Clinical Outcomes of Palliative Surgery Including a Systemic-to-Pulmonary Artery Shunt in Infants With Cyanotic Congenital Heart Disease

Does Aspirin Make a Difference?

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Background—Aspirin (ASA) often is used to prevent thrombosis in infants with congenital heart disease after placement of a systemic-to–pulmonary artery shunt, but its effect on outcomes is unknown.

Methods and Results—The present multicenter study prospectively collected data on 1-year postoperative rates of death, shunt thrombosis, or hospitalization age <4 months for bidirectional Glenn/hemi-Fontan surgery in 1004 infants. The use and dose of ASA were recorded. Kaplan-Meier event rates were calculated for each event and the composite outcome, and a Cox regression model was constructed for time to event. Model terms were ASA use and type of surgery, with adjustment for age at surgery. Diagnoses were hypoplastic left heart syndrome (n=346), tricuspid atresia (n=103), tetralogy of Fallot (n=127), pulmonary atresia (n=177), heterotaxy syndrome (n=38), and other (n=213). There were 344 shunts placed without cardiopulmonary bypass (closed shunt), 287 shunts with bypass (open shunt), 323 Norwood procedures, and 50 Sano procedures. Overall, 80% of patients received ASA. One-year postoperative events rates were high: 38% for the composite end point, 26% for death, and 12% for shunt thrombosis. After the exclusion of patients with early mortality, patients receiving ASA had a lower risk of shunt thrombosis (hazard ratio, 0.13; P=0.008) and death (closed shunt: hazard ratio, 0.41, P=0.057; open shunt: hazard ratio, 0.10, P<0.001; Norwood: hazard ratio, 0.34, P<0.001; Sano: hazard ratio, 0.68, P=NS) compared with those not receiving ASA.

Conclusions—The morbidity and mortality for infants after surgical placement of a systemic-to–pulmonary artery shunt are high. ASA appears to lower the risk of death and shunt thrombosis in the present observational study. (Circulation. 2007;116:293-297.)

Key Words: aspirin ▪ heart defects, congenital ▪ mortality ▪ shunts ▪ thrombosis

Optimal care of infants surgically palliated for complex congenital heart lesions with reduced pulmonary blood flow and other cardiac malformations with single-ventricle physiology continues to be a challenge. The multicenter outcomes of infants with cyanotic congenital heart disease palliated with a systemic-to–pulmonary artery shunt are not well established. Historically, the Blalock-Taussig shunt was considered the primary management option for tetralogy of Fallot. In the current era, primary repair for tetralogy of Fallot is preferred at many institutions,1,2 and thus systemic-to–pulmonary artery shunts are more commonly indicated for infants with complex single-ventricle physiology. Intermediate-term outcomes for these patients have been incompletely defined, with most outcome data reported from single institutions3–5 or focused on a specific congenital heart defect.6–8

In addition, despite an overall reduction in mortality for single-ventricle palliation procedures in the current era, shunt

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thrombosis and interstage attrition remain significant problems. Although the use of aspirin (ASA) was reported to reduce the rate of occlusion of aortopulmonary shunts in a small case series of 37 infants, its efficacy was not confirmed in a larger study of 478 patients.

The purpose of the present study was to evaluate the morbidity and mortality of infants with systemic-to-pulmonary shunts and the effect of ASA use on these outcomes. As part of a large, multinational registry of infants with complex congenital heart disease palliated with a systemic-to-pulmonary artery shunt, we collected data on medical morbidity, mortality, and the use of ASA over a follow-up period of 1 year. We hypothesized that the outcomes would differ, depending on the type of cardiac surgical procedure, and that ASA use would be variable but would affect outcome.

Methods

Patient Population

Between January 2001 and August 2005, patients at 15 institutions in the United States, France, and Germany were identified who underwent one of the following surgeries: (1) a systemic-to-pulmonary artery shunt via a closed procedure (without cardiopulmonary artery bypass), (2) systemic-to-pulmonary artery shunt via an open procedure (with cardiopulmonary bypass done in conjunction with an intracardiac operation), (3) Norwood procedure (for hypoplastic left heart syndrome with a modified Blalock-Taussig shunt), or (4) Sano procedure (for hypoplastic left heart syndrome with a right ventricle-to-pulmonary artery shunt). The study was approved by the investigational review board at each institution. Data collected included cardiac diagnosis, type of initial procedure performed, age, center, and ASA use. Follow-up data were collected over 1 year from the time of procedure for the outcomes of death, shunt thrombosis, and hospitalization for bidirectional Glenn/hemi-Fontan procedure performed in patients <4 months of age. Shunt thrombosis was defined by any one of the following: (1) absence of a murmur by clinical examination in conjunction with increasing cyanosis with supportive evidence of narrowing or thrombosis of a shunt or of stenosis at the shunt insertion site; (2) absence of flow on echo Doppler, angiography, magnetic resonance imaging, or computerized tomography; (3) surgical or postmortem observation; or (4) need for an urgent repeated shunt as a result of prohibitive cyanosis. Forms were sent to the data coordinating center at Duke Clinical Research Institute, where data entry, validation, and query resolution were performed. All patient identifiers were kept at the individual center and were not sent to the data coordinating center.

Data Analysis

Outcomes of interest were defined as the time from initial procedure to death, shunt thrombosis, hospitalization for bidirectional Glenn/hemi-Fontan surgery at <4 months of age, and a composite of these 3 outcomes. Only patients with single-ventricle physiology were included in the hospitalization for bidirectional Glenn/hemi-Fontan procedure and the composite outcome. One-year event rates (defined as 1 minus the probability of freedom from event at 1 year) were estimated within the Kaplan-Meier framework for the population as a whole, for each category of cardiac diagnosis, and for each surgical category. To assess the effect of ASA use (any amount of ASA or none), a Cox regression model was constructed for death with the model terms ASA use, type of surgery, and interaction term for ASA use, cardiac diagnosis, and ASA dose. For patients who received any amount of ASA, Kaplan-Meier survival analyses were performed according to procedure type and ASA dose. Low-dose ASA was defined as ≤¼ baby ASA (20 mg) per day; high-dose ASA was defined as ≥½ baby ASA (40 mg) per day. Patients with early events (≤14 days) were excluded to minimize the effect of events related to the initial surgical procedure. The model was adjusted for age at surgery, cardiac diagnosis, and center. For both 1-degree and multidegree variables, Wald $χ^2$ values and probability values were computed. Reported probability values and 95% CIs are 2-tailed. To assess for differences in outcome according to cardiac diagnosis and ASA use, the model was additionally evaluated with the interaction term for ASA by cardiac diagnosis. We used SAS statistical software (version 8.2, SAS Institute, Inc, Cary, NC) to perform the analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 1004 patients were evaluated with the following diagnoses: hypoplastic left heart syndrome (n=346), tricuspid atresia (n=103), complex tetralogy of Fallot (n=127), pulmonary atresia (n=177), heterotaxy syndrome (n=38), and other forms of complex single ventricle (n=213). There were 344 shunts performed without cardiopulmonary bypass (closed shunt), 287 shunts performed with bypass (open shunt), 323 Norwood procedures, and 50 Sano procedures. The median age at surgery was 8 days (25th and 75th percentiles, 5 and 18 days). The type of modified Blalock-Taussig shunt placed was a Gore-Tex shunt ranging from 3.0 to 3.5 mm in all neonates. The overall ASA use in the cohort was 806 of 1002 (80%). In 2 patients, ASA use was not recorded. The number of procedures performed and ASA use by type of procedure are shown in Figure 1. Among patients who received ASA, the dose was <¼ baby ASA (20 mg) in 9%, ¼ baby ASA (20 mg) in 30%, ½ baby ASA (40 mg) in 51%, and >½ baby ASA (40 mg) in 10%. None of the patients were on other antithrombotic agents.

Event Rates

The Kaplan-Meier event rates for each event and the composite event are given in Table 1 for closed shunts, open shunts, Norwood procedures, and Sano procedures. In aggregate for all procedures combined, the incidence of shunt thrombosis was 99 of 1004 (12%; 95% CI, 10 to 15; 1-year event rate); hospitalization for bidirectional Glenn/hemi-Fontan procedure in patients <4 months of age was 98 of 877 (14%; 95% CI, 11 to 16); death was 223 of 1004 (26%; 95% CI, 23 to 29); and composite was 306 of 877 (38%; 95% CI, 35 to 42). Table 2 shows the event rates for each event and the composite event according to cardiac diagnosis. For the patients with tetralogy of Fallot, the hospitalization for surgery reflects the biventricular repair at <4 months of age and was not included in the hospitalization for bidirectional Glenn/hemi-Fontan procedure in patients <4 months of age or the composite outcome in aggregate. Those patients with tetralogy of Fallot generally had lower individual event rates.
TABLE 1. One-Year Postplacement Kaplan-Meier Event Rate Estimates With 95% CIs Summarized by Procedure Type

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Closed Shunt</th>
<th>Open Shunt</th>
<th>Norwood</th>
<th>Sano</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt thrombosis, n/N, KM event rate† (95% CI)</td>
<td>28/344, 11 (7 to 15)</td>
<td>37/287, 16 (11 to 21)</td>
<td>31/323, 11 (7 to 14)</td>
<td>3/50, 8 (0 to 17)</td>
<td>99/1004, 12 (10 to 15)</td>
</tr>
<tr>
<td>Hospitalization for Glenn at &lt; 4 mo of age, n/N, KM event rate† (95% CI)</td>
<td>19/257, 9 (5 to 12)</td>
<td>37/248, 18 (13 to 24)</td>
<td>38/323, 15 (10 to 19)</td>
<td>4/49, 11 (1 to 20)</td>
<td>98/877, 14 (11 to 16)</td>
</tr>
<tr>
<td>Death, n/N, KM event rate† (95% CI)</td>
<td>37/344, 13 (9 to 16)</td>
<td>71/287, 30 (24 to 36)</td>
<td>101/323, 34 (28 to 39)</td>
<td>14/50, 37 (20 to 55)</td>
<td>223/1004, 26 (23 to 29)</td>
</tr>
<tr>
<td>Composite, n/N, KM event rate† (95% CI)</td>
<td>55/257, 21 (18 to 29)</td>
<td>101/248, 46 (39 to 53)</td>
<td>133/323, 43 (38 to 49)</td>
<td>17/49, 42 (26 to 59)</td>
<td>306/877, 38 (35 to 42)</td>
</tr>
</tbody>
</table>

* n/N is defined as the number of patients with at least 1 event over the total number of patients.
† Kaplan-Meier (KM) event rate is defined as 1 minus the Kaplan-Meier survival rate at 1 year after procedure with 95% CIs.

Aspirin Effect

We evaluated the relationship between ASA use and the individual outcomes through a Cox regression model, excluding events ≤ 14 days (64 patients; 55 not on ASA, 9 on ASA). A beneficial effect of ASA was indicated by a significantly lower rate of shunt thrombosis when ASA was used (hazard ratio, 0.13; 95% CI, 0.03 to 0.59; \( P = 0.008 \)). Similarly, the use of ASA also was associated with a significantly lower mortality (Table 3), particularly in patients who underwent an open shunt or a Norwood procedure (Table 4). Low-dose ASA (≤ 1/2 baby ASA; 20 mg) and high-dose ASA (≥ 1/2 baby ASA; 40 mg) were associated with similar mortality rates for patients who had undergone these procedures (Figure 2). When evaluated by cardiac diagnosis, use of ASA was associated with a significantly lower mortality in patients who had hypoplastic left heart syndrome, tricuspid atresia, tetralogy of Fallot, and other cardiac diagnoses (Table 5). ASA use was not associated with a significant effect on the incidence of hospitalization for surgery in patients < 4 months of age.

Discussion

The systemic-to-pulmonary artery shunt, including the modified Blalock-Taussig shunt, is an effective surgical therapy for the initial palliation of cyanotic congenital heart disease. Knowledge of the outcomes of infants with a systemic-to-pulmonary shunt in the current era is based mostly on reports from single institutions.3–5 Limited multicenter reports have focused largely on hypoplastic left heart syndrome.6–8 Management strategies including the use of antplatelet agents might affect outcome. Although ASA often is used in children with congenital heart disease at risk for thrombotic complications, its efficacy has not been demonstrated. Cenazzo et al11 showed no difference in shunt patency index (angiographic Gore-Tex diameter/preoperative Gore-Tex diameter) between patients receiving ASA and those not receiving ASA. Motz et al10 showed that ASA reduced the incidence of partial or complete shunt occlusion in a study of 37 infants (ASA, 13%; no ASA, 54%). This finding, however, was not confirmed in a larger study conducted by Al Jubair et al9 of 546 shunts in 478 patients (ASA, 7%; no ASA, 11%; \( P = \text{NS} \)). We therefore sought to evaluate the morbidity and mortality of infants with systemic-to-pulmonary shunts from a contemporary multinational registry and to assess the effect of ASA use on these outcomes.

We evaluated the outcomes of death, shunt thrombosis, and hospitalization for bidirectional Glenn/hemifont procedure in patients < 4 months of age. Reported mortality in infants palliated with a systemic-to-pulmonary artery shunt is low in patients with tetralogy of Fallot4 but is high in patients with hypoplastic left heart syndrome, ranging from 35% to 42% over 1 year in several recent series.6,7,12 We also evaluated shunt obstruction, which is common after placement of modified Blalock-Taussig shunts resulting from myofibroblastic proliferation, often associated with organized thrombus. A recent histopathological study demonstrated that at a median time of 8.1 months after shunt placement, the mean value for maximal narrowing of the shunt lumen was

TABLE 2. One-Year Postplacement Kaplan-Meier Event Rate Estimates With 95% CIs Summarized by Cardiac Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HLHS</th>
<th>PA</th>
<th>Heterotaxy</th>
<th>Tricuspid Atresia</th>
<th>TOF</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt thrombosis, n/N, KM event rate† (95% CI)</td>
<td>34/346, 11 (7 to 15)</td>
<td>22/177, 16 (10 to 23)</td>
<td>6/38, 34 (8 to 61)</td>
<td>12/103, 15 (7 to 22)</td>
<td>5/127, 5 (1 to 9)</td>
<td>20/213, 10 (6 to 14)</td>
</tr>
<tr>
<td>Hospitalization for Glenn or biventricular repair at &lt; 4 months of age, n/N, KM event rate† (95% CI)</td>
<td>34/346, 12 (8 to 16)</td>
<td>16/177, 10 (6 to 15)</td>
<td>5/38, 17 (3 to 32)</td>
<td>14/103, 15 (8 to 22)</td>
<td>10/127, 9 (4 to 15)</td>
<td>29/213, 16 (11 to 22)</td>
</tr>
<tr>
<td>Death, n/N, KM event rate† (95% CI)</td>
<td>115/346, 36 (31 to 42)</td>
<td>32/177, 21 (15 to 28)</td>
<td>12/38, 38 (20 to 55)</td>
<td>13/103, 14 (7 to 21)</td>
<td>14/127, 15 (7 to 23)</td>
<td>37/213, 20 (14 to 26)</td>
</tr>
<tr>
<td>Composite, n/N, KM event rate† (95% CI)</td>
<td>159/346, 48 (43 to 54)</td>
<td>58/177, 37 (29 to 45)</td>
<td>19/38, 61 (42 to 80)</td>
<td>36/103, 39 (28 to 49)</td>
<td>25/127, 24 (16 to 32)</td>
<td>73/213, 37 (31 to 44)</td>
</tr>
</tbody>
</table>

*HLHS indicates hypoplastic left heart syndrome; PA, pulmonary atresia; and TOF, tetralogy of Fallot.
† n/N is defined as the number of patients with at least 1 event over the total number of patients.
‡ Kaplan-Meier (KM) event rate is defined as 1 minus the Kaplan-Meier survival rate at 1 year after procedure with 95% CIs.
TABLE 3. Cox Regression Model Terms for Death, 1-Year Follow-Up, Deaths ≤14 Days Excluded

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>χ² Value*</th>
<th>df†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>ASA</td>
<td>68.71</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>16.70</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Interaction</td>
<td>15.49</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Log of age</td>
<td>2.84</td>
<td>1</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>Center</td>
<td>17.52</td>
<td>6</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>3.92</td>
<td>4</td>
<td>0.417</td>
</tr>
</tbody>
</table>

*A χ² value is the critical value corresponding to the magnitude of the effect such that a larger χ² value indicates a larger absolute effect.
†Degrees of freedom is number of levels of a variable minus 1; it is used in the calculation of the test statistic.

34% ± 22%, with 21% of patients having >50% stenosis.13 We also evaluated hospitalization for bidirectional Glenn/hemi-Fontan in patients <4 months of age. We believed that this outcome would reflect a subgroup of patients experiencing early shunt morbidity as a result of cyanosis requiring the need for earlier intervention. Although there are some reports from single centers that a bidirectional Glenn/hemi-Fontan operation can be performed earlier than 4 months of age with good results and favorable effects on growth,13,14 multicenter studies have demonstrated that early age (<4 months) at operation is associated with a significantly higher mortality.5,16

Our results reflect a large, multinational, multicenter study and indicate that the mortality and morbidity for infants after surgical palliation including a systemic-to-pulmonary artery shunt are high, particularly for those receiving an open shunt or a Norwood operation. Approximately one third of infants in the present study receiving open shunts and Norwood operations had died by 1 year of age, and nearly one half reached a composite end point of shunt thrombosis, hospitalization for bidirectional Glenn/hemi-Fontan procedure before 4 months of age, or death by 1 year of age.

The present study also suggests that antiplatelet therapy with ASA improves outcome for infants palliated with a systemic-to-pulmonary artery shunt. ASA blocks the action of both cyclooxygenase-1 and -2. Inhibition of cyclooxygenase-1 leads to inhibition of platelet adhesion and aggregation. Cyclooxygenase-2 inhibition decreases inflammation at the site of the thrombus and reduces mononuclear cell infiltration.17,18 ASA has established benefits in adult patients with unstable angina, cerebrovascular disease, and peripheral arterial disease by reducing atherothrombotic events across a wide range of high-risk patients (relative risk reduction, ≥25%).19,20 ASA use in the present study was associated with a lower risk of death and shunt thrombosis in infants with systemic-to-pulmonary artery shunts. Low-dose ASA (≤1/4 baby ASA; 20 mg) and high-dose ASA (≥1/2 baby ASA; 40 mg) appeared to be equally protective. Our study is the first to demonstrate that ASA use is associated with a lower risk of death in this high-risk patient population for both patients with remaining antegrade pulmonary blood flow and those who are entirely shunt dependent.

It is noteworthy that the mortality rate is much higher than the incidence of shunt thrombosis for the entire group and for each subgroup. The high death rate among patients who did not receive ASA and had open shunts or Norwood procedures is alarming. One might speculate that an insidious reduction in the shunt lumen size as a result of accumulation of platelet thrombi may produce a gradual decline in baseline oxygen saturation, so any stressful event, eg, respiratory or gastrointestinal disease, may precipitate an irreversible degree of hypoxemia and acidosis. Constant seeding of emboli into the systemic and pulmonary circuits is another possible mechanism of death. Antiplatelet therapy is likely to be beneficial for improved endothelial function, particularly in the coronary circulation in patients with hypoplastic left heart syndrome and in the prevention of systemic or pulmonary microthrombi, in addition to reducing shunt thrombosis.

Our present study is limited in several ways. First, this was a nonrandomized, observational study, and patients not treated with ASA may have had confounding conditions precluding its use or increasing their risk. In addition, these registry data did not include investigation in the cause of death or other details of the clinical history such as ventricular function and comorbidities. In addition, we did not relate the incidence of thrombosis to physical characteristics of the shunt (such as length, size, and vessel of origin) that may have influenced the outcome. Another limitation is that these patients were not receiving other antiplatelet or antithrombotic agents (eg, dipyridamole, heparin, low-molecular-

TABLE 4. ASA Versus No ASA Hazard Ratio Estimates With 95% Cl, 1-Year Follow-Up, Deaths ≤14 Days Excluded

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA Hazard Ratio (95% Cl)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed shunt</td>
<td>0.41 (0.16 to 1.03)</td>
<td>0.057</td>
</tr>
<tr>
<td>Norwood</td>
<td>0.10 (0.06 to 0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Open shunt</td>
<td>0.34 (0.19 to 0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sano</td>
<td>0.68 (0.09 to 5.33)</td>
<td>0.714</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
weight heparin, clopidogrel, or warfarin); therefore, we are unable to present data concerning the use of these agents. We also did not collect bleeding complications potentially attributable to aspirin use during therapy or at the time of subsequent surgery. Additionally, with regard to the outcome of bidirectional Glenn/hemi-Fontan operation in patients <4 months of age, none of the participating centers was routinely performing this operation before 4 months of age; thus, we assumed that this outcome was reflective of a subgroup with early shunt morbidity and associated higher mortality. Nevertheless, we cannot exclude the possibility that the early operations were performed because of poor ventricular function, increasing atroventricular valve regurgitation, or worsening heart failure in individual patients. Finally, the number of patients undergoing the Sano procedure was limited; thus, the CIs around the events were large, and the effects of ASA on events were not statistically significant in this subgroup. We do not know if ASA is not effective in this type of surgery or if the number of patients was insufficient to demonstrate an effect.

Conclusions

The multicenter outcomes of infants palliated with a systemic-to-pulmonary artery shunt in the current era are poor. ASA appears to be associated with a reduction in shunt thrombosis and death. Investigations into additional mechanisms of the benefits of antiplatelet and antithrombotic therapy are needed. Clinical trials of antiplatelet and antithrombotic therapies are clearly warranted in this high-risk patient population.

Source of Funding

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Disclosures

Drs Bokesch, Graham, Takahashi, Juggers, and Sanders served on the Steering Committee and received honoraria from sanofi-aventis. Dr Rakhit is an employee of Bristol-Myers Squibb, and Dr Fontecave is an employee of sanofi-aventis Paris. All authors, excluding Dr Michel-Behnke, who reports no conflicts, indicate that their institutions have received research grants from Bristol-Myers Squibb and sanofi-aventis. Drs Califf and Li received funding from grant 1UL 1R0124128–01 from the National Center for Research Resources and the National Institutes of Health.

References


CLINICAL PERSPECTIVE

Aspirin often is used to prevent thrombosis in infants with congenital heart disease after placement of a systemic-to-pulmonary artery shunt, but its effect on outcomes is unknown. The present multicenter study prospectively collected data on 1-year postoperative rates of death, shunt thrombosis, or hospitalization age <4 months for bidirectional Glenn/hemi-Fontan surgery in 1004 infants. The use and dose of aspirin were recorded. Overall, 80% of patients received aspirin. One-year postoperative events rates were high: 38% for the composite end point, 26% for death, and 12% for shunt thrombosis. After the exclusion of patients with early mortality, patients receiving aspirin had a lower risk of shunt thrombosis (hazard ratio, 0.13; P = 0.008) and death (closed shunt: hazard ratio, 0.41, P = 0.057; open shunt: hazard ratio, 0.10, P < 0.001; Norwood: hazard ratio, 0.34, P < 0.001; Sano: hazard ratio, 0.68, P = NS) compared with those not receiving aspirin. Aspirin appears to lower the risk of death and shunt thrombosis in the present observational study.