

ORIGINAL ARTICLE

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

Deepak L. Bhatt, M.D., Keith A.A. Fox, M.B., Ch.B., Werner Hacke, M.D., Peter B. Berger, M.D., Henry R. Black, M.D., William E. Boden, M.D., Patrice Cacoub, M.D., Eric A. Cohen, M.D., Mark A. Creager, M.D., J. Donald Easton, M.D., Marcus D. Flather, M.D., Steven M. Haffner, M.D., Christian W. Hamm, M.D., Graeme J. Hankey, M.D., S. Claiborne Johnston, M.D., Koon-Hou Mak, M.D., Jean-Louis Mas, M.D., Gilles Montalescot, M.D., Ph.D., Thomas A. Pearson, M.D., P. Gabriel Steg, M.D., Steven R. Steinhubl, M.D., Michael A. Weber, M.D., Danielle M. Brennan, M.S., Liz Fabry-Ribaudou, M.S.N., R.N., Joan Booth, R.N., and Eric J. Topol, M.D., for the CHARISMA Investigators*

From Cleveland Clinic, Cleveland (D.L.B., D.M.B., L.F.-R., J.B.); University and Royal Infirmary of Edinburgh, Edinburgh (K.A.A.F.); University of Heidelberg, Heidelberg, Germany (W.H.); Duke University, Durham, N.C. (P.B.B.); Rush Medical College, Chicago (H.R.B.); Hartford Hospital, Hartford, Conn. (W.E.B.); Hôpital Pitié-Salpêtrière (P.C.), Sainte-Anne Hospital (J.-L.M.), Institut de Cardiologie-CHU Pitié-Salpêtrière (G.M.), and Hôpital Bichat (P.G.S.) — all in Paris; Sunnybrook and Women's College Health Science Centre, Toronto (E.A.C.); Brigham and Women's Hospital and Harvard Medical School, Boston (M.A.C.); Rhode Island Hospital and Brown University, Providence (J.D.E.); Royal Brompton Hospital, London (M.D.F.); University of Texas Health Science Center at San Antonio, San Antonio (S.M.H.); Kerckhoff-Klinik Center, Bad Nauheim, Germany (C.W.H.); Royal Perth Hospital and School of Medicine and Pharmacology, University of Western Australia, Perth (G.J.H.); University of California, San Francisco, San Francisco (S.C.J.); Gleneagles Medical Centre, Singapore (K.-H.M.); University of Rochester School of Medicine, Rochester, N.Y. (T.A.P.); University of Kentucky, Lexington (S.R.S.); SUNY Downstate Medical Center, Brooklyn, N.Y. (M.A.W.); and Case Western Reserve University, Cleveland (E.J.T.). Address reprint requests to Dr. Topol at the Department of Genetics, Case Western Reserve University, BRB 724, 10900 Euclid Ave., Cleveland, OH 44106-4955, or at eric.topol@case.edu.

*The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) committees, national coordinators, and investigators are listed in the Appendix.

This article was published at www.nejm.org on March 12, 2006.

N Engl J Med 2006;354:1706-17.

Copyright © 2006 Massachusetts Medical Society.

ABSTRACT

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.)

ATHEROSCLEROTIC VASCULAR DISEASE has a propensity to engender arterial thrombosis, a sequence that has been characterized as an “atherothrombotic” process.^{1,2} Collectively, atherothrombotic disorders of the coronary, cerebrovascular, and peripheral arterial circulation are the leading cause of death and disability in the world.³ Their prevalence is increasing; they are significantly undertreated, and better means of prevention are needed.⁴

Platelets have been shown to play a central role in the pathogenesis of atherothrombosis.^{1,2} Low-dose aspirin has been shown to reduce ischemic outcomes in patients above a certain risk threshold.⁵ 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.⁶⁻⁹

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.¹⁰ 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 to

Table 1. Inclusion Criteria for Patients with Multiple Atherothrombotic Risk Factors and for Those with Established Cardiovascular Disease.

Patients and Criteria	Clopidogrel plus Aspirin	Placebo plus Aspirin
	<i>no. of patients (%)</i>	
Patients with multiple atherothrombotic risk factors*	1659	1625
Major risk factors	1535 (92.5)	1490 (91.7)
Type 1 or 2 diabetes (with drug therapy)	1360 (82.0)	1295 (79.7)
Diabetic nephropathy	716 (43.2)	687 (42.3)
Ankle–brachial index <0.9	94 (5.7)	92 (5.7)
Asymptomatic carotid stenosis ≥70% of luminal diameter	123 (7.4)	132 (8.1)
≥1 Carotid plaque, as evidenced by intima–media thickness	198 (11.9)	213 (13.1)
Minor risk factors	1474 (88.8)	1454 (89.5)
Systolic blood pressure ≥150 mm Hg, despite therapy for at least 3 mo	809 (48.8)	744 (45.8)
Primary hypercholesterolemia	993 (59.9)	1030 (63.4)
Current smoking >15 cigarettes/day	284 (17.1)	271 (16.7)
Male sex and age ≥65 yr or female sex and age ≥70 yr	841 (50.7)	853 (52.5)
Patients with established cardiovascular disease†	6062	6091
Documented coronary disease	2892 (47.7)	2943 (48.3)
Angina with documented multivessel coronary disease	888 (14.6)	885 (14.5)
History of multivessel percutaneous coronary intervention	398 (6.6)	434 (7.1)
History of multivessel coronary-artery bypass grafting	736 (12.1)	733 (12.0)
Myocardial infarction	1903 (31.4)	1943 (31.9)
Documented cerebrovascular disease	2157 (35.6)	2163 (35.5)
Transient ischemic attack during previous 5 yr	617 (10.2)	616 (10.1)
Ischemic stroke during previous 5 yr	1634 (27.0)	1611 (26.4)
Documented symptomatic peripheral arterial disease	1418 (23.4)	1420 (23.3)
Current intermittent claudication and ankle–brachial index ≤0.85	885 (14.6)	892 (14.6)
History of intermittent claudication and previous intervention (e.g., amputation, peripheral bypass, or angioplasty)	835 (13.8)	801 (13.2)

* Data on the other 166 patients enrolled but not categorized were not adequately differentiated on the basis of medical records. To meet the criterion for enrollment on the basis of multiple risk factors, patients were required to have two major or three minor or one major and two minor atherothrombotic risk factors.

† To meet the criterion for enrollment on the basis of established cardiovascular disease, patients were required to have one of the listed conditions.

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 end points 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, inotropic support, or surgical intervention.¹¹ 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 symptomatic patients (defined as patients enrolled on the basis of established cardiovascular disease) as compared with asymptomatic 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

Table 2. Baseline Characteristics.

Characteristic	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)
Demographic characteristics		
Age — yr		
Median	64.0	64.0
Range	39.0–95.0	45.0–93.0
Female sex — no. (%)	2316 (29.7)	2328 (29.8)
Race or ethnic group — no. (%)*		
White	6272 (80.4)	6230 (79.9)
Hispanic	776 (9.9)	837 (10.7)
Asian	387 (5.0)	388 (5.0)
Black	252 (3.2)	234 (3.0)
Other	115 (1.5)	112 (1.4)
Inclusion subgroup		
Documented vascular disease — no. (%)	6062 (77.7)	6091 (78.1)
Multiple risk factors — no. (%)	1659 (21.3)	1625 (20.8)
Neither subgroup — no. (%)	81 (1.0)	85 (1.1)
Selected clinical characteristics		
Smoking status — no. (%)		
Current	1571 (20.1)	1584 (20.3)
Former	3811 (48.9)	3802 (48.7)
Hypertension — no. (%)	5719 (73.3)	5764 (73.9)
Hypercholesterolemia — no. (%)	5748 (73.7)	5787 (74.2)
Congestive heart failure — no. (%)	469 (6.0)	457 (5.9)
Prior myocardial infarction — no. (%)	2672 (34.2)	2725 (34.9)
Atrial fibrillation — no. (%)	298 (3.8)	285 (3.7)
Prior stroke — no. (%)	1942 (24.9)	1895 (24.3)
Prior transient ischemic attack — no. (%)	938 (12.0)	926 (11.9)
Diabetes — no. (%)	3304 (42.3)	3252 (41.7)
Peripheral arterial disease — no. (%)	1760 (22.6)	1771 (22.7)
Prior percutaneous coronary intervention — no. (%)	1750 (22.4)	1804 (23.1)
Prior coronary-artery bypass grafting — no. (%)	1525 (19.5)	1554 (19.9)
Prior carotid endarterectomy	420 (5.4)	405 (5.2)
Prior peripheral angioplasty or bypass — no. (%)	879 (11.3)	858 (11.0)
Diabetic nephropathy — no. (%)	1006 (12.9)	1003 (12.9)

* Race or ethnic group was self-reported.

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,¹² 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

Table 3. Concomitant Medications.*

Medication	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)
	no. of patients (%)	
Aspirin	7775 (99.7)	7777 (99.7)
Study drug	7750 (99.3)	7760 (99.5)
Open-label clopidogrel	773 (9.9)	814 (10.4)
Diuretics	3757 (48.2)	3671 (47.1)
Nitrates	1812 (23.2)	1877 (24.1)
Calcium antagonists	2866 (36.7)	2879 (36.9)
Beta-blockers	4292 (55.0)	4344 (55.7)
Angiotensin II–receptor blockers	1990 (25.5)	2020 (25.9)
Ramipril	1387 (17.8)	1424 (18.3)
Other angiotensin-converting–enzyme inhibitors	3607 (46.2)	3612 (46.3)
Other antihypertensive agents	966 (12.4)	968 (12.4)
Statins	5991 (76.8)	6001 (76.9)
Atorvastatin	2777 (35.6)	2808 (36.0)
Simvastatin	2672 (34.2)	2695 (34.5)
Pravastatin	976 (12.5)	953 (12.2)
Fluvastatin	260 (3.3)	234 (3.0)
Lovastatin	273 (3.5)	283 (3.6)
Other statins	474 (6.1)	458 (5.9)
Other lipid-lowering agents	1114 (14.3)	1094 (14.0)
Fibrates	678 (8.7)	654 (8.4)
Binding resins	338 (4.3)	313 (4.0)
Nicotinic acid	277 (3.6)	262 (3.4)
Antidiabetic medications	3259 (41.8)	3237 (41.5)
Insulin	1360 (17.4)	1334 (17.1)
Thiazolidinediones	624 (8.0)	634 (8.1)
Other oral hypoglycemic agents	2677 (34.3)	2678 (34.3)

* 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).

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 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Efficacy end points				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

* CI denotes confidence interval.

† The 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).

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 atherosclerotic 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.

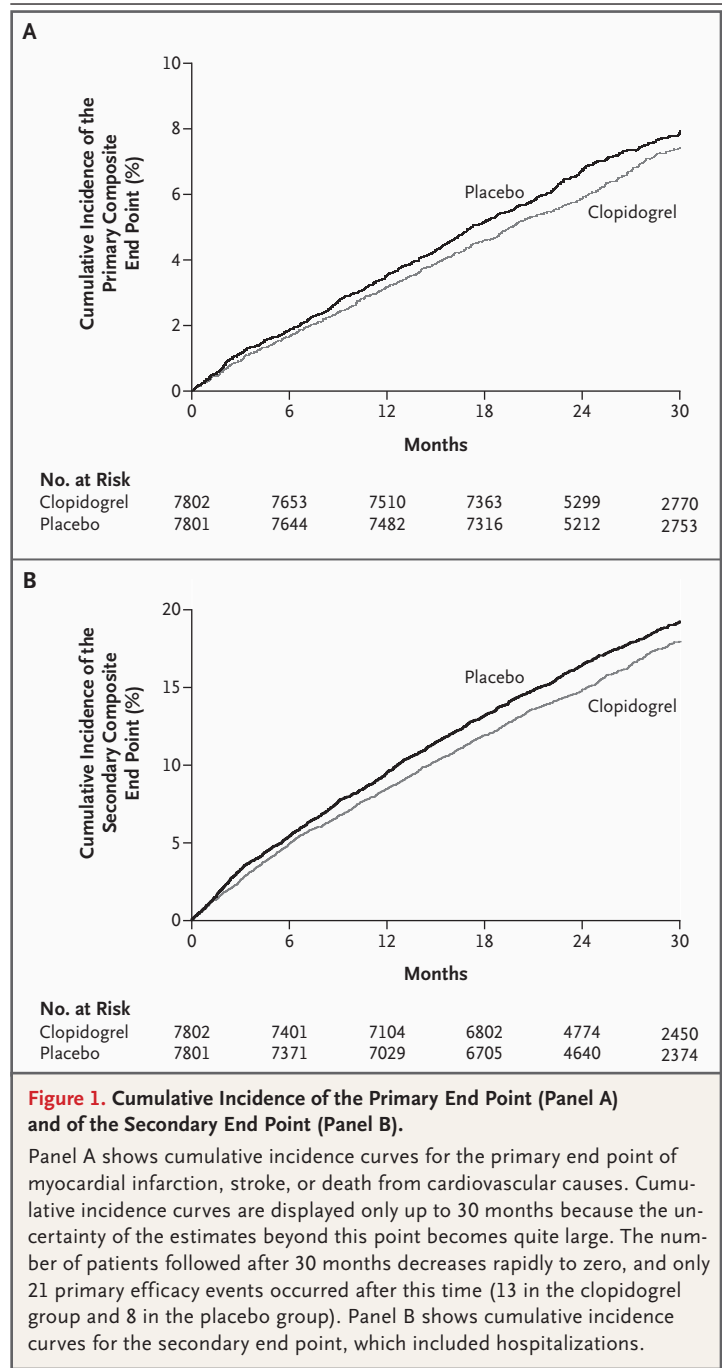
The patients in our trial received evidence-based pharmacologic treatment, with frequent use of concomitant statins, ACE inhibitors, and other background medical therapy. The incidence of the primary end point with such therapy, as predicted, was approximately 3 percent per year.

In the original, large-scale Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,¹³ 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 P2Y₁₂-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.⁶⁻⁹ 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

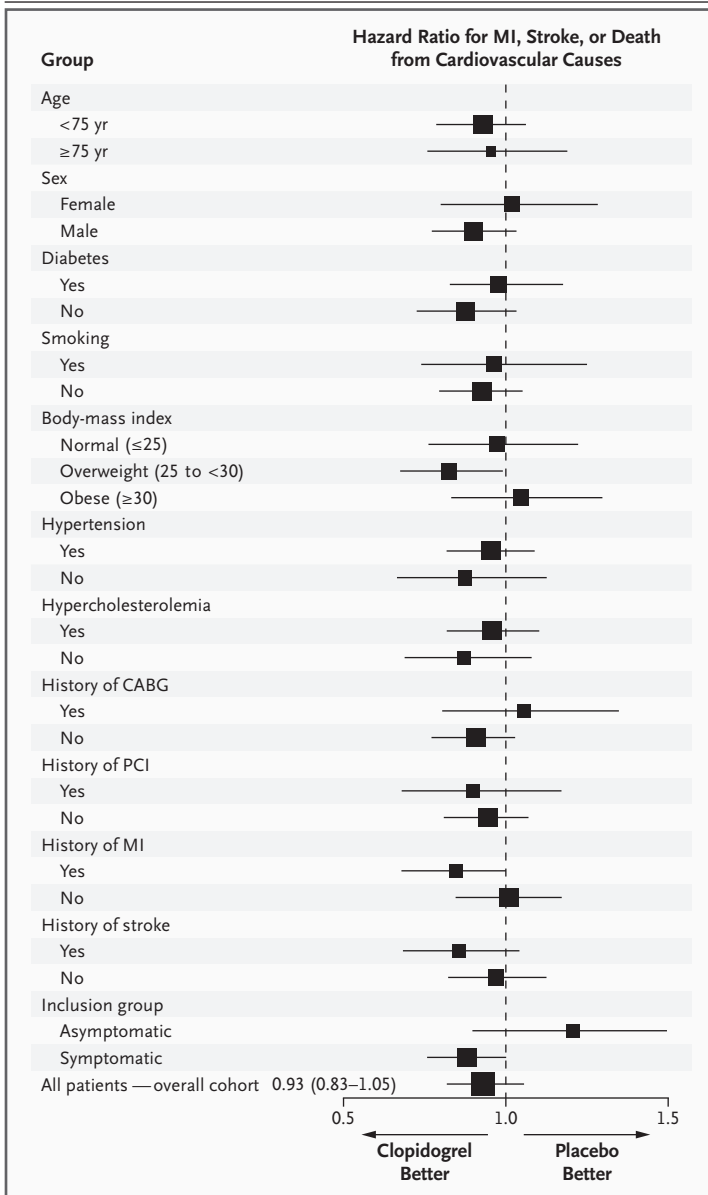


Figure 2. Hazard Ratios for Myocardial Infarction (MI), Stroke, or Death from Cardiovascular Causes in Each of the Subgroups Examined. Hazard ratios are shown with their 95 percent confidence intervals. The sizes of the symbols are roughly proportional to the number of patients in the analysis. Body-mass 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.

infarction and atherosclerosis have revealed a marked difference among persons in the biologic basis of disease susceptibility. Whereas multiple genes have been demonstrated to confer susceptibility to heart attack, little has been reported on the molecular determinants of atherosclerosis in

humans.¹⁴ Atherosclerosis is far more common than are vascular events such as sudden death, heart attack, and stroke, which occur in a relatively small subgroup of patients. One hypothesis that could be consistent with a benefit of dual antiplatelet therapy in symptomatic patients (those with established vascular disease) is that this group has already shown a predisposition to arterial plaque rupture, fissure, or erosion. That dual antiplatelet therapy is best used in patients who are most liable to have such arterial injury appears to be a worthy hypothesis for prospective evaluation.

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.

Sponsored and funded by Sanofi-Aventis and Bristol-Myers Squibb. Dr. Topol is supported by grants (P50 HL077101 and HL081011) from the National Institutes of Health.

Dr. Bhatt reports having received consulting fees from Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Millennium, Sanofi-Aventis, Schering-Plough, and the Medicines Company; lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, and the Medicines Company; and having provided expert testimony regarding clopidogrel (the compensation was donated to a nonprofit organization). Dr. Fox reports having received consulting fees from Sanofi-Aventis; lecture fees from Sanofi-Aventis and Bristol-Myers Squibb; and grant support from Sanofi-Aventis. Dr. Hacke reports having received consulting and lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Berger reports having received consulting and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Johnson & Johnson, Genentech, Guilford, Arginox, Schering-Plough, and Boston Scientific, and is the medical director and owns equity in Lumen. Dr. Black reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Merck, Pfizer, Novartis, and Myogen and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and Novartis. Dr. Boden reports having received consulting fees and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, KOS Pharmaceuticals, PDL BioPharma, and CV Therapeutics. Dr. Cacoub reports having received consulting fees from Servier, Schering-Plough, Roche, and Chiesi and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, Servier, Schering-Plough, Abbott, and Chiesi. Dr. Cohen reports having received consulting fees from Hoffmann-La Roche, Eli Lilly Canada, Oryx Pharmaceuticals, and GlaxoSmithKline Cana-

da and lecture fees from Sanofi-Aventis, Oryx Pharmaceuticals, Eli Lilly Canada, and Key Schering. Dr. Creager reports having received consulting fees and grant support from the Sanofi-Aventis/Bristol-Myers Squibb partnership and lecture fees from Sanofi-Aventis/Bristol-Myers Squibb. Dr. Easton reports having received consulting fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Flather reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Boehringer Ingelheim; lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Menarini; and grant support from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Novartis. Dr. Haffner reports having received consulting and lecture fees from Sanofi-Aventis. Dr. Hamm reports having received consulting and lecture fees from Sanofi-Aventis. Dr. Hankey reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Bayer, and Boehringer Ingelheim and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, Bayer, and Boehringer Ingelheim. Dr. Johnston reports having received a grant from Johnson & Johnson. Dr. Mas reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, and Servier and lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Montalescot reports having received consulting and

lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Pearson reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Bayer, Forbes Medi-Tech, and Merck and lecture fees from Bristol-Myers Squibb, Abbott, AstraZeneca, Bayer, KOS Pharmaceuticals, Merck, Pfizer, and Merck/Schering-Plough. Dr. Steg reports having received consulting fees from Sanofi-Aventis, AstraZeneca, Takeda, and GlaxoSmithKline and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, AstraZeneca, Servier, Merck, Novartis, Sankyo, Boehringer Ingelheim, Pfizer, and Nycomed. Dr. Steinhubl reports having received consulting fees from Sanofi-Aventis, AstraZeneca, Eli Lilly, and the Medicines Company. Dr. Weber reports having received lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Topol reports having served as a consultant to and having received lecture fees from Sanofi-Aventis and Bristol-Myers Squibb before 2005. No other potential conflict of interest relevant to this article was reported.

We are indebted to Bernard Job, M.D., and Christophe Gaudin, M.D., from Sanofi-Aventis and Mel Blumenthal, M.D., and Ravi Saini, M.D., from Bristol-Myers Squibb for their efforts on behalf of the CHARISMA trial, as well as to the 15,603 patients in 32 countries who participated in the trial.

APPENDIX

The CHARISMA committees, national coordinators, and investigators are as follows: **Executive committee:** E.J. Topol (chair), K.A.A. Fox (cochair), W. Hacke (cochair), D.L. Bhatt (principal investigator), P.B. Berger, H.R. Black, W.E. Boden, P. Cacoub, E.A. Cohen, M.A. Creager, J.D. Easton, M.D. Flather, S.M. Haffner, C.W. Hamm, G.J. Hankey, S. Claiborne Johnston, K.-H. Mak, J.-L. Mas, G. Montalescot, T.A. Pearson, P.G. Steg, S.R. Steinhubl, M.A. Weber; **Independent data and safety monitoring board:** R.L. Frye (chair), P. Amarrenco, L.M. Brass, M. Buyse, L.S. Cohen, D.L. DeMets, V. Fuster, R.G. Hart, J.R. Marler, C. McCarthy, A. Schömig; **Clinical events committee:** A.M. Lincoff (chair), C.A. Sila (neurology), A. Albuquerqu, G. Aroutiounov, D. Artemiev, B.G. Atkeson, T. Bartel, D.C.G. Basart, A. Bastos Lima, G. Belli, A.L. Bordalo e Sá, X. Bosch, G. Boysen, E.W.A. Busch, A. Cavallini, A. Chamorro Sánchez, J.H. Chiu, T. Dahl, E. Danielsson, R.B. Fathi, P. Grande, K. Groundstroem, M. Hamon, M. Haude, C. Held, B. Hesse, M.A. Hook, J.C. Hostetter, J.C. Huang, R.C. Jones, A. Kamińska, K. Karlócai, S. Marcheselli, J. Martí-Fàbregas, R. Mikulík, J.P. Neau, Y. Nişancı, H.J. Nordal, T. Okay, G. Opala, I.A. Orlova, V. Parfomenko, T.J. Pasierski, G. Permyanov-Miralda, A. Plomaritoglou, P. Pruszczyk, G. Rasmanis, R.O. Roine, A. Rónaszéki, M.L. Rossi, K. Sas, R.W. Shields, J. Sitar, B. Srichai, J. Stam, P.J. Sweeney, M.S. Svänne, D. Tschopp, K. Urbánek, M. Vavuranakis, L. Vécsei, M.V. Baptista, P. Vojtúšek, F. Woimant, and F. J. Zidar; **National coordinators:** *Argentina* — S.F. Ameriso, F.A. Cura; *Australia* — P. Aylward, G.J. Hankey; *Belgium* — B.J. Boland; *Brazil* — A. Amato, V. De Paola; *Canada* — E.A. Cohen, A. Roussin, P. Teal; *Czech Republic* — E. Ehler; *Denmark* — H. Sillesen; *Finland* — M.S. Nieminen; *France* — P.G. Steg; *Germany and Austria* — U. Hoffmann, F.-J. Neumann; *Greece* — A.P. Dimas; *Hungary* — T. Forster; *Italy* — D. Ardissino; *Mexico* — R. Alvarado; *the Netherlands* — H.R. Büller; *Norway* — B. Indredavik; *Poland* — Z.A. Gaciong; *Portugal* — J. Morais; *Russia* — V. Mareev; *Spain* — A. Batriu, L.M. Rulope; *South Africa* — A.J. Dalby; *Sweden* — J.B. Östergren; *Switzerland* — T.F. Luscher; *Turkey* — H. Kultursay; *United Kingdom* — M.D. Flather, K.A.A. Fox; and *United States* — W.E. Boden, J.D. Easton, S.M. Haffner, T.A. Pearson, S.R. Steinhubl; **Investigators:** *Argentina* — A. Alvarisqueta, S. Ameriso, L. Maria Amuchastegui, A. Caccavo, I. Casas Parera, S. Chekherdemian, F. Cura, M.M. Esnaola y Rojas, M. Fernandez Pardal, J. Ferrari, H. Fideleff, E. Hasbani, R. La Mura, J.L. Presta, R. Rey, R. Rey, R. Rivas, D.G. Starosiliz, A. Villamil, J. Waitman, and P. Zaefferer; *Australia* — J. Amerena, C. Bladin, D. Chew, D. Crimmins, D. Cross, S. Davis, T. Davis, G. Donnan, R. Fitridge, D. Freilich, H. Gibbs, J. Graham, A. Hill, J. Horowitz, D. Hunt, N. Ingham, J. Karrasch, I. Meredith, R. Moses, P. Phillips, J. Rankin, S. Read, D. Rees, S. Roger, J. Sampson, R. Schwartz, P. Walker, G. Watts, A. Whelan, and R. Whitbourn; *Austria* — B. Eber, H. Niessner, E. Pilger, R. Schmidt, T. Wascher, and J. Willeit; *Belgium* — S. Blecic, B.J. Boland, J. Boland, G. Boxho, P.P. De Deyn, J. Duchateau, J. Ducobu, G.R. Heyndrickx, F. Sanchez-Ruiz, A. Scheen, V. Thijs, W. Van Mieghem, and E. Verjans; *Brazil* — Á.A.V. de Paola, A. Francischetti, E. Francischetti, F.A. Frota Bezerra, R. Gagliardi, A. Massaro, Y. Nagato, K. Nakiri, S. Rassi, C. Scherr, J.A. Sgarbi, J. Soares Felício, and H. Suplicy; *Canada* — R. Arts, P. Auger, C.E.H. Baer, G. Bailey, P. Bailey, M. Beaudry, J. Bédard, L. Berger, J.D. Berlingieri, R.K. Bhargava, P. Bogaty, D. Bruckschwaiger, M.H. Cameron, M. Chilvers, S. Connolly, C. Constance, H.S. Conter, R. Cote, J. Cusson, H. Desai, L. Desjardins, R.A. Dlin, A. Durocher, C. Fortin, Y.-D. Gagnon, A. Glanz, S.G. Goodman, D. Gossard, M.K. Gupta, V. Hachinski, D. Hambly, R.D. Hamilton, B. Hejdankova, J. Hii, W. Hughes, W.K.K. Hui, J. Janzen, D. Johnston, C. Joyner, W.P. Klinka, S. Kouz, P.L. Allier, R. Labbé, S.S.Y. Lam, D.A. Landry, C. Laroche, B.J. Lawlor, J.H.F. Lenis, P. Ma, A. Mackey, D.R. Marr, J. Milton, J. Minuk, M.-J. Miron, K.K.A. Misik, G. Moddel, T. Monchesky, P. Nault, W.F. O'Mahony, A. Panju, A. Penn, P. Perron, S. Phillips, K. Pistawka, B.R. Ramjattan, J.A. Ricci, J. Rodés, D. Sahlas, D. Selchen, M. Sharma, A. Shuaib, D. Spence, D.C. Steeves, D. Studney, J. Sullivan, B.A. Sussex, P. Teal, J. Teitelbaum, H.D. Tildesley, S.J. Tishler, A.G.G. Turpie, C. Voll, J.W. Warnica, M.A. Weigel, T. Winder, M. Winger, V.C. Woo, P. Wozniak, J.-F. Yale, L.C.H. Yao, G. Zimakas, and R. Zimmermann; *Chile* — R. Corbalan, P. Lavados, and J. Yovanovich; *Czech Republic* — M. Bar, M. Branny, J. Charvat, E. Ehler, B. Filipensky, M. Filipova, J. Smid, J. Spac, J. Spinar, F. Stanek, and E. Zidkova; *Denmark* — M. Carstensen, S.E. Husted, H. Kraemmer-Nielsen, and K. Lindvig; *Finland* — J. Airakinen, M.S. Nieminen, and J. Sivenius; *France* — N. Abenhaim, B. Agraou, M. Bismuth, H. Boccalon, M. Bourgoin, M.-G. Boussier, P. Carpentier, I. Cibois-Honorat, C. Conri, B.D. Hautefeuille, P. Dambrine, M. David, H. Decousus, B. Devulder, J.-L. Dubois-Rande, E. Ferrari, R. Fonteny, L. Fuchs, M. Giroud, J.-L. Guilmot, M. Krempf, M.-H. Mahagne, J.-L. Mas, A. Medvedowsky, G. Montalescot, T. Moulin, J.-F. Pinel, J. Puel, I. Quere, G. Rodier, T. Rosolacci, F. Rouanet, D. Saillard, G. Steg, D. Stephan, C. Tribouilloy, J.-Y. Vogel, and Y. Samson; *Germany* — C. Baran, J. Berrouschot, O. Busse, M. Dichgans, H.-C. Diener, H.-G. Fritz, M. Goertler, B. Grewing, T. Haak, R. Haberl, C. Hamm, J. Hein, T. Heitzer, M. Hennerici, U. Hoffmann, T. Horacek, G. Klausmann, H. Lawall, G. Mahla, H. Mauersberger, G. Meinhardt, A. Müller-Jensen, T. Münzel, P. Nawroth, F.-J. Neumann, H. Ochs, P. Ringleb, H. Samer, D. Sander, P.

Scheffler, K.-L. Schulte, S. Silber, U. Speier, K. Stangl, E. Stark, C. Tiefenbacher, P. von Bilderling, M. Weisbach, and J. Wunderlich; *Greece* — A. Dimas, M. Elisaf, D. Karamitsos, A. Melidonis, E. Pagkalos, A. Polydorou, C. Saopoulos, K. Vemmos, and G. Ziakas; *Hong Kong* — J. Chan, W. Kwong Chan, W.-H. Chen, R. Cheung, S.-K. Li, K. Tan, K. Sing, L. Wong, and K.-S. Woo; *Hungary* — G. Acsády, K. Cseh, L. Csiba, M. Csornai, T. Forster, C. Kerekes, L. Kollár, V. Kristóf, Z. László, A. Murányi, J. Sebestyén, and M. Sereg; *Italy* — E. Agabiti Rosei, P. Bassi, D. Cucinotta, E. Degli Esposti, F. Federico, S. Forconi, N. Glorioso, P. Gresele, D. Guidetti, E. Mannarino, F. Masini, G. Micieli, A. Morganti, R. Pasquali, P. Carlo Rossi, L. Saccà, M.L. Sacchetti, A. Spissu, P. Terrosu, and F. Violi; *Malaysia* — N.A. bin Kamaruddin, S. Pheng Chan, and K.-S. Tan; *Mexico* — C. Aguilar, R. Alvarado, A. Arauz, C.-G. Ascanio, N.-S. Barroso, L.-F. Flota, S. Hernandez, R. Herrera, J.-L. Leyva, E. Meaney, A. Miranda, E. Morales, B. Ramirez, A. Ranero, M.A. Rivera, J.L. Ruiz, C.-J. Sanchez, and J.-A. Tamez; *Norway* — D. Atar, B. Indredavik, and P.A. Sirnes; *Poland* — P. Andziak, F. Brakowiecki, A. Cencora, M. Cholewa, Z. Gaciong, P. Gutowski, J. Huczynski, K. Janik, A. Jawien, G. Kania, D. Kleczkowski, J. Kotowicz, W. Krasowski, M. Kruk, A. Kuczynska-Zardzewialy, H. Kwieciński, J. Lopatynski, M. Muszynska-Polaszewska, M. Piepiorka, K. Pilarska, R. Podemski, J. Rudzinski, A. Rynkiewicz, M. Strzelecka-Gorzynska, A. Szczudlik, M. Szpajer, B. Wierusz-Wysocka, D. Wojciechowski, B. Wyrzykowski, P. Zaleski, B. Zalska, and K. Ziaja; *Portugal* — L. Cunha, D. Ferreira, J. Ferro, L. Gardete Correia, P. Marques da Silva, J. Morais, L. Mota Capitaço, J. Puig, and V. Salgado; *Russia* — J. Belousov, N. Gratsiansky, V. Mareev, A. Sinopalnikov, A. Skoromets, V. Skvortsova, L. Stratchounsky, and Z. Suslina; *Singapore* — A. Auchus, H.-M. Chang, K. Hou Mak, N.V. Ramani, and J. Chin Tay; *South Africa* — P. Blomere, S. Balkan, M. Bryer, L. Burgess, A.J. Dalby, L. Distiller, I.O. Ebrahim, G.C. Ellis, M.R. Essop, J. King, E. Lloyd, R. Moore, R. Sommers, L. Steingo, and M. Van Niekerk; *Spain* — J.M. Aguilera, J. Alvarez-Sabin, M. Cairols, C. Calvo, J. Castillo, A. Coca, A. Davalos, F. De Alvaro, A. Flores, J. García Puig, A. Gil-Peralta, P. Gomez, M. Heras, C. Macaya, A.M. Hidalgo, J. Matías-Guiu, E. Mostacero, R. Romero, E. Ros Die, L.M. Ruilope, J. Serena, N. Vila, and J. Vivancos; *Sweden* — L. Bokemark, B. Cederin, S. Karacagil, J. Östergren, T. Strand, and S. Undén-Göransson; *Switzerland* — I. Baumgartner, J.H. Beer, J. Bogousslavsky, H. Bounameaux, B. Caduff, A. Cerny, A. Gallino, T. Luescher, P. Lyrer, and A. Pagnamenta; *Taiwan* — J.-J. Cheng, H.-T. Chou, H.-W. Huang, and S.-J. Ryu; *the Netherlands* — D.H. Biesma, D.P.M. Brandjes, H.R. Büller, F.R. den Hartog, D.W.J. Dippel, M.H.H. Kramer, J.W.M. Lenders, H.R. Michels, M.G. Niemeijer, P.R. Nierop, J.U.R. Niewold, M.G.C. Pieterse, E.A.C.M. Sanders, P.J.H. Smak Gregoor, J. Tejjink, R.P.T. Troquay, and B. van Vlies; *Turkey* — S. Balkan, M. Bayazit, K. Gol, B. Ince, H. Kultursay, E. Kumral, K. Kutluk, and H. Tuzun; *United Kingdom* — J. Adgey, P. Bath, J. Belch, M.J. Brack, L.A. Corr, R. Curless, R. Donnelly, J.A. Dormandy, P. Durrington, S.J. Ellis, M.D. Flather, K.A.A. Fox, D. Jenkinson, K.R. Lees, R.S. MacWalter, D. McEneaney, A. Mehrzad, K. Muir, C. Murphy, J.A. Purvis, T. Robinson, H.G.M. Shetty, D. Springings, G. Stansby, and G.S. Venables; *United States* — A. Abou-Zamzam, H. Adams, F.V. Aguirre, B. Ahmad, J.R. Allison III, A. Almahameed, I. Altafulah, J. Anderson, R. Arakaki, G. Arnold, R. Avva, A. Axelrod, J.M. Bacharach, D. Banish, A. Bank, G.G. Banks, S. Bansal, C. Bayron, K.J. Becker, L. Becnel, A. Belber, J.R. Belden, D. Bernstein, H.S. Bhatia, J. Bittrick, W.E. Boden, K.K. Bordenave, T. Bowers, A.J. Bradley, J.R. Brady, S. Brady, J. Brandes, A. Brateanu, D. Brautigam, D. Brill, J. Brillman, R.E. Broker, D. Brotman, C. Brown, T.E. Bruya, J. Kern Buckner, D. Buth, T. Byer, L. Cannon, R. Capodilupo, J.M. Cappleman, E.L. Chaikof, J. Chambers, H. Chandna, Y. Pragada Chandrashekhara, C. Chen, T. Chippendale, S. Chokshi, P. Clagett, K. Cohen, M. Collins, A. Comerota, J.R. Cook, J. Corbelli, M.A. Creager, F.H. Cucher, F.E. Cummins, B. Dandapani, K. Dave, G.E. DeGent, M. DeGregorio, D.P. DeHart, J. DeLeon, T. Devlin, B. DeVries, M. Drehobl, M.N. Drossner, M. Dryjski, D. Dulli, D. Eisenberg, W.T. Ellison, S. Erlmeier, W. Felten, W. Felton, P.E. Fenster, H. Fields, T. Fischel, A. Furlan, M. Gandhi, R. Gaona, S. Gazda, J. Gelormini, A. George, J. George, W. George, S. Gill, J.M. Glass, M.C. Goldberg, S. Goldman, J. Goldstein, M.A. Goodman, B.P. Grayum, J. Greenberg, G. Grewal, J. Griffin, R. Griffin, Jr., E. Gross-Sawicka, D. Gupta, S. Gupta, L. Gutnik, B. Haake, J.L. Haist, J. Hanna, J. Harris, B. Harrison, M.V. Hart, R. Hendley, T. Henry, P. Hermans, C. Herrera, J. Hoch, J. Hollander, V.N. Howard, T. Huber, R. Hull, R.J. Hye, B. Iteld, S.A. Jackson, B. Jacobs, L. Jacobs, C. Jenkins, C. Johnson, L. Toyono Jong, K. Kaplan, R.A. Kaplan, S. Katz, C.J. Kavinsky, R. Kelley, B. Kerzner, E.J. Klein, G. Koshkarian, M. Kozak, V. Krisciunas, K. Kutoloski, N. Lakkis, M. Lasala, J.R. LaSalle, B. Latthe, P. Lee-Kwen, K.G. Lehmann, D. Leifer, J. LeLevier, D. Lender, K. Levin, M. Levine, P. Lewis, R. Libman, T. Little, G. Locke, R. Loeffler, D. Lorch, T.J. Lowenkopf, M. Lurie, F. Maggiamo, J.D. Martin, B. Massie, E.K. Massin, T.G. Mattio, W. McGuinn, R.J. Meckler, M. Meredith, J.H. Mersey, A. Miller, J. Miller, L. Miller, P. Misch, J. D. Orr, F. Moradali, A.D. Mooradian, J.T. Morelli, A. Nafziger, S.D. Nash, K. Ng, A. Niederman, J.P. O'Bryan, P. Ogden, J. Miller Oppy, J.D. Orr, F. Ovalle, P. Overlie, C.K. Ozaki, T. Pacheco, B. Peart, C. Perkins, F. Pettyjohn, I. Pines, J. Pita, T. Poling, A.R. Pollack, S. Pollock, G.L. Post, J.B. Powers, R. Prashad, G. Raad, M. Raikhel, M. Rajachandran, R. Reichwein, M. Rendell, P.S. Reynolds, M. Rich, T. Richardson, K. Rictor, M.E. Ring, M. Rocco, B. Rogers, E.M. Roth, W.M. Ryan, J. Salmon, R. Sanchez, J.A. Schecter, K.C.J. Scherbarth, J. Schrenker, U. Schubart, A. Schussheim, J. Seaworth, P. Seigel, S. Shah, N. Shammass, W.S. Sheldon, L. Shelhamer, D. Sherman, R. Shey, T.L. Shook, R. Shor, R. Sievert, S. Silliman, B. Silver, H. Simon, W. Slater, G. Sloan, J. Smith III, W.B. Smith, B. Snyder, D. Som, C. Sotolongo, A. Spaedy, D. Spriggs, S. Steen, S. Stenstrom, L.D. Stonesifer, D. Subich, D.P. Suresh, R. Tamayo, W.A. Tan, G. Tefera, U. Thadani, R. Tidman, A. Tilikian, M.J. Tonkon, A. Turel, D. VanSickle, C. Vernon, W. Voyles, J. Walder, M. Warren, K. Weber, K. Weeks, R.J. Weiss, N. Weiss, J.H. Whitaker, D. Wolinsky, W. Wu, J. Yadav, and G.D. Yeoman.

REFERENCES

1. Ruggeri ZM. Platelets in atherothrombosis. *Nat Med* 2002;8:1227-34.
2. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque. I. Evolving concepts. *J Am Coll Cardiol* 2005;46:937-54.
3. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nat Med* 1998;4:1241-3.
4. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-9.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
6. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Errata, *N Engl J Med* 2001;345:1506, 1716.]
7. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21.
8. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized con-

trolled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]

9. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.

10. Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management,

and Avoidance (CHARISMA) trial. *Am Heart J* 2004;148:263-8.

11. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.

12. Bhatt DL, Fox KA, Hacke W, et al. A global view of atherothrombosis: baseline characteristics in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2005;

150(3):401.e1-401.e7. (Accessed March 24, 2006, at <http://www.ahjonline.com/article/PIIS000287030500284X/fulltext#abstract>.)

13. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.

14. Topol EJ. Simon Dack Lecture: the genomic basis of myocardial infarction. *J Am Coll Cardiol* 2005;46:1456-65.

Copyright © 2006 Massachusetts Medical Society.