ORIGINAL ARTICLE

Clopidogrel in Infants with Systemic-to-Pulmonary-Artery Shunts

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ABSTRACT

BACKGROUND

Infants with cyanotic congenital heart disease palliated with placement of a systemic-to-pulmonary-artery shunt are at risk for shunt thrombosis and death. We investigated whether the addition of clopidogrel to conventional therapy reduces mortality from any cause and morbidity related to the shunt.

METHODS

In a multicenter, double-blind, event-driven trial, we randomly assigned infants 92 days of age or younger with cyanotic congenital heart disease and a systemic-to-pulmonary-artery shunt to receive clopidogrel at a dose of 0.2 mg per kilogram of body weight per day (467 infants) or placebo (439 infants), in addition to conventional therapy (including aspirin in 87.9% of infants). The primary efficacy end point was a composite of death or heart transplantation, shunt thrombosis, or performance of a cardiac procedure due to an event considered to be thrombotic in nature before 120 days of age.

RESULTS

The rate of the composite primary end point did not differ significantly between the clopidogrel group (19.1%) and the placebo group (20.5%) (absolute risk difference, 1.4 percentage points; relative risk reduction with clopidogrel, 11.1%; 95% confidence interval, –19.2 to 33.6; P=0.43), nor did the rates of the three components of the composite primary end point. There was no significant benefit of clopidogrel treatment in any subgroup, including subgroups defined by shunt type. Clopidogrel recipients and placebo recipients had similar rates of overall bleeding (18.8% and 20.2%, respectively) and severe bleeding (4.1% and 3.4%, respectively).

CONCLUSIONS

Clopidogrel therapy in infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary-artery shunt, most of whom received concomitant aspirin therapy, did not reduce either mortality from any cause or shunt-related morbidity. (Funded by Sanofi-Aventis and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00396877.)

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Congenital heart disease is the most common type of birth defect and a common cause of death in the first year of life.[1,2] Although many forms of congenital heart disease can be repaired in early infancy, provision of pulmonary blood flow with a systemic-to-pulmonary-artery shunt remains an essential component of initial treatment for some forms of complex cyanotic congenital heart disease. Shunts are most commonly placed for primary palliation or as a component of staged reconstruction in infants with single-ventricle disease, such as a hypoplastic left ventricle.[3,4] They are also used as initial palliation for two-ventricle disease when the risk of definitive repair in early infancy is high.[5]

Infants who undergo placement of a systemic-to-pulmonary-artery shunt for palliation are at risk for shunt thrombosis and sudden death.[6-8] Effective preventive therapy for thrombosis in young infants has not been tested in a randomized trial, but aspirin treatment has been associated with significantly reduced risks of mortality and shunt thrombosis in a prospective registry.[6,9] In adults with atherosclerotic cardiovascular disease, prophylactic antiplatelet therapy often consists of a combination of aspirin and the thienopyridine clopidogrel.[10-13] As happens with many drugs that are approved for use in adults, clopidogrel use is spreading into pediatric practice in the absence of sound evidence of its efficacy in the pediatric population. Indeed, clopidogrel use increased by a factor of 15 from 2001 to 2009 in children's hospitals in the United States.[14] Some pediatric cardiovascular practitioners have already claimed that clopidogrel is safe and effective on the basis of retrospective single-center reviews.[15]

The objective of our trial was to evaluate the efficacy of clopidogrel as compared with placebo in reducing mortality from any cause and shunt-related morbidity in young infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary-artery shunt. The safety of clopidogrel was also evaluated on the basis of adverse events, especially those related to bleeding.

Methods

Study Design

The Clopidogrel to Lower Arterial Thrombotic Risk in Neonates and Infants Trial (CLARINET) was a double-blind, randomized, placebo-controlled, parallel-group, event-driven trial. The original study design was developed by two of the academic authors in conjunction with representatives of the sponsors, Sanofi-Aventis and Bristol-Myers Squibb. The trial was designed in consultation with the Food and Drug Administration as part of the written request process for pediatric exclusivity (a 6-month extension of patent protection for drugs studied in children). The investigators at each study site gathered the data. The steering committee had unrestricted access to the raw data and participated in the analysis, which was performed by statisticians employed by the sponsors. The primary end point was additionally validated by statisticians who were not employed by the sponsor, and the final interpretation of data was provided by the steering committee. The first draft of the manuscript was written by two of the academic authors and subsequently revised by all the authors. The academic authors vouch for the accuracy and completeness of the data and all analyses, and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

Patients

Patients were recruited and followed from November 2006 through February 2010 at 134 sites in Europe, Asia, North America, South America, and Africa. Infants 92 days of age or younger at the time of randomization were eligible if they had cyanotic congenital heart disease palliated with a systemic-to-pulmonary-artery shunt (i.e., a modified Blalock–Taussig shunt, right ventricular-to-pulmonary shunt, central shunt, or stent of ductus arteriosus). Patients were excluded if they had active bleeding or had an increased risk of bleeding; a full list of exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org. Before randomization, written informed consent was obtained from a parent or legal guardian of each patient in accordance with the guidelines of local institutional review boards, which approved the study protocol.

Study Procedures

After shunt placement and as soon as possible within a 92-day window, infants were randomly assigned, in a 1:1 ratio, to receive clopidogrel (Plavix, Bristol-Myers Squibb and Sanofi-Aventis) at a dose of 0.2 mg per kilogram of body weight per day or matching placebo. Randomization was performed with the use of a central interactive

voice response system, with stratification according to center only. The study drug was formulated as a syrup (see the Supplementary Appendix). Concomitant aspirin use was permitted, but the use of nonsteroidal anti-inflammatory drugs was discouraged.

Efficacy and safety assessments were conducted by means of scheduled telephone contact, as well as in-person evaluations at baseline (day 1); at weeks 4, 12, 24, and 36; and at the final visit, defined as the time of the first occurrence of an event marking termination of the study (shunt thrombosis, performance of elective surgery for correction of the congenital heart disease, death, the first birthday, or the common study end date). Compliance with study medication was assessed on the basis of study drugs returned to the study investigator at the end of each 12-week period. If necessary, treatment with the study drug could be temporarily discontinued and reinitiated. Temporary discontinuation for more than 2 consecutive days was recorded on the case report form. It was recommended that treatment be discontinued 5 days before elective surgery.

END POINTS

The primary efficacy end point was defined as the earliest occurrence of any of the following: death or heart transplantation, shunt thrombosis requiring intervention, or a cardiac procedure performed before 120 days of age because of an event adjudicated to be thrombotic. The third component was ascertained by an event-adjudication committee whose members were unaware of the group assignments. Detailed definitions of end-point events and a description of the event-adjudication process are provided in the Supplementary Appendix.

We analyzed adverse events and serious adverse events, including reports of any bleeding. Bleeding events were classified according to their intensity as judged by the investigator: mild, if they required no active intervention other than withholding medication or monitoring; moderate, if they required medical intervention to treat bleeding or clot formation; and severe, if they required any procedural intervention.

STATISTICAL ANALYSIS

We assumed a rate of the primary end point of 40% in the placebo group, on the basis of data compiled at several of the participating centers. Using this estimate, we designed the study to detect a 30% relative reduction in the primary event rate in the clopidogrel group, with a statistical power of 80% and a 5% overall type I error rate. Interim analyses were performed when approximately 40%, 60%, and 80% of the required 172 events occurred. The data and safety monitoring committee recommended continuing the study after each interim analysis. At the final analysis, a P value of less than 0.035 was considered to indicate statistical significance.

The intention-to-treat principle was applied to all efficacy analyses. The time to occurrence of the primary end point was compared between the two study groups with the use of a two-sided log-rank test. Study-group comparisons were expressed as the relative risk reduction with clopidogrel versus placebo and the corresponding 95% confidence interval, estimated with the use of a Cox proportional-hazards model. The Cox proportional-hazards model was also used to assess the relationship between the treatment effect and the following prespecified characteristics: age (neonates vs. older infants), sex, race or ethnic group, age at the time of shunt palliation (≤1 week vs. >1 week), interval between shunt palliation and randomization, type of initial surgery, type of cardiac defect, and status with respect to prior and concomitant aspirin use.

Adverse events were analyzed in the population of patients who received one or more doses of the study drug and also in the per-protocol population. The Pearson chi-square test was used to compare the rates of adverse events occurring during treatment in the clopidogrel and placebo groups.

RESULTS

RANDOMIZATION AND FOLLOW-UP

A total of 906 patients were enrolled and randomly assigned to either clopidogrel or placebo (Fig. 1). The baseline characteristics and time from shunt palliation to randomization were similar in the two study groups (Table 1); administration of other medications (including aspirin) and compliance with medication were also similar between the two groups. Aspirin was administered in 87.0% of placebo recipients and 88.7% of clopidogrel recipients as part of routine care.

The median duration of follow-up, which was similar in the two groups, was 5.8 months overall (range, 0 to 12). Study-drug administration was temporarily suspended in 53.6% of the patients for

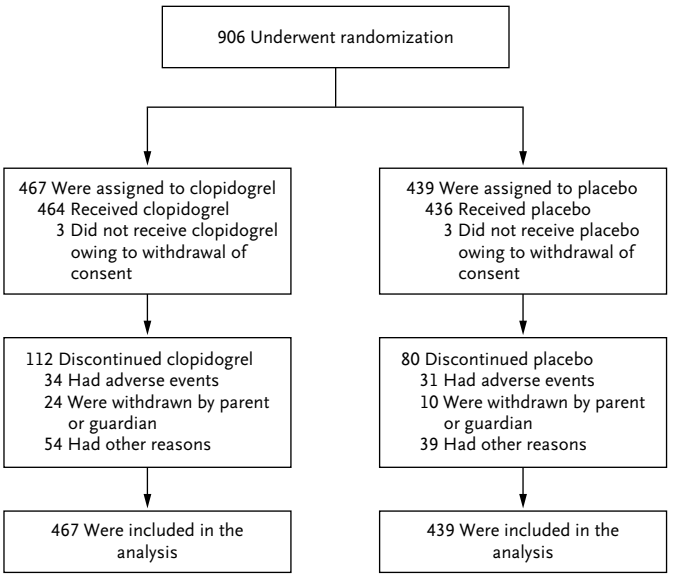

Figure 1. Enrollment and Follow-up of the Study Patients, According to Study Group.

"Other reasons" for early discontinuation of study drug included the investigator's decision to discontinue the study drug more than 5 days before surgery because of the risk of bleeding (in 36 patients in the clopidogrel group and 27 patients in the placebo group).

a median of 8 days (range, 2 to 156). The study drug was permanently discontinued early in a significantly greater proportion of patients receiving clopidogrel than patients receiving placebo (24.0% vs. 18.2%, P=0.03) (Fig. 1); the overall median time to permanent discontinuation was 96 days (range, 2 to 312). Reasons for premature study termination were similar in the two groups (Fig. 1).

EFFICACY END POINTS

The primary end point occurred in 89 clopidogrel recipients and 90 placebo recipients (19.1% and 20.5%, respectively; absolute risk difference, 1.4 percentage points; relative risk reduction with clopidogrel, 11.1%; 95% confidence interval [CI], –19.2 to 33.6; P=0.43) (Table 2 and Fig. 2). We further analyzed each component of the primary end point. The rate of heart transplantation or death from any cause was slightly lower with clopidogrel than with placebo (11.8% vs. 13.9%), but this difference did not reach statistical significance (Table 2, and Fig. S1 in the Supplementary Appendix). The rates of death and heart transplantation according to specific causes were similar in the two groups (Table 2), as were the incidence of shunt thrombosis and the rate of cardiac procedures performed before 120 days of age and related to thrombotic events (Table 2, and Fig. S2 and S3 in the Supplementary Appendix).

In post hoc analyses, patients in the overall study population who received concomitant aspirin, as compared with those who did not, had a significantly lower rate of the primary end point (18.6% vs. 28.2%; absolute risk difference, 9.6 percentage points; relative risk reduction, 40.1%; 95% CI, 11.8 to 59.3; P=0.009 by the log-rank test) (Table S1 in the Supplementary Appendix).

We explored the effect of clopidogrel on efficacy end points in prespecified subgroup analyses. There was no significant interaction between study-group assignment and the incidence of the primary end point in subgroups defined by age, sex, race or ethnic group, type of palliative surgery, number of days from palliation to randomization, type of cardiac defect, or status with respect to aspirin use before or during the study (Fig. S4 in the Supplementary Appendix). Event rates for the primary efficacy end point according to whether the patient received no antiplatelet therapy, aspirin alone, clopidogrel alone, or aspirin plus clopidogrel are presented in Fig. S5 and Table S2 in the Supplementary Appendix.

SAFETY END POINTS

Among all randomized patients who received one or more doses of the study drug, at least one adverse event of any severity occurred in 353 patients (76.1%) in the clopidogrel group and 310 (71.1%) in the placebo group (P=0.09); serious adverse events occurred in 234 patients (50.4%) in the clopidogrel group and 196 (45.0%) in the placebo group (P=0.10) (Table S3 in the Supplementary Appendix). The percentage of patients with adverse events leading to permanent treatment discontinuation was similar in the clopidogrel group and the placebo group (7.3% and 7.1%, respectively; P=0.90). More neurologic events occurred in the clopidogrel group than in the placebo group — most notably, seizure (in 14 patients [3.0%] vs. 7 [1.6%]) and stroke (in 8 patients [1.7%] vs. 0).

Overall, approximately one in five patients had at least one bleeding episode (18.8% in the clopidogrel group and 20.2% in the placebo group) (Fig. 3). The two groups did not differ signifi-

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Study Group.*

Characteristic	Clopidogrel (N=467)	Placebo (N=439)	Total (N=906)
Age — days	36.1±22.3	36.0±22.5	36.1±22.4
Male sex — no. (%)	269 (57.6)	254 (57.9)	523 (57.7)
Weight — kg	3.4±0.7	3.5±0.7	3.5±0.7
Congenital cardiac defect — no. (%)			
Hypoplastic left heart syndrome	120 (25.7)	104 (23.7)	224 (24.7)
Pulmonary atresia with intact ventricular septum	75 (16.1)	77 (17.5)	152 (16.8)
Tetralogy of Fallot	42 (9.0)	31 (7.1)	73 (8.1)
Tetralogy of Fallot with pulmonary atresia	63 (13.5)	62 (14.1)	125 (13.8)
Tricuspid atresia	49 (10.5)	56 (12.8)	105 (11.6)
Other single-ventricle defect	81 (17.3)	70 (15.9)	151 (16.7)
Other two-ventricle defect	61 (13.1)	64 (14.6)	125 (13.8)
Ebstein's anomaly	11 (2.4)	8 (1.8)	19 (2.1)
Cardiac arrest before surgery — no. (%)	7 (1.5)	7 (1.6)	14 (1.5)
Type of initial systemic-to-pulmonary-artery shunt — no. (%)†			
Modified Blalock–Taussig shunt			
With Norwood procedure	62 (13.3)	51 (11.6)	113 (12.5)
Without Norwood procedure	257 (55.0)	252 (57.4)	509 (56.2)
Right ventricular-to-pulmonary shunt			
With Norwood procedure	60 (12.8)	54 (12.3)	114 (12.6)
Without Norwood procedure	5 (1.1)	2 (0.5)	7 (0.8)
Central shunt	40 (8.6)	38 (8.7)	78 (8.6)
Stent in ductus arteriosus	42 (9.0)	42 (9.6)	84 (9.3)
Age at shunt palliation — days			
Median	8.0	8.0	8.0
Range	0–92	0–91	0–92
Time from shunt palliation to randomization — no. (%)			
≤1 wk	113 (24.2)	116 (26.4)	229 (25.3)
>1 to ≤2 wk	126 (27.0)	105 (23.9)	231 (25.5)
>2 to ≤4 wk	119 (25.5)	117 (26.7)	236 (26.0)
>4 wk	109 (23.3)	101 (23.0)	210 (23.2)
Duration of follow-up — mo			
Median	5.9	5.6	5.8
Range	0–12	0–12	0–12
Duration of treatment — days			
Median	162.0	161.5	—
Range	2–367	1–371	
Aspirin use within 10 days before randomization — no. (%)	389 (83.3)	371 (84.5)	760 (83.9)

* Plus–minus values are means ±SD. There were no significant differences ($P<0.05$) between the two study groups in any of the characteristics listed.

† Data do not include one infant, in the clopidogrel group, with tetralogy of Fallot and pulmonary atresia who twice underwent stenting of the right ventricular outflow tract but did not undergo palliation with a systemic-to-pulmonary-artery shunt.

Table 2. Incidence of the Primary Efficacy End Point in the Intention-to-Treat Population, According to Study Group.

End Point	Clopidogrel (N=467)	Placebo (N=439)	Absolute Risk Difference	Relative Risk Reduction with Clopidogrel	P Value
	no. of patients/total no. (%)		*percentage points*	*percent (95% CI)*	
Primary end point*	89 (19.1)	90 (20.5)	1.4	11.1 (–19.2 to 33.6)	0.43
Death or heart transplantation	55 (11.8)	61 (13.9)	2.1	19.4 (–16.1 to 44.0)	0.25
Death from cardiovascular cause	27 (5.8)	28 (6.4)		—	—
Death related to cardiac procedure	2 (0.4)	3 (0.7)		—	—
Death of unknown cause	8 (1.7)	14 (3.2)		—	—
Death from noncardiovascular cause	18 (3.9)	15 (3.4)		—	—
Heart transplantation	0	1 (0.2)		—	—
Shunt thrombosis†	27 (5.8)	21 (4.8)	1.0	–16.1 (–105.3 to 34.4)	0.61
Decreased murmur and increased cyanosis	16/27 (59.3)	14/21 (66.7)		—	—
Impairment of shunt flow	24/27 (88.9)	19/21 (90.5)		—	—
Surgical observation	6/27 (22.2)	2/21 (9.5)		—	—
Postmortem observation	2/27 (7.4)	0		—	—
Progressive cyanosis requiring a procedure	19/27 (70.4)	10/21 (47.6)		—	—
Cardiac procedure at <120 days of age, after thrombotic event	21 (4.5)	14 (3.2)	1.3	–38.0 (–171.4 to 29.8)	0.35

* The primary end point was a composite of death or heart transplantation, shunt thrombosis requiring intervention, or a cardiac procedure performed before 120 days of age, after an event adjudicated as thrombotic. Only the first event was counted.

† Shunt thrombosis was confirmed by detection of one or more of the following: decreased murmur and increased cyanosis; impairment of shunt flow observed on Doppler echocardiography, on angiography during surgery, or on magnetic resonance imaging or computed tomography after death; or progressive cyanosis requiring urgent shunt revision or a revascularization procedure.

cantly with respect to the incidence of mild, moderate, or severe bleeding (Table S4 in the Supplementary Appendix). The majority of bleeding events were spontaneous, and the most common sites of bleeding were gastrointestinal. The numbers of bleeding events and other adverse events were consistent across the prespecified subgroups defined by age, sex, race or ethnic group, type of palliative surgery, days from palliation to randomization, and status with respect to aspirin use before or during the study. Bleeding complications according to use or nonuse of concomitant aspirin therapy are summarized in Table S5 in the Supplementary Appendix.

In per-protocol analyses, adverse events occurred in 260 patients (73.9%) in the clopidogrel group and 238 patients (66.9%) in the placebo group (P=0.04) (Table S6 in the Supplementary Appendix). (The results of per-protocol analyses of bleeding events and events according to use or nonuse of concomitant aspirin therapy are given in Tables S7 and S8 in the Supplementary Appendix.)

DISCUSSION

Our trial shows that adding clopidogrel to conventional therapy did not reduce mortality from any cause or shunt-related morbidity in neonates or infants with congenital heart disease palliated with a systemic-to-pulmonary-artery shunt. The rate of the primary end point (the earliest occurrence of death or heart transplantation, shunt thrombosis, or a cardiac procedure before 120 days of age after an event considered to be thrombotic in nature) was similar with clopidogrel and placebo. The study did not show the efficacy of clopidogrel for any component of the composite primary end point, including shunt thrombosis.

There are several plausible explanations for our finding that clopidogrel lacked clinical efficacy as compared with placebo. Cyanotic congenital heart disease comprises a heterogeneous group of disorders that are managed in diverse ways.[16] The percentage of the variance in end points explained by any single factor, such as use of a medication,

may be smaller in our study population than in a more homogeneous population of adults with atherosclerotic cardiovascular disease.

The efficacy of aspirin in preventing shunt thrombosis has never been tested in a randomized, controlled trial. Nonetheless, aspirin is widely used for this purpose, and most infants in our study received aspirin treatment as part of their routine care. Indeed, the results of our post hoc analysis are consistent with prospective registry data suggesting that aspirin prevents death and shunt-related morbidity in patients like ours.[6] It is possible that clopidogrel would have been effective had aspirin not been used concomitantly. However, the effect of clopidogrel treatment on the primary composite end point did not differ according to whether aspirin was used concomitantly.

Platelets in neonates, as compared with platelets in older children and adults, have a decreased response to standard physiologically relevant agonists, as reflected in decreased aggregation, granule secretion, and expression of activation markers after stimulation with adenosine diphosphate (ADP), collagen, epinephrine, thromboxane analogues, or low-dose thrombin.[17] The baseline mean percentage of platelet aggregation after stimulation with 5 μM ADP is approximately 50% in adults but approximately 15% in neonates.[18] A clopidogrel dose of 0.2 mg per kilogram, which was the dose used in the infants in this trial, provides a level of inhibition of the baseline response that is similar to the level of inhibition provided by a dose of 75 mg in an adult (30 to 50% inhibition after stimulation with 5 μM ADP), as determined in a previous dose-finding trial in infants.[18] However, the normal baseline aggregation rate is lower in infants than in adults,[19] so blocking ADP with clopidogrel may be less protective against thrombosis in infants. A low baseline aggregation rate could also explain the absence of an increase in the risk of bleeding with the clopidogrel dose used in this trial. We chose this dose because it provided a level of inhibition of baseline platelet aggregation in infants that was similar to the level in adults and because we believed it provided the safest addition to standard postoperative therapy in infants with systemic-to-pulmonary-artery shunts. However, the results of our trial do not preclude the efficacy or safety of higher-dose regimens.

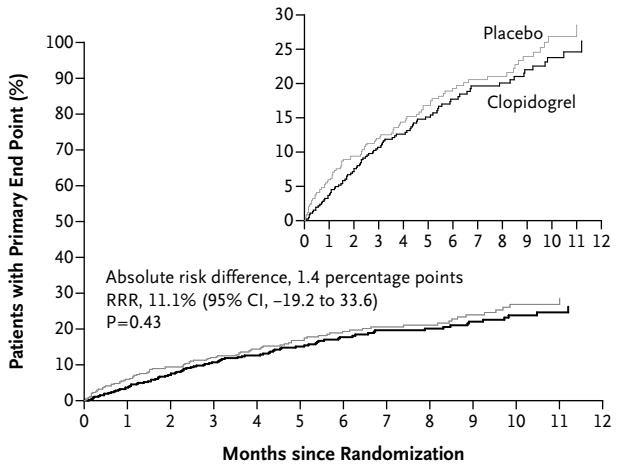

Figure 2. Kaplan–Meier Event Rates for the Primary Efficacy End Point.
The primary efficacy end point was defined as death or heart transplantation, shunt thrombosis, or a cardiac procedure performed before 120 days of age, after an event adjudicated to be thrombotic. CI denotes confidence interval, and RRR relative risk reduction.

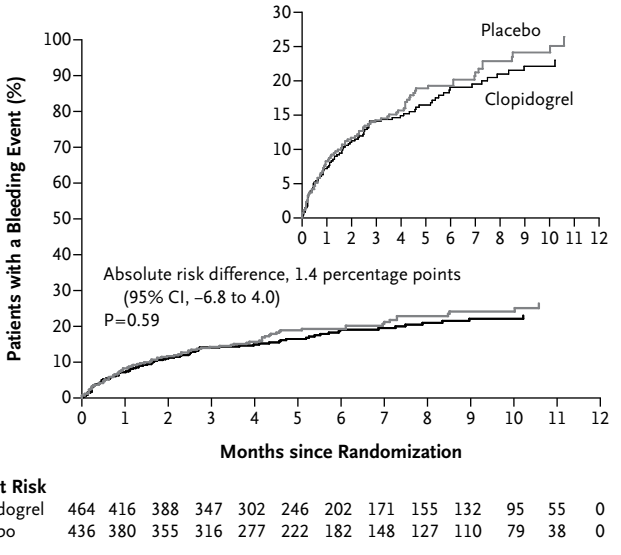

Figure 3. Kaplan–Meier Event Rates for Bleeding.

In the present study, we established a standardized approach to assessing bleeding events by developing defined criteria appropriate for use in this infant population. This approach has not been used in previous trials, and we do not have spe-

cific validation of the clinical usefulness or reproducibility of these criteria. Although we did not find significant differences in the percentage of adverse events between the two study groups, the power of our study to detect such differences was limited.

There are other important limitations of this trial. Information about the young infants who were screened and excluded was not collected, limiting insight into the generalizability of our study population. Aspirin therapy was the standard of care for infants with systemic-to-pulmonary-artery shunts at most centers, so we could not use a factorial design in which patients were randomly assigned to receive aspirin with clopidogrel or clopidogrel alone. Despite the independent adjudication of thrombotic events, the clinical diagnosis of shunt occlusion and its mechanisms is imprecise. We did not collect data on the many postrandomization factors, such as the number of central catheters or total days in the cardiac intensive care unit, which might increase thrombotic complications. However, because these factors occurred after randomization, we believe it is unlikely that they affected the results. The estimated treatment effects had large confidence intervals. This highlights the challenges of conducting a trial of treatment in children with a rare disease; despite an aggressive enrollment campaign spread over 134 sites in 31 countries, our study did not have adequate statistical power to test the equivalence of clopidogrel and placebo.

In conclusion, we found no benefit of clopidogrel, as compared with placebo, in reducing the rate of death for any cause or shunt-related morbidity, particularly shunt thrombosis, among infants with congenital heart disease palliated with a systemic-to-pulmonary-artery shunt.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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