Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis
A Randomized Controlled Trial

Laura M. Dember, MD
Gerald J. Beck, PhD
Michael Allon, MD
James A. Delmez, MD
Bradley S. Dixon, MD
Arthur Greenberg, MD
Jonathan Himmelfarb, MD
Miguel A. Vazquez, MD
Jennifer J. Gassman, PhD
Tom Greene, PhD
Milena K. Radeva, MS
Gregory L. Braden, MD
T. Alp Ikizler, MD
Michael V. Rocco, MD, MSCE
Ingemar J. Davidson, MD
James S. Kaufman, MD
Catherine M. Meyers, MD
John W. Kusek, PhD
Harold I. Feldman, MD, MSCE
for the Dialysis Access Consortium Study Group

Approximately 470,000 Americans have end-stage renal disease, and most are treated with hemodialysis.1 A major challenge in caring for patients undergoing hemodialysis is maintaining a functioning vascular access, which is essential for performing the dialysis procedure. The effect of vascular access dysfunction is substantial—it is a leading reason for hospitalization among patients with end-stage renal disease and has associated annual costs in the United States that exceed $1 billion.2,3

Context The arteriovenous fistula is the preferred type of vascular access for hemodialysis because of lower thrombosis and infection rates and lower health care expenditures compared with synthetic grafts or central venous catheters. Early failure of fistulas due to thrombosis or inadequate maturation is a barrier to increasing the prevalence of fistulas among patients treated with hemodialysis. Small, inconclusive trials have suggested that antiplatelet agents may reduce thrombosis of new fistulas.

Objective To determine whether clopidogrel reduces early failure of hemodialysis fistulas.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial conducted at 9 US centers composed of academic and community nephrology practices in 2003-2007. Eight hundred seventy-seven participants with end-stage renal disease or advanced chronic kidney disease were followed up until 150 to 180 days after fistula creation or 30 days after initiation of dialysis, whichever occurred later.

Intervention Participants were randomly assigned to receive clopidogrel (300-mg loading dose followed by daily dose of 75 mg; n = 441) or placebo (n = 436) for 6 weeks starting within 1 day after fistula creation.

Main Outcome Measures The primary outcome was fistula thrombosis, determined by physical examination at 6 weeks. The secondary outcome was failure of the fistula to become suitable for dialysis. Suitability was defined as use of the fistula at a dialysis machine blood pump rate of 300 mL/min or more during 8 of 12 dialysis sessions.

Results Enrollment was stopped after 877 participants were randomized based on a stopping rule for intervention efficacy. Fistula thrombosis occurred in 53 (12.2%) participants assigned to clopidogrel compared with 84 (19.5%) participants assigned to placebo (relative risk, 0.63; 95% confidence interval, 0.46-0.97; P = .018). Failure to attain suitability for dialysis did not differ between the clopidogrel and placebo groups (61.8% vs 59.5%, respectively; relative risk, 1.05; 95% confidence interval, 0.94-1.17; P = .40).

Conclusion Clopidogrel reduces the frequency of early thrombosis of new arteriovenous fistulas but does not increase the proportion of fistulas that become suitable for dialysis.

Trial Registration clinicaltrials.gov Identifier: NCT00067119

©2008 American Medical Association. All rights reserved.
The arteriovenous fistula is the preferred type of vascular access because thrombosis rates, infection rates, access-related expenditures, and total health care expenditures all are lower for patients with fistulas than for those with either synthetic arteriovenous grafts or central venous catheters. Recognition of these advantages is reflected in the clinical practice guidelines of several professional societies and has triggered a major initiative by the Centers for Medicare & Medicaid Services to increase the prevalence of fistulas. However, the advantages of fistulas are counterbalanced by the substantially higher proportion of fistulas than grafts that are never able to be used for dialysis because of failure to mature adequately or central venous catheters, which are the least desirable type of vascular access because of their high rates of catheter-associated bacteremia and inadequate solute clearance.

Several small placebo-controlled trials observed lower rates of early fistula thrombosis with short-term use of antiplatelet agents in the postoperative period. However, none of these studies had adequate power to demonstrate statistically significant differences between the treatment groups and none reported the proportion of fistulas that ultimately matured into a functional vascular access. To further evaluate the effect of platelet inhibition on fistula thrombosis and maturation failure, we performed a multicenter, randomized, double-blind, placebo-controlled trial of clopidogrel administered following fistula creation in a large group of patients with advanced chronic kidney disease or end-stage renal disease.

Methods

Participants

The study design has previously been reported in detail. Briefly, participants were enrolled from 9 centers in the United States. Individuals undergoing creation of a new upper extremity fistula were eligible for enrollment if they were receiving maintenance treatment with hemodialysis or were expected to begin maintenance hemodialysis within 6 months. Major exclusion criteria included active bleeding or bleeding events requiring red blood cell transfusions within the previous 12 weeks, a platelet count less than $75 \times 10^9/µL$, known coagulopathy, acute ulcer disease, systolic blood pressure higher than 200 mm Hg or diastolic blood pressure higher than 115 mm Hg, advanced liver disease, inability to discontinue antithrombotic or anticoagulant therapy including aspirin during the study drug administration period, pregnancy, and current substance abuse. Unless there was a history of myocardial infarction or cerebrovascular accident within the previous 12 months, the use of antiplatelet agents did not preclude enrollment if the investigator and the patient's physicians thought their discontinuation for 7 weeks was medically safe. Race/ethnicity data were collected based on patient self-report. The institutional review board at each center approved the protocol and all participants provided written informed consent.

Primary Outcomes

The study was designed to assess the ability of clopidogrel to reduce early fistula failure (is, the primary outcome) compared with placebo. Study endpoints were early primary uptake defined as patency at 6 weeks after fistula creation as confirmed by the participant's vascular surgeon, and monthly thereafter until ascertainment of fistula suitability. Adverse events were recorded until 30 days after discontinuation of the study medication. Study medication was discontinued before 6 weeks in the event of fistula thrombosis confirmed by the participant's vascular surgeon or the investigator.

Study Design and Procedures

Participants were assigned in equal proportions to receive clopidogrel or placebo using a computer-generated permuted block randomization with stratification by location of the fistula (forearm vs upper arm) and by center. Randomization was performed within 1 calendar day after fistula creation surgery following confirmation that a fistula was created and that it was patent by physical examination. Participants and members of the study team were blinded to treatment assignment. Study drug administration began immediately after randomization. Clopidogrel was administered orally, with a loading dose of 300 mg on day 1 followed by 75 mg each day thereafter for an additional 41 days. Clopidogrel and matching placebo tablets were provided by Synthelabo (Ambares, France) and packaged by Fisher Clinical Services (Allentown, Pennsylvania). Participants receiving antiplatelet or anticoagulant agents prior to enrollment discontinued such treatment for at least 7 days prior to surgery. Resumption of these medications was permitted after the 6 weeks of study drug administration. Adherence to study medication was assessed by pill counts and expressed as: [(number of pills dispensed−number of pills returned)/number of pills prescribed] × 100%.

Decisions regarding fistula creation, initiation of use of the fistula, and procedures performed to enhance fistula maturation were made by the participant's physicians and not dictated by the study protocol. Data collection was performed at baseline, 6 weeks after fistula creation, and monthly thereafter until ascertainment of fistula suitability. Adverse events were recorded until 30 days after discontinuation of the study medication. Study medication was discontinued before 6 weeks in the event of fistula thrombosis confirmed by the participant's vascular surgeon or the investigator.

Outcomes

The primary outcome was thrombosis (ie, patency failure) 6 weeks after fistula creation. The fistula was classified as patent if a bruit was audible with a stethoscope throughout systole and diastole at least 8 cm proximal to the arteriovenous anastomosis. Fistula patency was assessed by trained study personnel.

The major secondary outcome was failure to attain suitability for dialysis. Fistula suitability was defined as the ability to use the fistula for dialysis with 2 needles and maintain a dialysis machine blood flow rate adequate for optimal dialysis ($\geq 300$ mL/min) during 8 of 12 dialysis sessions occurring during a 30-day suitability ascertainment period. For participants receiving maintenance hemodialysis at the time of enrollment and for participants who started maintenance hemodialysis within 120 days after fistula creation.
creation, the suitability ascertainment period began between 120 and 150 days after fistula creation surgery. The start of the suitability ascertainment period was the first dialysis session within days 120 and 150 during which fistula cannulation was performed. If dialysis initiation occurred after day 120, the ascertainment period began at dialysis initiation. During each dialysis session of the suitability ascertainment period, all blood flow measurements recorded after the first hour and before the last 15 minutes of the dialysis session were included in the determination of the suitability outcome. If a fistula was not being used during the fistula suitability ascertainment period, the fistula was classified as not suitable, even if it had been successfully used prior to the ascertainment period.

Bleeding was classified as minor, intermediate, major, life-threatening, or fatal, as previously described. The classifications of major, life-threatening, and fatal bleeding were reviewed by a quality control committee consisting of a subset of the investigators, but the categorization made by the clinical center investigator was maintained for analyses.

Statistical Analysis

The primary and secondary outcomes in the 2 treatment groups were compared using the Mantel-Haenszel $\chi^2$ test stratified according to clinical center and the location of the fistula (forearm or upper arm). Treatment effects were expressed as a weighted average of the strata-specific relative risks. Poisson regression models were used to test for differences in the relative risks (interactions) among the clinical center and fistula location strata.

The comparisons of the primary and secondary outcomes were based on the participants' randomized treatment assignments, irrespective of adherence to the intervention. However, participants who could not have patency or suitability ascertained were censored from the analyses of these outcomes. In sensitivity analyses performed to address missing data, bounds on the minimum and maximum relative risks for the primary outcome were obtained by imputing all missing outcomes in 1 treatment group as "patent" and all missing outcomes in the other treatment group as "not patent." For sensitivity analyses of the secondary outcome, suitability was imputed for participants without suitability assessments based on vital status and the 6-week patency outcome.

A data and safety monitoring board (DSMB) approved the protocol prior to implementation, reviewed adverse events every 6 months, and reviewed the interim analyses of efficacy. A formal stopping guideline based on a Lan-DeMets spending function was used to approximate the O'Brien-Fleming boundary for 4 interim efficacy analyses. The stopping guideline also included a boundary for early termination in the absence of trends for a treatment effect at the third or fourth interim analysis. The majority of the total type I error ($\alpha$) was allocated to the later interim analyses. At the actual interim analyses, the estimated information fractions (defined as the proportion of total projected patency assessments completed at each analysis) were 0.241, 0.479, 0.733, and 0.813, with corresponding nominal 2-sided $\alpha$ levels of .0001, .0015, .020, and .024. The $P$ values and 95% confidence intervals (CIs) for the primary analysis were adjusted for interim monitoring using the repeated CI approach.

All other CIs and 2-sided $P$ values are reported on a comparison-wise basis without adjustment for interim analyses or multiple comparisons. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

Sample Size

The trial was designed to enroll a total of 1284 participants (642 in each treatment group). This sample size would have provided 85% power to detect a relative reduction in the fistula thrombosis rate of 30% in the clopidogrel group at a 2-sided $\alpha$ level of .05, assuming a thrombosis rate of 25% in the placebo group. We based our prediction of the thrombosis rate in the placebo group on a pooled analysis of previously published placebo-controlled trials evaluating antiplatelet agents on thrombosis of new fistulas. We viewed an effect size of 30% as clinically compelling, and it was also consistent with the findings of the previous small trials of antiplatelet therapy. The power calculation incorporated a 3% rate of treatment drop-in (ie, initiation of antiplatelet therapy by treating physicians to participants randomized to placebo) and a 3% rate of treatment dropout (ie, discontinuation of study drug among participants randomized to clopidogrel), a loss to follow-up prior to the 6-week patency assessment of 5%, and an upward adjustment of 2.7% to account for the O'Brien-Fleming stopping rule. The target sample size also provided 81% power at a 2-sided $\alpha$ level of .05 to detect a 20% relative reduction in failure to attain fistula suitability for dialysis, assuming a failure rate of 40% in the placebo group.

RESULTS

Early Termination of Enrollment

At the recommendation of the DSMB, enrollment was terminated on October 24, 2006, after the fourth interim analysis, when the study information fraction had reached 0.813. The recommendation for termination was based on the prespecified stopping rule for efficacy of the intervention on the primary end point. Recognizing the importance of determining the effect of clopidogrel on the secondary outcome (fistula suitability), the DSMB considered conditional power calculations for suitability before making the decision to terminate enrollment. These calculations indicated that continuing the trial could not have shown a statistically significant benefit of clopidogrel on the suitability outcome and was unlikely (conditional probability < .05) to yield a relative risk in a qualitatively different direction than that observed at the fourth interim analysis.
For participants randomized prior to the early termination date, study drug administration continued for a full 6 weeks, and follow-up continued until the earlier of the following: ascertainment of the suitability outcome or June 18, 2007, the date investigators were unblinded to the trial results and the reason for early termination.

**Patients**

Between January 7, 2003, and October 24, 2006, 1036 participants consented and 877 were randomized (Figure). Four hundred forty-one participants were randomized to receive clopidogrel and 436 to receive placebo. Two participants randomized to the clopidogrel group and 2 participants randomized to the placebo group had placement of a synthetic graft rather than creation of a fistula. These participants discontinued study medication immediately after it was recognized that a fistula was not created. Fistula surgeries were performed at 27 hospitals by 71 surgeons, and dialysis was performed at 125 facilities affiliated with the 9 clinical centers. The median time from surgery to study drug administration was 1.5 hours (10th-90th percentile, 0.2-17 hours). Adherence to study medication was greater than 90% for 87% of participants assigned to clopidogrel and for 86% of participants assigned to placebo.

As shown in Table 1, baseline characteristics of the participants were similar in the 2 treatment groups. Fifty-four percent of the participants received a forearm fistula. Among the upper arm fistulas, 69% were created by an anastomosis between the brachial artery and cephalic vein and 25% were created using the brachial artery and a transposed basilic vein.

Thirty-seven participants (8.4%) in the clopidogrel group and 33 participants (7.6%) in the placebo group discontinued the study medication early. The reasons for early discontinuation of study medication did not differ between treatment groups (Figure). Assessment of fistula patency was performed in 433 participants (98.9%) and 431 participants (98.9%) in the clopidogrel and placebo groups, respectively (Figure).

**Fistula Thrombosis at 6 Weeks**

Among the 866 participants who had patency assessed, the primary outcome of fistula thrombosis at 6 weeks occurred in 53 participants (12.2%) in the clopidogrel group compared with 84 participants (19.5%) in the placebo group (relative risk, 0.63; 95% CI, 0.46-0.97; P = .018) (Table 2). Ten participants in the placebo group and 7 participants in the clopidogrel group had a surgical or percutaneous intervention to restore patency or promote maturation before 6 weeks. There was no significant interaction between fistula location (forearm vs upper arm) and treatment assignment (P = .15). Similarly, there was no significant interaction between clinical center and treatment assignment (P = .57). In sensitivity analyses evaluating extreme best- and worst-case imputation scenarios for the 11 participants (1.3%) without patency assessments, the lower and upper bounds on the possible relative risk associated with clopidogrel ranged between 0.63 and 0.69.

---

**Table 1. Baseline Characteristics**

- **Patients enrolled:** 1036
- **Randomized:** 877
- **Completed study drug treatment:** 400
- **Included in analysis of suitability (primary outcome):** 385
- **Included in analysis of suitability (secondary outcome):** 373
- **Excluded:** 31

**Table 2. Fistula Thrombosis at 6 Weeks**

- **Randomized to receive clopidogrel:** 437
- **Received treatment as assigned:** 431
- **Completed study drug treatment:** 399
- **Included in analysis of patency (primary outcome):** 385
- **Included in analysis of suitability (secondary outcome):** 373

**Figure. Participant Flow Through the Trial**

©2008 American Medical Association. All rights reserved.
**Fistula Suitability for Dialysis**

Fistula suitability was assessed in 758 randomized patients (86.4%) and in 95.8% of those who initiated dialysis soon enough to have suitability assessed (Figure). Of the fistulas assessed for suitability, the percentage with suitability failure did not differ between the clopidogrel group and the placebo group (61.8% vs 59.5%; relative risk, 1.05; 95% CI, 0.94-1.17; P = .40) (Table 3). The estimated relative risk of 1.05 was unchanged in the sensitivity analyses that incorporated imputation for the missing suitability outcomes. Similarly, there was no difference between groups in the percentage with suitability failure when fistulas that were treated with a percutaneous or surgical intervention because of poor maturation were classified as suitability failures (67.5% vs 65.4%; relative risk, 1.04; 95% CI, 0.94-1.15; P = .42).

In both treatment groups, most of the fistula suitability failure outcomes were due to lack of use of the fistula during the ascertainment period, either because the fistula had already been abandoned or because the treating physician thought that it had not yet matured adequately (Table 3). Because of the possibility that our criteria for fistula suitability were too stringent, as a sensitivity analysis we removed the dialysis machine blood flow criteria from the definition of suitability and classified fistulas as suitable solely on the basis of use during 8 dialysis sessions during the suitability ascertainment period. Using this modified definition, the overall fistula suitability failure rate was 49.0% and there was no difference between treatment groups (47.8% in the clopidogrel group vs 52.1% in the placebo group; relative risk, 0.92; 95% CI, 0.81-1.07; P = .30).

**Adverse Events**

Adverse events were similar in the 2 treatment groups (Table 4). In particular, neither the frequency nor the severity of bleeding events was greater among participants treated with clopidogrel than among those who received placebo.

**COMMENT**

We found that clopidogrel reduced the frequency of early thrombosis of new arteriovenous fistulas. The drug was well-tolerated and did not increase bleeding events during a 6-week administration period. The beneficial

---

**Table 1. Baseline Participant Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clopidogrel (n = 441)</th>
<th>Placebo (n = 436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>52.7 (14.7)</td>
<td>54.5 (14.4)</td>
</tr>
<tr>
<td>Male</td>
<td>273 (61.9)</td>
<td>275 (63.1)</td>
</tr>
<tr>
<td>Black</td>
<td>221 (50.1)</td>
<td>201 (46.1)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>30.2 (6.6)</td>
<td>29.3 (7.5)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>141.0 (21.4)</td>
<td>139.9 (21.4)</td>
</tr>
<tr>
<td>Systolic</td>
<td>141.0 (21.4)</td>
<td>139.9 (21.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.8 (13.4)</td>
<td>78.7 (14.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>217 (49.2)</td>
<td>205 (47.0)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>110 (24.9)</td>
<td>107 (24.5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>23 (5.2)</td>
<td>31 (7.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>16 (3.6)</td>
<td>12 (2.7)</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td>12 (2.7)</td>
<td>15 (3.4)</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>103 (23.4)</td>
<td>102 (23.4)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB use</td>
<td>246 (55.8)</td>
<td>262 (60.1)</td>
</tr>
<tr>
<td>Statin use</td>
<td>164 (37.2)</td>
<td>171 (39.2)</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>91 (20.6)</td>
<td>81 (18.6)</td>
</tr>
<tr>
<td>Hemooglobin, mean (SD), g/dL</td>
<td>11.6 (1.8)</td>
<td>11.6 (1.7)</td>
</tr>
<tr>
<td>Serum albumin, mean (SD), g/dL</td>
<td>3.7 (0.6)</td>
<td>3.7 (0.6)</td>
</tr>
<tr>
<td>Preoperative vascular mapping</td>
<td>330 (75.9)</td>
<td>318 (73.8)</td>
</tr>
<tr>
<td>Previous arteriovenous access</td>
<td>79 (17.9)</td>
<td>81 (18.6)</td>
</tr>
<tr>
<td>Hemodialysis initiation before fistula creation</td>
<td>239 (54.2)</td>
<td>233 (53.4)</td>
</tr>
</tbody>
</table>

**Table 2. Fistula Thrombosis**

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Clopidogrel (n = 435)</th>
<th>Placebo (n = 431)</th>
<th>Relative Risk Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis at 6 wks (all patients)</td>
<td>53 (12.2)</td>
<td>84 (19.5)</td>
<td>0.63 (0.46-0.97)</td>
</tr>
<tr>
<td>By location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm fistula</td>
<td>31 (12.9)</td>
<td>60 (24.7)</td>
<td>0.53 (0.36-0.77)</td>
</tr>
<tr>
<td>Upper arm fistula</td>
<td>22 (11.3)</td>
<td>24 (12.8)</td>
<td>0.89 (0.52-1.53)</td>
</tr>
</tbody>
</table>

---

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Adverse events were similar in the 2 treatment groups (Table 4). In particular, neither the frequency nor the severity of bleeding events was greater among participants treated with clopidogrel than among those who received placebo.

**COMMENT**

We found that clopidogrel reduced the frequency of early thrombosis of new arteriovenous fistulas. The drug was well-tolerated and did not increase bleeding events during a 6-week administration period. The beneficial
The proportion of fistulas with suitability failure was substantial and higher than we anticipated. Previous studies, mostly from single centers, have reported fistula maturation failure rates ranging from 18% to 53%. During the period in which the trial was conducted there was an increased emphasis in clinical practice guidelines and by regulatory agencies on creating fistulas rather than synthetic grafts. It is likely that efforts by treating physicians at the participating centers to increase fistula use led to liberalization of selection criteria for fistula creation. We speculate that these changes in criteria for attempting fistula creation contributed to the high rate of fistula suitability failure observed in our trial.

We considered the possibility that our criteria for fistula suitability were too stringent and that a benefit of clopidogrel on suitability would have been apparent had we used a different definition of suitability. However, in a sensitivity analysis that eliminated the dialysis machine blood flow criteria, the suitability failure rate remained high and the proportions of participants with

Table 3. Fistula Suitability Failure

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n = 385)</th>
<th>Placebo (n = 373)</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitability failure (all patients)</td>
<td>230 (61.6)</td>
<td>222 (59.5)</td>
<td>1.05 (0.94-1.17)</td>
</tr>
<tr>
<td>By location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm fistula</td>
<td>144 (66.9)</td>
<td>137 (64.0)</td>
<td>1.05 (0.92-1.20)</td>
</tr>
<tr>
<td>Upper arm fistula</td>
<td>94 (56.3)</td>
<td>85 (53.4)</td>
<td>1.05 (0.87-1.27)</td>
</tr>
<tr>
<td>By failure reason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistula abandoned with no expectation of future use</td>
<td>115 (29.9)</td>
<td>134 (35.9)</td>
<td>0.85 (0.69-1.03)</td>
</tr>
<tr>
<td>Fistula not yet in use despite treatment with dialysis</td>
<td>57 (14.8)</td>
<td>47 (12.6)</td>
<td>1.17 (0.83-1.66)</td>
</tr>
<tr>
<td>Fistula in use during ascertainment period but failed to meet suitability criteria</td>
<td>66 (17.1)</td>
<td>41 (11.0)</td>
<td>1.56 (1.08-2.24)</td>
</tr>
</tbody>
</table>

Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Events</th>
<th>No. (%) of Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n = 441)</td>
<td>Placebo (n = 436)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>67 (15.2)</td>
<td>81 (18.6)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>13 (2.9)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Minor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>6 (1.4)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Major</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>4 (0.9)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>64 (14.5)</td>
<td>77 (17.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3 (0.7)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (1.4)</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (0.2)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Infection</td>
<td>4 (0.9)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Vascular access event: study fistula</td>
<td>5 (1.1)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Vascular access event: nonstudy access</td>
<td>15 (3.4)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.9)</td>
<td>4 (0.9)</td>
</tr>
</tbody>
</table>

©2008 American Medical Association. All rights reserved.

(Reprinted) JAMA, May 14, 2008—Vol 299, No. 18 2169
suitability failure remained similar in the 2 treatment groups. Thus, it is unlikely that the definition of suitability used in the trial masked a benefit of clopidogrel.

It is possible that clopidogrel could indirectly improve fistula suitability by maintaining patency long enough to enable the performance of maturation-enhancing interventions such as percutaneous angioplasty of vessel stenosis or surgical revision of the arteriovenous anastomosis.22-24 Although such procedures were performed in the trial at the discretion of the treating physicians, they were performed on only a small proportion of fistulas; thus, it is possible that a modest beneficial effect of clopidogrel on fistula suitability would have been observed had a more aggressive approach to repairing anatomic lesions been taken.

Our trial has several strengths. It is the first large, multicenter trial evaluating an intervention to improve outcomes of new fistulas and the first trial that includes fistula suitability for dialysis as an outcome. The participants were enrolled from both urban and rural settings and from both academic and community practices in multiple geographic regions within the United States. The treatment groups were balanced with respect to baseline characteristics. Adherence to study medication was good and the primary outcome was assessed in nearly all of the participants.

Our trial has some limitations. We excluded patients taking antiplatelet agents or anticoagulants if they were unable to discontinue the medication, and interventions to enhance fistula maturation failure, criteria for selecting suitable candidates for fistula creation, and interventions to enhance fistula suitability were balanced with respect to baseline characteristics. The performance of fistula suitability failure in this large trial conducted at centers with a particular interest in hemodialysis vascular access provides a compelling argument for additional efforts to identify mechanisms underlying fistula maturation failure, criteria for selecting suitable candidates for fistula creation, and interventions to enhance fistula suitability.

Author Affiliations: Boston University (Drs Dember and Kaufman) and VA Boston Healthcare System (Dr Kaufman), Boston, Massachusetts; Cleveland Clinic Foundation, Cleveland, Ohio (Drs Beck and Gassman and Ms Radeva); University of Alabama at Birmingham (Dr Allon); Washington University in St Louis, St Louis, Missouri (Dr Dembele); University of Iowa, Iowa City (Dr Dixon); Duke University, Durham, North Carolina (Dr Greenberg); Maine Medical Center, Portland (Dr Himmelharp); University of Texas-Southwestern, Dallas (Drs Vazquez and Davidson); University of Utah, Salt Lake City (Dr Greene); Baystate Medical Center, Springfield, Massachusetts (Dr Braden); Vanderbilt University, Nashville, Tennessee (Dr Ikizler); Wake Forest University, Winston-Salem, North Carolina (Dr Rocco); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (Drs Meyers and Kusek); and University of Pennsylvania, Philadelphia (Dr Feldman).

Author Contributions: Dr Beck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dember, Beck, Allon, Delmez, Dixon, Greenberg, Himmelharp, Vazquez, Gassman, Greene, Radeva, Davidson, Kaufman, Meyers, Kusek, Feldman. Acquisition of data: Dember, Beck, Allon, Delmez, Dixon, Greenberg, Himmelharp, Vazquez, Gassman, Greene, Radeva, Davidson, Kaufman, Meyers, Kusek. Analysis and interpretation of data: Demer, Beck, Allon, Delmez, Dixon, Greenberg, Himmelharp, Gassman, Greene, Radeva, Braden, Ikizler, Rocco, Kaufman, Meyers, Kusek, Feldman. Drafting of the manuscript: Dember, Beck. Critical revision of the manuscript for important intellectual content: Dember, Beck, Allon, Delmez, Dixon, Greenberg, Himmelharp, Vazquez, Gassman, Greene, Radeva, Braden, Ikizler, Rocco, Kaufman, Meyers, Kusek, Feldman. Administrative, technical, or material support: Dember, Beck, Delmez, Dixon, Greenberg, Davidson, Meyers, Kusek, Feldman. Study supervision: Dember, Beck, Allon, Delmez, Dixon, Greenberg, Himmelharp, Vazquez, Gassman, Greene, Radeva, Braden, Ikizler, Rocco, Davidson, Kaufman, Meyers, Kusek, Feldman.

Financial Disclosures: Dr Dember reports having received consulting fees from Proteon Therapeutics. Dr Allon reports having received consulting fees from Arrow International. Dr Dixon reports having received consulting fees from Proteon Therapeutics and Provasis Therapeutics. Dr Greenberg reports having received consulting fees from Sanofi-Synthelabo. Dr Kaufman reports having received consulting fees from Proteon Therapeutics. Dr Kusek reports that he owns stock in Pfizer, Lilly, and Decode Genetics. Dr Feldman reports having received grant support from Amgen, Hoffman La Roche, General Electric, and Watson Pharmaceuticals; having received consulting fees from Kirin Pharmaceuticals; and having provided expert testimony for General Electric. No other disclosures were reported.

Funding/Support: The trial was funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (grants U01DK058986, U01DK059882, U01DK058968, U01DK058978, U01DK058978, U01DK058985, U01DK058966, and U01DK058973). Study drug was donated by Sanofi-Synthelabo, Ambarès, France.

Role of the Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases project officers (Drs Meyers and Kusek) worked collaboratively with the investigators and members of the data coordinating center in designing the study, monitoring the study performance, interpreting data, and preparing the manuscript. The drug manufacturer had no involvement in designing or conducting the study, analyzing or interpreting the data, or preparing the article.

CLOPIDOGREL AND EARLY FAILURE OF ARTERIOVENOUS FISTULAS FOR HEMODIALYSIS

K. Welch, F. Darrau, B. Banerero, B. Ketel, A. Wounded Arrow, C. Grant, J. Deep, L. Pyszka; University of Texas-Southwestern; M. Vazquez, I. Davidson, R. Toto, L. Littmon, C. Ying, T. Lightfoot, H. Quinones, R. Saxena, P. Clagett, J. Valentine, B. Dolmatch, J. Thompson; Baylor University Medical Center; A. Feneves, G. Pearl; Vanderbilt University Medical Center; T. Kizler, P. Egbert; Wake Forest University; M. Rocco, P. Daehnagh, A. Tuttley, V. Mauck, T. Hooiser, D. McInr; Washington University in St Louis; J. Delmez, D. Win- dus, D. Coyne, M. Rothstein, S. Shenoy, R. Creagh- an, B. Luka; National Institute of Diabetes and Digestive and Kidney Diseases; J. Kusek, C. Meyers; Steering Committee Chair: H. Feldman (University of Pennsylvania); Data Coordinating Center (Cleveland Clinic Foundation): G. Beck, J. Gassman, T. Greene, B. Hu, S. Bi, A. Liu, M. Radeva, L. Tuason, B. Weiss; Data and Safety Monitoring Board: N. Levin (chair), A. Besarab, G. Chertow, M. Diener-West, T. Louis, W. McClellan, C. Stelmahan-Breen.

Previous Presentation: The findings of this trial were presented at the annual meeting of the American Society of Nephrology; November 7, 2007; San Francisco, California.

Additional Contributions: We are grateful to the participating patients, to our colleagues who referred patients for enrollment, and to the dialysis unit staff members who facilitated conduct of the trial.

REFERENCES


©2008 American Medical Association. All rights reserved.