DOI:
10.1056/NEJMoa1512021

Document Version
Publisher's PDF, also known as Version of record

ORIGINAL ARTICLE

A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events

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ABSTRACT

BACKGROUND

Sickle cell anemia is an inherited blood disorder that is characterized by painful vaso-occlusive crises, for which there are few treatment options. Platelets mediate intercellular adhesion and thrombosis during vaso-occlusion in sickle cell anemia, which suggests a role for antiplatelet agents in modifying disease events.

METHODS

Children and adolescents 2 through 17 years of age with sickle cell anemia were randomly assigned to receive oral prasugrel or placebo for 9 to 24 months. The primary end point was the rate of vaso-occlusive crisis, a composite of painful crisis or acute chest syndrome. The secondary end points were the rate of sickle cell–related pain and the intensity of pain, which were assessed daily with the use of pain diaries.

RESULTS

A total of 341 patients underwent randomization at 51 sites in 13 countries across the Americas, Europe, Asia, and Africa. The rate of vaso-occlusive crisis events per person-year was 2.30 in the prasugrel group and 2.77 in the placebo group (rate ratio, 0.83; 95% confidence interval, 0.66 to 1.05; P=0.12). There were no significant differences between the groups in the secondary end points of diary-reported events. The safety end points, including the frequency of bleeding events requiring medical intervention, of hemorrhagic and nonhemorrhagic adverse events that occurred while patients were taking prasugrel or placebo, and of discontinuations due to prasugrel or placebo, did not differ significantly between the groups.

CONCLUSIONS

Among children and adolescents with sickle cell anemia, the rate of vaso-occlusive crisis was not significantly lower among those who received prasugrel than among those who received placebo. There were no significant between-group differences in the safety findings. (Funded by Daiichi Sankyo and Eli Lilly; ClinicalTrials.gov number, NCT01794000.)

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*A complete list of investigators in the Determining Effects of Platelet Inhibition on Vaso-Occlusive Events (DOVE) trial is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on December 8, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1512021

Sickle cell anemia, which is estimated to affect 100 million persons worldwide, is an inherited blood disorder characterized by hemolytic anemia and recurrent vaso-occlusive crises that are associated with hospitalizations, impaired quality of life, and early death.[1-3] The pathophysiological mechanism of vaso-occlusion in sickle cell anemia is complex. The polymerization of sickle hemoglobin initiates a cascade of thrombotic and inflammatory insults that result in progressive vascular damage and ischemic end-organ injury.[4] Hydroxyurea is partially effective in reducing the frequency of acute vaso-occlusive events, but it has not been shown to prevent organ damage.[5] There is an unmet need for additional agents that target the pathophysiological basis of the disease.[6]

Platelets play a role in the pathogenesis of sickle cell disease. Induced in part by adenosine diphosphate (ADP) released by lysed erythrocytes, activated platelets mediate the formation of multicellular aggregates and promote inflammation during vaso-occlusion.[7-10] Abnormalities in platelet count, turnover, and survival, as well as markers of platelet activation, are found at steady state and are exacerbated during vaso-occlusive crises.[11-13] Several studies have suggested a benefit of ADP-directed antiplatelet therapy in reducing markers of platelet activation, as well as the rate and intensity of pain in patients with sickle cell disease.[14,15]

Prasugrel is an oral, third-generation thienopyridine that inhibits ADP-mediated platelet activation and aggregation by irreversibly binding to the P2Y12 class of ADP receptors.[11,16] Previous studies involving patients with sickle cell disease who were treated with prasugrel documented levels of platelet inhibition similar to those in healthy persons,[17] as well as reductions in platelet activation and in vaso-occlusive pain[18]; the studies also established the basis for a dose-adjustment strategy for the treatment of children with sickle cell anemia.[19] Together, these studies provided the rationale for the Determining Effects of Platelet Inhibition on Vaso-Occlusive Events (DOVE) trial.

METHODS

STUDY DESIGN AND OVERSIGHT

The DOVE trial was a phase 3 double-blind, placebo-controlled, parallel-group, multinational trial designed to assess the efficacy of prasugrel in reducing the rate of vaso-occlusive crisis, a composite end point of painful crisis or acute chest syndrome, in children and adolescents with sickle cell anemia. The design of the trial has been described previously.[20]

The protocol and steering committees, which were made up of academic investigators and representatives of the sponsors (Daiichi Sankyo and Eli Lilly), designed the study and supervised its conduct (a complete list of the members of each committee is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). In each country, the study was approved by national regulatory authorities and by local ethics committees, institutional review boards, or both and abided by local regulations. Periodic safety assessments were conducted by an independent external data and safety monitoring committee. The principal investigators had full access to the data, and the data analyses were independently verified by the Harvard Clinical Research Institute for both accuracy and adherence to the protocol and to the approved statistical analysis plan, which are available at NEJM.org.

STUDY POPULATION

The study population included children and adolescents, 2 through 17 years of age, who had sickle cell anemia (homozygous hemoglobin S [HbSS] or hemoglobin Sβ^0 thalassemia) and who had had two or more vaso-occlusive crises during the previous year. The definition of vaso-occlusive crisis that we used to assess eligibility for inclusion in the trial was identical to that used for the primary end point. Details of the inclusion and exclusion criteria[20] are provided in Table S1 in the Supplementary Appendix. Information on race and ethnic background was reported by the patient or the patient's family. Participants from 51 sites in 13 countries underwent randomization. Patients who were being treated with hydroxyurea at a dose that had been stable for more than 60 days before screening were eligible to participate. Transcranial Doppler ultrasonographic screening for primary stroke risk was required to have been performed within the preceding year in all patients 2 through 16 years of age. The eligibility criteria were intended to identify the patients with the greatest potential for benefit from prasugrel while minimizing the risk of bleeding or stroke. Therefore, in accordance with evidence-based consensus guidelines for sickle cell

disease, the exclusion criteria included an abnormal or conditional result of transcranial Doppler ultrasonography within the preceding year; current or past regular red-cell transfusions for stroke prevention; a history of transient ischemic attack, stroke, or head trauma; regular treatment with an antiplatelet agent, anticoagulant, or nonsteroidal antiinflammatory drug; and clinical findings associated with an increased risk of bleeding.[21] The child's parent or legal representative provided written informed consent. The participating children also gave documented assent, as required under local regulations.

RANDOMIZATION AND STUDY PROCEDURES

The study included a 2-week screening period followed by a double-blind period during which the participant took prasugrel or placebo (treatment period), a period that was planned to last a minimum of 9 months and a maximum of 24 months; this allowed participants who enrolled early to participate for a longer time. Participants were randomly assigned, in a 1:1 ratio, with the use of an interactive voice-response system, to receive either oral prasugrel or placebo; assignments were balanced according to receipt or no receipt of hydroxyurea treatment, country, and age group (2 through 5, 6 through 11, and 12 through 17 years of age) on the basis of a minimization algorithm.[22] Prasugrel treatment was initiated at a dose of 0.08 mg per kilogram of body weight; with the use of an individualized dose-adjustment strategy, the treatment was then adjusted to a dose between 0.04 mg per kilogram and 0.12 mg per kilogram (maximum absolute dose, 10 mg) that provided a targeted level of platelet reactivity.[20] The placebo was identical in appearance to prasugrel, and the dose of placebo was mock-adjusted in the same manner as the dose of prasugrel.[20]

Platelet reactivity was measured with the use of the Verify*Now* P2Y12 assay, a whole-blood point-of-care assay that reports ADP-induced platelet aggregation results as P2Y12 reaction units (PRUs) and percentage inhibition. A target range of 231 to 136 PRUs (30 to 60% inhibition) was chosen on the basis of previous studies of prasugrel involving patients with sickle cell anemia, as well as studies of clopidogrel involving infants with congenital heart disease who were found to have no increased risk of bleeding in association with similar levels of inhibition after treatment.[23,24] After the 45-day dose-adjustment period, participants returned for follow-up visits every 3 months, with dose adjustments made according to changes in body weight.[20] Adherence was monitored by direct questioning and by pill counts conducted at each visit. Participants were considered to be adherent if they took 80 to 120% of the assigned regimen (study drug or placebo).

A handheld, mobile, electronic patient-reported outcome (ePRO) device was used to alert the patients and caregivers to record information on several of the secondary end points.[20,25-27] Caregivers of participants 4 years of age or older or the participants themselves completed this ePRO pain diary daily during the 2-week screening period and for the first 9 months of the double-blind treatment period.

END POINTS

The primary end point was the rate of vaso-occlusive crisis, which was a composite of painful crisis or acute chest syndrome. A painful crisis was defined as the onset of moderate-to-severe pain that lasted for at least 2 hours, for which there was no explanation other than sickle cell disease and that required therapy with oral or parenteral opioids, ketorolac, or other analgesics prescribed by a health care provider in a medical setting, such as a hospital, clinic, or emergency department, or in the context of documented telephone management.[3,20,28,29] Acute chest syndrome was defined as acute illness characterized by fever, respiratory symptoms, or both, accompanied by a new pulmonary infiltrate on chest radiography. Vaso-occlusive crisis end points meeting these definitions required documentation, which included completion by a medical professional of a trial-specific telephone management tool when applicable. Events that recurred within 7 days of each other were considered to be a single episode.[30,31]

The major secondary end points were the diary-documented rate and intensity of sickle cell–related pain, with intensity assessed on a scale of 0 to 10 with the use of a modified version of the Faces Pain Scale–Revised (in which 0 denotes no pain and 10 denotes the worst pain possible)[20]; the rates of hospitalization for vaso-occlusive crisis, painful crisis, and acute chest syndrome; the rate of sickle cell–related red-cell transfusion; and the diary-documented rate of analgesic use and school attendance. Safety assessments included

the incidence of hemorrhagic events requiring medical intervention, the incidence of hemorrhagic and nonhemorrhagic adverse events that occurred while the participant was taking the study drug or placebo, and the rate of permanent discontinuation of the study drug or placebo owing to hemorrhagic and nonhemorrhagic adverse events.

STATISTICAL ANALYSIS

We estimated that 220 patients would need to be enrolled for the study to have approximately 85% power to detect a 35% lower rate of vaso-occlusive crisis in the prasugrel group than in the placebo group, with the use of a two-sided test at a significance level of 0.05, as analyzed with the Andersen–Gill model, which is an extension of the Cox proportional-hazards model for the analysis of recurrent events. Although the sample size for the safety analysis was not formally assessed, we planned to have at least 204 patients completing at least 9 months of treatment. All efficacy analyses were performed with data from the intention-to-treat population, and safety analyses were performed with data from patients who received at least one dose of the assigned regimen (study drug or placebo).

The time to a recurrent episode of vaso-occlusive crisis was analyzed with the use of the Andersen–Gill model. A robust variance estimate was used, with treatment, hydroxyurea use, and age group included as factors in the model. The major secondary efficacy end points were also analyzed with the use of the Andersen–Gill model. The pain-diary end points were computed and analyzed by means of a mixed-effects model repeated-measures analysis. The mixed-effects model included the fixed effects of treatment, the baseline value of the pain-diary measure, hydroxyurea use, age group, time, and treatment-by-time interaction. A covariance-structure selection process was used to determine the best-fit covariance structure for the estimation of within-patient variability.

If a significant reduction in the primary end point was achieved, a fixed-sequence gatekeeping testing strategy for the major secondary efficacy end points was planned to control the overall type I error rate.[20] We also explored the consistency of the treatment effect on the primary and key secondary efficacy end points in prespecified subgroups. A prespecified landmark analysis of the primary efficacy end point was performed with the use of a time-dependent Andersen–Gill model to estimate the rate ratios before and after 6 months, 9 months, and 12 months across all age groups.

RESULTS

ENROLLMENT AND FOLLOW-UP

The randomization and follow-up of participants, including a breakdown according to age group, are shown in Figure S1 in the Supplementary Appendix. From May 2013 through June 2015, a total of 341 patients underwent randomization at 51 sites in 13 countries, with 171 assigned to the prasugrel group and 170 assigned to the placebo group. A total of 275 participants completed the 9-month follow-up visit; of these, 9 participants discontinued the assigned regimen after the 9-month visit, and 2 participants completed 24 months of the assigned regimen before the database lock. The remaining 264 patients were continuing their participation in the study at the time of the database lock. Because the youngest age group was the slowest to enroll, fewer participants in this age group than in the older age groups had reached the 9-month visit at the time of the database lock. The duration of study follow-up was similar in the two study groups (median, 303 days in the prasugrel group and 306 days in the placebo group). No participants were lost to follow-up.

The percentage of participants who were adherent to the assigned regimen was similar in the two study groups (78.2% of participants in the prasugrel group and 81.2% of participants in the placebo group, $P=0.59$). Diary data from 268 patients 4 years of age or older were collected for up to 9 months.

BASELINE CHARACTERISTICS OF PARTICIPANTS

The demographic and baseline clinical characteristics of the participants are shown in Table 1. Distributions of age, sex, weight, and hydroxyurea use were similar in the two groups. Of the 341 patients who underwent randomization, 308 (90.3%) had HbSS sickle cell disease, and 153 (44.9%) were receiving hydroxyurea.

END POINTS

Vaso-Occlusive Crisis Events

A total of 736 vaso-occlusive crisis events occurred during the study: 328 events among 115 patients (67.3%) in the prasugrel group and 408 events

among 123 patients (72.4%) in the placebo group. The rate of vaso-occlusive crisis events (the number per person-year) was somewhat lower, but not significantly so, in the prasugrel group than in the placebo group: 2.30 events per person-year and 2.77 events per person-year, respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.66 to 1.05; P=0.12) (Table 2 and Fig. 1).

In the landmark analyses, the rate ratio of vaso-occlusive crisis through 9 months was 0.88 (95% CI, 0.69 to 1.12); after 9 months, the rate ratio decreased to 0.63 (95% CI, 0.42 to 0.94), but the difference in rate ratios between these periods was not significant (P=0.09 for interaction) (Table S2 in the Supplementary Appendix). The rate ratio continued to decrease numerically at 12 months, but only 26% of the participants (88 of 341) reached 12 months of treatment.

Subgroup Analyses

The results of the subgroup analyses are shown in Figure 2. Although the effect of prasugrel on vaso-occlusive crises was greatest in the group of participants who were 12 through 17 years of age (P=0.06) and in patients who were not receiving hydroxyurea (P=0.06), no significant interaction was observed between the study groups with regard to any of the characteristics of patients.

Secondary End Points

Prasugrel had no significant effect on the rate of hospitalization for vaso-occlusive crises, the rate of red-cell transfusion, the rate of pain, the intensity of pain, the rate of analgesic use, or the rate of absence from school owing to sickle cell–related pain, as assessed with the use of daily pain diaries (Table 2). Treatment with prasugrel had no significant effect on other secondary end points, including the duration of hospitalization for vaso-occlusive crises, the time from randomization to the first or second vaso-occlusive crisis, and the incidence of transient ischemic attack or ischemic stroke. After adjustment to the final maintenance dose of the study drug or placebo, platelet reactivity was lower in the prasugrel group than in the placebo group (mean difference, –72.4 PRUs; 95% CI, –83.7 to –61.1; P<0.001).

Safety and Adverse Events

There was no significant difference between the study groups in the incidence of hemorrhagic events requiring medical intervention, in the incidence of hemorrhagic and nonhemorrhagic adverse events that occurred during the treatment period (Table 3, and Table S3 in the Supplementary Appendix), or in the side-effect profile of the study drug when administered with or without hydroxyurea (Table S4 in the Supplementary Appendix). There were three deaths during the treatment period, two in the placebo group and one in the prasugrel group; none were judged by the investigator as being related to the study drug or placebo. In the prasugrel group, the death was due to a ruptured intracerebral aneurysm and cerebral hemorrhage.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Placebo Group (N=170)	Prasugrel Group (N=171)
Age — yr	10.6±4.3	10.6±4.3
Age group — no. (%)		
2 through 5 yr	33 (19.4)	34 (19.9)
6 through 11 yr	66 (38.8)	66 (38.6)
12 through 17 yr	70 (41.2)	71 (41.5)
18 yr	1 (0.6)	0
Hydroxyurea use — no. (%)	76 (44.7)	77 (45.0)
Female sex — no. (%)	86 (50.6)	87 (50.9)
Weight — kg	31.9±14.8	33.2±15.4
Body-mass index	16.5±2.8	17.1±3.6
Race — no./total no. (%)†		
White	58/169 (34.3)	58/171 (33.9)
Black	109/169 (64.5)	113/171 (66.1)
Multiple	2/169 (1.2)	0
Location of enrollment — no. (%)		
Ghana or Kenya	72 (42.4)	76 (44.4)
Egypt, Lebanon, or Turkey	52 (30.6)	51 (29.8)
United States or Canada	29 (17.1)	27 (15.8)
Brazil	0	1 (0.6)
Saudi Arabia or Oman	4 (2.4)	3 (1.8)
Belgium, Italy, or United Kingdom	13 (7.6)	13 (7.6)
Vaso-occlusive crises in previous year — no.	4.0±7.9	3.5±2.0

* Plus–minus values are means ±SD. Body-mass index, the weight in kilograms divided by the square of the height in meters, was the only characteristic that differed significantly between the study groups (P=0.04).
† Race was self-reported.

DISCUSSION

In this phase 3 multinational, placebo-controlled trial evaluating the efficacy of prasugrel

Table 2. Primary and Secondary Efficacy End Points.

End Point	Placebo Group (N=170)	Prasugrel Group (N=171)	Rate Ratio (95% CI)	P Value
Vaso-occlusive crisis				
Patients with events — no. (%)	123 (72.4)	115 (67.3)		
Total events	408	328		
Length of follow-up — patient-yr	147.44	142.89		
Event rate per patient-yr	2.77	2.30	0.83 (0.66 to 1.05)	0.12
Painful crisis				
Patients with events — no. (%)	122 (71.8)	113 (66.1)		
Total events	401	320		
Length of follow-up — patient-yr	147.44	142.89		
Event rate per patient-yr	2.72	2.24	0.82 (0.65 to 1.04)	0.11
Acute chest syndrome				
Patients with events — no. (%)	15 (8.8)	15 (8.8)		
Total events	17	16		
Length of follow-up — patient-yr	147.44	142.89		
Event rate per patient-yr	0.12	0.11	0.96 (0.48 to 1.93)	0.92
Hospitalization for vaso-occlusive crisis				
Patients with events — no. (%)	76 (44.7)	69 (40.4)		
Total events	166	152		
Length of follow-up — patient-yr	147.44	142.89		
Event rate per patient-yr	1.13	1.06	0.94 (0.65 to 1.37)	0.76
Red-cell transfusions due to sickle cell disease				
Patients with events — no. (%)	37 (21.8)	37 (21.6)		
Total events	62	71		
Length of follow-up — patient-yr	147.44	142.89		
Event rate per patient-yr	0.42	0.50	1.17 (0.71 to 1.91)	0.54
			Least-Squares Mean Difference (95% CI)	
Least-squares mean monthly rate of daily pain — %*	17.7	17.5	–0.24 (–4.6 to 4.1)	0.91
Least-squares mean monthly intensity of daily pain*	0.61	0.71	0.10 (–0.11 to 0.31)	0.37
Least-squares mean monthly rate of analgesic use — %†	22.8	24.3	1.51 (–4.19 to 7.21)	0.60
Least-squares mean quarterly rate of absence from school — %†	10.3	11.5	1.27 (–2.11 to 4.65)	0.46
Platelet reactivity — PRU‡				
Baseline	276	276	0.19 (–10.1 to 10.5)	0.97
Fully adjusted dose	275	203	–72.4 (–83.7 to –61.1)	<0.001
At 9 months	281	214	–66.9 (–79.6 to –54.2)	<0.001

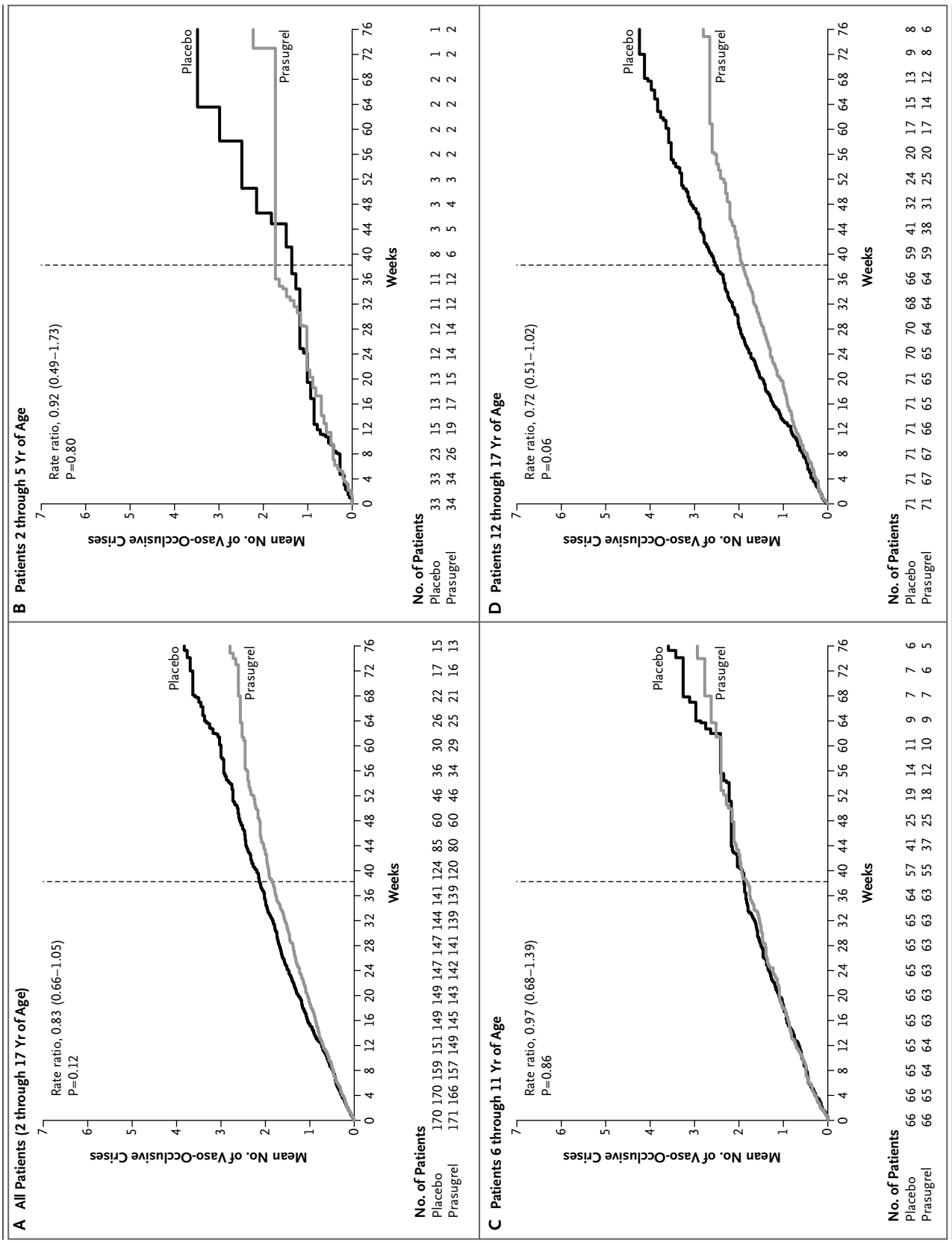
* The rate and mean intensity of daily pain were evaluated only for patients 7 years of age or older; data were available for 127 participants in the placebo group and for 127 participants in the prasugrel group. The rate of daily pain is the percentage of days during the course of a month during which a patient experienced pain. Pain intensity was assessed on a scale of 0 to 10 with the use of a modified version of the Faces Pain Scale–Revised (in which 0 denotes no pain and 10 denotes the worst pain possible).

† The rates of analgesic use and school absence were evaluated only for patients 4 years of age or older. For the rate of analgesic use, data were available for 153 participants in the placebo group and 153 participants in the prasugrel group; for the rate of absence from school, data were available for 115 participants in the placebo group and for 105 participants in the prasugrel group

‡ Platelet reactivity was measured with an assay that reports adenosine diphosphate–induced platelet aggregation results as P2Y12 reaction units (PRUs). Values for the fully adjusted dose and at 9 months were not adjusted for the baseline value. Data were available for 163 participants in the placebo group and for 161 participants in the prasugrel group.

Figure 1 (facing page). Mean Number of Vaso-Occlusive Crises.

The data at each time point are the estimated mean number of events that occurred in the patient population up to that point. In each panel, the vertical dashed line represents 9 months (270 days) after randomization. Because of the declining numbers of patients at risk, the mean cumulative function plots were truncated at 76 weeks.



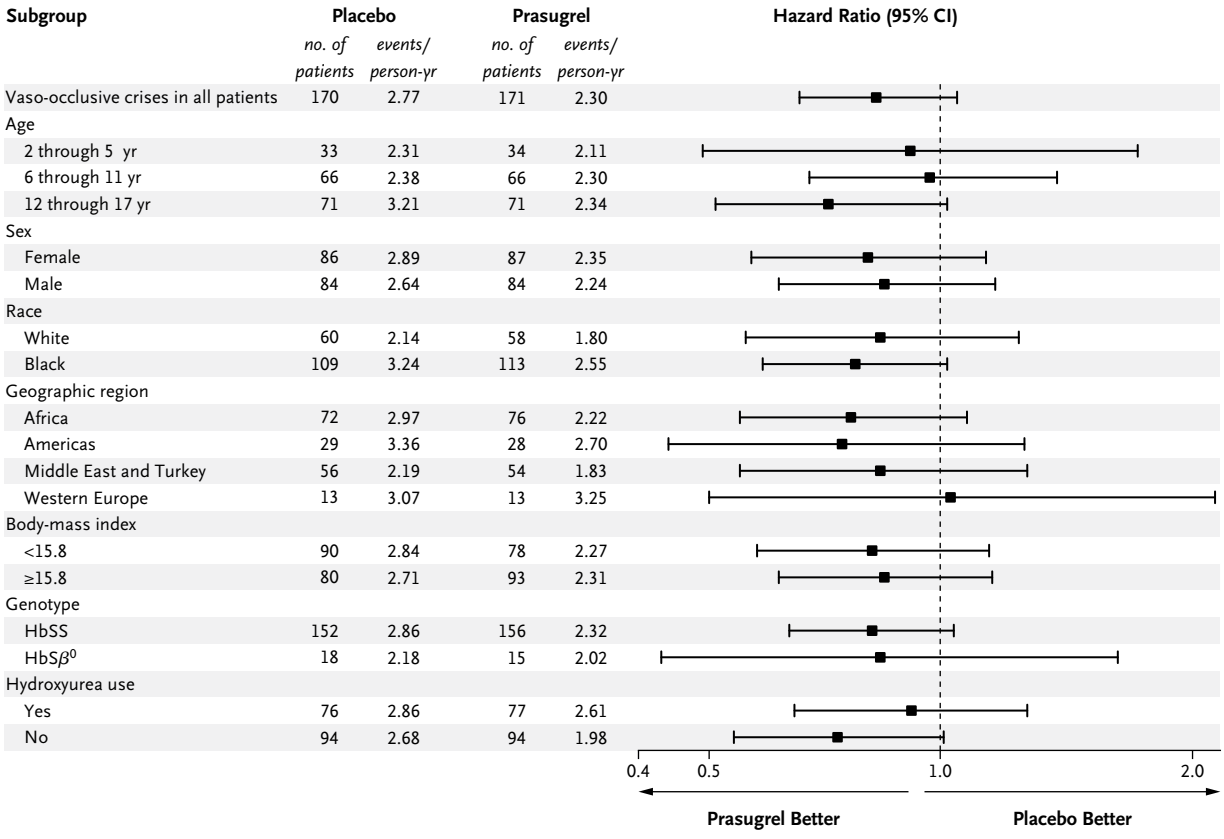


Figure 2. Rates of Vaso-Occlusive Crises According to Demographic Group.

The Africa subgroup includes Ghana and Kenya; the Americas subgroup includes Brazil, the United States, and Canada; the Middle East and Turkey subgroup includes Saudi Arabia, Oman, Egypt, Lebanon, and Turkey; and the western Europe subgroup includes Belgium, Italy, and the United Kingdom. A body-mass index (the weight in kilograms divided by the square of the height in meters) of 15.8, the median among participants at baseline, was used as the cutoff for the subgroups based on this characteristic. None of the results of the subgroup analyses were significant. HbSβ^0 denotes hemoglobin Sβ^0 thalassemia, and HbSS homozygous hemoglobin S.

in children and adolescents with sickle cell anemia, the primary end point — the rate of vaso-occlusive crisis — did not differ significantly between the prasugrel group and the placebo group. In addition, prasugrel treatment had no significant effect on any of the prespecified secondary end points. These results suggest that treatment with prasugrel alone, at the levels of platelet inhibition attained in this study, is not effective in significantly reducing the frequency of acute vaso-occlusive crises in children 2 through 17 years of age who have sickle cell anemia. The overall rate of hemorrhagic and nonhemorrhagic adverse events — including deaths, serious adverse events, adverse events leading to discontinuation of the study drug or placebo, adverse events that occurred during the treatment period, and adverse events that were judged as being possibly related to the study drug or placebo or to the study procedure — did not differ significantly between the study groups.

Sickle cell anemia is a heterogeneous and complex disease in which platelet activation is only one of several mechanisms of vascular injury, which perhaps explains why prasugrel was ineffective. This result is consistent with those of previous trials of other agents directed at a single pathologic process, in which treatment has generally failed.[6] However, the nonsignificant effect of prasugrel in the oldest age group may suggest that platelet activation is relatively more important in these older patients, a hypothesis that is consistent with the fact that endothe-

Table 3. Adverse Events.*

Adverse Event	Placebo Group (N=170)	Prasugrel Group (N=170)†	P Value
	no. of patients (%)		
Hemorrhagic adverse events			
Hemorrhagic events requiring medical intervention	8 (4.7)	11 (6.5)	0.64
Discontinuation of study drug or placebo because of an adverse event	1 (0.6)	2 (1.2)	0.99
Adverse event during treatment period	33 (19.4)	32 (18.8)	0.99
Death	0	1 (0.6)	0.99
Serious adverse event	3 (1.8)	5 (2.9)	0.72
Nonhemorrhagic adverse events			
Discontinuation of study drug or placebo because of an adverse event	4 (2.4)	4 (2.4)	0.99
Adverse event during treatment period	162 (95.3)	157 (92.4)	0.37
Death	2 (1.2)‡	0	0.50
Serious adverse event	96 (56.5)	87 (51.2)	0.38

* Adverse events included events that occurred from the first dose until 10 days after the last dose of the study drug or placebo. A patient could have more than one event, and each patient could have both nonhemorrhagic and hemorrhagic events and be counted in both categories.
† One patient did not receive the study drug after randomization and was not included in the safety analyses.
‡ One of the two deaths in the placebo group was reported after the database lock.

lial dysfunction in sickle cell disease is progressive.[1,31-33] The results in the oldest subgroup (Fig. 1D) were largely responsible for the separation of the treatment and placebo curves that was observed at 3 months (Fig. 1A), whereas little treatment effect was observed in the two younger subgroups (Fig. 1B and 1C). Event rates were similar in the two younger age groups, although relatively few participants in the youngest age group had completed 9 months of treatment, which limited the interpretation of the results in this age group. In this intercontinental study, we succeeded in enrolling patients with sickle cell anemia who were from various regions worldwide. Although no significant differences in the rates of vaso-occlusive crisis were seen between treatment groups according to geographic region, it is possible that randomization did not completely eliminate bias related to disease heterogeneity (e.g., beta globin haplotype), environmental factors, or coexisting conditions (e.g., malaria), and cross-cultural differences may have influenced the results.

We found no synergistic effect between hydroxyurea and prasugrel, and in fact prasugrel seemed to be less effective in participants who were also receiving hydroxyurea (Fig. 2). This is perhaps surprising, but it suggests that antiplatelet agents may have a role in the treatment of patients in whom hydroxyurea therapy has failed. It is difficult to further analyze any interaction between hydroxyurea and prasugrel, because we did not specifically collect information on responses to hydroxyurea. Although data on routine complete blood counts were collected for safety assessments and revealed no significant safety concerns, blood counts have not been used to assess adherence to hydroxyurea therapy. There was no a priori reason to believe that levels of hemoglobin F would modify the response to prasugrel. Future studies of adherence and response to hydroxyurea in which hemoglobin F levels are measured may make it possible to accurately assess the effect of hydroxyurea in combination with prasugrel. Similarly, sickle cell anemia is a highly variable condition; more detailed laboratory information, such as hemoglobin F levels and alpha globin genotype, may allow better identification of the patients who are most likely to have a response to treatment. It should be noted that hydroxyurea-treated patients who were receiving prasugrel had no more adverse events than did those who were not receiving prasugrel.

No new safety issues were identified in as-

sociation with prasugrel treatment in this population. The single death in the prasugrel group was from an intracerebral hemorrhage. A postmortem examination revealed a ruptured cerebral aneurysm, and the death was not considered by the investigator to be treatment-related. The participant had had normal results of transcranial Doppler ultrasonography at study entry and no previous neuroimaging or clinical history of neurologic symptoms.

Because safety was a priority in this study, we aimed for modest platelet inhibition and chose a narrower target range (231 to 136 PRUs, corresponding to 30 to 60% platelet inhibition) than the range used in studies of adults with acute coronary syndrome (235 to 95 PRUs).[34] The lack of effect of the administered dose of prasugrel may be related to the fact that the effect on platelet inhibition was smaller than had been anticipated. An adjustment of the dose to a lower PRU limit (i.e., greater platelet inhibition) may have offered therapeutic benefit but potentially would have been associated with an increased risk of bleeding.

In summary, in our study, the rate of vaso-occlusive crises was not significantly lower with prasugrel than with placebo among children with sickle cell anemia, although the smaller number of vaso-occlusive crises in the prasugrel group, particularly among the older children, is encouraging. Antiplatelet agents, such as prasugrel, may have a therapeutic role as part of a multidrug approach targeting multiple aspects of the complex pathophysiological mechanisms of sickle cell anemia. The DOVE trial included patients in Africa and the Middle East, where sickle cell anemia is most prevalent. The successful completion of the DOVE trial provides guidance for future multicontinental clinical trials of treatment for sickle cell anemia.

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

We thank all the patients who agreed to participate; the study coordinators, nurses, and monitors in the participating countries; LeRoy LeNarz, M.D. (Eli Lilly), for his support of the study; Julie Sherman, A.A.S., for graphical support; and Keri Poi, Ph.D. (Eli Lilly), for editorial assistance.

APPENDIX

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