Preventing Thrombosis After the Fontan Procedure

Not There Yet*

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In 2007 (1), a review of the experience with thromboembolism and use of anticoagulation after the Fontan procedure in patients with single-ventricle lesions came to 4 conclusions: 1) thromboembolic events occur both early and late after the Fontan procedure at a frequency higher than any other cardiac surgery in children other than prosthetic valve replacement; 2) these thromboembolic events contribute to the failure of Fontan physiology and their occurrence increases in a “failed Fontan”; 3) these thromboembolic events occur in the presence of absence of standard anticoagulation schemes, including combinations of heparin and warfarin; and 4) the factors predisposing to thromboembolism after the Fontan procedure likely represented a complex interaction of multiple factors. They speculated that it would be unlikely that any single anticoagulation agent would provide a solution to such a complex problem.

In this issue of the Journal, Monagle et al. (2) present the findings of a study that would appear to confirm this opinion. Their study began as an ambitious randomized trial comparing a regimen of acetylsalicylic acid (ASA) with post-operative heparin followed by oral warfarin therapy to prevent thromboembolism in children undergoing the Fontan procedure. In addition to perspective randomization of patients to ASA or heparin/warfarin, the study’s primary endpoint was innovative because it included both thrombus that led to clinical events and the presence of asymptomatic or silent thromboemboli that were detected by transesophageal echocardiography (TEE), a relatively invasive procedure not usually in done in the routine clinical management of Fontan patients.

Unfortunately, the execution of the study fell short of its initial intent. The targeted recruitment goal was 242 patients to attain statistical power. Only 111 patients were eventually enrolled. Although 81% of the population underwent at least 1 surveillance TEE, only 48% of the subjects had both surveillance TEEs; thus, the true prevalence of silent thromboemboli was not fully ascertained. The numbers of silent and clinically evident thromboemboli were nearly identical in the ASA and heparin/warfarin groups. However, the sample size is too small to confirm noninferiority of either therapy as the possible differences between ASA and heparin/warfarin therapies range from ASA therapy conferring a 1.6 times greater risk of thromboembolism compared with heparin/warfarin and heparin/warfarin conferring a 3 times greater risk than ASA.

Although this study did not accomplish its initial purpose as a clinical trial, it does offer important data in its final form as 3 large multicenter observational studies rolled into one: 1) a large prospective intention-to-treat study of ASA prophylaxis after the Fontan procedure; 2) a similar intention-to-treat study for heparin/warfarin prophylaxis in Fontan patients; and 3) an assessment of TEE as a means for surveillance for thromboembolism in Fontan patients. The study confirms results from a contemporary Fontan experience (3) demonstrating the rate of clinical events associated with thromboemboli in the first years after the Fontan procedure to be low. In the current study (2), symptoms from a clot in the Fontan connection developed in only 3 of the 111 patients. The rest of the clinically detected thrombi were in the femoral (n = 3) and jugular (n = 1) veins where previous cardiac catheterization and/or the placement of central intravenous lines may have also influenced thrombus formation. This study also confirms another recent experience (4) demonstrating a low, clinically evident prevalence of thromboemboli using ASA as prophylaxis.

The study clearly illustrates the challenges of using warfarin as prophylactic therapy in children. Nearly one-fifth of the patients started on warfarin stopped the drug before the end of the study. Forty-one percent of international normalized ratio measurements were below the recommended therapeutic range. Poor compliance with warfarin therapy (patients who had <30% of international normalized ratio measurements in the therapeutic range) had a significant greater risk of thrombosis. Thus, even discounting the extra need for performing periodic blood testing with warfarin therapy, “maintenance” of anticoagulation with warfarin was suboptimal and frequently erratic.

This study also confirmed findings from previous experience (5) that surveillance TEE frequently detects emboli without clinical symptoms and/or not seen on standard transthoracic echocardiography. In all cases, the intensity of anticoagulation was increased and no clinical events occurred. However, it appears that routine periodic TEE surveillance was difficult because only one-half of the subjects had 2 TEE studies.

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A recent large, single-center experience (6) of long-term Fontan survivors identified thromboembolism as an important continuing cause of mortality in this patient group and that no anticoagulation therapy confers a substantial risk (hazard ratio: >90) for thromboembolic death. Another study (7) found a higher rate of thromboembolic events in patients not treated with anticoagulation compared with treatment with ASA or warfarin. Thus, it is unlikely that most clinicians would not attempt some form of anticoagulation therapy in patients after the Fontan procedure. Monagle et al. have provided evidence that currently used therapies are not as effective as we would like them to be. However, their experience also suggests that primary prevention antithrombotic strategies using recurrent invasive surveillance must be associated with a high enough benefit/risk and/or inconvenience ratio to gain acceptance by patients and their families.

Optimal strategies to reduce mortality and morbidity with thromboembolism after the Fontan procedure clearly remain to be determined. It is likely that the newer anticoagulants undergoing evaluation in adults with atrial fibrillation (8) will be tested in Fontan patients. Antithrombotic strategies should also not be limited to primary prophylaxis. Screening for hereditary thrombophilia before surgery may be helpful. Care needs to be taken to avoid creation of areas of stagnant flow such as pulmonary artery stumps (9) or ascending aortas in aortic atresia (10) that predispose to arterial thrombi and stroke. Individualization of antithrombotic strategies for patients who demonstrate prothrombotic states such as increased levels of factor VIII (11) may be efficacious. As patients who underwent the Fontan procedure age, and complications develop such as ventricular systolic dysfunction, atrial arrhythmias, and chronic lower extremity venous insufficiency (12) that increase the risk of thromboembolic events, the surveillance and therapy to prevent such events should become more intense and aggressive. Ultimately, tailored antithrombotic therapy for individual Fontan patients as they age will likely be more effective than a “one-size-fits-all” approach.

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