In summary, although this analysis produces reassuring information about temporal trends and sparks renewed debate over the question of aspirin dosing, it is increasingly clear that we have reached the limits of where existing aspirin data can take us. Placebo-controlled trials of aspirin are no longer practical, but dose-range studies of aspirin in these cohorts certainly are. Thus, although the question of optimal aspirin therapy continues to be a long and continued debate, these findings show sufficient merit to warrant further investigation and direct, large, randomized comparisons.

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Amplified Benefit of *Clopidogrel* Versus *Aspirin* in Patients With Diabetes Mellitus

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Following an ischemic event, diabetic patients have a higher rate of recurrence than patients without diabetes mellitus.[1–6] Patients with diabetes but without prior myocardial infarction (MI) have a risk of MI during follow-up that is similar to that of nondiabetic patients who have already had a prior MI.[7] The mechanisms for the heightened risk are multifactorial.[8] However, a greater thrombotic predisposition exists with diabetes, which is largely mediated by platelets.[9–13] Aspirin has been shown to have a modest benefit over placebo in reducing vascular events in patients with diabetes mellitus.[14] The intravenous antiplatelet agent abciximab has been found to be particularly efficacious in patients with diabetes who are undergoing percutaneous revascularization.[15,16] Platelet glycoprotein IIb/IIIa inhibitors, when used for acute coronary syndromes, appear to have their greatest benefit in diabetic patients.[17] The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study randomized 19,185 patients with recent ischemic stroke, recent MI, or established peripheral arterial disease to the adenosine diphosphate (ADP) receptor antagonist clopidogrel or to aspirin.[18] An 8.7% relative risk reduction was seen in vascular death, MI, or ischemic stroke with use of clopidogrel.

TABLE 1 Baseline Characteristics of Patients With a History of Diabetes in the Two Treatment Groups

	Clopidogrel (n = 1,914)	Aspirin (n = 1,952)
Age (yrs)	63.9	64.1
Men	69%	68%
Unstable angina	9%	10%
Hypertension	68%	64%
Hyperlipidemia	45%	46%
Heart failure	10%	10%
Prior MI	22%	21%
Prior stroke	15%	14%
Claudication	7%	7%
Current smoker	22%	23%

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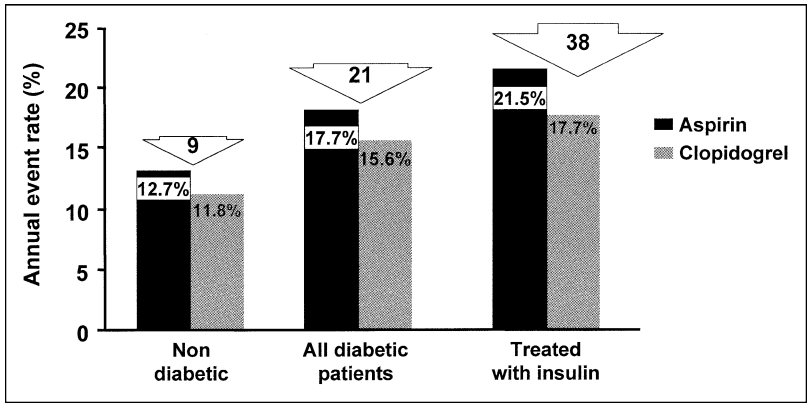

FIGURE 1. The number of events (vascular death, MI, stroke, or rehospitalization for ischemia or bleeding) prevented per 1,000 patients per year treated by clopidogrel instead of aspirin in nondiabetic patients, diabetic patients, and diabetic patients who require insulin.

TABLE 2 Number (%) of Patients Rehospitalized for Ischemia (transient ischemic attack, angina, or limb ischemia) or Bleeding

	Clopidogrel (n = 1,914)	Aspirin (n = 1,952)	RRR (95% CI)	p Value
Any ischemic or bleeding event	255 (13.3%)	304 (15.6%)	14.5% (0.2–26.7)	0.047
Any ischemic event	222 (11.6%)	260 (13.3%)	12.9% (−3.0–26.4)	0.105
Any bleeding event	34 (1.8%)	55 (2.8%)	37.0% (3.8–58.7)	0.031

CI = confidence interval; RRR = relative risk reduction.

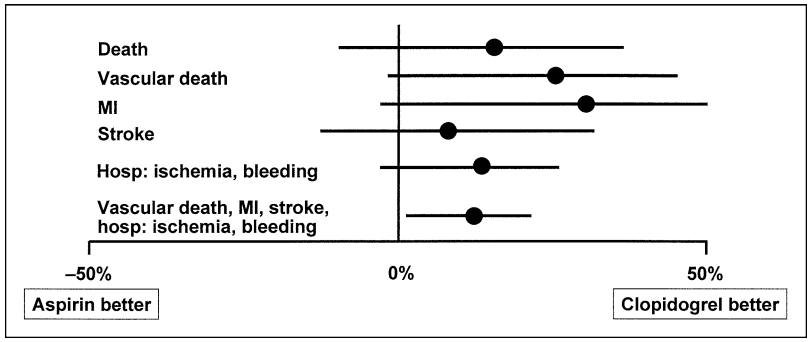

FIGURE 2. Relative risk reductions (with 95% confidence intervals) in individual and composite end points for diabetic patients, demonstrating a consistent benefit in favor of clopidogrel over aspirin.

A subsequent analysis of CAPRIE found an additional 8.7% reduction in rehospitalization for ischemia or bleeding.[19]

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We sought to determine whether clopidogrel compared with aspirin would be particularly efficacious in preventing ischemic events in diabetic patients with atherosclerosis. Patients with a history of diabetes mellitus at enrollment were identified. Diabetes was defined by each investigator at the time of entry, without specific laboratory confirmatory testing. The rates of vascular death, MI, all-cause stroke, and rehospitalization for ischemic events (angina, transient ischemic attack, or limb ischemia), or for bleeding were determined for 3,866 diabetic patients randomized to either clopidogrel or aspirin in the CAPRIE study, without any double counting of events. The prespecified primary composite end point for this analysis consisted of vascular death, all-cause stroke, MI, or rehospitalization for ischemia or bleeding. The 2 treatment groups were compared using a 2-sided log-rank test. The proportions of patients who were rehospitalized for ischemic events (angina, transient ischemic attack, or limb ischemia) or bleeding were compared using the Pearson chi-square test. A multivariate Cox proportional hazards model was used to adjust for baseline variables, including age, sex, race, weight, hypertension, prior MI, prior cerebrovascular event, congestive heart failure, smoking, claudication, and angina. A significance level of 0.05 was used. All analyses were performed on an on-treatment basis, with each patient's time at risk censored 28 days after early discontinuation of the study drug. All statistical analyses were performed using SAS software (version 6.12, SAS Institute Inc., Cary, North Carolina).

Baseline characteristics of the 1,914 patients with a history of diabetes randomized to clopidogrel and the 1,952 diabetic patients who were randomized to aspirin are listed in Table 1. There were no significant differences between the 2 groups, except for a slightly higher percentage of hypertension in patients who were randomized to clopidogrel (68% vs 64%; $p = 0.025$). The event rate per year was 12.7% in the 7,594 nondiabetic patients randomized to aspirin and 11.8% in the 7,639 nondiabetic patients randomized to clopidogrel ($p = 0.096$). In diabetic patients, the event rate per year was 15.6% in the 1,914 patients randomized to clopidogrel and 17.7% in the 1,952 patients with diabetes who received aspirin, with an absolute risk reduction of 2.1% ($p = 0.042$). In the subset of 1,134 diabetic patients who received insulin at baseline, the annual event rates for the primary composite end point were higher: 17.7% in the clopidogrel group and 21.5% in the aspirin group, with an absolute risk reduction of 3.8% ($p = 0.106$). As Figure 1 illustrates, there is a greater benefit with clopidogrel versus aspirin. Although the absolute risk reduction was larger in the diabetic patients due to their higher event rates, the relative risk reduction achieved with clopidogrel was similar in diabetics and nondiabetics (12.5% vs 6.1%, p value for interaction = 0.36). Data on rehospitalization rates for diabetic pa-

TABLE 3 Multivariate Model Showing the Benefit of Clopidogrel Over Aspirin in Reducing Death, Myocardial Infarction (MI), Stroke, or Rehospitalization for Ischemia or Bleeding After Adjustment for Baseline Characteristics

Variable	Risk Ratio	p Value
Clopidogrel	0.869	0.032
Age	1.103/10 yrs	0.012
Angina	1.559	0.001
Prior stroke	1.246	0.072
Prior MI	1.236	0.020
Claudication	1.732	0.001

tients treated with clopidogrel and aspirin are listed in Table 2. The incidence of rehospitalization for bleeding events and for either ischemic or bleeding events was significantly lower with clopidogrel therapy than with aspirin therapy ($p = 0.031$ and $p = 0.047$, respectively). The incidence of rehospitalization for ischemia was also lower in the clopidogrel group compared with the aspirin group, although this difference was not statistically significant. There was a consistent benefit favoring clopidogrel over aspirin in diabetic patients among all of the individual and composite end points examined (Figure 2).

In a multivariate model incorporating baseline clinical characteristics, clopidogrel therapy was independently associated with a decrease in vascular death, MI, stroke, and rehospitalization for ischemia or bleeding in diabetic patients (Table 3). In this model, the relative risk reduction for clopidogrel compared with aspirin was 13.1% (95% confidence interval 1.2% to 23.7%; $p = 0.032$). Significant predictors of an event in this model included age, angina, prior MI, and claudication.

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As expected, there is a greater risk observed as one examines cumulative event rates in nondiabetic patients, diabetic patients, and diabetic patients who require insulin. Importantly, these data demonstrate that there is also a greater benefit observed with use of clopidogrel as the primary antiplatelet instead of aspirin. Similar to other analyses of intravenous antiplatelet agents, more potent oral antiplatelet therapy is of particular benefit in the presence of diabetes.[15,16]

Compared with aspirin, clopidogrel is especially effective in reducing the elevated risk for recurrent ischemic events in diabetic patients with a history of atherothrombosis. Given the synergistic benefits of combination therapy with clopidogrel and aspirin observed in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study,[20] diabetic patients with evidence of vascular disease, even in the absence of overt ischemic events, may potentially benefit from dual antiplatelet therapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, a study that includes such patients, is currently underway to prospectively test this hypothesis.

There are certain limitations to this analysis. It was not prespecified, nor was it powered to examine individual end points. However, treatment with clopidogrel or aspirin was randomized. The duration and severity of diabetes were unknown. Specific details regarding control of diabetes, such as glycosylated hemoglobin levels or glycemic control, were not collected.

The ADP receptor antagonist clopidogrel is superior to aspirin in reducing recurrent ischemic events in patients with diabetes, while causing fewer bleeding complications. Due to the elevated event rates in diabetic patients, the absolute benefit of clopidogrel is amplified in this clinical setting. The significant benefit of clopidogrel over aspirin is in addition to the modest protection conferred by aspirin over placebo in this high-risk population.

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Abciximab Survival Advantage Following Percutaneous Coronary Intervention Is Predicted by Clinical Risk Profile

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Periprocedural platelet activation has been correlated with ischemic adverse clinical outcomes following percutaneous coronary intervention (PCI).[1,2] Early (≤30 days) post-PCI major adverse cardiovascular events (MACE), which include death, myocardial infarction, or need for urgent repeat coronary revascularization may occur as a consequence of procedure-related atherosclerotic plaque disruption with subsequent platelet activation, aggregation, and thrombus formation. Enhanced platelet inhibition following platelet glycoprotein (GP) IIb/IIIa inhibitor therapy suppresses the occurrence of periprocedural MACE.[3–8] Randomized comparative trials of parenteral platelet GP IIb/IIIa inhibition versus placebo have measured early (48 hours to 30 days) composite MACE to define the relative efficacy of treatment.[3–8] Although all currently available GP IIb/IIIa inhibitors suppress periprocedural MACE, to date only abciximab has demonstrated a significant late (1 to 3 years) survival advantage.[8–10] The present study was undertaken to determine if patients who derive a survival benefit from abciximab can be predicted by baseline demographics and disease history.

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A total of 5,799 patients enrolled into 3 large-scale randomized, double-blind placebo-controlled trials of abciximab administered at the time of PCI had their long-term (3-year) vital status determined. Protocol algorithms, inclusion and/or exclusion criteria, and trial end points have been previously described.[3,7,8] Briefly, the primary end point for each trial was similar and included the composite occurrence of death, myocardial infarction (defined as creatine kinase [CK]-MB more than the threefold upper limit of normal and/or the development of new Q waves), or need for urgent repeat percutaneous or surgical revascularization within 30 days after enrollment. In all 3 trials, CK and CK-MB measurements were obtained at baseline (pre-PCI) and every 8 hours for 48 hours or until hospital discharge. One treatment group in the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial received only a bolus abciximab injection (no 12-hour infusion) and 1 treatment group in the Evaluation of Platelet IIb-IIIa Inhibition in Stenting (EPISTENT) trial was randomly assigned to balloon angioplasty in combination with abciximab bolus plus infusion administration (no randomized placebo control for balloon intervention).[3,8] These 2 patient cohorts were not included in this analysis. Mortality data through September 30, 2000, was collected on a case report form by the original study sites for all patients. All treated patients included in this analysis were administered the study agent as a bolus injection of 0.25 mg/kg plus 12-hour infusion at a rate of 10 μg/min or as a weight-adjusted 12-hour infusion at a rate of 0.125 μg/kg/min to a maximum of 10 μg/min.

Survival of abciximab and control (placebo treated) patients was compared using a proportional hazards regression model. A 95% confidence interval for the hazard ratio for mortality for abciximab versus placebo was computed. Corresponding p values using the Wald method are presented. The Kaplan-Meier method was used to estimate the probability of death in each treatment group for the duration of follow-up. Kaplan-Meier estimates were combined across studies, weighting each study by the number of patients included from all treatment groups. A multivariate proportional hazards model was developed using a step-down procedure on available baseline clinical characteristics to identify factors associated with increased risk of death to 3-year follow-up. The minimum p value required for retention of variables in the model was 0.05. Clinical variables available for all patients included age, gender, weight, serum creatinine, history of coronary bypass graft surgery, history of PCI, multiple vessels attempted at the time of PCI, history of congestive heart failure, presence of diabe-

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