and stroke ranged from 3% to 16% and 3% to 19%, respectively, in the studies in which thromboembolism was the primary outcome^{6, 7, 19-25} (Table II) and from 1% to 7% in studies assessing multiple outcomes^{1, 3, 26-32} (Table III).

In assessing the validity of incidence estimates one must consider the diagnostic methods used.³³ The most common methods used to detect venous and intracardiac thrombosis were transthoracic and transesophageal echocardiography, followed by angiography. Other diagnostic methods reported included autopsy (11 cases) and reoperation (6 cases). The most common diagnostic methods used to detect stroke were computed tomography, magnetic resonance imaging, angiography, and clinical diagnosis. The two cross-sec-

Table IV. Outcome of thromboembolic events after Fontan procedures according to antithrombotic treatment

Treatment	Number treated	Outcome of treatment			
		Successful Complete resolution	Death	Treatment failure	
				Subsequent embolization, extension, or incomplete resolution	Subsequent takedown of Fontan
Surgery	4	1	2	1	—
Surgery + anticoagulation	14	7	6	—	1
Thrombolysis	6	3	1	3	—
Thrombolysis + anticoagulation	11	3	4	8	—
Heparin	5	3	1	1	—
Coumadin	23	14	2	7	1
Aspirin	2	—	—	2	—
Total	65	31	16	22	2

tional studies compared transesophageal and transthoracic echocardiography for intracardiac thromboembolism.^{17, 18} Had the point prevalences from these studies been estimated using transthoracic echocardiography, the results would have been 5% and 3% instead of 17% and 20%. Several other publications reported thromboembolism diagnosed by transesophageal echocardiography or angiography that were not detected using transthoracic echocardiography.^{6, 7, 19}

In addition to nonstandardized diagnostic tests, many studies assessed only survivors, with no information on mortality. Mean time from Fontan procedure to thromboembolism was at times greater than mean time of follow-up.⁶ The incidence of thromboembolism was increased in recent studies compared with earlier studies, reflecting increased survival, longer duration of follow-up, improved diagnostic tests, or increased awareness of the potential for thrombosis.⁶ The retrospective nature of the studies, frequent lack of sensitive diagnostic tests, and limited follow-up not only account for variation in reported incidences but also suggest that the reported incidences of thromboembolism after Fontan procedures are minimal estimations.

The timing of thromboembolism after Fontan procedures is important in determining the optimal duration of prophylactic anticoagulation. The exact duration of time from Fontan procedure to thromboembolism could be calculated for 109 events reported in 16 case series^{3, 7, 17, 19-31} and 15 case reports.^{8-10, 32, 34-44} Of these 109 cases of thromboembolism, 54 occurred within the first 3 months after the procedure and 55 occurred after 3 months. Two large series that assessed the timing of thromboembolism both concluded that the period of risk

extended beyond 3 months after the procedure,^{6, 7} with a mean time of 6.1 years in one series.⁶ Prophylactic anticoagulation for 3 months after Fontan procedures is frequently advocated; however, it is unjustified on the basis of the existing literature.

Identification of predisposing factors for thromboembolism could allow stratification of patients into high- or low-risk groups that require different intensities of prophylactic anticoagulation. A number of authors have analyzed a variety of possible predisposing factors, including demographic and surgical factors (patient age at operation⁶; type of Fontan procedure performed,^{6, 7} including the presence or absence of fenestration^{19, 20}; type of material used for the conduit; use of valved or nonvalved conduits⁶) and hemodynamic factors (arrhythmias,^{6, 19, 20} right-to-left shunts,²⁰ polycythemia,¹⁹ and low cardiac output²⁴). Although some studies claimed statistically significant relationships, predisposing risk factors were not identified with consistency or certainty because of lack of statistical power, use of retrospective data, and incomplete reporting of data. Consequently, no conclusions can be made about the relative contribution of patient demographic, surgical, or hemodynamic factors in causing thromboembolism after Fontan procedures.

Two studies assessed the role of coagulation deficiencies in the etiology of thromboembolism. Both studies had major inadequacies.^{31, 45} The reference ranges used to determine normal from abnormal were not age specific, and most children labeled as abnormal were in fact normal for age. Case reports with similar findings also used inappropriate reference ranges, whereas cases reporting normal coagulation factors did not.^{6, 20, 25, 37} No

accurate data implicate abnormalities of the coagulation system in thromboembolism after Fontan procedures.

All episodes of thromboembolism in the series by Shirai and colleagues were detected on routine transthoracic echocardiographic screening of asymptomatic patients. Warfarin therapy was begun and the patients remained well, although the duration of follow-up was not stated. Routine evaluation with transthoracic echocardiography leading to the detection and treatment of asymptomatic thrombi has previously been reported to improve outcome and reduce the incidence of stroke.⁶ However, other cases are reported in which subsequent stroke was not prevented.^{17, 19} Prospective studies are required to confirm the usefulness of routine screening, in particular with a sensitive test such as transesophageal echocardiography.^{46, 47}

The management of thromboembolism after Fontan procedures is also controversial. Literature on the management and outcome of thromboembolism was scarce and often poorly documented (Table IV). Therapeutic options include surgical embolectomy, with or without further surgical modifications of the intracardiac anatomy; thrombolytic therapy; and anticoagulation therapy. Total resolution of thrombosis was achieved in only 48% of cases. Death occurred in 25% despite aggressive treatment.* Many children do not survive long enough to be given effective antithrombotic treatment.³⁸

The incidence and poor prognosis of thromboembolism after Fontan procedures has caused most authors to postulate that routine prophylactic anticoagulation with warfarin or antiplatelet agents is warranted. However, only one small retrospective series has been published in which all patients received prophylactic anticoagulation. Despite warfarin administration for 3 months, the incidence of venous thrombosis alone was 7.4%.³ The target international normalized ratio, which reflects the level of anticoagulation, was not stated. In total, from all other case series and reports in the literature, only 16 patients received prophylactic anticoagulation therapy with either warfarin ($n = 12$), aspirin ($n = 3$), or heparin ($n = 1$).^{6, 7, 10, 17, 19, 20, 25, 35} The rationale for prophylaxis in these particular patients was the presence of fenestration ($n = 7$), previous thrombosis ($n = 2$), atrial fibrillation ($n = 1$), and immobility ($n = 1$). No rationale was given for a further five cases. Of the 12 patients who

received warfarin (target international normalized ratios not stated), five had thromboembolism during or after the prophylactic therapy. In one patient warfarin was discontinued because of bleeding and a subsequent thromboembolus occurred.³⁵ The three patients given prophylactic aspirin and one patient given heparin all had thromboemboli while receiving prophylactic therapy. In summary, the usefulness of prophylactic anticoagulation therapy remains to be proven. Virtually no information regarding the safety and efficacy of prophylactic anticoagulation with oral anticoagulants or antiplatelet agents exists.

The current study by Shirai and colleagues is useful because it reaffirms the high risk of thromboembolism after Fontan procedures. With increased follow-up and using a more sensitive diagnostic method like transesophageal echocardiography, the incidence of thromboembolism after Fontan procedures is likely greater than 20%. In combination with the reported poor outcome of thromboembolism, prophylaxis seems logical. The optimal type and duration of any such therapy is unknown. Returning to our framework of evidence-based medicine, we can find little evidence documenting the benefits or risks of routine prophylaxis. Measures such as relative risk and number needed to treat cannot be applied because the appropriate studies have not been done. Current practices can only be viewed as opinions based, at best, on theory and personal experiences. As we approach the next millennium, this level of evidence is insufficient grounds for management of an important issue that has remained unresolved for 25 years. By design, retrospective case series like that of Shirai and colleagues and those published previously cannot resolve this issue.¹⁵ These questions can only be answered in well-controlled, prospective studies.^{13, 14} Single institutions are unlikely to successfully complete such studies. Multicenter randomized controlled trials comparing prophylactic antiplatelet and anticoagulation therapies are urgently required to provide rational scientific guidelines for the future management of Fontan procedures in children.

REFERENCES

1. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five to fifteen year follow-up after Fontan operation. *Circulation* 1992;85:469-96.
2. Gale AW, Danielson G, McGoon D, Wallace D, Mair D. Modified Fontan operation for univentricular heart and complicated congenital lesions. *J Thorac Cardiovasc Surg* 1979;78:831-8.
3. Prenger K, Hess J, Cromme-Dijkhuis A, Eijgelaa A. Por-

*6,7,10,17-19,22,23,25-27,32,34-36,39-44

- cine-valved Dacron conduits in Fontan procedures. *Ann Thorac Surg* 1988;46:526-30.
4. Jonas RA. Intracardiac thrombus after the Fontan procedure. *J Thorac Cardiovasc Surg* 1995;110:1502-3.
5. Cetta F, Feldt RH, O'Leary PW, Mair DD, Warnes CA, Driscoll DJ, et al. Improved early morbidity after Fontan operation: the Mayo Clinic experience, 1987 to 1992. *J Am Coll Cardiol* 1996;28:480-6.
6. Rosenthal D, Friedman A, Kleinman S, Kopf G, Rosenfeld L, Hellenbrand W. Thromboembolic complications after Fontan operations. *Circulation* 1995;92(Suppl):II287-93.
7. Jahangiri M, Ross DB, Redington AN, Lincoln C, Shinebourne EA. Thromboembolism after the Fontan procedure and its modifications. *Ann Thorac Surg* 1994;58:1409-14.
8. Okita Y, Miki S, Kusuwhara K, Ueda Y, Tahata T, Komeda M, et al. Massive systemic venous thrombosis after Fontan operation: report of a case. *Thorac Cardiovasc Surg* 1988;36:335-6.
9. Shannon FL, Campbell DN, Clarke DR. Right atrial thrombosis: rare complication of the modified Fontan procedure. *Pediatr Cardiol* 1986;7:209-12.
10. Wilson D, Wisheart J, Stuart A. Systemic thromboembolism leading to myocardial infarction and stroke after fenestrated total cavopulmonary connection. *Br Heart J* 1995;73:483-5.
11. Oxman AD, Sackett DL, Guyatt GH. Evidence-Based Medicine Working Group. I. How to get started. *JAMA* 1993;270:2093-5.
12. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. For the Evidence-Based Medicine Working Group. IX. A method for grading health care recommendations. *JAMA* 1995;274:1800-4.
13. Guyatt GH, Sackett DL, Cook DJ. Evidence-Based Medicine Working Group. II. How to use an article about therapy or prevention. A. Are the results of the study valid? *JAMA* 1993;270:2598-601.
14. Guyatt GH, Sackett DL, Cook DJ. Evidence-Based Medicine Working Group. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? *JAMA* 1994;271:59-63.
15. Naylor CD, Guyatt GH. Evidence-Based Medicine Working Group. X. How to use an article reporting variations in the outcomes of health services. *JAMA* 1996;275:554-8.
16. Wilson MC, Hayward RSA, Tunis SR, Bass EB, Guyatt G. Evidence-Based Medicine Working Group. VIII. How to use clinical practice guidelines. B. What are the recommendations and will they help you in caring for your patients? *JAMA* 1995;274:1630-2.
17. Fyfe DA, Kline CH, Sade RM, Gillette PC. Transesophageal echocardiography detects thrombus formation not identified by transthoracic echocardiography after the Fontan operation. *J Am Coll Cardiol* 1991;18:1733-7.
18. Stumper O, Sutherland G, Geuskens R, Roelandt J, Bos E, Hess J. Transesophageal echocardiography in evaluation and management after a Fontan procedure. *J Am Coll Cardiol* 1991;17:1152-60.
19. du Plessis A, Chang A, Wessel D, Lock J, Wernovsky G, Newburger J, et al. Cerebrovascular accidents following the Fontan operation. *Pediatr Neurol* 1995;12:230-6.
20. Day RW, Boyer RS, Tait VF, Ruttenberg HD. Factors associated with stroke following the Fontan procedure. *Pediatr Cardiol* 1995;16:270-5.
21. Matthews K, Bale J, Clark E, Marvin W, Doty D. Cerebral infarction complicating Fontan surgery for cyanotic congenital heart disease. *Pediatr Cardiol* 1986;7:161-6.
22. Fletcher SE, Case CL, Fyfe DA, Gillette PC. Clinical spectrum of venous thrombi in the Fontan patient. *Am J Cardiol* 1991;68:1721-2.
23. Dobell ARC, Trusler GA, Smallhorn JF, Williams WG. Atrial thrombi after the Fontan operation. *Ann Thorac Surg* 1986;42:664-7.
24. Danielson G. Invited commentary. *Ann Thorac Surg* 1994;58:1413-4.
25. Kaulitz, Ziemer G, Bergmann F, Luhmer I, Kallfelz H. Atrial thrombus after a Fontan operation: predisposing factors, treatment, and prophylaxis. *Cardiol Young* 1997;7:37-43.
26. Fontan F, Deville C, Quaegebeur J, Ottenkamp J, Sourdille N, Choussat A, et al. Repair of tricuspid atresia in 100 patients. *J Thorac Cardiovasc Surg* 1983;85:647-60.
27. Laks H, Milliken J, Perloff J, Hellenbrand W, George B, Chin A, et al. Experience with the Fontan procedure. *J Thorac Cardiovasc Surg* 1984;88:939-51.
28. Anecchino F, Brunelli F, Borghi A, Abbruzzese P, Merlo M, Parenzan L. Fontan repair for tricuspid atresia: experience with 50 consecutive patients. *Ann Thorac Surg* 1988;45:430-6.
29. Myers J, Waldhausen J, Weber H, Arenas J, Cyran S, Gleason M, et al. A reconsideration of risk factors for the Fontan operation. *Ann Surg* 1990;211:738-44.
30. Mair DD, Rice MJ, Hagler DJ, Puga FJ, McGoon DC, Danielson GK. Outcome of the Fontan procedure in patients with tricuspid atresia. *Circulation* 1985;72:88.
31. Cromme-Dijkhuis AH, Hess J, Hahlen K, Henkens CMA, Bink-Boelkens MTE, Eygelaar AA, et al. Specific sequelae after Fontan operation at mid- and long-term follow-up. *J Thorac Cardiovasc Surg* 1993;106:1126-32.
32. Dajee H, Deutsch LS, Benson LN, Perloff JK, Laks H. Thrombolytic therapy for superior vena caval thrombosis following superior vena cava-pulmonary anastomosis. *Ann Thorac Surg* 1984;38:637-9.
33. Laupacis A, Wells G, Richardson WS, Tugwell P. Evidence-Based Medicine Working Group. V. How to use an article about prognosis. *JAMA* 1994;272:234-7.
34. Downing TP, Danielson G, Ritter D, Julsrud P, Seward J. Pulmonary artery thrombosis associated with anomalous pulmonary venous connection: an unusual complication following the modified Fontan procedure. *J Thorac Cardiovasc Surg* 1985;90:441-5.
35. Asante-Korang A, Sweeram N, McKay R, Arnold R. Thrombolysis with tissue type plasminogen activator following cardiac surgery in children. *Int J Cardiol* 1992;35:317-22.
36. Hedrick M, Elkins RC, Knott-Craig CJ, Razook JD. Successful thrombectomy for thrombosis of the right side of the heart after the Fontan operation. *J Thorac Cardiovasc Surg* 1992;105:297-301.
37. Hutto RL, Williams JP, Maertens P, Wilder WM, Williams RS. Cerebellar infarct: late complication of the Fontan procedure? *Pediatr Neurol* 1991;7:161-6.
38. Kreutzer G, Galindez E, Bono H, de Palma J. An operation for the correction of tricuspid atresia. *J Thorac Cardiovasc Surg* 1973;66:613-21.
39. Lam J, Neirotti R, Becker AE, Planche C. Thrombosis after the Fontan procedure: transesophageal echocardiography may replace angiocardiology. *J Thorac Cardiovasc Surg* 1994;108:194-5.
40. Mahony L, Nikaidoh H, Fixler D. Thrombolytic treatment

- with streptokinase for late intraatrial thrombosis after modified Fontan procedure. *Am J Cardiol* 1988;62:343-4.
41. Putnam JB, Lemmer JH, Rocchini AP, Bove EL. Embolectomy for acute pulmonary artery occlusion following Fontan procedure. *Ann Thorac Surg* 1988;45:335-6.
42. Sharratt G, Lacson A, Cornel G, Virmani S. Echocardiography of intracardiac filling defects in infants and children. *Pediatr Cardiol* 1986;7:189-94.
43. Kao JM, Alejos J, Grant PW, Williams RG, Shannon KM, Laks H. Conversion of atriopulmonary to cavopulmonary anastomosis in management of late arrhythmias and atrial thrombosis. *Ann Thorac Surg* 1994;58:1510-4.
44. Beitzke A, Zobel G, Zenz W, Gamillscheg A, Stein JJ. Catheter-directed thrombolysis with recombinant tissue plasminogen activator for acute pulmonary embolism after Fontan operation. *Pediatr Cardiol* 1996;17:410-2.
45. Cromme-Dijkhuis AH, Henkens CMA, Bijleveld CMA, Hillge HL, Bom VJJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. *Lancet* 1990;336:1087-90.
46. Jaeschke R, Guyatt GH, Sackett DL, Evidence-Based Working Group. III. How to use an article about a diagnostic test. A. Are the results of the study valid? *JAMA* 1994;271:389-91.
47. Jaeschke R, Guyatt GH, Sackett DL, Evidence-Based Medicine Working Group. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients. *JAMA* 1994;271:703-7.