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EXPEDITED REVIEW

Patients With Prior Myocardial Infarction, Stroke, or Symptomatic Peripheral Arterial Disease in the CHARISMA Trial

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Objectives The purpose of this study was to determine the possible benefit of dual antiplatelet therapy in patients with prior myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease (PAD).

Background Dual antiplatelet therapy with clopidogrel plus aspirin has been validated in the settings of acute coronary syndromes and coronary stenting. The value of this combination was recently evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, where no statistically significant benefit was found in the overall broad population of stable patients studied.

Methods We identified the subgroup in the CHARISMA trial who were enrolled with documented prior MI, ischemic stroke, or symptomatic PAD.

Results A total of 9,478 patients met the inclusion criteria for this analysis. The median duration of follow-up was 27.6 months. The rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel plus aspirin arm than in the placebo plus aspirin arm: 7.3% versus 8.8% (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.72 to 0.96, $p = 0.01$). Additionally, hospitalizations for ischemia were significantly decreased, 11.4% versus 13.2% (HR 0.86, 95% CI 0.76 to 0.96, $p = 0.008$). There was no significant difference in the rate of severe bleeding: 1.7% versus 1.5% (HR 1.12, 95% CI 0.81 to 1.53, $p = 0.50$); moderate bleeding was significantly increased: 2.0% versus 1.3% (HR 1.60, 95% CI 1.16 to 2.20, $p = 0.004$).

Conclusions In this analysis of the CHARISMA trial, the large number of patients with documented prior MI, ischemic stroke, or symptomatic PAD appeared to derive significant benefit from dual antiplatelet therapy with clopidogrel plus aspirin. Such patients may benefit from intensification of antithrombotic therapy beyond aspirin alone, a concept that future trials will need to validate. (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA]; http://clinicaltrials.gov/ct/show/NCT00050817?order=1; NCT00050817) (J Am Coll Cardiol 2007;49:1982–8) © 2007 by the American College of Cardiology Foundation

Dual antiplatelet therapy with aspirin plus clopidogrel has been studied extensively and found to be superior to aspirin alone in patients with acute coronary syndromes and after stent implantation for up to a year of therapy (1–3). The combination was most recently evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial (4). The overall trial found a nonsignificant 7.1% relative risk reduction in the primary efficacy end point of cardiovascular death, myocardial infarction (MI), or stroke over a median of 28 months and a similar but statistically significant 7.7% relative risk reduction in the secondary efficacy end point, which included hospitalization for ischemia or revascularization (4).

The CHARISMA study enrolled a stable population with either established atherothrombotic disease or multiple risk factors for atherothrombotic events (5). In a prespecified analysis of the CHARISMA trial, the 12,153 patients enrolled with established disease (documented cardiovascular, cerebrovascular, or peripheral arterial disease [PAD]) seemed to derive a significant benefit from combination therapy, while the 3,284 patients without documented disease but with multiple risk factors did not derive any benefit (4).

The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial had previously demonstrated in a stable secondary prevention population that clopidogrel monotherapy was superior to aspirin monotherapy for reducing the composite of vascular death, MI, or stroke, as well as hospitalization for ischemic events (6,7), and that this benefit was further amplified in higher-risk subgroups from the CAPRIE trial such as those with prior ischemic events (8). We hypothesized that if the CHARISMA trial had examined only a "CAPRIE-like" high-risk secondary prevention population instead of a broader and overall lower-risk population, as was actually done, greater benefit of dual antiplatelet therapy over aspirin might have been evident.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
MI = myocardial infarction
PAD = peripheral arterial disease

Methods

The design of the CHARISMA trial has been published previously (9). Briefly, patients with documented coronary artery disease, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis were enrolled and randomized in double-blind fashion to clopidogrel plus aspirin or placebo plus aspirin and followed for a median of 28 months. Patients were excluded if they had indications for open-label clopidogrel use or were at high risk of bleeding.

For the purposes of this post hoc analysis, patients were identified as "CAPRIE-like" if they were enrolled with a documented prior MI, documented prior ischemic stroke, or symptomatic PAD. Symptomatic PAD was defined as either current intermittent claudication with an ankle brachial index ≤0.85 or a history of intermittent claudication with a previous related intervention (amputation, peripheral bypass surgery, endovascular procedure). In the CAPRIE trial, the time limit for entry for stroke was ≥1 week to ≤6 months after the event and ≤35 days for MI; unlike the inclusion criteria in the CAPRIE trial, for the current analysis, no time limit was set with respect to the occurrence of the prior ischemic event.

The primary efficacy end point was cardiovascular death (including hemorrhagic death), MI, or stroke (from any cause). The primary safety end point was severe bleeding as defined by the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) criteria, which includes fatal bleeding, primary intracranial hemorrhage, or bleeding that causes hemodynamic compromise and requires blood or fluid replacement, inotropic support, or surgical intervention (10). These events were validated by the Cleveland Clinic Clinical Events Adjudication Committee. The secondary efficacy end point consisted of cardiovascular death, MI, stroke, or rehospitalization for unstable angina, transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral). Moderate bleeding as determined by the GUSTO criteria was the secondary safety end point; this end point captures bleeding that leads to transfusion but that does not lead to hemodynamic compromise that requires intervention (10).

Statistical analysis. The efficacy of clopidogrel plus aspirin versus placebo plus aspirin was assessed using a 2-sided log-rank test. Treatment effect, as measured by the hazard ratio (HR) (relative risk) and its associated 95% confidence interval (CI), was estimated using Cox's proportional hazards model. Cumulative Kaplan-Meier estimates of the event rates were also calculated. Statistical comparisons of the safety event rates in the 2 treatment groups were performed using a 2-sided

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Table 1 Baseline Characteristics

Characteristic	Clopidogrel + Aspirin (n = 4,735)	Placebo + Aspirin (n = 4,743)
Demographics		
Age (yrs), median (Q1, Q3)	64 (56, 71)	64 (56, 71)
Female patients, n (%)	1,292 (27.3)	1,275 (26.9)
Ethnicity, n (%)		
Caucasian	3,859 (81.5)	3,851 (81.2)
Hispanic	454 (9.6)	481 (10.1)
Asian	226 (4.8)	222 (4.7)
Black	141 (3.0)	137 (2.9)
Other	55 (1.2)	52 (1.1)
Inclusion group, n (%)		
Prior myocardial infarction	1,903 (40.2)	1,943 (41.0)
Prior ischemic stroke	1,634 (34.5)	1,611 (34.0)
Symptomatic PAD	1,418 (29.9)	1,420 (29.9)
Selected clinical characteristics, n (%)		
Smoking status		
Current	1,024 (21.6)	1,055 (22.2)
Former	2,434 (51.4)	2,435 (51.3)
Hypertension	3,236 (68.3)	3,317 (69.9)
Hypercholesterolemia	3,307 (69.8)	3,343 (70.5)
Congestive heart failure	298 (6.3)	308 (6.5)
Prior myocardial infarction	2,193 (46.3)	2,248 (47.4)
Atrial fibrillation	172 (3.6)	160 (3.4)
Prior stroke	1,764 (37.3)	1,726 (36.4)
Transient ischemic attack	326 (6.9)	300 (6.3)
Diabetes	1,457 (30.8)	1,484 (31.3)
PAD	1,529 (32.3)	1,530 (32.3)
Percutaneous coronary intervention	1,209 (25.5)	1,239 (26.1)
Coronary artery bypass graft surgery	809 (17.1)	829 (17.5)
Carotid endarterectomy	257 (5.4)	235 (5.0)
Peripheral angioplasty or bypass	829 (17.5)	812 (17.1)
Diabetic nephropathy	195 (4.1)	211 (4.4)

PAD = peripheral arterial disease.

log-rank test. No adjustments for multiple comparisons were made. Multivariate analysis incorporating baseline demographics, concomitant medications, and time from enrolling ischemic event was performed to examine any independent effect of the randomized treatment. The instantaneous hazard functions of primary efficacy and safety end points were estimated by the life-table method as the first 30 days, 30 to 90 days, 90 to 180 days, and then every 180 days. All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 9,478 patients fulfilled the "CAPRIE-like" criteria for this analysis. A total of 3,846 patients had prior MI, with a median time from the qualifying event to randomization of 23.6 months; 3,245 patients had prior stroke, with a median time from event of 3.5 months; 2,838 patients had symptomatic PAD, with a median time from diagnosis of 23.6 months. Note that 443 (4.7%) patients fell into multiple categories because they actually had more than 1 prior event or disease location. The baseline characteristics of these patients in the 2 randomized arms were well matched, with no significant differences (Table 1). Concomitant medication use was also similar in the 2 arms of the study except nitrate use, which was 25.8% in the aspirin plus placebo arm and 23.5% in the aspirin plus clopidogrel arm (p = 0.008) (Table 2).

The overall rate of cardiovascular death, MI, or stroke in this cohort was 8.8% in the placebo plus aspirin arm and 7.3% in the clopidogrel plus aspirin arm (HR 0.83, 95% CI 0.72 to 0.96, p = 0.01) (Fig. 1). The interaction term for the benefit in this subgroup was 0.005. Significant benefit was also evident for the secondary efficacy end point incorporating hospitalization for ischemic events (Table 3). Patients with prior MI or prior stroke appeared to have a similar relative risk reduction as those with symptomatic PAD, although the risk reduction in the PAD subgroup did not reach statistical significance (Fig. 2). Overall, those patients with disease in multiple (that is, 2 or 3) vascular locations (prior events such as MI or stroke or established PAD) had a 14.7% rate of cardiovascular death, MI, or stroke versus a 7.7% rate in those having only 1 vascular location (either prior MI or prior stroke or established PAD) (HR 2.0, 95%

Table 2 Concomitant Medications

Medication	Clopidogrel + Aspirin (n = 4,735)	Placebo + Aspirin (n = 4,743)
Aspirin	4,720 (99.7)	4,732 (99.8)
Diuretics	2,102 (44.4)	2,086 (44.0)
Nitrates	1,112 (23.5)	1,225 (25.8)
Calcium antagonists	1,601 (33.8)	1,647 (34.7)
Beta-blockers	2,639 (55.7)	2,696 (56.8)
Angiotensin II receptor blockers	1,035 (21.9)	1,048 (22.1)
Ramipril	872 (18.4)	893 (18.8)
Other angiotensin-converting enzyme inhibitors	2,129 (45.0)	2,161 (45.6)
Other antihypertensives	496 (10.5)	528 (11.1)
Statins	3,651 (77.1)	3,646 (76.9)
Atorvastatin	1,651 (34.9)	1,663 (35.1)
Simvastatin	1,686 (35.6)	1,682 (35.5)
Pravastatin	622 (13.1)	607 (12.8)
Fluvastatin	139 (2.9)	139 (2.9)
Lovastatin	156 (3.3)	156 (3.3)
Other statins	258 (5.4)	239 (5.0)
Other lipid-lowering agents	580 (12.2)	543 (11.4)
Fibrates	337 (7.1)	291 (6.1)
Binding resins	171 (3.6)	171 (3.6)
Nicotinic acid	156 (3.3)	140 (3.0)
Antidiabetic medications	1,445 (30.5)	1,490 (31.4)
Insulin	592 (12.5)	582 (12.3)
Thiazolidinediones	214 (4.5)	230 (4.8)
Other oral hypoglycemics	1,171 (24.7)	1,205 (25.4)

Values are expressed as n (%).

CI 1.55 to 2.57, $p < 0.001$). Patients with disease in multiple vascular locations had an 18.5% rate of cardiovascular death, MI, or stroke in the placebo plus aspirin arm versus a 10.6% rate with clopidogrel plus aspirin (HR 0.55, 95% CI 0.33 to 0.91, $p = 0.018$).

In the 2,675 patients who were excluded from the original CHARISMA group of "established cardiovascular disease" to derive the current study population, there were patients with angina and documented multivessel coronary artery disease, a history of percutaneous coronary intervention, a history of coronary artery bypass surgery, and those with transient ischemic attacks. In this excluded cohort of patients with stable cardiovascular disease without documented thrombotic events, there was no benefit of clopidogrel plus aspirin versus placebo plus aspirin; the rate of cardiovascular death, MI, or stroke was 5.5% versus 4.7% (HR 1.16, 95% CI 0.83 to 1.63, $p = 0.38$); for the end point of cardiovascular death, MI, stroke, or hospitalization for ischemic events, the rate was 17.7% versus 17.1% (HR 1.04, 95% CI 0.87 to 1.24, $p = 0.69$). Figure 3 shows the primary efficacy end point for the patients enrolled with MI (Fig. 3A) versus those enrolled with coronary artery disease other than MI (Fig. 3B).

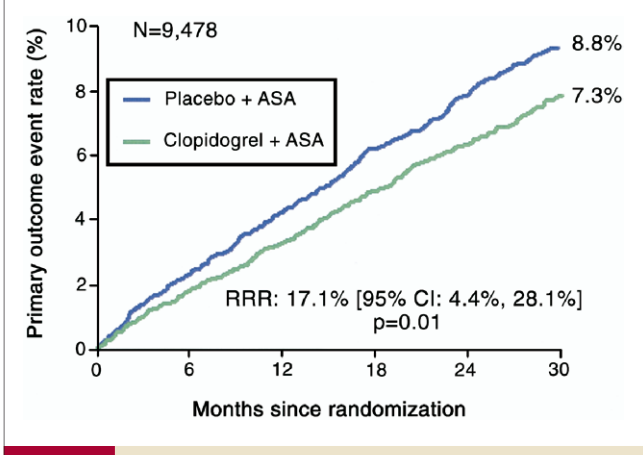

Figure 1 Kaplan-Meier Curves for Cardiovascular Death, MI, or Stroke for Clopidogrel + ASA Versus Placebo + ASA

Kaplan-Meier event curves for the primary end point of cardiovascular death, myocardial infarction (MI), or stroke. ASA = aspirin; CI = confidence interval; RRR = relative risk reduction.

For the "CAPRIE-like" cohort, the individual components of the composite end point as well as additional secondary end points and bleeding end points are listed in Table 3. There was no significant difference in severe bleeding, though moderate bleeding was significantly increased with dual antiplatelet therapy: 2.0% versus 1.3% (HR 1.60, 95% CI 1.16 to 2.20, $p = 0.004$). In an attempt to define net clinical benefit, the rate of cardiovascular death, MI, stroke, or severe GUSTO bleeding was examined and found to be 9.4% in the placebo plus aspirin arm versus 8.3% in the clopidogrel plus aspirin arm (HR 0.87, 95% CI 0.76 to 1.00, $p = 0.051$).

Multivariate analysis revealed treatment with clopidogrel plus aspirin to be an independent predictor of freedom from

Table 3 Primary and Secondary Efficacy and Bleeding End Points

End Point	Clopidogrel + Aspirin (n = 4,735)	Placebo + Aspirin (n = 4,743)	HR (95% CI)	p Value
Efficacy end points				
Primary efficacy	347 (7.3)	416 (8.8)	0.829 (0.719–0.956)	0.010
All-cause mortality	235 (5.0)	257 (5.4)	0.914 (0.765–1.090)	0.316
Cardiovascular mortality	142 (3.0)	163 (3.4)	0.870 (0.695–1.090)	0.224
Myocardial infarction*	117 (2.5)	145 (3.1)	0.805 (0.631–1.027)	0.080
Ischemic stroke*	126 (2.7)	152 (3.2)	0.828 (0.654–1.048)	0.115
Stroke*	144 (3.0)	179 (3.8)	0.802 (0.644–0.998)	0.048
Secondary efficacy	831 (17.6)	938 (19.8)	0.872 (0.794–0.958)	0.004
Hospitalization†	542 (11.4)	626 (13.2)	0.855 (0.762–0.960)	0.008
Safety end points				
Severe bleeding	79 (1.7)	71 (1.5)	1.114 (0.808–1.535)	0.509
Fatal bleeding	15 (0.3)	11 (0.2)	1.362 (0.626–2.966)	0.434
Primary intracranial hemorrhage	17 (0.4)	20 (0.4)	0.849 (0.445–1.621)	0.619
Moderate bleeding	97 (2.0)	61 (1.3)	1.597 (1.159–2.200)	0.004

*Fatal plus nonfatal events. †For unstable angina, transient ischemic attack, or revascularization.
CI = confidence interval; HR = hazard ratio.

cardiovascular death, MI, or stroke; the HR for cardiovascular death, MI, or stroke in patients randomized to clopidogrel plus aspirin instead of placebo plus aspirin was 0.84 (95% CI 0.73 to 0.97, p = 0.019). The effect of time from the ischemic event or diagnosis to randomization was included in the model and there was no significant effect of time with regard to outcome, although such testing may have been underpowered. Therefore, the primary end points at various times from the ischemic event are presented (Table 4); these data are also presented as an instantaneous hazard function from the time of randomization (Fig. 4). Besides randomization to clopidogrel, other predictors of decreased risk of cardiovascular death, MI, or stroke were female gender, concomitant statin use, and concomitant use of other lipid-lowering therapies. Significant predictors of cardiovascular death, MI, or stroke were increasing age, history of congestive heart failure, history of stroke, diastolic blood pressure ≥80 mm Hg, increasing neutrophil count, concomitant anticoagulants, concomitant antidiabetic medications, and current smoking.

Discussion

Ten years ago, the CAPRIE trial demonstrated the superiority of clopidogrel monotherapy over aspirin monotherapy in patients with recent MI, stroke, or symptomatic PAD over the 36-month study duration (6). The combination of clopidogrel plus aspirin was then validated as a therapeutic strategy in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) and CREDO (Clopidogrel to Reduce Events During Observation) trials of acute coronary syndromes and stenting, respectively (2,3). The CHARISMA trial was an ambitious

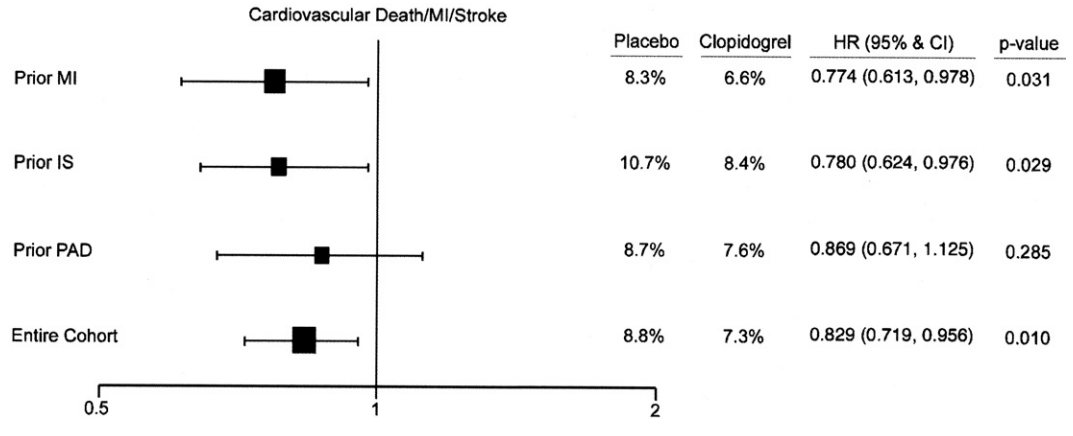

Figure 2 Hazard Ratio for the Primary End Point in Patients Enrolled With Prior MI, Stroke, or PAD

Hazard ratio (HR) and 95% CI for the composite of cardiovascular death, MI, or stroke for patients randomized to placebo plus aspirin versus clopidogrel plus aspirin that were enrolled with a prior MI, prior ischemic stroke (IS), or symptomatic peripheral arterial disease (PAD). Abbreviations as in Figure 1.

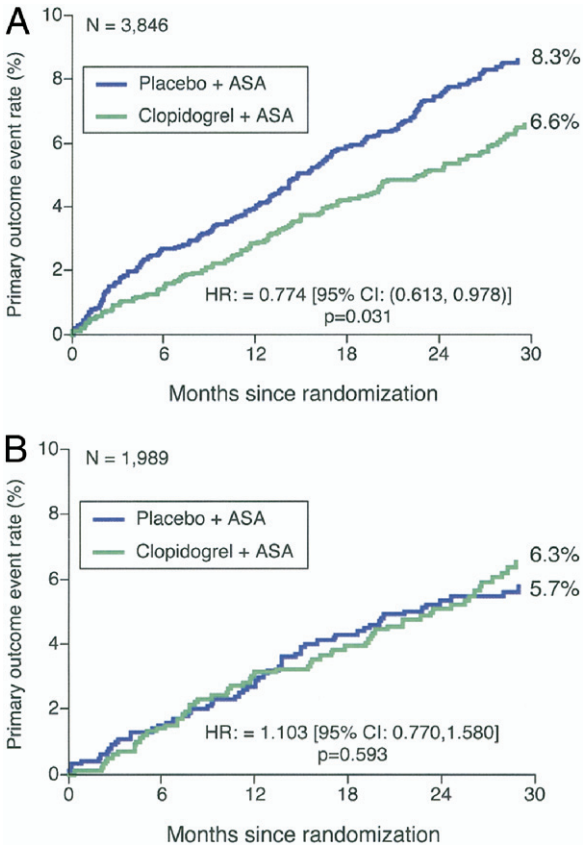

Figure 3 Kaplan-Meier Curves for the Primary End Point in Patients With CAD Either With or Without Prior MI

(A) Kaplan-Meier curves for the primary end point of cardiovascular death, MI, or stroke in patients enrolled with prior MI. **(B)** Kaplan-Meier curves for the primary end point in patients enrolled with coronary artery disease without prior MI. Abbreviations as in Figures 1 and 2.

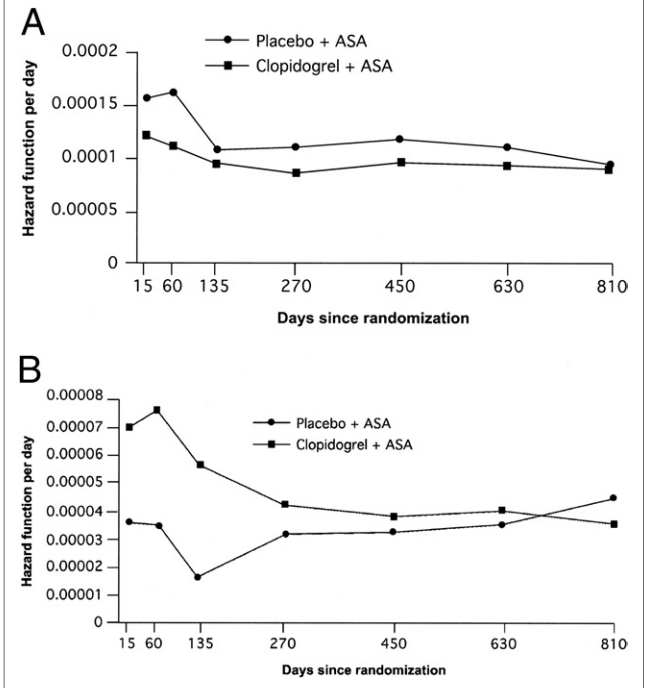

Figure 4 Instantaneous Hazard for Cardiovascular Death, MI, or Stroke or for Severe or Moderate Bleeding

(A) Instantaneous hazard for cardiovascular death, MI, or stroke. **(B)** Instantaneous hazard for severe or moderate bleeding. Abbreviations as in Figure 1.

attempt to examine dual antiplatelet therapy in a much broader population than the CAPRIE trial, with the additional inclusion of lower-risk secondary prevention as well as primary prevention types of patients (4). The CHARISMA trial overall did not show a statistically significant benefit in the primary efficacy end point, although it did show a significant benefit in the secondary efficacy end point. The current post hoc subgroup analysis of patients with prior MI, stroke, or symptomatic PAD from the CHARISMA trial shows a statistically significant 1.5% absolute risk reduction in the composite of cardiovascular death, MI, or stroke over a median of 27.6 months. This compares with a 2% absolute risk reduction in the same end point in the CURE trial over a median of 9 months.

Thus, there appears to be a gradient of benefit for dual antiplatelet therapy depending on the risk of thrombotic events of the patient. A reduction in all-cause mortality with short-term clopidogrel given in addition to aspirin was observed in the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) trial (11), with significant 2% to 3% absolute risk reductions in composite ischemic end points seen in the CURE and CREDO trials (~20 to 30 ischemic events prevented per 1,000 patients treated for about 1 year). In comparison, the CAPRIE-like cohort from the CHARISMA trial shows a more modest degree of benefit, with 14.4 episodes of cardiovascular death, MI, or stroke averted over the course of an average of 27.6 months per

Table 4 Rates of Cardiovascular Death, Myocardial Infarction, or Stroke at Different Time Intervals From the Ischemic Event to Randomization

Time of Ischemic Event Prior to Randomization	Clopidogrel + Aspirin	Placebo + Aspirin	HR (95% CI)
Within 30 days	8.2% (86/1,053)	10.5% (109/1,041)	0.773 (0.583–1.025)
Between 30 to 300 days	6.7% (68/1,014)	8.0% (83/1,036)	0.831 (0.603–1.146)
Between 300 days to 30 months	6.8% (68/997)	8.0% (81/1,018)	0.848 (0.614–1.171)
More than 30 months	6.6% (71/1,078)	7.2% (74/1,034)	0.918 (0.663–1.271)

Abbreviations as in Table 3.

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1,000 patients treated, at a cost of 1.7 severe bleeds. Of note, there was no statistically significant increase in severe bleeding, including fatal bleeding or intracranial hemorrhage. Additionally, during the median of 27.6 months, 17.5 hospitalizations for ischemic events (unstable angina, transient ischemic attack, worsening PAD) or revascularization were prevented at the cost of an additional 7.6 moderate bleeds (essentially, transfusions).

The benefit on ischemic outcomes started soon after randomization with increasing separation of the event curves as duration of therapy increased. Examination of the actual event rates showed that the largest absolute benefit appeared to be in patients whose ischemic event was within the prior month, with a lower absolute benefit seen between 30 days and 30 months, with further attenuation of observed benefit beyond 30 months; it is biologically plausible that the greatest degree of benefit would be in those whose ischemic event was most recent, although this analysis was underpowered to detect any definite time-related effect. Several patterns emerge upon examination of this data set. The benefit in preventing ischemic events is greatest early after randomization. The benefit in preventing ischemic events is less in patients who are further removed from the last previous ischemic event at the time of randomization. The bleeding excess is also "front-loaded," with more bleeding seen with dual antiplatelet therapy compared with aspirin plus placebo in the first few months of therapy and little difference afterward. All of these patterns are not statistically significant per se, as the study lacks power to make a definitive statement regarding these observations.

Based on the findings in the subgroup of 2,675 patients who were excluded from the original CHARISMA group of "established cardiovascular disease" to derive the current study population, it appears that patients with angina and documented multivessel coronary artery disease, a history of remote percutaneous coronary intervention, a history of coronary artery bypass surgery, or those with transient ischemic attacks may not benefit from dual antiplatelet therapy. Thus, it seems that it is those patients who have had plaque rupture and thrombosis in the past that are most likely to derive benefit from an extended duration of dual antiplatelet therapy.

There are evident limitations to this analysis. As a post hoc subgroup analysis, it can only be considered hypothesis generating. Even large subgroup analyses may be misleading and provide spurious results. Nevertheless, with over 9,000 patients, it is a large subgroup that consists of a logical cohort to analyze given the initial findings of the CAPRIE trial. Furthermore, in this subgroup, the baseline characteristics of the clopidogrel plus aspirin and placebo plus aspirin groups were well matched without any significant differences, and the results persisted after multivariable analysis.

In conclusion, patients with documented prior MI, stroke, or symptomatic PAD in the CHARISMA trial appeared to have significant benefit from a reduction in ischemic events from dual antiplatelet therapy with clopidogrel plus aspirin versus placebo plus aspirin, which was somewhat offset by an increase in moderate, although not severe, bleeding. Such patients may benefit from intensification of antithrombotic therapy beyond aspirin alone, a concept that future trials will need to validate.

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APPENDIX

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