

Risk of Stroke Associated With Abciximab Among Patients Undergoing Percutaneous Coronary Intervention

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INTRAVENOUS PLATELET GLYCOPROTEIN (GP) IIb/IIIa receptor inhibitors effectively reduce thrombotic complications in patients undergoing percutaneous coronary intervention (PCI).¹⁻⁶ In randomized studies, treatment with abciximab (a monoclonal antibody Fab fragment directed against the platelet GP IIb/IIIa receptor⁷) resulted in an approximate 50% reduction in the composite of death or myocardial infarction at 30 days.¹⁻⁴ However, inhibition of platelet aggregation by GP IIb/IIIa receptor blockers such as abciximab increases the risk of bleeding complications, particularly when these agents are combined with conventional doses of heparin.¹⁻⁸

Intracerebral hemorrhage is the most serious potential complication of anti-thrombotic or anticoagulant therapy and usually results in fatality or disability.⁹ Because of its potent inhibition of platelet aggregation, the effect of abciximab on the risk of stroke has been a concern. We performed a com-

Context Abciximab, a potent inhibitor of the platelet glycoprotein IIb/IIIa receptor, reduces thrombotic complications in patients undergoing percutaneous coronary intervention (PCI). Because of its potent inhibition of platelet aggregation, the effect of abciximab on risk of stroke is a concern.

Objective To determine whether abciximab use among patients undergoing PCI is associated with an increased risk of stroke.

Design Combined analysis of data from 4 double-blind, placebo-controlled, randomized trials (EPIC, CAPTURE, EPILOG, and EPISTENT) conducted between November 1991 and October 1997 at a total of 257 academic and community hospitals in the United States and Europe.

Patients A total of 8555 patients undergoing PCI with or without stent deployment for a variety of indications were randomly assigned to receive a bolus and infusion of abciximab (n=5476) or matching placebo (n=3079). One treatment group in EPIC received a bolus of abciximab only.

Main Outcome Measure Risk of hemorrhagic and nonhemorrhagic stroke within 30 days of treatment among abciximab and placebo groups.

Results No significant difference in stroke rate was observed between patients assigned abciximab (n=22 [0.40%]) and those assigned placebo (n=9 [0.29%]; $P=.46$). Excluding the EPIC abciximab bolus-only group, there were 9 strokes (0.30%) among 3023 patients who received placebo and 15 (0.32%) in 4680 patients treated with abciximab bolus plus infusion, a difference of 0.02% (95% confidence interval [CI], -0.23% to 0.28%). The rate of nonhemorrhagic stroke was 0.17% in patients treated with abciximab and 0.20% in patients treated with placebo (difference, -0.03%; 95% CI, -0.23% to 0.17%), and the rates of hemorrhagic stroke were 0.15% and 0.10%, respectively (difference, 0.05%; 95% CI, -0.11% to 0.21%). Among patients treated with abciximab, the rate of hemorrhagic stroke in patients receiving standard-dose heparin in EPIC, CAPTURE, and EPILOG was higher than in those receiving low-dose heparin in the EPILOG and EPISTENT trials (0.27% vs 0.04%; $P=.057$).

Conclusions Abciximab in addition to aspirin and heparin does not increase the risk of stroke in patients undergoing PCI. Patients undergoing PCI and treated with abciximab should receive low-dose, weight-adjusted heparin.

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combined analysis of 8555 patients from 4 large randomized trials¹⁻⁴ to compare stroke rates between patients treated

with abciximab (in addition to aspirin and heparin) and those receiving placebo during PCI.

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METHODS

Study Protocols and Population

Data were obtained from EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina), EPILOG (Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade), and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting), 4 studies conducted between November 1991 and October 1997 at a total of 257 academic and community hospitals in the United States and Europe.

The protocols and results of the 4 studies have been published in detail.¹⁻⁴ In brief, the studies were large, double-blind, placebo-controlled, randomized trials designed to evaluate the efficacy of the GP IIb/IIIa receptor inhibitor abciximab in reducing thrombotic complications in patients undergoing PCI for a variety of indications. The EPIC trial enrolled patients scheduled to undergo balloon angioplasty in high-risk clinical situations including unstable angina, evolving myocardial infarction, or high-risk coronary morphology.¹ CAPTURE evaluated the use of abciximab in patients with unstable angina refractory to conventional medical therapy for whom PCI was planned and performed after approximately 24 hours of pretreatment with abciximab or placebo.² EPILOG evaluated use of abciximab among patients undergoing elective balloon angioplasty.³ EPISTENT evaluated the hypothesis that stenting plus abciximab and balloon angioplasty plus abciximab would be superior to stenting plus placebo among patients scheduled to undergo elective or urgent percutaneous coronary revascularization.⁴

In the EPIC trial (median age [25th and 75th percentiles], 61 [52,68] years), patients were excluded if they were 80 years of age or older. In EPILOG (median age, 60 [51,69] years), patients were eligible for inclusion if they were older than 21 years. In the CAPTURE and EPISTENT trials (median age, 61 and 59 years, respectively), there were no limitations with respect to age. All

trials excluded patients with characteristics associated with an increased risk of bleeding, as well as those with a cerebrovascular accident within the preceding 2 years.

Patients were randomly assigned to receive a bolus and an infusion of abciximab (0.25 mg/kg bolus, 10 µg/min infusion in EPIC and CAPTURE and 0.125 µg/kg per minute [maximum 10 µg/min] in EPILOG and EPISTENT) or matching placebo. One treatment group in EPIC received a bolus of abciximab only. In EPIC, EPILOG, and EPISTENT, the study drug was administered from 1 hour before until 12 hours after PCI. The CAPTURE trial required administration of placebo or abciximab starting 18 to 24 hours prior to PCI and continuing until 1 hour after completion of the intervention.

All patients received aspirin and intravenous heparin. With the exception of EPIC, all trials adjusted the heparin dose for weight for all patients. In EPIC, heparin was given in an initial bolus of 10 000 to 12 000 U followed by incremental bolus doses to keep the activated clotting time between 300 and 350 seconds during the intervention.¹ CAPTURE and 1 abciximab treatment arm in EPILOG used a standard-dose, weight-adjusted heparin regimen that consisted of an initial bolus of 100 U of heparin per kilogram (maximum 10 000 U), with additional boluses as necessary to achieve and maintain an activated clotting time of at least 300 seconds.^{2,3} In addition to weight adjustment, patients in the second abciximab treatment arm in EPILOG and patients in both abciximab treatment arms in EPISTENT received a low-dose heparin regimen (70 U/kg bolus with maximum of 7 000 U, followed by additional boluses to keep the activated clotting time at least 200 seconds).^{3,4}

The study protocols were approved by the institutional review board at each study center and all patients gave written informed consent to participate.

Stroke Classification

Patients with suspected strokes were identified from the case report forms for

each study. Clinical notes, hospital discharge summaries, neurological consultation reports, results of computed tomographic or magnetic resonance imaging studies or reports, and, if applicable, autopsy reports were collected for all patients with suspected stroke for final adjudication and classification. Any suspected stroke that occurred during the 30-day follow-up period was independently adjudicated and confirmed by a central clinical events committee (blinded to patient treatment assignment) and was classified as hemorrhagic or nonhemorrhagic.

Statistical Analysis

The rate of stroke and intracranial bleeding was determined among all patients as randomized, and among all patients as treated, with exclusion of the abciximab bolus-only group in the EPIC trial. Compared with the abciximab bolus plus infusion treatment regimen, the abciximab bolus-only regimen in the EPIC trial did not result in sufficient efficacy in reducing thrombotic complications during PCI to warrant further clinical evaluation. Therefore, all subsequent abciximab PCI trials used a treatment strategy that consisted of a bolus followed by an infusion. For this reason, as well as to provide an unbiased basis for comparison across the 4 trials and to reflect actual clinical practice in which patients are being treated with abciximab bolus and infusion, the abciximab bolus-only group was excluded from the treatment analysis. Stroke rates in this group are reported separately.

Continuous variables are presented as means with SDs. Discrete variables are shown as frequencies and percentages. Baseline characteristics among patients with and without stroke were compared in univariable analysis using the *t* test for continuous variables and the Fisher exact test for proportions. Statistical software used was S-PLUS, version 3.3 (Insightful Corp, Seattle, Wash).

RESULTS

All Patients

Among the 8555 patients randomized in the 4 trials, there were 33 strokes re-

ported in 31 patients (0.36%) within the first 30 days following enrollment. Stroke occurred in 9 (0.29%) of the 3079 patients randomized to placebo and in 22 (0.40%) of the 5476 patients randomized to abciximab ($P=.46$), including nonhemorrhagic stroke in 6 patients assigned placebo (0.20%) and 13 patients assigned abciximab (0.24%) ($P=.81$); hemorrhagic stroke or intracranial bleeding occurred in 3 patients assigned pla-

cebo (0.10%) and in 9 patients assigned abciximab (0.16%) ($P=.56$). In 1 patient, the type of stroke could not be established.

Among the 695 patients in the EPIC abciximab bolus-only group, 1 patient (0.14%) experienced a hemorrhagic stroke, and 4 patients (0.58%) had a nonhemorrhagic stroke.

Two strokes occurred among patients in the EPIC trial who had been randomized to abciximab bolus plus in-

fusion but were not treated because the stroke occurred after randomization but before the angioplasty. Both patients (one with a hemorrhagic stroke and one with a nonhemorrhagic stroke) died prior to study drug administration and angioplasty. All patients who experienced strokes or intracranial bleeding events in the CAPTURE, EPILOG, and EPISTENT trials had received the allocated study drug.

Study Drug Bolus and Infusion

Among the 7703 patients who received study drug bolus and infusion, there were 24 strokes: 9 (0.30%) of 3023 patients treated with placebo and 15 (0.32%) of 4680 patients treated with abciximab bolus plus infusion. There were no statistically significant differences in the rates between these groups overall or in the rates of nonhemorrhagic stroke or intracranial bleeding/hemorrhagic stroke (TABLE 1). One of 3 patients with intracranial bleeding/hemorrhagic stroke in the placebo group died of stroke compared with 4 of 7 patients treated with abciximab.

Heparin Dosing

The rate of hemorrhagic stroke was higher in patients receiving abciximab and standard-dose heparin (patients from EPIC, CAPTURE, and the standard-dose heparin arm of EPILOG) compared with those receiving abciximab and low-dose heparin (patients from EPISTENT and the low-dose heparin arm of EPILOG) (0.27% vs 0.04%, respectively; $P=.057$) (Table 1). No differences were observed in the means of the maximum activated clotting time values achieved during the procedure between patients with hemorrhagic stroke and those without. A trend toward higher incidence of nonhemorrhagic stroke was apparent in patients receiving abciximab and low-dose heparin vs abciximab and standard-dose heparin (0.24% vs 0.09%, respectively; $P=.30$).

Predictive Value of Baseline Characteristics

Patients who experienced a stroke were older, more often had a history of hy-

Table 1. Rates of Stroke and Intracranial Bleeding*

| | Patients Receiving Abciximab, No. (%) | Patients Receiving Placebo, No. (%) | Difference in Stroke Rate, % (95% CI)† | P Value |
|--|---|---|--|------------|
| All strokes | | | | |
| Total of 4 trials | 15/4680 (0.32) | 9/3023 (0.30) | 0.02 (−0.23 to 0.28) | .86 |
| EPIC | 3/678 (0.44) | 4/681 (0.59) | −0.14 (−0.91 to 0.62) | >.99 |
| CAPTURE | 1/622 (0.16) | 4/631 (0.63) | −0.47 (−1.17 to 0.22) | .37 |
| EPILOG | 6/1811 (0.33) | 0/914 (0.00) | 0.33 (0.07 to 0.60) | .19‡ |
| Standard-dose heparin | 4/898 (0.45) | 0/914 (0.00) | 0.45 (0.01 to 0.88) | .06‡ |
| Low-dose heparin | 2/913 (0.22) | ... | ... | ... |
| EPISTENT | 5/1569 (0.32) | 1/797 (0.13) | 0.19 (−0.18 to 0.56) | .67 |
| Angioplasty | 2/785 (0.25) | ... | ... | ... |
| Stent | 3/784 (0.38) | 1/797 (0.13) | 0.26 (−0.24 to 0.75) | .37 |
| Intracranial bleeding/ hemorrhagic stroke | | | | |
| Total of 4 trials | 7/4680 (0.15) | 3/3023 (0.10) | 0.05 (−0.11 to 0.21) | .75 |
| EPIC | 2/678 (0.29) | 2/681 (0.29) | 0.00 (−0.57 to 0.58) | >.99 |
| CAPTURE | 0/622 (0.00) | 1/631 (0.16) | −0.16 (−0.47 to 0.15) | >.99 |
| EPILOG | 5/1811 (0.28) | 0/914 (0.00) | 0.28 (0.03 to 0.52) | .18‡ |
| Standard-dose heparin | 4/898 (0.45) | 0/914 (0.00) | 0.45 (0.01 to 0.88) | .06‡ |
| Low-dose heparin | 1/913 (0.11) | ... | ... | ... |
| EPISTENT | 0/1569 (0.00) | 0/797 (0.00) | 0.00 | >.99 |
| Angioplasty | 0/785 (0.00) | ... | ... | ... |
| Stent | 0/784 (0.00) | 0/797 (0.00) | 0.00 | >.99 |
| Nonhemorrhagic stroke | | | | |
| Total of 4 trials | 8/4680 (0.17) | 6/3023 (0.20) | −0.03 (−0.23 to 0.17) | .78 |
| EPIC | 1/678 (0.15) | 2/681 (0.29) | −0.15 (−0.64 to 0.35) | >.99 |
| CAPTURE | 0/622 (0.00) | 3/631 (0.48) | −0.48 (−1.01 to 0.06) | .25 |
| EPILOG | 2/1811 (0.11) | 0/914 (0.00) | 0.11 (−0.04 to 0.26) | .55 |
| Standard-dose heparin | 1/898 (0.11) | 0/914 (0.00) | 0.11 (−0.11 to 0.33) | .50 |
| Low-dose heparin | 1/913 (0.11) | ... | ... | ... |
| EPISTENT | 5/1569 (0.32) | 1/797 (0.13) | 0.19 (−0.18 to 0.56) | .67 |
| Angioplasty | 2/785 (0.25) | ... | ... | ... |
| Stent | 3/784 (0.38) | 1/797 (0.13) | 0.26 (−0.24 to 0.75) | .37 |

*Rate of stroke and intracranial bleeding among patients treated with bolus plus infusion of abciximab or placebo in the 4 abciximab percutaneous coronary intervention trials (EPIC, CAPTURE, EPILOG, and EPISTENT) with exclusion of the abciximab bolus-only treatment group from the EPIC trial.

†The difference in rates denotes the difference between the stroke rate in patients receiving abciximab and patients receiving placebo. The 95% confidence interval (CI) denotes the difference in rates between both groups.

‡Fisher exact test for comparison of stroke rates between both treatment groups. The CI of the difference corresponds to testing whether the difference in stroke rates is equal to 0. The results from both tests do not correspond because the event rate in the placebo arm is 0 and the test of the difference is therefore testing the event rate in the abciximab arm being equal to 0.

hypertension, and less frequently had a history of diabetes mellitus (TABLE 2). Nonsignificant higher prevalences of peripheral vascular disease and prior revascularization procedures were apparent among patients who experienced a stroke.

COMMENT

This combined analysis of 8555 patients suggests that abciximab in addition to aspirin and heparin does not increase the overall risk of stroke in patients undergoing PCI. These results were obtained in a diverse population of patients undergoing PCI, with or without stent deployment, varying from patients with a low-risk profile and stable coronary artery disease to those at increased risk during PCI because of unstable ischemic syndromes or unfavorable lesion morphology on angiography.¹⁻⁴

For comparison, the rate of stroke in patients treated with heparin undergoing PCI for stable coronary artery disease and unstable coronary syndromes, including primary angioplasty for acute myocardial infarction, has been reported to be between 0% and 1%.¹⁰⁻¹⁹ In the current analysis, the rate of nonhemorrhagic stroke, as well as the rate of intracranial hemorrhage, in patients treated with abciximab were comparable to those for patients undergoing PCI receiving heparin.¹⁰⁻¹⁹ The current data also are consistent with that of other intravenous GP IIb/IIIa receptor inhibitors. In patients undergoing PCI in the IMPACT-II and RESTORE trials, the incidence of intracranial hemorrhage associated with eptifibatid and tirofiban treatment was 0.1%, which was comparable with the placebo event rate.^{5,6} Similarly, in the 10948 patients with acute coronary syndromes without persistent ST-segment elevation in the PURSUIT trial, there were no differences in stroke rates between patients who received placebo (0.8%, with hemorrhagic stroke rate <0.1%) and those who received eptifibatid (0.6%, with hemorrhagic stroke rate <0.1%).²⁰

In this study, patients who experienced a stroke were older, more often

had a history of hypertension, but less frequently a history of diabetes mellitus. These findings are consistent with the established risk factors for both non-hemorrhagic and hemorrhagic stroke among patients with ST-segment elevation myocardial infarction treated with thrombolytic therapy,²¹⁻²⁵ and with the baseline clinical and demographic predictors of stroke in the non-ST-segment elevation acute coronary syndrome patient population in the PURSUIT trial.²⁰

In patients treated with abciximab, a trend toward a higher incidence of intracranial bleeding was observed among patients receiving standard-dose heparin compared with those receiving a low-dose heparin regimen. As the number of hemorrhagic strokes was small and the difference only reached borderline statistical significance, definitive conclusions cannot be made about the potential risk of heparin dosing on the incidence of hemorrhagic stroke in the patient population studied. However, other major bleeding complications are also reduced by the use of a low-dose heparin regimen compared with a standard-dose heparin regimen in patients receiving abciximab.¹⁻⁴ Furthermore, previous studies in patients with acute myocardial infarction treated with thrombolytic agents have shown that inappropriate high dosing of antithrombotic therapy has the potential to substantially increase the incidence of hemorrhagic stroke²⁶⁻²⁸ and suggest that caution should be exercised with respect to dosing of heparin in patients undergoing PCI and receiving abciximab. In fact, the EPILOG and EPISTENT trials have shown that the clinical benefit of abciximab can be uncoupled from the risk of hemorrhage by using low-dose, weight-adjusted heparin regimens.^{3,4} This approach should be regarded as a standard treatment strategy for patients undergoing PCI and treated with abciximab or any other GP IIb/IIIa receptor blocker.

On the other hand, surveillance with respect to the efficacy of the low-dose heparin regimen in protecting patients from nonhemorrhagic stroke is

Table 2. Baseline Demographics by Stroke Status*

| | All Stroke (n = 31) | No Stroke (n = 8524) | P Value† |
|--|------------------------|-------------------------|----------|
| Mean (SD), age, y | 67 (7) | 60 (11) | <.001 |
| Sex, % female | 35 | 27 | .29 |
| Mean (SD) weight, kg | 82 (17) | 84 (16) | .61 |
| Mean (SD) height, cm | 171 (9) | 172 (10) | .99 |
| Hypertension | 77 | 54 | .01 |
| Diabetes mellitus | 7 | 21 | .04 |
| Current smoker or quit within last year | 27 | 35 | .33 |
| Prior coronary artery bypass graft | 19 | 11 | .14 |
| Prior percutaneous coronary intervention | 24 | 20 | .56 |
| Prior congestive heart failure | 7 | 6 | .70 |
| History of peripheral vascular disease | 17 | 8 | .08 |
| Prior stroke | 3 | 2 | .45 |

*Data are expressed as percentages unless otherwise indicated.
†P values for comparison of continuous variables according to t test, for discrete variables according to the Fisher exact test.

equally needed. Similarly, the apparent small excess of nonhemorrhagic strokes in the abciximab bolus-only group in the EPIC trial compared with the overall rate of nonhemorrhagic stroke among patients receiving abciximab bolus plus infusion might also be an expression of the previously reported insufficient level of antithrombotic efficacy provided by this treatment regimen in this clinical setting.

The current analysis of 8555 patients undergoing PCI and treated with either abciximab or placebo was limited by the very low incidence of stroke in this patient population. As most strokes, and especially most hemorrhagic strokes, occur in older patients, data on a larger number of elderly patients are required to provide more definitive assurance of the lack of risk of stroke in this subpopulation. Continued surveillance for occurrence of stroke in patients treated with abciximab and systemic collection of follow-up data from clinical trials and in clinical practice are needed.

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REFERENCES

1. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med.* 1994;330:956-961.
2. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet.* 1997;349:1429-1435.
3. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med.* 1997;336:1689-1696.
4. 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.
5. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatid on complications of percutaneous coronary intervention: IMPACT-II. *Lancet.* 1997;349:1422-1428.
6. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation.* 1997;96:1445-1453.
7. Ronner E, Dykun Y, Van den Brand MJB, et al. Platelet glycoprotein IIb/IIIa receptor antagonists: an asset for treatment of unstable coronary syndromes and coronary intervention. *Eur Heart J.* 1998;19:1608-1616.
8. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med.* 1998;339:436-443.
9. Tung CY, Granger CB, Sloan MA, et al, for the GUSTO-I Investigators. Effects of stroke on medical resource use and costs in acute myocardial infarction. *Circulation.* 1999;99:370-376.
10. Dorros G, Cowley MJ, Simpson J, et al. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. *Circulation.* 1983;67:723-730.
11. Serruys PW, De Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med.* 1994;331:489-495.
12. Fischman DL, Leon MB, Baim DS, et al, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med.* 1994;331:496-501.
13. Schomig 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;334:1084-1089.
14. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med.* 1996;335:217-225.
15. Zijlstra F, de Boer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med.* 1993;328:680-684.
16. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1993;328:673-679.
17. The GUSTO-IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med.* 1997;336:1621-1628.
18. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review [published correction appears in *JAMA.* 1998;279:1876]. *JAMA.* 1997;278:2093-2098.
19. Tiefenbrunn AJ, Chandra NC, French WJ, et al. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMII-2). *J Am Coll Cardiol.* 1998;31:1240-1245.
20. Mahaffey KW, Harrington RA, Simoons ML, et al. Stroke in patients with acute coronary syndromes: incidence and outcomes in the PURSUIT trial. *Circulation.* 1999;99:2371-2377.
21. Gore JM, Granger CB, Simoons ML, et al. Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation.* 1995;92:2811-2818.
22. Longstreth WT Jr, Litwin PE, Weaver WD, and the MITI Project Group. Myocardial infarction, thrombolytic therapy, and stroke: a community-based study. *Stroke.* 1993;24:587-590.
23. De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. *J Am Coll Cardiol.* 1992;19:289-294.
24. Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet.* 1993;342:1523-1528.
25. Mahaffey KW, Granger CB, Sloan MA, et al. Risk factors for in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis: results from GUSTO-I. *Circulation.* 1998;97:757-764.
26. Antman EM. Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. *Circulation.* 1994;90:1624-1630.
27. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation.* 1994;90:1631-1637.
28. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation.* 1996;93:870-878.