

ORIGINAL ARTICLE

A Clinical Trial of Abciximab in Elective Percutaneous Coronary Intervention after Pretreatment with Clopidogrel

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ABSTRACT

BACKGROUND

Whether the glycoprotein IIb/IIIa inhibitor abciximab is beneficial in patients undergoing elective percutaneous coronary intervention after pretreatment with clopidogrel is unknown.

METHODS

We enrolled 2159 patients with coronary artery disease who underwent a percutaneous coronary intervention: 1079 patients were randomly assigned in a double-blind manner to receive abciximab and 1080 patients to receive placebo. All patients were pretreated with a 600-mg dose of clopidogrel at least two hours before the procedure. The primary end point of the trial was the composite of death, myocardial infarction, and urgent target-vessel revascularization within 30 days after randomization.

RESULTS

The incidence of the primary end point was 4 percent (45 patients) in the abciximab group, as compared with 4 percent (43 patients) in the placebo group (relative risk, 1.05; 95 percent confidence interval, 0.69 to 1.59; $P=0.82$). Most adverse events were myocardial infarctions: the incidence was 4 percent (40 patients) in the abciximab group and 4 percent (41 patients) in the placebo group ($P=0.91$). Twelve patients (1 percent) in the abciximab group and eight patients (1 percent) in the placebo group had major bleeding complications ($P=0.37$). Profound thrombocytopenia occurred in 10 patients (1 percent) in the abciximab group but in none in the placebo group ($P=0.002$).

CONCLUSIONS

Our data suggest that in patients at low-to-intermediate risk who undergo elective percutaneous coronary intervention after pretreatment with a high loading dose of clopidogrel, abciximab is associated with no clinically measurable benefit within the first 30 days.

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PROGRESS IN THE FIELD OF ADJUNCTIVE antithrombotic therapy has had a decisive role in improving the outcome of percutaneous coronary interventions.¹ Dual antiplatelet therapy with aspirin and a thienopyridine has strikingly improved both the efficacy and the safety of coronary-artery stenting.^{2,3} Thienopyridines act by blocking one of the three adenosine 5'-diphosphate (ADP) receptors.⁴⁻⁶ An important limitation of ticlopidine is its delayed onset of action: maximal inhibition of ADP-induced platelet aggregation is achieved several days after administration.^{4,7-9} Although the use of large loading doses of clopidogrel results in a more rapid onset of action than that of ticlopidine, at least six hours is required for the antiplatelet effect of a loading dose of 300 mg to be maximal.¹⁰⁻¹⁴ This delay may have adverse consequences for patients who undergo percutaneous coronary interventions before the antiplatelet effect is maximal.¹⁵

Although the development of platelet glycoprotein IIb/IIIa antagonists has been a remarkable achievement in the field of percutaneous coronary interventions,⁶ studies suggest that the benefit provided by these agents is greater if patients are not adequately pretreated with thienopyridines.^{16,17} It is unclear whether and to what extent additional benefit can be obtained from the administration of glycoprotein IIb/IIIa inhibitors to patients in whom clopidogrel-induced inhibition of platelet aggregation is maximal.¹⁸ Data indicate that the use of a 600-mg loading dose of clopidogrel results in a maximal antiplatelet effect within two hours^{10,13,19}; this pretreatment dose has been safe in patients who are undergoing coronary-artery stenting with or without abciximab.²⁰ We designed this trial to evaluate whether abciximab provides additional clinical benefit in patients who are undergoing elective percutaneous coronary intervention after pretreatment with a 600-mg dose of clopidogrel.

METHODS

PATIENTS

Patients with coronary artery disease were eligible for the study if they were to undergo elective percutaneous coronary intervention in native coronary vessels between May 2000 and February 2003 and had been pretreated with 600 mg of clopidogrel at least two hours before the intervention. Patients were excluded if they had had a myocardial infarction within the prior 14 days; had unstable angina with ST-segment changes of at least 0.1 mV in at

least two electrocardiographic leads at rest, a troponin T level of more than 0.03 ng per milliliter, or both; had a target lesion in a venous bypass graft; had a chronic occlusion (present for longer than 3 months); had a target lesion with angiographically visible thrombus; had a left ventricular ejection fraction of less than 30 percent; had hemodynamic instability, insulin-dependent diabetes mellitus, pericarditis, or cancer; had had a stroke in the prior 3 months; had active bleeding or bleeding diathesis; had had trauma or major surgery in the preceding month; had a suspected aortic dissection; were receiving oral anticoagulation therapy; had received a glycoprotein IIb/IIIa inhibitor within the preceding 14 days; had severe, uncontrolled hypertension (systolic blood pressure of more than 180 mm Hg); had a hemoglobin level of less than 10.0 g per deciliter or a hematocrit below 34 percent; had a platelet count of less than 100,000 per cubic millimeter or more than 600,000 per cubic millimeter; had had a known allergic reaction to the study medication; or were or might be pregnant. All patients provided written informed consent, and the study protocol was approved by the ethics committees of the participating centers.

STUDY PROTOCOL

Patients in both study groups received 600 mg of clopidogrel at least two hours before the percutaneous coronary intervention. They also received 325 to 500 mg of aspirin. After the decision to perform a percutaneous coronary intervention but before the guide wire had crossed the lesion, patients underwent randomization in a double-blind manner with the use of sealed envelopes containing the block randomization sequence for each participating center. Patients in the abciximab group received abciximab (a bolus of 0.25 mg per kilogram of body weight, followed by an infusion of 0.125 μ g per kilogram per minute [maximum, 10 μ g per minute] for 12 hours) along with 70 U of heparin per kilogram. Patients in the placebo group received a bolus of placebo, followed by a 12-hour infusion, and a bolus of 140 U of heparin per kilogram. Among patients who are not receiving a glycoprotein IIb/IIIa inhibitor, the use of large doses of heparin — more than 100 U per kilogram — is standard practice in most of Europe, where monitoring of the activated clotting time is not routinely performed during percutaneous coronary interventions. Patients at the participating center in the United States (in which fewer than 5 percent of patients were enrolled) received ei-

ther an abciximab bolus and infusion along with a total of 70 U of heparin per kilogram or a placebo bolus and infusion with 100 U of heparin per kilogram, along with monitoring to maintain an activated clotting time of approximately 250 to 300 seconds, according to the physician's preference and in accordance with practice patterns in the United States. Double-blinding was achieved by the use of similar-appearing vials in the two groups.

Coronary stenting was the target percutaneous coronary intervention according to the protocol. Postinterventional therapy included aspirin (100 to 325 mg a day indefinitely) and clopidogrel (75 mg twice a day until discharge but no longer than three days, followed by a daily dose of 75 mg for at least one month as indicated), as well as other cardiac medications thought to be required by the patient's physician. The protocol provided for the performance of electrocardiography and collection of blood samples for the determination of cardiac enzyme levels, hemoglobin levels, and platelet counts every 8 hours for the first 24 hours after the procedure and daily afterward, until discharge. Three or more cardiac enzyme measurements were obtained in 82 percent of the patients; two or more measurements were obtained in 99 percent of patients. Patients were interviewed by telephone at 30 days, and those with cardiac symptoms were seen in the outpatient clinic for a complete clinical, electrocardiographic, and laboratory checkup.

STUDY END POINTS AND DEFINITIONS

The primary end point of the study was the cumulative incidence of death from any cause, myocardial infarction, or urgent target-vessel revascularization (coronary bypass surgery or percutaneous intervention) owing to myocardial ischemia within 30 days after randomization. The diagnosis of myocardial infarction was based on either the development of pathologic Q waves in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of normal in at least two blood samples.¹⁶ The diagnosis of a large myocardial infarction was based on the presence of new pathologic Q waves in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to at least five times the upper limit of normal in at least two samples.¹⁶

The safety of the study medications was assessed on the basis of the 30-day incidence of major and minor bleeding, profound thrombocytopenia (less

than 20,000 platelets per cubic millimeter), or the need for transfusion. Major bleeding and minor bleeding were defined according to the Thrombolysis in Myocardial Infarction criteria.²¹ A bleeding complication was defined as major if it was intracranial or if clinically significant overt signs of hemorrhage were associated with a drop in hemoglobin of more than 5.0 g per deciliter (or, when a hemoglobin value was not available, an absolute drop in the hematocrit of at least 15 percent). Minor bleeding was defined as clinically overt hemorrhage (including that seen on imaging) associated with a fall in hemoglobin of 3.0 to 5.0 g per deciliter (or, when a hemoglobin value was not available, a fall in the hematocrit of 9 percentage points to less than 15 percentage points). All events were adjudicated and classified by an event-adjudication committee whose members were unaware of the patients' assigned treatment.

STATISTICAL ANALYSIS

The initial assumption was that the event rate would be 8 percent in the placebo group. The trial was designed on the basis of the superiority principle to have 80 percent power to detect a 50 percent reduction in the incidence of the primary end point with abciximab therapy at an α level of 0.05. On this basis, 550 patients were needed in each group. After the data and safety monitoring board identified a lower-than-expected overall event rate among the first 678 enrolled patients, the sample-size requirements were recalculated and the number of patients in the trial was doubled. The final design of the trial was to have 80 percent power to detect a 40 percent reduction in the incidence of the primary end point with abciximab therapy at an α level of 0.05, assuming an event rate of 7 percent in the placebo group. On this basis, 1050 patients were needed in each group.

The investigators had full access to the data and were fully involved in the data analysis. All analyses were performed in a blinded manner regarding the randomly assigned treatment. Unblinding of the study groups was done after completion of the statistical analyses. In no case was the treatment assignment revealed because of clinical needs, and no crossovers occurred. The data are presented as means \pm SD; medians, with 25th and 75th percentiles; or counts or percentages. The differences between the groups were assessed with the use of a two-sided chi-square test or Fisher's exact test for categorical data, as appropriate. Student's *t*-test or

a nonparametric Wilcoxon rank-sum test was used to compare continuous data. The main analysis was done by calculating the relative risk of the primary end point (with the 95 percent confidence interval) associated with the use of abciximab, as compared with the use of placebo. Secondary analyses addressed the comparison of abciximab with placebo in prespecified subgroups defined by older age (more than 70 years), sex, the presence of type 2 diabetes, the presence of angina class III or IV²² or a prior myocardial infarction, and the presence of complex (type B2 or C) lesions.²³ A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Base-line characteristics and the type of intervention performed for the 2159 patients enrolled in the study are shown in Tables 1 and 2. The mean age of the study population was 66 years, 40 percent had class III or IV angina, 74 percent had multivessel disease, 33 percent had a history of myocardial infarction, 20 percent had type 2 diabetes, and 65 percent of the target lesions were type B2 or C. Coronary stenting was the most commonly performed percutaneous coronary intervention. Intervention was performed in more than one lesion in 322 patients (30 percent) in the abciximab group and 330 patients (31 percent) in the placebo group (P=0.72). Thirty-day follow-up was complete in all patients.

EFFICACY ANALYSIS

Figure 1 shows the incidence of adverse events during the 30 days after randomization. Three patients in each group (0.3 percent) died. Q-wave myocardial infarction occurred in four patients (0.4 percent) in the abciximab group and five patients (0.5 percent) in the placebo group (P=1.0). A myocardial infarction occurred in 4 percent of patients in the abciximab group (40 patients) and 4 percent of patients in the placebo group (41 patients, P=0.91), and a large myocardial infarction occurred in 18 patients (2 percent) and 16 patients (1 percent), respectively (P=0.73). Ten patients (1 percent) in the abciximab group and seven patients (1 percent) in the placebo group (P=0.46) required urgent revascularization because of severe ischemia. In 8 of these 17 patients (5 in the abciximab group and 3 in the placebo group), aortocoronary bypass surgery was performed. The incidence of death or a large myocardial infarction was 2 percent (21 patients) in the abcix-

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Abciximab (N=1079)	Placebo (N=1080)
Age — yr	65.4±10.4	66.1±9.9
Women — no. (%)	253 (23)	256 (24)
Body-mass index	27.2±3.7	27.2±3.8
Arterial hypertension — no. (%)	581 (54)	591 (55)
Type 2 diabetes — no. (%)	227 (21)	214 (20)
Current smoker — no. (%)	191 (18)	184 (17)
Hypercholesterolemia — no. (%)	579 (54)	574 (53)
Prior myocardial infarction — no. (%)	343 (32)	360 (33)
Prior aortocoronary bypass surgery — no. (%)	111 (10)	96 (9)
Angina class III or IV — no. (%)	436 (40)	433 (40)
Multivessel disease — no. (%)	805 (75)	797 (74)
Left ventricular ejection fraction	0.596±0.123	0.587±0.123
Duration of clopidogrel pretreatment — hr		
Median	7.4	7.4
25th–75th Percentiles	4.0–18.0	3.9–20.2
Drug therapy at admission — no. (%)		
Aspirin	817 (76)	817 (76)
ACE inhibitors	594 (55)	613 (57)
Beta-blockers	729 (68)	742 (69)
Calcium-channel antagonists	161 (15)	153 (14)
Nitrates	272 (25)	286 (26)
Statins	605 (56)	622 (58)

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme. There were no significant differences between the groups. The body-mass index is the weight in kilograms divided by the square of the height in meters.

imab group and 2 percent (17 patients) in the placebo group (P=0.51). The combined incidence of death or any myocardial infarction was 4 percent (43 patients) in the abciximab group and 4 percent (42 patients) in the placebo group (P=0.91).

Figure 2 shows the cumulative incidence curves for the primary end point of the trial: death, myocardial infarction, or urgent target-vessel revascularization. The 30-day incidence of the primary end point was 4 percent (45 patients) in the abciximab group and 4 percent (43 patients) in the placebo group (relative risk associated with abciximab, 1.05; 95 percent confidence interval, 0.69 to 1.59; P=0.82). Figure 3 shows the results of the analyses in various subgroups of the population.

SAFETY ANALYSIS

Twelve patients (1 percent) in the abciximab group and eight patients (1 percent) in the placebo group had a major bleeding complication (P=0.37). The incidence of minor bleeding complications was

Table 2. Base-Line Characteristics of the Lesions and the Types of Intervention.*

Characteristic	Abciximab (N=1401)	Placebo (N=1410)
	<i>no. of lesions (%)</i>	
Location of treated lesion		
Left main coronary artery	31 (2)	29 (2)
Left anterior descending coronary artery	590 (42)	550 (39)
Left circumflex coronary artery	361 (26)	393 (28)
Right coronary artery	411 (29)	432 (31)
Bypass-vein graft	8 (1)	6 (<1)
Complex (type B2 or C) lesions	910 (65)	927 (66)
Total occlusion	61 (4)	71 (5)
Restenotic lesion	78 (6)	85 (6)
Type of intervention		
Stenting	1270 (91)	1276 (90)
Balloon angioplasty	131 (9)	134 (10)

* Plus-minus values are means ±SD. There were no significant differences between the groups.

2 percent (27 patients) in the abciximab group and 2 percent (21 patients) in the placebo group ($P=0.38$). Profound thrombocytopenia occurred in 10 patients (1 percent) in the abciximab group, as compared with none in the placebo group ($P=0.002$). Transfusion of blood products was required in 26 patients (2 percent) in the abciximab group and 10 patients (1 percent) in the placebo group ($P=0.007$).

DISCUSSION

We assessed whether the administration of the glycoprotein IIb/IIIa antagonist abciximab reduced the incidence of ischemic complications in patients undergoing elective stent placement after pretreatment with a 600-mg loading dose of clopidogrel. The chief finding was that the use of abciximab was associated with no clinically measurable benefit in the 30 days after the procedure. Although the overall incidence of bleeding complications was low in this trial, abciximab was associated with an increased frequency of profound thrombocytopenia and need for blood-product transfusion. The trial could not directly assess the benefits of a large loading dose of clopidogrel, since all patients in the trial received it. However, the event rate was lower than the event rate in low-risk subgroups in the placebo groups of similar controlled trials of a glycoprotein IIb/IIIa inhibitor.^{16,24} Since other trials have indicated a benefit from the glycoprotein IIb/IIIa inhibitor, our finding of the lack of such an effect after clopidogrel

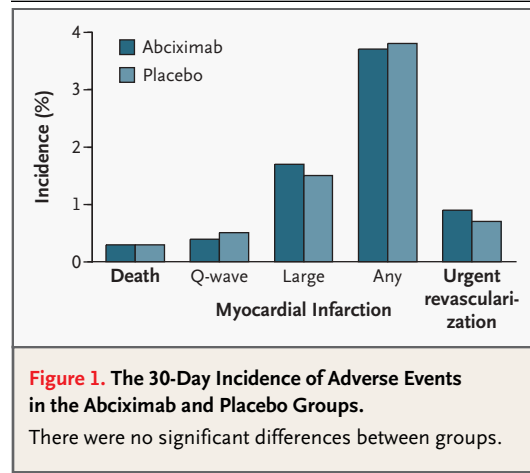


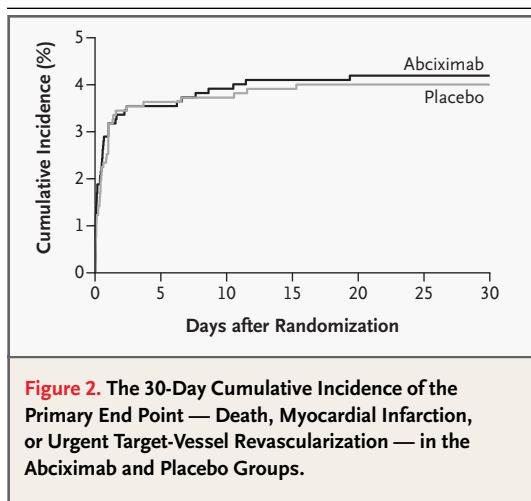
Figure 1. The 30-Day Incidence of Adverse Events in the Abciximab and Placebo Groups.

There were no significant differences between groups.

treatment suggests a favorable effect for this pretreatment regimen.

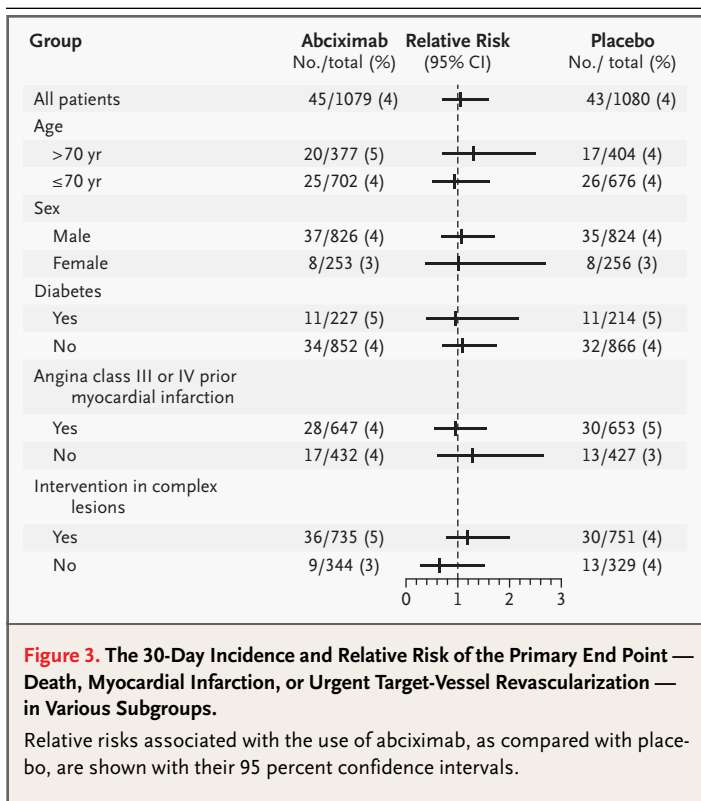
The European centers used a larger heparin bolus in the placebo group than is traditionally used in the United States (140 U per kilogram vs. 100 U per kilogram),¹⁶ but at the same time, there was no monitoring of the activated clotting time and no additional heparin doses were administered during the procedure. After accounting for the additional heparin doses that followed the bolus dose, analysis of pooled data from six randomized trials reveals a mean total heparin dose of more than 14,000 U in the placebo groups of those trials.²⁵ Therefore, our heparin strategy led to a higher bolus dose but less total heparin than was administered to patients in prior studies in which a glycoprotein IIb/IIIa inhibitor was not used. The abciximab group received a reduced dose of heparin of 70 U per kilogram. According to current guidelines, which are based on randomized trials, a reduced dose of 50 to 70 U per kilogram should be used in combination with glycoprotein IIb/IIIa inhibitors,²⁶ since higher doses of heparin increase the frequency of bleeding complications without improving efficacy.²⁷ Furthermore, the rates of bleeding complications in both the abciximab and placebo groups were similar to those in previous trials of glycoprotein IIb/IIIa antagonists,^{16,17,24,28} indirectly suggesting that the 600-mg loading dose of clopidogrel is safe.

The incidence of ischemic complications was 4 percent in the abciximab group. If we consider the glycoprotein IIb/IIIa inhibitor group in previous clinical trials, the incidence of ischemic complications ranged from 5.3 percent to 7.6 percent when all patients were included and from 4.4 percent to



6.8 percent when only patients with stable angina were analyzed.^{16,17,24} The low incidence of ischemic complications in our trial compares favorably with those reported in the trials cited above. Although differences in the patients' characteristics may have contributed to the low event rate, we believe that the antiplatelet effect of a 600-mg loading dose of clopidogrel was the most likely reason.

The lower-risk profile of our study population as compared with those of previous trials^{16,24} may largely be responsible for the lack of additional benefit with abciximab. However, two findings make this hypothesis highly improbable. First, abciximab did not tend to reduce the incidence of ischemic complications in any of the high-risk subgroups of our population. In fact, the findings of our subgroup analysis for patients with diabetes are not in line with those of a previous meta-analysis showing a benefit with abciximab therapy in patients with diabetes.²⁹ We should bear in mind, however, that patients with insulin-dependent diabetes, a subgroup at particularly high risk included in the meta-analysis,²⁹ were excluded from our trial. Second, a reduction in the risk of ischemic events of 25 to 50 percent was previously found with abciximab and eptifibatid, even when the analysis was restricted to the low-risk subgroup of patients with stable angina.^{16,24} We acknowledge, however, that the actual event rate in the placebo group was lower than expected, which reduced the power of the study; as a consequence, the 95 percent confidence interval included a 31 percent reduction with abciximab (from -31 percent to 59 percent). The lack of benefit of abciximab after a high loading dose of clopidogrel should



not be applied to patients at higher risk than those enrolled in this trial. In conclusion, in patients at low and intermediate risk who undergo elective percutaneous coronary intervention after pretreatment with a 600-mg loading dose of clopidogrel at least two hours before the procedure, the additional use of abciximab is associated with no clinically measurable benefit within the first 30 days.

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APPENDIX

The ISAR-REACT Study was organized as follows: **Steering committee** — A. Schömig (chair), A. Kastrati (principal investigator), J. Dirschinger, P.B. Berger; **Data and Safety Monitoring Board** — J. Mann (chair), F. Hofmann, M. Schwaiger, K. Ulm (statistician); **Event Adjudication Committee** — J. Dirschinger, H. Schühlen, J. Pache; **Data-Coordinating Center** — J. Mehilli (director), H. Bollwein, C. Volmer, M. Hadamitzky, C. Markwardt, J. Hausleiter, H. Holle, F. Rodrigues, K. Hösl; **Study Sites and Investigators** — *Germany*: Deutsches Herzzentrum, Munich: H. Schühlen (principal investigator), M. Gawaz, C. Schmitt, R. Blasini, N. von Beckerath; First Medizinische Klinik rechts der Isar, Munich: J. Dirschinger (principal investigator), J. Pache, M. Seyfarth; Medizinische Klinik I, Garmisch-Partenkirchen: F. Dotzer (principal investigator), M. Fleckenstein, C. Glatthor; Herz-Zentrum, Bad Krozingen: F.-J. Neumann (principal investigator), V. Bassignana, H.-J. Büttner, H.-P. Bestehorn, K. Peitz; *the Netherlands*: St. Antonius Ziekenhuis, Nieuwegein: J.M. ten Berg (principal investigator), K. Hamraoui, T. Herbots, M.J. Suttorp, B.J.W.M. Rensing, E.T. Bal, J.M.P.G. Ernst; *United States*: Mayo Clinic, Rochester, Minn.: P.B. Berger (principal investigator), D. Shelstad.

REFERENCES

1. Topol EJ, Serruys PW. Frontiers in interventional cardiology. *Circulation* 1998;98:1802-20.
2. Schömig A, Neumann F-J, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;334:1084-9.
3. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998;339:1665-71.
4. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998;129:394-405.
5. Hollopeter G, Jantzen HM, Vincent D, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 2001;409:202-7.
6. Bhatt DL, Topol EJ. Scientific and therapeutic advances in antiplatelet therapy. *Nat Rev Drug Discov* 2003;2:15-28.
7. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999;100:1667-72.
8. Steinhubl SR, Lauer MS, Mukherjee DP, et al. The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non-Q-wave myocardial infarctions. *J Am Coll Cardiol* 1998;32:1366-70.
9. Schühlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. *Circulation* 1998;98:104-11.
10. Thebault JJ, Kieffer G, Cariou R. Single-dose pharmacodynamics of clopidogrel. *Semin Thromb Hemost* 1999;25:Suppl 2:3-8.
11. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. *Semin Thromb Hemost* 1999;25:Suppl 2:15-9.
12. Helft G, Osende JI, Worthley SG, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. *Arterioscler Thromb Vasc Biol* 2000;20:2316-21.
13. Gawaz M, Seyfarth M, Müller I, et al. Comparison of effects of clopidogrel versus ticlopidine on platelet function in patients undergoing coronary stent placement. *Am J Cardiol* 2001;87:332-6.
14. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908-13.
15. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]
16. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;352:87-92.
17. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888-94.
18. Berger PB, Steinhubl S. Clinical implications of percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events (PCI-CURE) study: a US perspective. *Circulation* 2002;106:2284-7.
19. Müller I, Seyfarth M, Rüdiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* 2001;85:92-3.
20. Pache J, Kastrati A, Mehilli J, et al. Clopidogrel therapy in patients undergoing coronary stenting: value of a high-loading-dose regimen. *Catheter Cardiovasc Interv* 2002;55:436-41.
21. The TIMI Study Group. Definitions used in TIMI trials. (Accessed December 18, 2003, at <http://www.timi.org/>.)
22. Campeau L. Grading of angina pectoris. *Circulation* 1976;54:522-3.
23. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. *Circulation* 1990;82:1193-202.
24. The ESPRIT Investigators. Novel dosing regimen of eptifibatid in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356:2037-44. [Erratum, *Lancet* 2001;357:1370.]
25. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation* 2001;103:961-6.
26. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) — executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001;103:3019-41.
27. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689-96.
28. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853-63. [Erratum, *JAMA* 2003;289:1638.]
29. Bhatt DL, Marso SP, Lincoff AM, Woloski KE, Ellis SG, Topol EJ. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000;35:922-8.

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