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

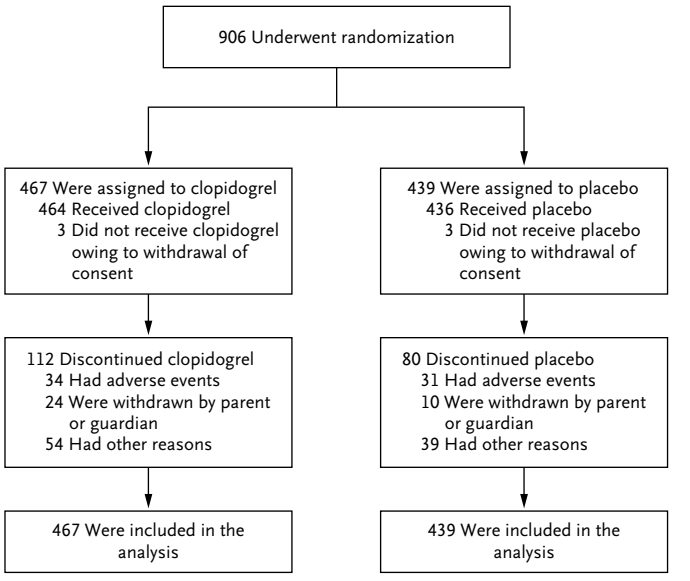

Figure 1. Enrollment and Follow-up of the Study Patients, According to Study Group.

"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.

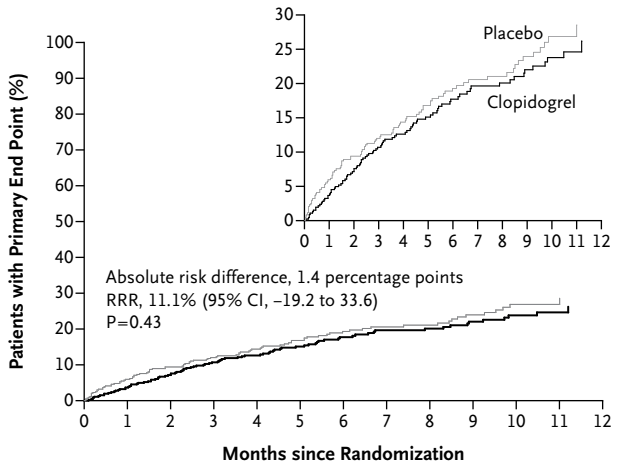

Figure 2. Kaplan–Meier Event Rates for the Primary Efficacy End Point.
The primary efficacy end point was defined as death or heart transplantation, shunt thrombosis, or a cardiac procedure performed before 120 days of age, after an event adjudicated to be thrombotic. CI denotes confidence interval,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

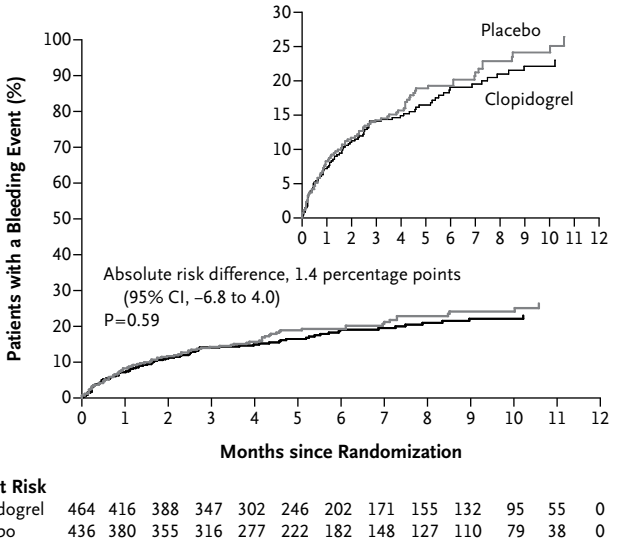

Figure 3. Kaplan–Meier Event Rates for Bleeding.

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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REFERENCES

1. Dastgiri S, Gilmour WH, Stone DH. Survival of children born with congenital anomalies. Arch Dis Child 2003;88:391-4.
2. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. Nat Rev Cardiol 2011;8:50-60.
3. Sano S, Ishino K, Kado H, et al. Outcome of right ventricle-to-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome: a multi-institutional study. Ann Thorac Surg 2004;78:1951-7.
4. Azakie T, Merklinger SL, McCrindle BW, et al. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. Ann Thorac Surg 2001;72:1349-53.
5. Yuan SM, Shinfeld A, Raanani E. The Blalock-Taussig shunt. J Card Surg 2009;24:101-8.
6. Li JS, Yow E, Berezny KY, et al. Clinical outcomes of palliative surgery including a systemic-to-pulmonary artery shunt in infants with cyanotic congenital heart disease: does aspirin make a difference? Circulation 2007;116:293-7.
7. Al Jubair KA, Al Fagih MR, Al Jarallah AS, et al. Results of 546 Blalock-Taussig shunts performed in 478 patients. Cardiol Young 1998;8:486-90.
8. Wells WJ, Yu RJ, Batra AS, Monforte H, Sintek C, Starnes VA. Obstruction in modified Blalock shunts: a quantitative analysis with clinical correlation. Ann Thorac Surg 2005;79:2072-6.
9. Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003;76:152-6.
10. Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database Syst Rev 2011;1:CD005158.
11. King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, writing on behalf of the 2005 Writing Committee. Circulation 2008;117:261-95. [Erratum, Circulation 2008;117(6):e161.]
12. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Errata, N Engl J Med 2001;345:1506, 1716.]
13. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20. [Erratum, JAMA 2003;289:987.]
14. Gentilomo C, Huang YS, Raffini L. Significant increase in clopidogrel use across U.S. children's hospitals. Pediatr Cardiol 2011;32:167-75.
15. Mertens L, Eyskens B, Boshoff D, Gewillig M. Safety and efficacy of clopidogrel in children with heart disease. J Pediatr 2008;153:61-4.
16. Schidlow DN, Anderson JB, Klitzner TS, et al. Variation in interstage outpatient care after the Norwood procedure: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. Congenit Heart Dis 2011;6:98-107.
17. Israels SJ, Michelson AD. Antiplatelet therapy in children. Thromb Res 2006;118:75-83.
18. Li JS, Yow E, Berezny KY, et al. Dosing of clopidogrel for platelet inhibition in infants and young children: primary results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial. Circulation 2008;117:553-9.
19. Jennings LK, Michelson AD, Jacoski MV, et al. Pharmacodynamic effects of clopidogrel in pediatric cardiac patients: a comparative study of platelet aggregation response. Platelets 2012;23:430-8.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Wessel DL, Berger F, Li JS, et al. Clopidogrel in infants with systemic-to-pulmonary-artery shunts. N Engl J Med 2013;368:2377-84. DOI: 10.1056/NEJMoa1114588

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1.4 Events Adjudication Committee

Jane W. Newburger, MD, MPH (Chairperson), Felix Berger, MD, Stephen Brown, MD, Carolyn Dunbar-Masterson, RN, Timothy Feltes, MD, Alain Fraisse, MD, Judith Geva, MSW, Constancio Medrano, MD, Luc Mertens, MD, Leonardo Andrade Mulinari, MD, Alexis Palacios-Macedo, MD, Suresh Rao, MD.

2. ENROLLMENT CRITERIA

2.1 Inclusion Criteria

1. Neonate or infant (age less than or equal to 92 days at the time of randomization) with cyanotic congenital heart disease.
2. Treated by any palliative systemic-to-pulmonary artery shunt (closed shunt or open shunt, Norwood, Sano, stent of ductus arteriosus).
3. Signed informed consent obtained from patient's legally acceptable representative (parents or guardians) according to local regulations.

2.2 Exclusion Criteria

1. Active bleeding, increased risk of bleeding (bleeding disorders [e.g., hemophilia, von Willebrand disease], arterio-venous malformations, aneurysms) or previous intracranial (Grades II–IV) or life-threatening hemorrhage.
2. Allergy to 2 or more classes of drug.
3. Current treatment with thienopyridine (open label clopidogrel or ticlopidine), dipyridamole or oral anticoagulant.
4. Adjusted gestational age less than 34 weeks.
5. Unable to receive study drug orally or enterically.
6. Concurrent use of another experimental drug/device or participation in another investigational drug or device trial within the last 30 days, except if the study involves an FDA approved drug/device.
7. Current clinically significant or persistent thrombocytopenia, neutropenia, severe hepatic or renal failure (i.e., more than 2.5 times the upper limit for age of hepatic enzymes or creatinine).
8. Inability to follow the study procedure

If a patient was initially excluded for randomization, re-evaluation for inclusion could be done later, and the patient randomized in the study, provided all inclusion/exclusion criteria were satisfied, including the requirement to be less than 92 days of age at the time of randomization.

3. STUDY DRUG

3.1 Information on study drug (formulation)

As clopidogrel bisulfate is not sufficiently stable in solution over long-term storage, the formulation approach consisted of the development of an extemporaneous solution: powder for solution reconstituted with a syrup for reconstitution.

The liquid formulation used in the phase 3 CLARINET study was a multi-dose formulation that could be used for a 14-day treatment period after reconstitution.

The formulation was a simple, unbuffered, sweetened solution of clopidogrel. A matching placebo in terms of appearance was also developed to ensure the study blinding.

For the constitution of this placebo formulation, a preservative was added into the sucrose syrup in order to comply with the antimicrobial preservation required by the US Pharmacopeia. The addition of preservative was shown not to be necessary for the constituted active syrup.

Both the active drug product and placebo were presented as a 10 mL amber glass vial (containing a powder either with or without clopidogrel) and a 125 mL amber glass bottle filled with 102 mL of sucrose syrup. Clinical supplies were packaged with a bottle adapter and oral syringes (1 and 3 mL) to facilitate dosing convenience and accuracy.

The clopidogrel active drug product was a syrup at a final strength of 1 mg/mL with the following composition after constitution:

Components	**Function**	**Quantity**
Clopidogrel bisulfate	Active ingredient	0.13964 g
Mannitol	Diluent	0.28836 g
Sucrose syrup (67%)[a]	Diluent/Sweetener	135.96000 g
Total mass		136.38800 g

[a]Depends on batch density of the syrup

The placebo matching the drug product was a syrup constituted as follows:

Components	Function	Quantity
Mannitol	Diluent	0.28836 g
Methylparaben/ methylparahydroxybenzoate	Preservative	0.102 g
Propylparaben sodium/propyl parahydroxybenzoate	Preservative	0.0408 g
Sucrose syrup (67%)*	Diluent/Sweetener	135.96000 g
Total mass		136.10000 g

Storage conditions were set based on stability results: clopidogrel active drug powder, placebo powder and solvent were stable for 24 months when stored between 15°C and 30°C in their clinical packaging.

Storage for constituted solutions was 14 days under refrigerated conditions (2°C–8°C) based on in-use stability studies performed on constituted solutions.

4. EFFICACY TRIAL ENDPOINT DEFINITIONS

The Events Adjudication Committee classified procedures and medical interventions prior to 120 days of age with respect to whether a thrombotic or platelet-related event was likely to have played a role. The procedure or intervention could involve:

- Surgery (i.e., bidirectional Glenn procedure, shunt revision), or
- Cardiac catheterization, or
- Administration of a medication targeted at controlling the thrombotic process, such as heparin, abciximab, or thrombolytic agents.

The thrombotic nature of the event could be manifest by:

- A documented or inferred thrombus, for example in a shunt or the aorta, adjacent vessels, or
- A finding, such as narrowing of a shunt, for which there is histologic and/or pathophysiologic data to suggest an etiologic role for platelets.

Principles for determining the thrombotic nature of the event were as follows:

- A thrombotic or platelet related process must have probably or definitely played a causal role in triggering the procedure or event.
- A thrombotic or platelet related process does not have to be the sole factor in causing the event, but should have made a substantial contribution.
- Sometimes two or more lesions were detected in a patient at cardiac catheterization, surgery, or in another type of intervention. If a thrombotic or platelet-related process probably or definitely played a causal role in at least one of these lesions, the event was classified as “YES” for component #3 of the primary composite outcome.
    - Stenosis at the site of insertion of either a Blalock-Taussig shunt or right ventricle-to-pulmonary artery conduit (i.e., “Sano” shunt) has been shown to involve a platelet-related process.
    - If balloon angioplasty was performed at the site of shunt insertion, the event was classified as “YES,” even if other procedures (for example angioplasty of a residual coarctation or restrictive atrial septum) were performed for lesions in which platelets did not probably or definitely play a causal role.

Procedures that usually were be considered to be probably or definitely related to a preceding thrombotic or platelet-related event (i.e., classified as YES, fulfilling the primary endpoint) included:

- Visualized clot in shunt or adjacent vessels.
- Visualized clot in aorta, with or without occlusion of a coronary orifice and myocardial infarction.
- Cardiac arrest or near-arrest attributed by study team to be potentially related to shunt thrombosis on the basis of at least one of the following:
    - Chest was opened in the intensive care unit to “milk” the shunt.
    - Surgeon took the patient back to the operating room for shunt revision.
    - Patient was taken to the catheterization lab to restore full shunt patency.
    - Caregivers began additional anti-thrombotic therapy (e.g., heparin, Coumadin, open-label Plavix and aspirin).
- Evidence of narrowing of modified Blalock-Taussig shunt or of stenosis at the shunt insertion site.
- Glenn (Stage II) procedure or other intervention prior to 120 days of age secondary to cyanosis under the following conditions:
    - For patients who underwent the Norwood procedure with modified Blalock-Taussig shunt, evidence of shunt narrowing or stenosis at site of anastomosis with the pulmonary artery.
    - For patients who underwent the Norwood procedure with Sano modification, evidence of narrowing of the right ventricular to pulmonary artery conduit, or stenosis at the site of insertion of the conduit into the pulmonary artery.
- Other confirmed thrombus in cardiac structure or arterial vessels
- Ischemic stroke confirmed or most probably due to embolic or thrombotic origin

Procedures that usually would be considered to be unlikely or only possibly related to a thrombotic or platelet-related event (i.e., classified as NO, not fulfilling primary endpoint):

- Glenn procedure prior to 120 days of age performed as part of a center’s routine clinical practice.
- Glenn procedure or other intervention prior to 120 days of age secondary to any of the following conditions:
    - Evidence of kinking or tenting of a modified Blalock-Taussig shunt.

- Pulmonary artery stenosis at a site remote from where a shunt was inserted (for example, left pulmonary artery stenosis from residual ductal tissue in a patient with a right modified Blalock Taussig shunt).
- Evidence of proximal Sano (right ventricular to pulmonary artery) conduit obstruction (e.g., muscle bundles at insertion of Sano conduit).
- Residual or recurrent coarctation.
- Restrictive atrial septal defect.
- Poor myocardial function.
- Severe tricuspid valve regurgitation.
- Pulmonary vein stenosis.

5. PROCESS FOR REVIEW OF REPORTED EVENTS AND ADJUDICATION

5.1 Review Process for Reported Events

- All documents contained in the dossiers of patients which needed adjudication were transmitted to the Events Adjudication Committee.
- Each event or a shunt narrowing leading to a bi-directional Glenn procedure or any cardiac-related intervention prior to 120 days of age was declared on a specific page of the Case Report Forms (CRFs), which were entered into the study clinical database on the same business day. Quality Control (QC) notes were sometimes required to confirm or correct responses given on the event CRFs page.
- Investigators were queried locally at the site level for their assessment of the thrombotic nature of the event CRFs.
- When the thrombotic nature was uncertain, this CRF form was entered into the Adjudication Tracking database by the study team and was updated daily.
- Those event dossiers deemed to be complete were prepared for initial review by the Events Adjudication Coordinator.
- Investigators were required to submit additional source documentation when the information recorded on the CRF did not match the source documentation received.
- Those events which were deemed to satisfy the protocol criteria with well-documented evidence were reviewed by one of the study Regional Coordinators following initial review by the study coordinator or research assistant (licensed registered nurse who was blinded to the study treatment). The Events Adjudication Coordinator recorded his/her assessment of the reported event (agreement/disagreement with the reporting investigator). All disagreements or those where a decision could not be made for any reason was sent to the Chair of the Events Adjudication Committee for complete adjudication.
- The Chair of the Events Adjudication Committee reviewed the events reviewed and verified by the Events Adjudication Coordinator to ensure validity of the process.
- The Chair was allowed to question any adjudicator when she disagreed with the adjudication.

5.2 Process for Adjudication

Reported events were adjudicated by at least one Events Adjudication Committee member. Dossiers of reported events requiring complete adjudication were prepared and distributed to Committee members on a regular basis to ensure that events were adjudicated in a timely fashion. Each Committee member was requested to review the dossiers and acknowledge in writing his/her agreement/disagreement with the Investigator's impression of the events of a specific form.

If the First Adjudicator and Events Adjudication Chair agreed with the Investigator's assessment of outcome events, this agreement was acknowledged in writing and in the adjudication report field. The Event Adjudication database was updated accordingly, with acceptance of the Investigator's report of outcome, and adjudication was considered complete.

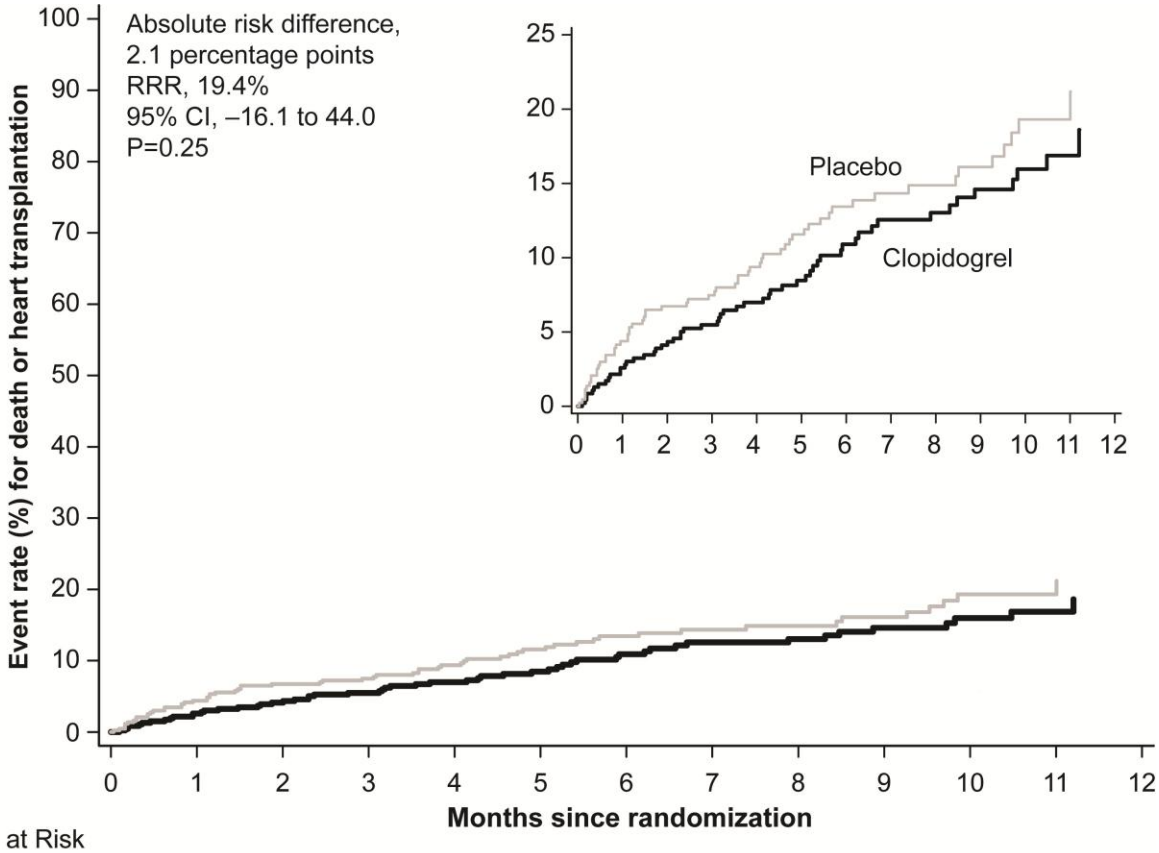
If the First Adjudicator disagreed with the Investigator' report of outcome events, the disagreement was acknowledged in writing and the Event Adjudication database was updated accordingly. The outcome event was forwarded to the Events Adjudication Chair. If the Chair agreed with Investigator's report of the outcome event, the agreement was acknowledged in writing and the Event Adjudication database was updated accordingly indicating that the Investigator's assessment of the outcome event was accepted, and the adjudication process was considered as complete. If the Chair disagreed with Investigator's report of the outcome event but agreed with the First Adjudicator, the disagreement was acknowledged in writing and in the adjudication report field, the Event Adjudication database was updated accordingly, the Adjudicators' assessment of outcome event was accepted, and the adjudication process was considered complete.

If the Chair of the Events Adjudication Committee was uncertain how to classify an outcome event, she and the First Adjudicator discussed and tried to resolve the issues surrounding the disagreement. If they subsequently agreed with the events as reported by the Investigator, this agreement was acknowledged in writing and in the adjudication reports field; the Event Adjudication database was updated accordingly; and the Investigator's report of the outcome event was accepted. Adjudication was then considered as complete.

If both adjudicators subsequently disagreed with the events as reported by the investigator, this disagreement was acknowledged in writing and in the adjudication reports field; the Event Adjudication database was updated accordingly, and adjudication considered as complete.

6. Supplementary Appendix Figures

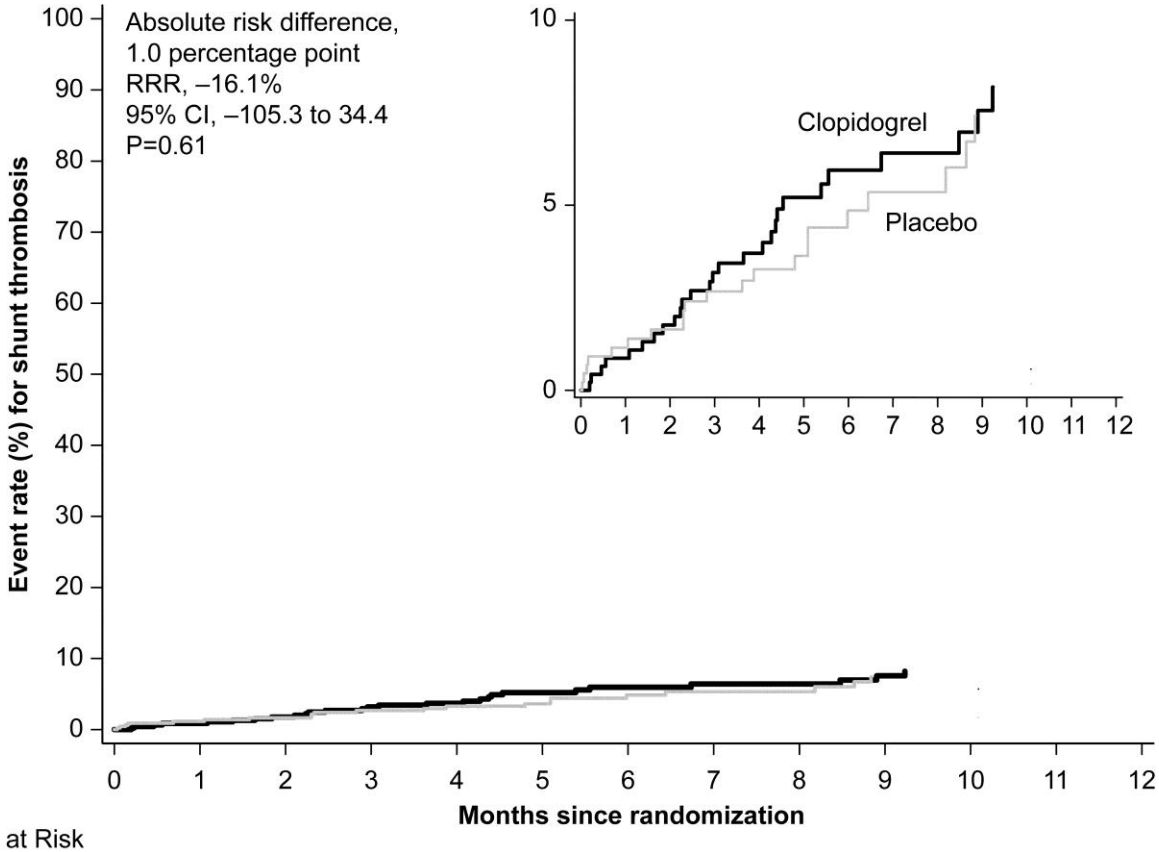
Supplementary Appendix Figure S1. Kaplan-Meier event rates for death or heart transplantation.



Number at Risk													
Clopidogrel	467	448	430	392	344	281	231	197	180	154	114	65	0
Placebo	439	410	391	356	313	256	204	166	144	127	89	43	0

CI, confidence interval; RRR, relative risk reduction.

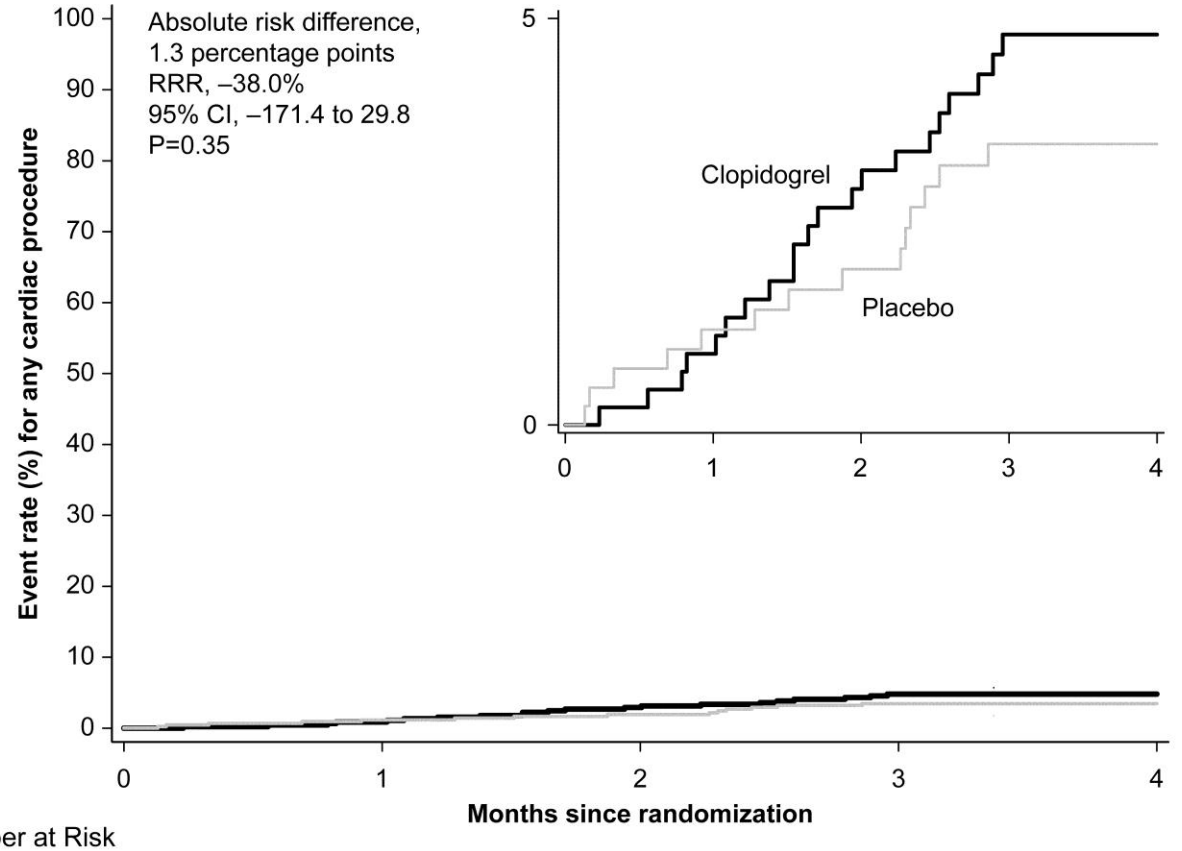
Supplementary Appendix Figure S2. Kaplan-Meier event rates for shunt thrombosis requiring intervention.



Number at Risk													
Clopidogrel	467	448	429	392	343	281	231	197	180	154	114	65	0
Placebo	439	410	391	356	313	256	204	166	144	127	89	43	0

CI, confidence interval; RRR, relative risk reduction.

Supplementary Appendix Figure S3. Kaplan-Meier event rates for any cardiac procedure prior to 120 days of age considered to be thrombotic in nature.

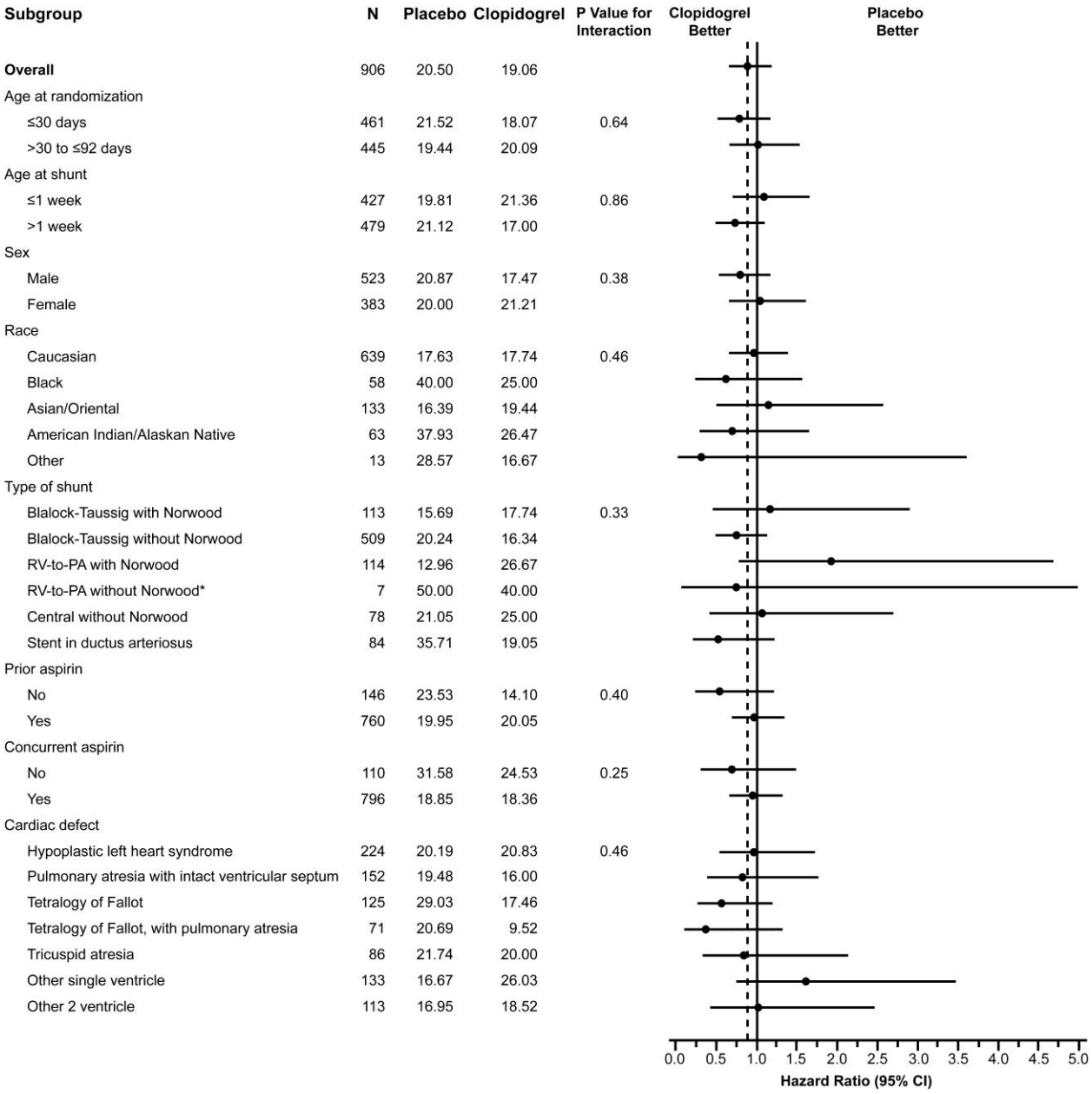


Number at Risk

Clopidogrel	467	446	422	386	341
Placebo	439	410	388	352	309

CI, confidence interval; RRR, relative risk reduction.

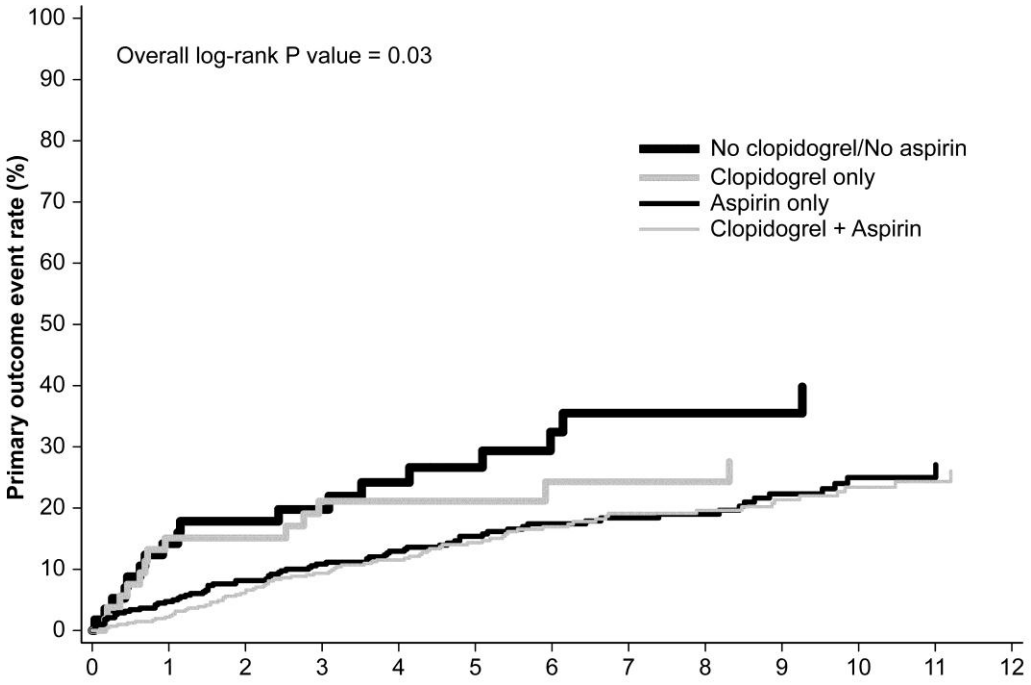
Supplementary Appendix Figure S4. Relative risk of the primary efficacy outcome of death or heart transplantation, shunt thrombosis, or cardiac procedure before 120 days of age following an event considered thrombotic in nature in different patient subgroups.



*The upper CI for patients with RV-to-PA shunt without Norwood is beyond the last value of the x-axis (8.42).

CI, confidence interval; RV-to-PA, right-ventricular-to-pulmonary artery shunt.

Supplementary Appendix Figure S5. Kaplan-Meier event rates for the primary efficacy outcome according to treatment with no antiplatelet therapy, aspirin alone, clopidogrel alone, or clopidogrel plus aspirin.



Number at Risk													
No clopidogrel/No aspirin	57	47	43	38	32	28	22	19	16	16	12	7	0
Clopidogrel only	53	45	44	37	35	32	24	24	24	21	13	6	0
Aspirin only	382	363	345	314	277	224	180	146	127	110	77	36	0
Clopidogrel + Aspirin	414	401	378	349	305	247	206	172	155	133	101	59	0

7. Supplementary Appendix Tables

Supplementary Appendix Table S1. Post hoc Analysis of Frequency of the Composite Primary Efficacy Outcome in the Overall Study Population by Concomitant Aspirin Use.

Frequency, n (%)	**No concomitant aspirin (N=110)**	**Concomitant aspirin (N=796)**
Primary outcome	31 (28.2)	148 (18.6)[a]
Death or heart transplantation	25 (22.7)	86 (10.8)
Shunt thrombosis	4 (3.6)	43 (5.4)
Cardiac procedure at age <120 days following an event considered thrombotic in nature	2 (1.8)	19 (2.4)

[a]Log-rank P=0.009; relative risk reduction, 40.1% (95% confidence interval, 11.8 to 59.3).

Supplementary Appendix Table S2. Frequency of Primary Outcome According to Treatment with no Antiplatelet Therapy, Aspirin Alone, Clopidogrel Alone, or Clopidogrel Plus Aspirin.

Frequency, n (%)	No aspirin/ No clopidogrel (N=57)	Aspirin only (N=382)	Clopidogrel only (N=53)	Clopidogrel + aspirin (N=414)
Primary outcome[a]	18 (31.6)	72 (18.8)[b]	13 (24.5)[c]	76 (18.4)[d,e]
Death or cardiac transplant	14 (24.6)	46 (12.0)	11 (20.8)	40 (9.7)
Shunt thrombosis	3 (5.3)	18 (4.7)	1 (1.9)	25 (6.0)
Cardiac intervention <120 days for event of thrombotic nature	1 (1.8)	8 (2.1)	1 (1.9)	11 (2.7)

[a]The earliest occurrence of death or heart transplantation, shunt thrombosis requiring intervention, or hospitalization for bidirectional Glenn procedure or other cardiac-related intervention prior to 120 days of age following a thrombotic event or narrowing of the shunt, determined by a blinded events adjudication committee.

[b]Log-rank P=0.01; relative risk reduction, 48.1% (95% confidence interval, 12.9 to 69.0).

[c]Log-rank P=0.35; relative risk reduction, 28.8% (95% confidence interval, –45.5 to 65.1).

[d]Log-rank P=0.005; relative risk reduction, 51.7% (95% confidence interval, 19.3 to 71.1).

[e]Overall log-rank test P=0.03.

Supplementary Appendix Table S3. Summary of Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in the Treated Population.

Adverse Event	Placebo (N=436), n (%)	Clopidogrel (N=464), n (%)	P value
Any adverse event	310 (71.1)	353 (76.1)	0.09
Bleeding events[a]	88 (20.2)	87 (18.8)	0.59
Non-bleeding events	222 (50.9)	266 (57.3)	0.54
Any serious adverse event	196 (45.0)	234 (50.4)	0.10
Bleeding events[a]	32 (7.3)	30 (6.5)	0.60
Non-bleeding events	164 (37.6)	204 (44.0)	0.053
Serious adverse event leading to death	14 (3.2)	16 (3.4)	0.84
Infections and infestations	215 (49.3)	247 (53.2)	0.24
Upper respiratory tract infection	65 (14.9)	68 (14.7)	0.91
Gastroenteritis	23 (5.3)	40 (8.6)	0.049
Pneumonia	11 (2.5)	23 (5.0)	0.056
Bronchiolitis	20 (4.6)	22 (4.7)	0.91
Nasopharyngitis	24 (5.5)	21 (4.5)	0.50
Urinary tract infection	14 (3.2)	16 (3.4)	0.84
Viral infection	10 (2.3)	13 (2.8)	0.63
Bronchitis	7 (1.6)	11 (2.4)	0.41
Wound infection	10 (2.3)	10 (2.2)	0.89
Lower respiratory tract infection	7 (1.6)	10 (2.2)	0.54
Postoperative wound infection	6 (1.4)	10 (2.2)	0.38
Pharyngitis	3 (0.7)	10 (2.2)	0.07
Influenza	9 (2.1)	9 (1.9)	0.89
Respiratory tract infection	11 (2.5)	8 (1.7)	0.40
Viral upper respiratory tract infection	11 (2.5)	8 (1.7)	0.40
Gastrointestinal disorders	97 (22.2)	121 (26.1)	0.18
Vomiting	21 (4.8)	37 (8.0)	0.054
Diarrhea	21 (4.8)	29 (6.3)	0.35
Hematochezia	21 (4.8)	16 (3.4)	0.30

Adverse Event	Placebo (N=436), n (%)	Clopidogrel (N=464), n (%)	P value
Gastroesophageal reflux disease	11 (2.5)	14 (3.0)	0.65
Gastrointestinal hemorrhage	5 (1.1)	10 (2.2)	0.24
Respiratory, thoracic, and mediastinal disorders	81 (18.6)	82 (17.7)	0.72
Hypoxia	13 (3.0)	18 (3.9)	0.46
Cough	16 (3.7)	14 (3.0)	0.59
Cardiac disorders	48 (11.0)	73 (15.7)	0.04
Cyanosis	13 (3.0)	26 (5.6)	0.054
Injury, poisoning, and procedural complications	50 (11.5)	54 (11.6)	0.94
Post-procedural hemorrhage	11 (2.5)	17 (3.7)	0.32
Skin and subcutaneous tissue disorders	50 (11.5)	40 (8.6)	0.15
Diaper dermatitis	8 (1.8)	10 (2.2)	0.73
Rash	14 (3.2)	9 (1.9)	0.23
General disorders and administration site conditions	32 (7.3)	38 (8.2)	0.63
Pyrexia	16 (3.7)	23 (5.0)	0.34
Nervous system disorders	10 (2.3)	36 (7.8)	<0.001
Seizures[b]	7 (1.6)	14 (3.0)	0.16
Strokes[c]	0	8 (1.7)	0.006
Metabolism and nutrition disorders	31 (7.1)	35 (7.5)	0.80
Investigations	28 (6.4)	22 (4.7)	0.27
Oxygen saturation decreased	11 (2.5)	15 (3.2)	0.53
Vascular disorders	20 (4.6)	19 (4.1)	0.72
Blood and lymphatic system disorders	12 (2.8)	17 (3.7)	0.44
Eye disorders	11 (2.5)	16 (3.4)	0.42
Conjunctivitis	8 (1.8)	12 (2.6)	0.44

[a]Patients having both a bleeding event and non-bleeding adverse event are counted only in the bleeding event row.

[b]Includes the following preferred terms: convulsion, clonic convulsion, partial seizures, convulsions local, hypoglycemic seizure, and febrile convulsion.

[c]Includes the following preferred terms: cerebral ischemia, cerebral infarction, ischemic cerebral infarction, and ischemic stroke.

Supplementary Appendix Table S4. Treatment-Emergent Bleeding Events in the Treated Population.

Bleeding	**Placebo (N=436), n (%)**	**Clopidogrel (N=464), n (%)**	**P value**
Severity			
Any	88 (20.2)	87 (18.8)	0.59
Mild	53 (12.2)	44 (9.5)	0.20
Moderate	20 (4.6)	24 (5.2)	0.68
Severe[a]	15 (3.4)	19 (4.1)	0.61
Type/etiology			
Spontaneous	60 (13.8)	56 (12.1)	0.45
Post-traumatic	6 (1.4)	11 (2.4)	0.27
Puncture (vascular access site)	16 (3.7)	9 (1.9)	0.11
Surgical	10 (2.3)	17 (3.7)	0.23
Associated with hemodynamic compromise	15 (3.4)	17 (3.7)	0.86
Criteria			
Blood loss more than expected	34 (7.8)	31 (6.7)	0.52
Bleeding requiring procedure	39 (8.9)	42 (9.1)	0.96

[a]Two severe bleeding events were fatal (one in each treatment group).

Supplementary Appendix Table S5. Patients with Any Treatment-Emergent Bleeding According to Concomitant Aspirin Use among Patients in the Treated Population.

Interaction Variable	Subgroup	Placebo, n (%)	Clopidogrel, n (%)	Odds ratio (95% CI)
Aspirin use[a]	No (N=109)	9 (16.1)	7 (13.2)	0.79 (0.27 to 2.31)
	Yes (N=791)	79 (20.8)	80 (19.5)	0.92 (0.65 to 1.30)
Aspirin (mg/kg)	No intake (N=109)	9 (16.1)	7 (13.2)	0.79 (0.27 to 2.31)
	≤3 mg/kg (N=137)	18 (28.6)	18 (24.3)	0.80 (0.38 to 1.72)
	>3 to ≤5 mg/kg (N=309)	26 (17.6)	25 (15.5)	0.86 (0.47 to 1.57)
	>5 to ≤10 mg/kg (N=310)	35 (22.7)	35 (22.4)	0.98 (0.58 to 1.68)
	>10 mg/kg (N=35)	0 (0.0)	2 (10.0)	

[a]P value for interaction = 0.44

CI, confidence interval.

Supplementary Appendix Table S6. Summary of Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in the Per-Protocol Population.

Adverse Event	Placebo (N=356), n (%)	Clopidogrel (N=352), n (%)	P value
Any adverse event	238 (66.9)	260 (73.9)	0.04
Bleeding events[a]	65 (18.3)	64 (18.2)	0.98
Non-bleeding events	173 (48.6)	196 (55.7)	0.06
Any serious adverse event	143 (40.2)	162 (46.0)	0.12
Bleeding events[a]	20 (5.6)	18 (5.1)	0.77
Non-bleeding events	123 (34.6)	144 (40.9)	0.08
Serious adverse event leading to death	7 (2.0)	10 (2.8)	0.45
Infections and infestations	174 (48.9)	190 (54.0)	0.17
Upper respiratory tract infection	58 (16.3)	60 (17.0)	0.79
Gastroenteritis	21 (5.9)	33 (9.4)	0.08
Bronchiolitis	18 (5.1)	19 (5.4)	0.84
Nasopharyngitis	22 (6.2)	18 (5.1)	0.54
Pneumonia	7 (2.0)	16 (4.5)	0.053
Urinary tract infection	10 (2.8)	11 (3.1)	0.08
Wound infection	9 (2.5)	9 (2.6)	0.98
Postoperative wound infection	6 (1.7)	9 (2.6)	0.42
Pharyngitis	3 (0.8)	9 (2.6)	0.08
Viral upper respiratory tract infection	9 (2.5)	8 (2.3)	0.82
Influenza	7 (2.0)	8 (2.3)	0.78
Viral infection	7 (2.0)	8 (2.3)	0.78
Bronchitis	6 (1.7)	8 (2.3)	0.57
Lower respiratory tract infection	6 (1.7)	8 (2.3)	0.57
Respiratory tract infection	10 (2.8)	6 (1.7)	0.32
Gastrointestinal disorders	71 (19.9)	80 (22.7)	0.37
Vomiting	16 (4.5)	28 (8.0)	0.057
Diarrhea	20 (5.6)	23 (6.5)	0.61
Hematochezia	16 (4.5)	12 (3.4)	0.46

Adverse Event	Placebo (N=356), n (%)	Clopidogrel (N=352), n (%)	P value
Gastroesophageal reflux disease	7 (2.0)	8 (2.3)	0.78
Respiratory, thoracic, and mediastinal disorders	52 (14.6)	60 (17.0)	0.37
Cough	13 (3.7)	8 (2.3)	0.28
Hypoxia	7 (2.0)	8 (2.3)	0.78
Epistaxis	3 (0.8)	8 (2.3)	0.12
Cardiac disorders	37 (10.4)	54 (15.3)	0.049
Cyanosis	11 (3.1)	18 (5.1)	0.17
Injury, poisoning, and procedural complications	38 (10.7)	42 (11.9)	0.60
Post-procedural hemorrhage	9 (2.5)	16 (4.5)	0.15
Skin and subcutaneous tissue disorders	39 (11.0)	34 (9.7)	0.57
Diaper dermatitis	6 (1.7)	8 (2.3)	0.57
Rash	13 (3.7)	7 (2.0)	0.18
General disorders and administration site conditions	28 (7.9)	29 (8.2)	0.86
Pyrexia	14 (3.9)	19 (5.4)	0.36
Metabolism and nutrition disorders	24 (6.7)	22 (6.3)	0.79
Nervous system disorders	10 (2.8)	21 (6.0)	0.04
Investigations	22 (6.2)	16 (4.5)	0.33
Oxygen saturation decreased	9 (2.5)	12 (3.4)	0.49
Eye disorders	9 (2.5)	15 (4.3)	0.20
Conjunctivitis	8 (2.2)	11 (3.1)	0.47
Blood and lymphatic system disorders	7 (2.0)	11 (3.1)	0.33
Vascular disorders	14 (3.9)	10 (2.8)	0.42

[a]Patients having both a bleeding event and non-bleeding adverse event are counted only in the bleeding event row.

Supplementary Appendix Table S7. Treatment-Emergent Bleeding Events in the Per-Protocol Population.

Bleeding	Placebo (N=356), n (%)	Clopidogrel (N=352), n (%)	P value
Severity			
Any	65 (18.3)	64 (18.2)	0.98
Mild	42 (11.8)	35 (9.9)	0.43
Moderate	14 (3.9)	15 (4.3)	0.83
Severe[a]	9 (2.5)	14 (4.0)	0.28
Type/etiology			
Spontaneous	40 (11.2)	40 (11.4)	0.96
Post-traumatic	5 (1.4)	10 (2.8)	0.18
Puncture (vascular access site)	16 (4.5)	6 (1.7)	0.03
Surgical	8 (2.2)	14 (4.0)	0.18
Associated with hemodynamic compromise	11 (3.1)	10 (2.8)	0.85
Criteria			
Blood loss more than expected	23 (6.5)	18 (5.1)	0.44
Bleeding requiring procedure	28 (7.9)	27 (7.7)	0.92

[a]One severe bleeding event was fatal in the clopidogrel group.

Supplementary Appendix Table S8. Patients with Any Treatment-Emergent Bleeding According to Concomitant Aspirin Use among Patients in the Per-Protocol Population.

Interaction Variable	Subgroup	Placebo, n (%)	Clopidogrel, n (%)	Odds Ratio (95% CI)
Aspirin use[a]	No (N=77)	5 (12.2)	4 (11.1)	0.90 (0.22 to 3.64)
	Yes (N=631)	60 (19.0)	60 (19.0)	1.00 (0.67 to 1.48)
Aspirin (mg/kg)	No intake (N=77)	5 (12.2)	4 (11.1)	0.90 (0.22 to 3.64)
	≤3 mg/kg (N=118)	17 (29.3)	17 (28.3)	0.95 (0.43 to 2.12)
	>3 to ≤5 mg/kg (N=249)	18 (14.8)	17 (13.4)	0.89 (0.44 to 1.83)
	>5 to ≤10 mg/kg (N=244)	25 (19.7)	24 (20.5)	1.05 (0.56 to 1.97)
	>10 mg/kg (N=20)	0 (0.0)	2 (16.7)	

[a]P value for interaction = 0.54

CI, confidence interval.