Randomized Trial of Intravenous Heparin Versus Recombinant Hirudin for Acute Coronary Syndromes

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators

**Background** Although intravenous heparin is routinely used in the treatment of patients with acute coronary syndromes, this anticoagulant requires antithrombin III as a cofactor, has no affinity for clot-bound thrombin, and is bound or inactivated by several plasma proteins and platelet factor 4. Recombinant hirudin, the prototypic direct thrombin inhibitor, has been demonstrated in pilot studies to yield improved angiographic and clinical outcomes compared with heparin. We compared these two antithrombins in a large-scale randomized trial.

**Methods and Results** At 275 participating hospitals in 12 countries, patients within 12 hours of the onset of ischemic chest discomfort with an abnormal ECG were randomly assigned to receive a 72- to 120-hour infusion of heparin (5000-U bolus and 1000- to 1300-U/h infusion, adjusted to activated partial thromboplastin time [APTT] of 60 to 90 seconds or hirudin (0.6-mg/kg bolus and 0.2-mg/kg per hour infusion without APTT adjustment) on a double-blind basis. Although recruitment of 12,000 patients was planned, the trial was stopped earlier because of an excess of intracerebral hemorrhagic events after 2564 patients were enrolled. The overall incidence of hemorrhagic stroke tended to be higher for patients receiving hirudin (1.3%) compared with heparin (0.7%), P=.1, but the incidence was significantly higher in patients receiving thrombolytic therapy (1264 patients, 1.8%) compared with those who did not (1168 patients, 0.3%), P<.001. The hemorrhagic stroke rate varied by the thrombolytic and antithrombin combination: tissue-type plasminogen activator and heparin, 0.9%; with hirudin, 1.7%; streptokinase with heparin, 2.7%; with hirudin, 3.2%. All these rates are higher than the overall incidence of hemorrhagic stroke in the patients receiving thrombolytic therapy and intravenous hirudin in the GUSTO I trial (30 892 patients with rate of 0.7%, 95% CI of 0.6 to 0.8%). Among the 26 patients who had intracerebral hemorrhages, the APTT was significantly elevated compared with the event-free patients (110±46 versus 87±36 seconds at 12 hours of therapy, respectively), P=.03.

**Conclusions** At the dose of hirudin tested, there was a trend of an excess of hemorrhagic stroke compared with heparin. Heparin, at a slightly higher dose than previously used in a large-scale trial (approximately 20% increase) was accompanied by a twofold risk of hemorrhagic stroke in patients receiving thrombolytic therapy. With both thrombin inhibitors, the APTT appears to be a useful index for predicting risk of hemorrhagic stroke in patients receiving thrombolytic therapy. (Circulation. 1994;90:1631-1637.)

**Key Words** • heparin • coronary disease • thrombosis • anticoagulants • myocardial infarction

Our contemporary approach to the treatment of patients with acute coronary syndromes, including unstable angina, non-Q-wave myocardial infarction (MI), and ST-segment elevation infarction, is to administer intravenous heparin along with acetylsalicylic acid. Heparin is not an ideal antithrombotic agent; it requires antithrombin III as a cofactor, does not have affinity for clot-bound thrombin, and is bound or inactivated by plasma proteins and platelet factor 4. Because of these theoretical deficiencies, direct thrombin inhibitors—which bind to the catalytic site of thrombin, bind to thrombin in clot, and are resistant to agents that degrade heparin—have been studied in patients with acute coronary syndromes. The prototypic direct thrombin inhibitor is hirudin, a 65-amino-acid peptide derived from the medicinal leech (Hirudo medicinalis), which represents the most potent known naturally occurring anticoagulant and has now been made available in clinically useful quantities through recombinant technology. Hirudin has been compared with heparin in pilot studies with conjunctive thrombolytic therapy and in patients with unstable angina and non-Q-wave MI. These results have been encouraging, suggesting the potential for improved efficacy of preventing coronary artery thrombosis or facilitating thrombolysis without an increased hemorrhagic risk. Hirudin also has yielded a more consistent effect on anticoagulation, requiring substantially less adjustment to achieve a stable anticoagulant effect. In addition, studies with a synthetic derivative of hirudin known as Hirulog have similarly been promising in the setting of coronary angioplasty, acute MI, and unstable angina pectoris. Collectively, the thrombin hypothesis—that potent, direct antithrombin therapy would prove superior to heparin for the treatment of patients with acute coronary syndromes—required more definitive testing in larger population studies. To address this hypothesis, we initiated a randomized, double-blind, multinational trial of heparin compared with recombinant hirudin.

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Methods

Patients at more than 275 participating sites were screened for eligibility. To enter, patients had to be <12 hours from the onset of chest discomfort and to present with an abnormal ECG characterized by either ST-segment elevation or depression of at least 0.05 mV or T-wave inversion of at least 0.1 mV. Patients with active bleeding, a serum creatinine >2.5 mg/dL, prior stroke within 1 year, or contraindication to heparin were excluded. All patients gave informed consent. The protocol was approved by each hospital’s institutional review board, and patients were stratified into two groups: those with ST-segment elevation of >0.1 mV in two or more contiguous leads and those without ST-segment elevation. Patients with ST-segment elevation were eligible to receive thrombolytic therapy with either accelerated tissue-type plasminogen activator (TPA) or streptokinase, as used in the GUSTO I trial.1,15

By telephone communication with the Coordinating Center, patients were randomly assigned to receive heparin or recombinant hirudin. Porcine heparin of a single lot was used (Elkins Sinn, Inc); the dose was a 5000-U bolus followed by 1000 U per hour for patients weighing <80 kg and 1300 U per hour for patients ≥80 kg. The dose of hirudin (recombinant desulfatohirudin, CIBA-GEIGY) was 0.6-6 mg/kg bolus and 0.2 mg/kg per hour. This dose was selected on the basis of angiographic pilot studies11 that demonstrated improved coronary thrombolytic or antithrombotic effects without excess of bleeding compared with heparin. Both infusions were maintained for 72 to 120 hours with a double-infusion bag to preserve a double-blind status for the patient and investigator team. The pharmacist or study nurse at the participating institution prepared two infusion bags for each patient; bag A represented heparin or placebo and bag B was hirudin or placebo. For patients assigned to heparin, the activated partial thromboplastin time (aPTT) was adjusted between 60 and 90 seconds; no adjustments were made based on elevated aPTT at 6 or 12 hours; for hirudin there was no adjustment recommended unless the aPTT was >150 seconds. The aPTT was serially measured at 6, 12, and 24 hours, and then at least once a day. Either the Ciba-Corning Biotack 512 portable unit or the site’s routine laboratory methods were used.

The primary end point was death or MI within 30 days. An MI was considered to have occurred at the time of enrollment if the creatine kinase (CK)-MB was elevated to above normal (and at least 3% of total CK) at the samples 0 (baseline) or 8 hours after enrollment. If the CK-MB was elevated at the 16-hour sample, and no symptoms occurred between enrollment and the 16-hour sample, this was considered an MI at enrollment. If the CK-MB was elevated at only the 16-hour sample, and symptoms consistent with MI occurred after enrollment, the events review committee coded the event according to information collected on the ECG, symptoms, and enzyme elevation. If CK-MB was not available, then total CK had to be greater than two times above the upper limit of normal. An MI was also to be classified in the event of new, significant Q waves in at least two contiguous leads.

For patients who had had an MI before enrollment, a new MI was defined as a rise in CK-MB to above normal limits or to at least twofold above a prior value if above the normal upper limit, with appropriate signs, symptoms, and ECG changes.

All events of death, stroke, and MI were reviewed by an independent adjudication committee blinded to therapy assignment. The trial’s sample size was calculated to be 12 000 patients assuming one third of patients entered in the ST-segment elevation stratum, two thirds of patients entered in the non–ST-segment elevation stratum, and an overall event rate of 8.5% with a 20% reduction by recombinant hirudin (α, 0.025; β, 0.10).

A data and safety monitoring committee was convened to review the data after the first 1000 patients were entered and to provide continued surveillance as necessary in the event of untoward bleeding events. If the data and safety monitoring committee recommended early cessation, the steering committee reviewed the recommendation and made the final decision. Members of the steering committee or data and safety monitoring committee were free of conflicts of interest, which included any financial linkage, such as equity, honoraria, consultancy, or travel reimbursement, with the primary sponsor (CIBA-GEIGY Corp).

Intracranial hemorrhage was defined as an acute new neurological deficit resulting in death or lasting >24 hours, classified by a neurologist, with a computed tomographic scan, magnetic resonance imaging scan, or autopsy demonstrating hemorrhage. All cases were reviewed and confirmed by a committee including an expert neurologist. Only the intracranial hemorrhage outcome data are included in this report. Final efficacy data, including detailed secondary outcomes, will be the subject of a future report. Furthermore, the final clinical baseline characteristics and treatment and outcome data will be available only after extensive quality-control procedures have been completed. These results, except for the verification of stroke cases, represent preliminary information that will be updated and completed in the final study report.

Continuous data were descriptively summarized using means and SDs and also medians with 25th and 75th percentiles. Discrete variables were summarized in terms of frequencies and percentages. Intracerebral hemorrhage incidence rates were expressed as percentages accompanied by 95% confidence intervals and were compared between treatment groups by use of the χ² test or Fisher’s exact test. Treatment comparisons were performed according to the intention-to-treat principle. All reported P values are two-tailed. The incidence of intracerebral hemorrhage was also compared with the corresponding rate in the GUSTO I trial in which more than 31 000 patients received thrombolytic therapy and intravenous heparin.3

Results

The trial was initiated September 1, 1993, and terminated earlier than planned on April 8, 1994, because of an excess of intracerebral hemorrhage. Selected baseline characteristics for the 2564 patients enrolled are summarized in Table 1 and compared with the GUSTO I patients receiving intravenous heparin as a reference group to demonstrate their increased age (P<.001) and preponderance of women (P<.001) compared with the patients enrolled in the previous large-scale trial.

As shown in Table 2, the overall incidence of hemorrhagic stroke was increased, albeit not a statistically significant difference, for hirudin compared with heparin: 17 of 1273 patients (1.3%; 95% CI, 0.7% to 2.0%) versus 9 of 1291 patients (0.7%; 95% CI, 0.2% to 1.2%), P=.11. All but 3 of the 26 intracerebral hemorrhages occurred in patients who also received thrombolytic therapy such that the incidence of intracerebral hemorrhage with thrombolytic therapy and conjunctive antithrombin therapy was 1.8% (1264 patients) compared with 0.3% (1168 patients) for patients not receiving thrombolytics (P<.001). The 3 patients who did not receive thrombolytic therapy but did experience intracerebral hemorrhage all were in the hirudin group. Thus, there was a trend of increased hemorrhagic stroke among nonthrombolytic patients in the hirudin group (0 of 599 patients for heparin versus 3 of 569 patients receiving hirudin, 0.5%; 95% CI, 0% to 1.1%). P=.08.

Patients who received thrombolytic therapy tended to have a higher rate of intracerebral hemorrhage with hirudin compared with heparin: 2.2% (95% CI, 1.0% to 3.3%) versus 1.5% (95% CI, 0.5% to 2.4%), P=.34. As
shown in Table 2, in GUSTO IIa, the hemorrhagic stroke rates were higher after thrombolytic therapy with both heparin and hirudin than the hemorrhagic stroke rates of patients treated with thrombolytic therapy and intravenous heparin in the GUSTO I trial. Furthermore, there was a high rate of intracerebral hemorrhage for both thrombolytic agents, which tended to be higher for streptokinase (2.9%) than for TPA (1.4%), P=0.06. Stroke with thrombolytics and hirudin tended to occur slightly earlier after enrollment than with heparin, although the differences were not significant (8 versus 17 hours [medians], P=.99). The baseline variables for the 26 patients with hemorrhagic stroke are presented in Table 3 and compared with the event-free cohort.

**Discussion**

Our findings are especially important in the context of the routine management of patients with acute coronary syndromes, who frequently receive thrombolytic therapy and intravenous heparin. From the GUSTO I trial it was clear that nearly 50% of the patients had an aPTT value below the 60- to 85-second prospectively defined therapeutic range, which led to the recommendation in the current trial to raise the dose of heparin in two ways. First, according to weight of patients, the infusion rate was increased to between 1000 and 1300 U per hour instead of the standard 1000 U per hour. Second, the upper range of aPTT adjustment was increased from 85 seconds to 90 seconds. These two changes resulted in an increase of approximately 20% in the actual amount of heparin administered in GUSTO IIa compared with the previous trial, yet there was up to a fourfold increase in hemorrhagic stroke rates using the same thrombolytic strategy and conjunctive medications such as acetylsalicylic acid. The increase in hemorrhagic stroke rate was

### Table 1. Selected Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>GUSTO IIa</th>
<th>GUSTO I</th>
<th>P*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Heparin</td>
<td>Hirudin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=1291)</td>
<td>(N=1273)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.2±11.8</td>
<td>63.5±12.5</td>
<td>60.9±11.9</td>
</tr>
<tr>
<td></td>
<td>56.65,73†</td>
<td>54.64,73</td>
<td>52.62,70</td>
</tr>
<tr>
<td>Sex, female, %</td>
<td>30</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135.9±24.8</td>
<td>135.7±25.6</td>
<td>129.0±23.4</td>
</tr>
<tr>
<td></td>
<td>120,134,150</td>
<td>120,133,150</td>
<td>112,130,144</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.4±16.9</td>
<td>79.1±16.5</td>
<td>79.4±15.6</td>
</tr>
<tr>
<td></td>
<td>68.77,89</td>
<td>69.78,89</td>
<td>70.78,88</td>
</tr>
</tbody>
</table>

*Comparison between GUSTO IIa overall cohort with patients in the GUSTO I thrombolytic trial who were assigned to intravenous heparin. †Values below the mean±SD represent the 25th percentile, median, and 75th percentile.

### Table 2. Incidence of Hemorrhagic Stroke

<table>
<thead>
<tr>
<th></th>
<th>GUSTO IIa</th>
<th>Corresponding GUSTO I Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heparin</td>
<td>Hirudin</td>
</tr>
<tr>
<td>Total patients, n</td>
<td>1291</td>
<td>1273</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>9 (0.7)</td>
<td>17 (1.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.2%-1.2%)</td>
<td>(0.7%-2.0%)</td>
</tr>
<tr>
<td>Thrombolytics only†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>620</td>
<td>644</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>9 (1.5)</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.5%-2.4%)</td>
<td>(1.0%-3.3%)</td>
</tr>
<tr>
<td>Thrombolytic agent TPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>436</td>
<td>460</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>4 (0.9)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0%-1.8%)</td>
<td>(0.5%-2.9%)</td>
</tr>
<tr>
<td>Thrombolytic agent SK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>189</td>
<td>189</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>5 (2.7)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.4%-4.9%)</td>
<td>(0.7%-5.7%)</td>
</tr>
</tbody>
</table>

*Does not apply — all patients received thrombolytics. †Incidence for combined thrombolytics in GUSTO IIa was 1.8% (95% CI, 1.1% to 2.6%). A limited number of patients in both groups received both TPA and SK.
TABLE 3. Relation of Selected Baseline Characteristics to Hemorrhagic Strokes

<table>
<thead>
<tr>
<th></th>
<th>Patients With Hemorrhagic Strokes</th>
<th>Patients With No Hemorrhagic Stroke</th>
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</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>26</td>
<td>2538</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.8±7.6</td>
<td>63.8±12.2</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>65,71.76</td>
<td>55,65.73</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>139.7±31.1</td>
<td>135.8±25.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.1±17.7</td>
<td>79.2±16.7</td>
</tr>
<tr>
<td>Weight ≥80 kg, n (%)</td>
<td>15 (58)</td>
<td>1170 (47)</td>
</tr>
<tr>
<td>aPTT at 12 h, s</td>
<td>110±46†</td>
<td>87±36†</td>
</tr>
<tr>
<td>Timing of stroke after enrollment, hr</td>
<td>30.5±48.1</td>
<td>Does not apply</td>
</tr>
</tbody>
</table>

*Values below the mean±SD represent the 25th percentile, median, and 75th percentile.
†P value for difference in aPTT is .031.

similarly confirmed in the Thrombolysis in Myocardial Infarction (TIMI) 9 trial, which used an identical thrombolytic and heparin regimen. Collectively, these data highlight a very narrow therapeutic window for heparin administration with thrombolytic therapy.

Up to this point, it remained unclear whether the aPTT, an in vitro measure of anticoagulation, represented a significant risk factor for intracranial hemorrhage. Furthermore, because of the distinct effects of hirudin on thrombin relative to heparin, it was uncertain whether the aPTT value after hirudin therapy had a similar meaning as that with heparin. The finding that an elevated aPTT was a significant risk factor for hemorrhagic stroke has several practical implications.

First, in the early hours after thrombolytic therapy, there is a significant anticoagulant effect caused by the generation of plasmin, proteolytic effects on coagulation factors, and fibrinogen breakdown. This anticoagulant effect is more extensive with streptokinase than with TPA. It is during this time frame when there may be an increased liability from the aggressive heparin and antithrombin therapies that are co-administered with thrombolitics, evidenced in the current study by the very early occurrence of intracerebral hemorrhage in the group of patients receiving thrombolytic therapy and hirudin.

Second, serial monitoring of the aPTT value appears to be warranted during antithrombin therapy, as upward deviation from the target range of 60 to 85 seconds is linked with a higher rate of catastrophic hemorrhage. It remains unclear what the preferred range of aPTT should be, and this is further complicated by the multiplicity of methods for assessing this measure that are currently in use, each yielding somewhat different values as a function of the reagents and instruments of testing.

Third, our data suggest that the aPTT derived from hirudin therapy is associated with risks very similar to those of heparin, such that the data from this trial for the first time indicate a need to monitor and titrate hirudin therapy, just as is conventionally done with heparin, and to be concerned when the aPTT level exceeds 100 seconds. In a pilot study for the current project, it was demonstrated that, at matched aPTT targets for heparin and hirudin, there was increased inhibition of thrombin activation and more evidence of culprit vessel clot lysis in patients with unstable angina. Unlike the safety findings that suggest similar risks with heparin and hirudin as a function of elevated aPTT, the pilot findings suggest that there may be heightened efficacy for hirudin compared with heparin in spite of an equivalent ex vivo anticoagulant effect. Of note, the effects on clot lysis for hirudin did not demonstrate a dose-response curve. Although it was assumed that higher doses of hirudin would have more pronounced effects, more recent data from multiple studies performed to date suggest a step-function rather than dose-response curve, with no clear-cut benefit of increasing the hirudin dose beyond the infusion level of 0.1 mg/kg per hour.

Fourth, the increased rate of intracerebral hemorrhage with streptokinase and heparin or hirudin, up to fourfold that documented in GUSTO I, raises the issue of need for and risk of conjunctive antithrombin therapy with this thrombolytic agent. In GUSTO I there was no difference in outcome for streptokinase with intravenous heparin compared with subcutaneous heparin; in previous large trials there have been no differences between streptokinase and subcutaneous heparin in contrast to no heparin. The potential simplicity of streptokinase without the need for conjunctive antithrombin therapy has been advocated, but there are conflicting data, which include facilitation of the clinical benefits of streptokinase with Hirulog and improved patency at 5 to 7 days after intravenous heparin and streptokinase compared with subcutaneous heparin. Thus, the increased rate of hemorrhagic stroke associated with the use of streptokinase in the current trial deserves further study, particularly in light of the extensive prior trial experience with streptokinase that documents its safety with respect to hemorrhagic strokes.

On the basis of the findings, the trial has been re-initiated at lower doses of heparin (the same as used in GUSTO I) and hirudin (0.1-mg/kg bolus and 0.1-mg/kg per hour infusion). The aPTT target range has been adjusted downward (back to 60 to 85 seconds), and recombinant hirudin as well as heparin will be titrated so as to avoid high aPTT values. Both agents will be down-titrated for marked aPTT prolongation in the early (6- and 12-hour) determinations. Because it remains uncertain whether the higher risk population, with older patients and more women, may at least in part have accounted for the excessive risk in the current project, we have added the exclusion of prior stroke and uncontrolled hypertension, the latter defined by systolic blood pressure >200 mm Hg. In addition, because clearance of hirudin relies on intact renal function, and at least two hemorrhagic strokes occurred in the setting...
of renal dysfunction, there will be increased attention to serum creatinine at the time of enrollment, with exclusion of patients with creatinine >2.0 mg/dL, and fluxes of renal dysfunction during therapy. With these modifications, we hope to test the original thrombin hypothesis without an undue hazard of serious bleeding complications. Our findings emphasize the importance of safety studies following and complementing angiographic studies.

**Appendix**

The following centers and investigators collaborated in the GUSTO IIA Trial.

**Steering Committee:** E. Topol, chairman, USA; R. Califf, director, Coordinating Center, USA; V. F. van der Werf, director, European Coordinating Center, Belgium; D. Ardissino, Italy; P. Armstrong, Canada; P. Aylward, Australia; G. Barbach, Israel; E. Bates, USA; K. Beatt, United Kingdom; A. Betriu, Spain; J. Chesebro, USA; J. Col, Belgium; S. Ellis, USA; H. Emanuelsson, Sweden; V. Fuster, USA; W. Gibler, USA; J. Gore, USA; A. Guerci, USA; J. Hochman, USA; D. Holmes, USA; N. Kleinemeier, USA; D. Morris, USA; K. Neuhaus, Germany; M. Ohman, USA; M. Pfisterer, Switzerland; H. Phillips, USA; W. Rutsch, Germany; J. Simes, Australia; M. Simonos, Netherlands; A. Vahanian, France; D. Weaver, USA; H. White, New Zealand.


**Executive Center:** The Cleveland Clinic Foundation, Ohio: E. Topol, V. Stosis, P. Brickenden, D. Passmore, D. Shyne, J. White.

**European Coordinating Center:** University of Leuven, Belgium: F. Van der Werf, R. Brower, A. de Clerck, E. Lesaffre, A. Loeb, A. Meuris.

**Australian Coordinating Center:** National Medical Research Council Clinical Trials Centre, University of Sydney, Australia: P. Aylward, J. Simes, S. Cho, J. Fabri, M. Kava, K. Lawergren, R. McCredie, M. Mijailovici, C. Thomas, F. Williams.

**New Zealand Coordinating Center:** Green Lane Hospital, Auckland, New Zealand: H. White, M. Scott.

**Clinical Events Committee:** Steering Committee Members: G. Barbash, J. Gore, M. Pfisterer, W. Rutsch, W.D. Weaver, R. White; Review Members: S. Bandy, J. Bohrer, B. Brott, A. DeFrancesco, J. Elliott, J. Hall, R. Harrington, W. Hathaway, W. Hillegass, J. Lifkowitz, A. Maelsaak, D. Moliterno, N. Omoigui, E. Peterson, M. Zabel.

**Data Safety Monitoring Board:** R. Frye, chairman, M. Cheitlin, D. DeMets, L. Fisher, J. Hirsh, P. Serruys, L. Walters.

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