Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

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BACKGROUND

Dual antiplatelet therapy with clopidogrel plus low-dose aspirin has not been studied in a broad population of patients at high risk for atherothrombotic events.

METHODS

We randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

RESULTS

The rate of the primary efficacy end point was 6.8 percent with clopidogrel plus aspirin and 7.3 percent with placebo plus aspirin (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; P = 0.22). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7 percent and 17.9 percent (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; P = 0.04), and the rate of severe bleeding was 1.7 percent and 1.3 percent (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61 percent; P = 0.09). The rate of the primary end point among patients with multiple risk factors was 6.6 percent with clopidogrel and 5.5 percent with placebo (relative risk, 1.2; 95 percent confidence interval, 0.91 to 1.59; P = 0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9 percent vs. 2.2 percent, P = 0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9 percent with clopidogrel and 7.9 percent with placebo (relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P = 0.046).

CONCLUSIONS

In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. (ClinicalTrials.gov number, NCT00050817.)
ATHROSCLOTIC VASCULAR DISEASE has a propensity to engender arterial thrombosis, a sequence that has been characterized as an “atherothrombotic” process. Collectively, atherothrombotic disorders of the coronary, cerebrovascular, and peripheral arterial circulation are the leading cause of death and disability in the world. Their prevalence is increasing; they are significantly undertreated, and better means of prevention are needed.

Platelets have been shown to play a central role in the pathogenesis of atherothrombosis. Low-dose aspirin has been shown to reduce ischemic outcomes in patients above a certain risk threshold. However, aspirin alone in many instances is not sufficient to prevent ischemic events in patients at high risk. Furthermore, aspirin inhibits only the cyclooxygenase pathway, leaving the adenosine diphosphate P2Y12 receptor unaffected. Dual antiplatelet therapy with clopidogrel (Plavix, Sanofi-Aventis), a P2Y12-receptor antagonist, plus aspirin has been shown to reduce ischemic events in patients with unstable angina, myocardial infarction without ST-segment elevation, or myocardial infarction with ST-segment elevation, as well as those undergoing angioplasty and stenting.

Accordingly, we tested the hypothesis that long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk.

METHODS

TRIAL DESIGN

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was a prospective, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of clopidogrel plus aspirin as compared with aspirin alone in patients at high risk for a cardiovascular event. The details of the trial design have been published previously. The trial was approved by the institutional ethics committee of each participating institution as well as the appropriate national ethics committees.

The trial was designed by Dr. Topol, who was responsible for obtaining funding and executing the trial, and it was planned and conducted by the executive committee, with extensive review of the data for its interpretation. The trial was managed by the Cleveland Clinic Cardiovascular Coordinating Center and by the national coordinators in each country in which patients were enrolled. Data collection and entry were performed by the sponsor and cosponsor. The locked, cleaned database was transferred to the Cleveland Clinic Cardiovascular Coordinating Center, where data analysis was performed. Dr. Bhatt prepared the first draft of the manuscript, and the executive committee helped to revise it. Dr. Topol had full access to an independent database for any query regarding the analyses and assumes responsibility for the integrity of the data.

Funding for the CHARISMA trial was provided by Sanofi-Aventis and Bristol-Myers Squibb. The sponsor and cosponsor had advisory input in the design of the study, had nonvoting input in the executive committee, and were responsible for auditing at individual study sites. The executive committee bears complete responsibility for the analysis of the results, the veracity and completeness of the reporting, and the writing of the manuscript; the sponsors did have the opportunity to review the manuscript.

PATIENTS

Patients were eligible to enroll in the trial if they were 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. The inclusion criteria for those with multiple risk factors and for those with established vascular disease are shown in Table 1.

Patients were excluded from the trial if they were taking oral antithrombotic medications or nonsteroidal antiinflammatory drugs on a long-term basis (although cyclooxygenase-2 inhibitors were permitted). Patients were also excluded if, in the judgment of the investigator, they had established indications for clopidogrel therapy (such as a recent acute coronary syndrome). Patients who were scheduled to undergo a revascularization were not allowed to enroll until the procedure had been completed; such patients were excluded if they were considered to require clopidogrel after revascularization.

TRIAL PROCEDURES

After providing written informed consent, patients were randomly assigned either to clopidogrel (75 mg per day) plus low-dose aspirin (75 mg per day) or to placebo plus aspirin (80 mg per day). Patients were enrolled in the study after undergoing a diagnostic catheterization and if they were considered to require acute intervention. After diagnostic catheterization, patients were randomized to one of the two treatment groups. No significant differences between the groups were noted in terms of baseline characteristics; however, patients assigned to the treatment group were more likely to have diabetes mellitus and to have had a coronary intervention or previous stroke.

All patients were started on aspirin 325 mg per day, with or without a different dose of aspirin on an as-needed basis, and were maintained on this dosage throughout the trial. The median duration of treatment was 16 months, with a range of 0 to 32 months.

The primary end point of the trial was the occurrence of a major vascular event, defined as a composite of cardiovascular death, nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or hospitalization for stable angina requiring antianginal therapy.

The incidence of major vascular events in the treatment and placebo groups was comparable, with 7.3% versus 7.5%, respectively, at 1 year and 11.6% versus 11.8%, respectively, at 2 years. The relative risk reduction for the primary end point was 5% (95% confidence interval, 1% to 12%; P=0.075; adjusted for prespecified risk factors).

The results of the CHARISMA trial suggest that dual antiplatelet therapy with clopidogrel plus aspirin is not superior to aspirin alone in patients at high risk for cardiovascular disease. However, further studies are needed to determine the role of dual antiplatelet therapy in high-risk patients.
162 mg per day) or to placebo plus low-dose aspirin. Study-drug assignment was performed centrally by an interactive voice-response system on the basis of a preestablished randomization scheme, stratified according to site. All patients also received standard therapy as appropriate (e.g., statins or beta-blockers) at the discretion of the investigator and other responsible clinicians. The use of appropriate background therapy was emphasized to the investigators, who were provided with international guidelines.

Follow-up evaluations were performed at one month, three months, and six months and every six months thereafter until the end of the trial. At these visits, patients’ compliance was assessed, standard medication was adjusted as appropriate, and all interventions, outcome events, and adverse events were recorded. According to the power calculations described below and the event-driven design of the trial, all patients were followed until a common study end date based on the pre-specified target of 1040 primary efficacy endpoints was reached.
END POINTS
All primary trial end points were adjudicated by the clinical events committee, whose members were unaware of patients’ treatment assignments. The primary efficacy end point was the first occurrence of myocardial infarction, stroke (of any cause), or death from cardiovascular causes (including hemorrhage). The principal secondary efficacy end point was the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral). Other efficacy end points included death from any cause and death from cardiovascular causes as well as myocardial infarction, ischemic stroke, any stroke, and hospitalization for unstable angina, transient ischemic attack, or revascularization, considered separately.

The primary safety end point was severe bleeding, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition, which includes fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, isotropic support, or surgical intervention. Moderate bleeding according to the GUSTO criteria (bleeding that led to transfusion but did not meet the criteria for severe bleeding) was also examined, as were fatal bleeding and primary intracranial hemorrhage.

Analyses of the primary end point were also performed in several prospectively defined subgroups. The subgroups included asymptomatic patients (defined as patients enrolled on the basis of established cardiovascular disease) as compared with symptomatic patients (those enrolled on the basis of multiple atherothrombotic risk factors), as well as patients with and those without a history of diabetes, hypertension, hypercholesterolemia, peripheral arterial disease, prior cardiac or vascular surgery, prior myocardial infarction, prior stroke, prior transient ischemic attack, or prior use of other antiplatelet agents, angiotensin-converting–enzyme (ACE) inhibitors (overall and ramipril vs. other ACE inhibitors), statins (overall and atorvastatin, simvastatin, and pravastatin), beta-blockers, calcium antagonists, antidiabetic agents, angiotensin II–receptor blockers, cyclooxygenase-2 inhibitors, and anticoagulants.

STATISTICAL ANALYSIS
We estimated that 15,200 patients (7600 per group) and 1040 primary events would be necessary to detect a 20 percent relative risk reduction in the primary efficacy end point, with 90 percent power at the two-sided 0.05 significance level in this event-driven trial, assuming an annual event rate of 3.1 percent in the control group and 18 to 42 months of follow-up. The primary efficacy outcome was monitored with use of a Peto–Haybittle type of stopping rule based on the P value of the log-rank test. Two preplanned interim analyses were conducted by a statistician associated with the independent data and safety monitoring board. A two-sided type I error of 0.001 was used at each analysis. A type I error of 0.049 was preserved for the final analysis.

Data were analyzed on an intention-to-treat basis, with the inclusion of all patients according to their randomly assigned treatment group and the inclusion of outcomes occurring from randomization to a common study end date (August 29, 2005). The time to the first occurrence of any event in the composite cluster was used for analysis. Data on patients who did not reach the primary end point by the study end date were censored on the date of the patients’ last assessment visit. Death from noncardiovascular causes was treated as a competing event, and follow-up was censored on the date of death.

The primary efficacy of clopidogrel as compared with placebo was assessed with the use of a two-sided log-rank test. The treatment effect as measured by the hazard ratio (the relative risk) and its associated 95 percent confidence interval was estimated with the use of the Cox proportional-hazards model. Cumulative incidence event curves were also calculated. Statistical comparisons of the primary safety-event rates in the two treatment groups were performed with Pearson’s chi-square test. No adjustments for multiple comparisons were made. All analyses were performed with SAS software (version 8.0, SAS Institute).

RESULTS
CHARACTERISTICS OF THE PATIENTS
A total of 15,603 patients from 32 countries and 768 sites were enrolled between October 1, 2002, and November 14, 2003, in the CHARISMA trial. Of these patients, 7802 were assigned to receive
clopidogrel plus aspirin and 7801 were assigned to receive placebo plus aspirin. Treatment was permanently discontinued by 20.4 percent of the patients in the clopidogrel group, as compared with 18.2 percent in the placebo group (P<0.001). A total of 4.8 percent of the patients in the clopidogrel group and 4.9 percent of those in the placebo group discontinued treatment because of an adverse event (P=0.67).

The baseline characteristics of the patients in the trial have been described previously, and selected features are listed in Table 2. The median age was 64 years; 29.8 percent of the patients were women. More than three quarters of the participants had established cardiovascular disease, as defined by the enrollment criteria, and most of the remaining patients had multiple atherothrombotic risk factors. On retrospective review of the enrollment information, 166 patients did not fall into either of these categories but were still considered in the broad population analysis.

Medications taken by the patients are shown in Table 3; these figures indicate the maximal frequency of use of each agent at any time during the trial (with use assessed at baseline and at every follow-up visit). Almost all the patients (aside from those who died or dropped out) took aspirin and the study drug, and 10.2 percent also took open-label clopidogrel. Three quarters took a statin, and more than half took a beta-blocker. Nearly two thirds took an ACE inhibitor, and a quarter took angiotensin II–receptor blocking agents.

**Efficacy End Points**

Follow-up with respect to the primary efficacy end point (the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes) was complete in 99.5 percent of the patients randomly assigned to receive clopidogrel and aspirin and 99.6 percent of those randomly assigned to receive placebo and aspirin. The efficacy results are shown in Table 4. With a median of 28 months of follow-up, the rate of the primary event was 6.8 percent in the clopidogrel group and 7.3 percent in the placebo group (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; P=0.22) (Fig. 1A). The rate of the principal secondary efficacy end point (the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, transient ischemic attack, or a revascularization procedure) was 16.7 percent in the clopidogrel group, as compared with 17.9 percent in the placebo group (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; P=0.04) (Fig. 1B).
SAFETY END POINTS
The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 1.7 percent in the clopidogrel group and 1.3 percent in the placebo group (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61; P=0.09). The rate of moderate bleeding was 2.1 percent in the clopidogrel group, as compared with 1.3 percent in the placebo group (relative risk, 1.62; 95 percent confidence interval, 1.27 to 2.08; P<0.001). The rate of intracranial hemorrhage was similar in the two treatment groups (Table 4).

There was one documented nonfatal case of thrombotic thrombocytopenic purpura among the clopidogrel-treated patients; this patient died one month later from end-stage chronic obstructive pulmonary disease. No other serious adverse events were reported.

SUBGROUP ANALYSES
Several prespecified subgroup analyses classified patients according to their criteria for enrollment (Fig. 2). Patients who were enrolled because they had documented cardiovascular disease were designated “symptomatic,” whereas those who were enrolled because they had multiple atherothrombotic risk factors without documented cardiovascular disease were designated “asymptomatic.” (Some of the latter patients had a reported history of cardiovascular events, including 10.4 percent with a prior myocardial infarction, 5.8 percent with a prior stroke, 5.2 percent with a prior transient ischemic attack, 7.7 percent who had undergone a percutaneous coronary intervention, and 9.8 percent who had undergone coronary-artery bypass grafting, although they did not meet the inclusion criteria for established cardiovascular disease as outlined in Table 1.)

Among the 3284 asymptomatic patients, there was a 20 percent relative increase in the rate of primary events with clopidogrel (6.6 percent, vs. 5.5 percent with placebo; P=0.20), whereas among the 12,153 symptomatic patients, there was a marginally significant reduction in the primary end point with clopidogrel (6.9 percent, vs. 7.9 percent with placebo; relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P=0.046). The interaction term for this analysis, when the differential treatment response in asymptomatic and symptomatic patients was examined, was marginally significant (P=0.045).

In the subgroup of asymptomatic patients, there was a significant increase in the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as compared with those assigned to placebo plus aspirin (5.4 percent vs. 3.8 percent, P=0.04) as well as an increase in the rate of death from cardiovascular causes among those assigned to clopidogrel (3.9 percent vs. 2.2 percent, respectively; P=0.01). In contrast, clopidogrel had no significant effect on death from cardiovascular causes in the symptomatic subgroup.

The rates of GUSTO-defined severe bleeding among the asymptomatic patients were 2.0 percent

### Table 3. Concomitant Medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clopidogrel plus Aspirin (N = 7802)</th>
<th>Placebo plus Aspirin (N = 7801)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>7775 (99.7)</td>
<td>7777 (99.7)</td>
</tr>
<tr>
<td>Study drug</td>
<td>7750 (99.3)</td>
<td>7760 (99.5)</td>
</tr>
<tr>
<td>Open-label clopidogrel</td>
<td>773 (9.9)</td>
<td>814 (10.4)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3757 (48.2)</td>
<td>3671 (47.1)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1812 (23.2)</td>
<td>1877 (24.1)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>2866 (36.7)</td>
<td>2879 (36.9)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4292 (55.0)</td>
<td>4344 (55.7)</td>
</tr>
<tr>
<td>Angiotensin II–receptor blockers</td>
<td>1990 (25.5)</td>
<td>2020 (25.9)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1387 (17.8)</td>
<td>1424 (18.3)</td>
</tr>
<tr>
<td>Other angiotensin-converting–enzyme inhibitors</td>
<td>3607 (46.2)</td>
<td>3612 (46.3)</td>
</tr>
<tr>
<td>Other antihypertensive agents</td>
<td>966 (12.4)</td>
<td>968 (12.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>5991 (76.8)</td>
<td>6001 (76.9)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>2777 (35.6)</td>
<td>2808 (36.0)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>2672 (34.2)</td>
<td>2695 (34.5)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>976 (12.5)</td>
<td>953 (12.2)</td>
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<td>Fluvastatin</td>
<td>260 (3.3)</td>
<td>234 (3.0)</td>
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<tr>
<td>Lovastatin</td>
<td>273 (3.5)</td>
<td>283 (3.6)</td>
</tr>
<tr>
<td>Other statins</td>
<td>474 (6.1)</td>
<td>458 (5.9)</td>
</tr>
<tr>
<td>Other lipid-lowering agents</td>
<td>1114 (14.3)</td>
<td>1094 (14.0)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>678 (8.7)</td>
<td>654 (8.4)</td>
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<tr>
<td>Binding resins</td>
<td>338 (4.3)</td>
<td>313 (4.0)</td>
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<tr>
<td>Nicotinic acid</td>
<td>277 (3.6)</td>
<td>262 (3.4)</td>
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<td>Antidiabetic medications</td>
<td>3259 (41.8)</td>
<td>3237 (41.5)</td>
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<td>Insulin</td>
<td>1360 (17.4)</td>
<td>1334 (17.1)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>624 (8.0)</td>
<td>634 (8.1)</td>
</tr>
<tr>
<td>Other oral hypoglycemic agents</td>
<td>2677 (34.3)</td>
<td>2678 (34.3)</td>
</tr>
</tbody>
</table>

* These values indicate the maximal frequency of use of each agent at any time during the trial (assessed at baseline and at every follow-up visit).
with clopidogrel and 1.2 percent with placebo \( (P=0.07) \); the corresponding rates among the symptomatic patients were 1.6 percent and 1.4 percent \( (P=0.39) \). Although both these differences favored the placebo group, neither was significant. The rates of GUSTO-defined moderate bleeding among asymptomatic patients were increased (2.2 percent with clopidogrel and 1.4 percent with placebo, \( P=0.08 \)), as were the rates of moderate bleeding among symptomatic patients (2.1 percent and 1.3 percent, respectively; \( P<0.001 \)). Again, both differences favored the placebo group, but this difference was significant only among the symptomatic patients.

### DISCUSSION

In this trial of patients with established atherothrombotic disease or at high risk for such disease, there was no significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary end point of myocardial infarction, stroke, or death from cardiovascular causes. There was a moderate, though significant, benefit in reducing the secondary composite end point of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, transient ischemic attack, or revascularization.

The rate of severe bleeding was not significantly greater with clopidogrel than with placebo, but a trend prompting concern was noted, and clopidogrel was associated with a significant increase in the rate of moderate bleeding. A total of 94 ischemic (secondary) end points were prevented with clopidogrel, at a cost of 93 moderate or severe bleeding events.

The patients in our trial received evidence-based pharmacologic treatment, with frequent use of concomitant statins, ACE inhibitors, and other background medical therapy. The incidence of the primary end point with such therapy, as predicted, was approximately 3 percent per year.

In the original, large-scale Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,\(^1^3\) clopidogrel alone was found to
be superior to aspirin alone in reducing the risk of ischemic stroke, myocardial infarction, or death from vascular causes. However, there was debate as to whether P2Y<sub>12</sub>-receptor blockade provided uniform benefit. Since CAPRIE, four large clinical trials have added to the body of evidence that supports the use of dual antiplatelet therapy in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention. CHARISMA represented the logical next step of evaluation of the potential role of this approach in a broad population of patients with established vascular disease or multiple cardiovascular risk factors.

A subgroup analysis suggested that clopidogrel was beneficial with respect to the primary efficacy end point in patients who were classified as symptomatic for the purposes of the trial (i.e., who were enrolled because of a documented history of established vascular disease). However, the P value for this association and the P value for the interaction between enrollment status and therapy were only marginally significant, suggesting that this observation should be interpreted with caution, especially since this subgroup analysis was only one of several such analyses performed. Furthermore, the risk of moderate or severe bleeding in symptomatic patients was greater with clopidogrel than with placebo, although there was no significant increase in intracranial or fatal bleeding. Finally, as a practical matter, it is unclear how such a classification could be implemented clinically, since some patients in the asymptomatic subgroup actually had a history of symptoms or cardiovascular events. The issue of whether dual antiplatelet therapy is beneficial in more specific subgroups of the population of patients with atherothrombotic disease or risk will require further study.

On the other hand, the risk associated with dual antiplatelet therapy in the asymptomatic group was not anticipated. The excess fatalities in this subgroup and the heightened risk of bleeding complications suggest that we should be cautious about too quickly dismissing this unexpected finding as the play of chance. It is possible that established vascular disease represents a crude proxy for hyperactive platelets. If this concept is accepted, dual antiplatelet therapy would be anticipated to be associated with greater efficacy and a lower rate of bleeding in the subgroup of symptomatic patients. However, reduced basal platelet activity in asymptomatic patients would be expected to be a liability, increasing the risk of bleeding complications, including possible hemorrhage into an arterial plaque. Whatever the explanation, it appears that until proven otherwise, clinicians should avoid dual antiplatelet therapy in patients without established vascular disease.

Recent studies of the genomics of myocardial

**Figure 1. Cumulative Incidence of the Primary End Point (Panel A) and of the Secondary End Point (Panel B).**

Panel A shows cumulative incidence curves for the primary end point of myocardial infarction, stroke, or death from cardiovascular causes. Cumulative incidence curves are displayed only up to 30 months because the uncertainty of the estimates beyond this point becomes quite large. The number of patients followed after 30 months decreases rapidly to zero, and only 21 primary efficacy events occurred after this time (13 in the clopidogrel group and 8 in the placebo group). Panel B shows cumulative incidence curves for the secondary end point, which included hospitalizations.
Figure 2. Hazard Ratios for Myocardial Infarction (MI), Stroke, or Death from Cardiovascular Causes in Each of the Subgroups Examined.

Hazard ratios are shown with their 95 percent confidence intervals. The sizes of the symbols are roughly proportional to the number of patients in the analysis. Body-mass index is the weight in kilograms divided by the square of the height in meters. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

In summary, the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. Furthermore, the risk of moderate-to-severe bleeding was increased. Our findings do not support the use of dual antiplatelet therapy across the broad population tested. There was a potential benefit in symptomatic patients (those with established vascular disease); this finding requires further study. Data on mortality rates suggest that dual antiplatelet therapy should not be used in patients without a history of established vascular disease.
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