The Interventional Management of Stroke (IMS) II Study

The IMS II Trial Investigators

Background and Purpose—The purpose of this study was to further investigate the feasibility and safety of a combined intravenous and intra-arterial approach to recanalization for ischemic stroke.

Methods—Subjects, ages 18 to 80, with a baseline NIHSS \( \geq 10 \) had intravenous recombinant tissue plasminogen activator (rt-PA) started (0.6 mg/kg over 30 minutes) within 3 hours of onset. For subjects with an arterial occlusion at angiography, additional rt-PA was administered via the EKOS micro-infusion catheter or a standard microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until thrombolysis.

Results—The 81 subjects had a median baseline NIHSS score of 19. The median time to initiation of intravenous rt-PA was 142 minutes as compared with 108 minutes for placebo and 90 minutes for rt-PA–treated subjects in the NINDS rt-PA Stroke Trial (\( P < 0.0001 \)). The 3-month mortality in IMS II subjects was 16% as compared with the mortality of placebo (24%) and rt-PA–treated subjects (21%) in the NINDS rt-PA Stroke Trial. The rate of symptomatic intracerebral hemorrhage in IMS II subjects (9.9%) was not significantly different than that for rt-PA treated subjects in the NINDS t-PA Stroke Trial (6.6%). IMS II subjects had significantly better outcomes at 3 months than NINDS placebo-treated subjects for all end points (OR \( \approx 2.7 \)) and better outcomes than NINDS rt-PA–treated subjects as measured by the Barthel Index and Global Test Statistic.

Conclusions—A randomized trial of standard intravenous rt-PA as compared with a combined intravenous and intra-arterial approach is warranted and has begun. (Stroke. 2007;38:2127-2135.)

Key Words: acute ischemic stroke ■ controlled clinical trials ■ intra-arterial therapy ■ tissue plasminogen activator

It has been 10 years since the Food and Drug Administration approved the administration of intravenous (IV) recombinant tissue plasminogen activator (rt-PA; Activase [Aletplase recombinant]; Genentech, Inc.) within 3 hours of symptom onset for the treatment of patients with acute ischemic stroke.\(^1\) Over the past 20 years, thrombolytic and recanalization studies have demonstrated that the effectiveness of thrombolytic therapy is time-dependent\(^2\) and that >80% of patients with an NIHSSS of 10 or more have persisting arterial occlusion lesions on subsequent angiography, even after initial treatment with IV rt-PA.\(^3\)–\(^9\) Controlled trials of IV thrombolytic therapy as well as intra-arterial (IA) administration of thrombolytic agents or use of devices to remove arterial clots have demonstrated that patients with recanalization of occluded arteries have improved clinical outcome as compared with those patients without recanalization.\(^10\)–\(^13\)

The concept of combining the advantages of IV rt-PA (speed of and certainty of initiation of therapy as well as widespread availability) and IA recanalization therapy when possible (titrated dosing, mechanical aids to recanalization, and possibly superior and earlier recanalization) has been evaluated in 2 previous controlled pilot trials. The Emergency Management of Stroke Trial\(^1\) and the Intervventional Management of Stroke (IMS) Trial,\(^6\) hereafter referred to as IMS I, demonstrated that the combined IV/IA approach had similar rates of mortality and symptomatic intracerebral hemorrhage (ICH) as compared with subjects of similar severity and age treated with IV rt-PA alone in the NINDS rt-PA Stroke Trial. In addition, as compared with placebo-treated subjects of similar baseline severity and age in the NINDS rt-PA Stroke Trial, IMS I subjects were significantly more likely to have an excellent outcome at 3 months, both before and after adjustment for baseline NIHSSS, age, and time to treatment (OR \( \approx 2 \)).

The completion of IMS I 1.5 years earlier than expected presented an opportunity to continue to accrue more data and explore new micro-catheter technology for the combined IV/IA approach while plans were undergoing development for a large randomized phase III trial. IMS II was therefore designed to evaluate the safety and effectiveness of the combined IV/IA approach using, whenever possible, the investigational EKOS small-vessel ultrasound infusion system (hereafter referred to as the EKOS micro-infusion system) in vessel-appropriate lesions. The EKOS System consists of 2 main components, a single-use sterile 0.014-inch (0.010-inch first generation) EKOS micro-infusion catheter consisting of an end-hole infusion lumen with an ultrasound
element at the distal tip, and a reusable control unit that provides the ultrasound energy source and the user interface (Figure 1). This system uses low-energy ultrasound to alter reversibly the structure of the thrombus and facilitate access of the thrombolytic agent rt-PA to potentially accelerate thrombolysis.

Materials and Methods
The IMS II Study was a 13-center, open-labeled, single-arm pilot study. The 3 objectives of the trial were: (1) to obtain reliable estimates of the efficacy and safety of combining low-dose IV rt-PA (0.6 mg/kg) followed by delivery of additional IA rt-PA (up to 22 mg) in the setting of low-energy ultrasound via the EKOS micro-infusion catheter at the site of IA occlusion in acute ischemic stroke patients with large strokes (NIHSS ≥10) treated within 3 hours of symptoms onset; (2) to determine if the estimated efficacy of combined IV/IA rt-PA at 3 months, as compared with the 3-month outcome of placebo-treated subjects in the NINDS rt-PA Stroke Trial, warrants proceeding to a large Phase III randomized Trial; and (3) to determine whether the recanalization rate of combined IV rt-PA followed by IA rt-PA and low-intensity ultrasound energy is greater than the rate of recanalization for the IMS I study subjects treated only with combined IV/IA rt-PA via a standard micro-catheter.

Study Protocol
The IMS II study protocol was the same as the IMS I Trial, except for the EKOS micro-infusion catheter, and was approved by the NINDS, DSMB, and Institutional Review Board/Ethics Committee at each participating center for enrollment initially of 72 subjects. After completing enrollment of the planned 72 subjects, the protocol was amended and again approved by the NINDS, DSMB, and participating Institutional Review Board/Ethics Committee for enrollment of up to an additional 48 subjects to accrue further experience with the EKOS catheter before start of the phase III randomized trial.

After verifying a potential subject met all inclusion and exclusion criteria (Table 1) and obtaining subject or legally authorized representative informed consent/HIPAA authorization per institutional protocol, subjects received IV rt-PA (Activase 0.6 mg/kg, 60 mg maximum, 15% of the dose as a bolus over 1 minute with the remainder administered over 30 minutes). After initiation of IV therapy, subjects were immediately transferred to the neuroangiography suite for cerebral angiography.

IA therapy had to be initiated within 5 hours of stroke onset and completed or stopped by 7 hours of onset. No more than a total of 22 mg of IA rt-PA could be administered. The total maximum dose of rt-PA (both IV and IA) in the study was 82 mg as compared with a maximum dose of 90 mg in the NINDS rt-PA Stroke Trial. No angioplasty or stenting was allowed as part of the protocol.

If the subject did not have a treatable occlusion visualized angiographically in the vascular territory appropriate for the patient’s symptoms, then no IA therapy was administered and the angiographic procedure was terminated. If a thrombus was identified in an EKOS catheter-appropriate intracranial artery such as the internal cerebral artery, middle cerebral artery (M1 or M2 segments), vertebral or basilar artery, then no further requisite imaging was performed and IA thrombolytic and ultrasound therapy was immediately initiated, as per the protocol outlined here. Thrombus identified in the anterior cerebral artery; posterior cerebral artery; superior cerebellar artery; posterior inferior cerebellar artery; and anterior inferior cerebellar artery could not be treated with the EKOS micro-infusion catheter but could receive IA therapy as per the IMS I protocol with a standard micro-catheter. In addition, any subject with etiology or an arterial occlusion that prevented safe passage of
A local infusion is an infusion in the EKOS catheter could be placed as close as technically feasible to the thrombus (local infusion). A local infusion is an infusion in the femoral access sheath, the guide catheter, and micro-catheter as per previously activated.

For subjects who had an EKOS-accessible occlusion, the micro-infusion catheter was passed over a micro-guide wire to the site of the clot. Alternatively, the EKOS catheter could be placed as close as technically feasible to the thrombus (local infusion). A local infusion is an infusion in which the catheter is as close to the thrombus as physically possible, but not imbedded within the thrombus. There should be no vessels or branches between the tip of the micro-catheter and the thrombus to divert the rt-PA infusion away from the target occlusion. Should the aforementioned criteria not be met, the infusion was considered to be regional (vessels or branches between catheter tip and clot). In the case of either a local or regional infusion, the ultrasound was not activated.

**EKOS Catheter Administration of IA rt-PA**

For subjects who had an EKOS-accessible occlusion, the micro-infusion catheter was passed over a micro-guide wire to the site of the arterial occlusive lesion where the micro-catheter tip was positioned within the proximal portion of the thrombus. After angiographic confirmation of the micro-catheter tip location, a 2-mg bolus of rt-PA was hand-injected over 4 minutes; then, using an infusion pump or syringe pump, rt-PA was administered at a rate of

### Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Age 18 through 80 years (ie, candidates must have had their 18th birthday, but not had their 81st birthday)</td>
</tr>
<tr>
<td>Initiation of intravenous rt-PA within 3 hours of onset of stroke symptoms. Time of onset is defined as the last time when the subject was witnessed to be at baseline (ie, subjects who have stroke symptoms on awakening will be considered to have their onset at beginning of sleep)</td>
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<tr>
<td>An NIHSSS ≥10 at the time that intravenous rt-PA is begun</td>
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<thead>
<tr>
<th>Clinical Exclusion Criteria</th>
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<tbody>
<tr>
<td>History of stroke in the past 3 months</td>
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<tr>
<td>Previous intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation</td>
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<tr>
<td>Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal</td>
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<tr>
<td>Hypertension at time of treatment; systolic blood pressure &gt;190* or diastolic blood pressure &gt;110 mm Hg) or aggressive measures to lower blood pressure to below these limits are needed*</td>
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<tr>
<td>Presumed septic embolus</td>
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<tr>
<td>Presumed pericarditis, including pericarditis after acute myocardial infarction</td>
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<tr>
<td>Recent (within 30 days) surgery or biopsy of parenchymal organ</td>
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<tr>
<td>Recent (within 30 days) trauma, with internal injuries or ulcerative wounds</td>
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<tr>
<td>Recent (within 90 days) severe head trauma or head trauma with loss of consciousness</td>
</tr>
<tr>
<td>Any active or recent (within 30 days) hemorrhage</td>
</tr>
<tr>
<td>Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy with INR &gt;1.5 or institutionally equivalent prothrombin time</td>
</tr>
<tr>
<td>Females of childbearing potential who are known to be pregnant and/or lactating or who have positive pregnancy tests on admission</td>
</tr>
<tr>
<td>Baseline laboratory values: glucose &lt;50 mg/dL*, platelets &lt;100,000, or hematocrit &lt;25</td>
</tr>
<tr>
<td>Subjects who have received heparin within 48 hours must have a normal partial thromboplastin time to be eligible</td>
</tr>
<tr>
<td>Subjects with an arterial puncture at a non-compressible site or a lumbar puncture in the previous 7 days</td>
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<tr>
<td>Subjects with a seizure at onset of stroke</td>
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<tr>
<td>Subjects with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations</td>
</tr>
<tr>
<td>Other serious, advanced, or terminal illness</td>
</tr>
<tr>
<td>Any other condition that the investigator feels would pose a significant hazard to the subject if Activase® (Alteplase) therapy is initiated</td>
</tr>
<tr>
<td>Current participation in another research drug treatment protocol; subject cannot start another experimental agent until after 90 days</td>
</tr>
<tr>
<td>Informed consent is not or cannot be obtained. For example, obtunded subjects are not automatically excluded from the study. However, if the next of kin or legal guardian (ie, the individual legally empowered in the state where the consent is obtained) cannot provide consent, randomization and entry into the study could not proceed</td>
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</tbody>
</table>

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<thead>
<tr>
<th>CT Scan Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>High density lesion consistent with hemorrhage of any degree</td>
</tr>
<tr>
<td>Significant mass effect with midline shift</td>
</tr>
<tr>
<td>Large (more than one-third of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan. Sulcal effacement and/or loss of grey–white differentiation alone are not contraindications for treatment</td>
</tr>
</tbody>
</table>

*INR indicates international normalized ratio. |

*SSubjects in the IMS Ia extension were treated by an identical protocol as IMS II and IMS I, except that the exclusion entry criteria for systolic blood pressure was tightened to >185 mm Hg, an upper limit of >400 mg/dL on blood glucose was added, and subjects on renal dialysis were excluded from entry into the trial.
10 mg/h (20 mL/h [0.5 mg/mL]) in the presence of ultrasound, which was activated on initiation of the rt-PA infusion. Infusion of rt-PA continued for up to 120 minutes for a maximum of 22 mg of rt-PA.

Angiographic assessment of the occlusion was conducted every 15 minutes to determine whether recanalization had occurred, and to monitor for new mass effect. If complete recanalization was detected, the rt-PA infusion and ultrasound delivery was terminated. If the angiogram revealed partial clot lysis, the micro-catheter was advanced into the new proximal clot surface for the remainder of the infusion. No mechanical disruption of the thrombus, with or through the EKOS micro-infusion catheter, was allowed under this protocol.

**Standard Micro-Catheter Administration of IA rt-PA**

When the EKOS catheter could not be used, a 2.3-French tapered, variable-stiffness, standard end-hold micro-catheter, such as the Rapid Transit or Prowler, was passed over the micro-guide wire to the level of occlusion; 2 mg of rt-PA was hand-injected through the catheter over 2 minutes beyond the thrombus. The catheter was then retracted into the thrombus, and 2 mg of rt-PA was hand-injected over 2 minutes directly into the thrombus. Infusion of rt-PA was then started at the rate of 9 mg/h (18 mL/h) for up to 2 hours of infusion time using an infusion or syringe pump. The procedure for IA administration of rt-PA, guide wire, or micro-catheter manipulation timetable for repeated arteriogram was performed as per previous IMS I protocol.6

Early termination of the IA treatment procedure occurred if there was: (1) arteriographic mass effect that could not be explained by early edema; (2) suspicion of extravasation of contrast suggesting vessel rupture; (3) CT demonstration of hemorrhage (ie, for a subject whose condition deteriorated and the procedure interrupted for a CT, the procedure could be re-started if the CT showed no hemorrhage); (4) worsening of clinical deficit that was not explained by arteriographic findings; (5) seizure; (6) achievement of thrombolysis in the ECASS Trials: parenchymal hematoma (PH-1, PH-2) and hemorrhagic infarction (HI-1, HI-2).18

The primary measure of outcome for this pilot study was mRS of 0 or 1 at 3 months. Predefined secondary clinical efficacy end points included: (1) mRS of 0 to 2 at 3 months; (2) NIHSSS ≥2 at 24 hours; (3) other 3-month favorable subject outcomes as measured by a Barthal Index score of 95 to 100, Glasgow Outcome Scale score of 0 to 1, and NIHSSS score of 0 or 1; (4) quality of life at 3 months as defined by the EuroQol Questionnaire; and (5) a 3-month global outcome end point that included the mRS, NIHSSS, Barthel index, and Glasgow Outcome Scale.19 To minimize treatment bias, the 90-day outcome assessment in which the primary efficacy end point is collected was performed by study personnel not involved with the initial treatment of the study subject.

Revascularization was measured according to both recanalization of the primary arterial occlusive lesion and thrombolysis in myocardial infarction (TIMI)/TICI reperfusion parameters (Table 2). The modified TICI reperfusion score was equivalent to TIMI score applied in IMS I, with grade 2 divided into A and B for post-hoc analysis.20 The primary revascularization end point was complete (arterial occlusive lesion III) recanalization of the targeted arterial occlusion at 60 minutes after the start of IA rt-PA and ultrasound therapy, as compared with the IMS I trial. Secondary angiographic end points included the rate of arterial occlusive lesion 2 or 3 recanalization of the targeted occluded vessel as well as the rate of TICI grade 3 or grade 2 (complete or partial) reperfusion at 1 hour and at completion of angiography. The revascularization end points were scored at the University of Cincinnati Clinical Coordinating Center by Dr Thomas A. Tomisk.

The NINDS appointed Data Safety Monitoring Committee reviewed all safety and outcome results of the IMS II Study. The late Dr Lawrence Brass, Professor of Neurology at Yale University, acted as the external Medical Monitor for ongoing review of serious clinical adverse identified in IMS II.

**Medical Management and Evaluation**

Medical management of subjects enrolled into the study followed the NINDS rt-PA Stroke Trial protocol and IMS I protocol.14 The NIHSSS was performed in every subject at baseline, before initiation of IA rt-PA, after completion of IA rt-PA therapy, at 24 (±6) hours, at day 5 or discharge from the hospital, and at 90 (±7) days after the stroke. In addition, a modified Rankin scale (mRS)15 to indicate the subject’s functional status before the qualifying stroke (pre-event) was obtained at baseline. Functional outcome at 3 months was assessed by the Barthel Index13 mRS,14 and the Glasgow Outcome Scale.16 Quality of life at 90 (±7) days was also assessed by the EuroQol Questionnaire.17

### TABLE 2. AOL Recanalization and TIMI/TICI Reperfusion Scores

<table>
<thead>
<tr>
<th>Grade</th>
<th>AOL Recanalization</th>
<th>Grade</th>
<th>TIMI/TICI Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No recanalization of the primary occlusive lesion</td>
<td>0</td>
<td>No perfusion</td>
</tr>
<tr>
<td>1</td>
<td>Incomplete or partial recanalization of the primary occlusive lesion with no distal flow</td>
<td>1</td>
<td>Perfusion past the initial occlusion, but limited distal branch filling</td>
</tr>
<tr>
<td>2</td>
<td>Incomplete or partial recanalization of the primary occlusive lesion with any distal flow</td>
<td>2</td>
<td>Perfusion with incomplete or slow distal branch filling</td>
</tr>
<tr>
<td>3</td>
<td>Complete recanalization of the primary occlusion with any distal flow</td>
<td>2A</td>
<td>Perfusion of ≥50% MCA distribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2B</td>
<td>Perfusion &gt;50% MCA distribution</td>
</tr>
</tbody>
</table>

**Primary Measures of Safety and Outcome**

The primary safety measure of the study was life-threatening bleeding complications during the first 36 hours after completion of rt-PA infusion, as it was for the NINDS rt-PA Stroke Trial and IMS I Trial.14 A significant life-threatening bleeding complication is defined as: (1) development of intracerebral hematoma or hemorrhagic infarction with clinical deterioration likely to result in permanent disability or death, or other severe systemic bleeding complications such as groin hematoma, retroperitoneal hematoma, or gastrointestinal bleeding requiring transfusion of ≥3 U of blood replacement or major surgical intervention. Intracerebral hemorhages were classified radiographically according to the method used in the ECASS Trials: parenchymal hematoma (PH-1, PH-2) and hemorrhagic infarction (HI-1, HI-2).18

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### Statistical Methodology

The hypotheses to be tested were: $H_0: p \geq 0.29$ versus $H_a: p < 0.29$ ($=0.17$), where $p$ is the proportion of subjects whose 3-month mRS score was 0 or 1. The 29% and 17% were obtained from the results of the Emergency Management of Stroke Trial and placebo group of the NINDS rt-PA Stroke Trial, respectively. If the null hypothesis
TABLE 3. Baseline Comparisons Between IMS II and NINDS t-PA Trial Cohorts

<table>
<thead>
<tr>
<th></th>
<th>IMS 2 Study (n=81)</th>
<th>NINDS Placebo (n=211)</th>
<th>NINDS t-PA (n=182)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±stddev)</td>
<td>64±11.5</td>
<td>64±10.4</td>
<td>65±10.5</td>
<td>NS†</td>
<td>NS‡</td>
</tr>
<tr>
<td>Age (median)</td>
<td>67</td>
<td>66</td>
<td>68</td>
<td>NS‡</td>
<td>NS§</td>
</tr>
<tr>
<td>Baseline NIHSS (mean±stddev)</td>
<td>19±5.3</td>
<td>18±5.4</td>
<td>18±5.7</td>
<td>NS‡</td>
<td>NS‡</td>
</tr>
<tr>
<td>Baseline NIHSS (median)</td>
<td>19</td>
<td>17</td>
<td>17</td>
<td>NS§</td>
<td>NS§</td>
</tr>
<tr>
<td>African American</td>
<td>9/81 (11%)</td>
<td>64/211 (30%)</td>
<td>57/182 (31%)</td>
<td>0.005†</td>
<td></td>
</tr>
<tr>
<td>Early Ischemic Changes on Baseline CT</td>
<td>49/81 (60%)</td>
<td>78/211 (37%)</td>
<td>62/182 (34%)</td>
<td>&lt;0.001¶</td>
<td></td>
</tr>
<tr>
<td>Serum glucose (mg/dl) (mean±stddev)</td>
<td>128±52.6</td>
<td>156±84.5</td>
<td>151±75.3</td>
<td>0.0055‡</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19/80 (24%)</td>
<td>39/210 (19%)</td>
<td>25/181 (14%)</td>
<td>0.0480¶</td>
<td></td>
</tr>
<tr>
<td>History of MI</td>
<td>9/79 (11%)</td>
<td>46/203 (23%)</td>
<td>38/174 (22%)</td>
<td>0.0477‡</td>
<td></td>
</tr>
<tr>
<td>Baseline Systolic BP (mm of Hg) (mean±stddev)</td>
<td>147±22.5</td>
<td>153±20.7</td>
<td>151±20.4</td>
<td>NS‡</td>
<td></td>
</tr>
<tr>
<td>Baseline Diastolic BP (mm of Hg) (mean±stddev)</td>
<td>80±14.0</td>
<td>86±13.2</td>
<td>85±11.6</td>
<td>0.0127‡</td>
<td></td>
</tr>
<tr>
<td>Stroke onset to IV-tPA (mean±stddev)</td>
<td>140±31.3</td>
<td>118±35.3</td>
<td>115±36.7</td>
<td>&lt;0.0001‡</td>
<td></td>
</tr>
<tr>
<td>Stroke onset to IV-tPA (median)</td>
<td>142</td>
<td>108</td>
<td>90</td>
<td>&lt;0.0001§</td>
<td></td>
</tr>
</tbody>
</table>

*P corresponding to comparison of IMS to NINDS-Placebo. 
†P corresponding to comparison of IMS to NINDS-t-PA.
‡From Student t test.
§From Wilcoxon nonparametric rank-sum test.
¶From χ² test.
Additional comparisons of IMS diastolic blood pressure, current smoking, previous diabetes, prior hypertension, and previous coronary heart failure were not significant.

was rejected, then we would conclude that it would be futile to proceed with a large phase III study of the IV/IA approach.

For the sample size estimation, the previously published methodology for IMS I was used, which included the proportions of successful outcomes obtained from subsets of placebo and rt-PA–treated subjects from parts I and II of the NINDS rt-PA Stroke Trial.

Successful outcomes obtained from subsets of placebo and rt-PA–treated subjects.

For binomial proportions using normal approximation. Given the statistical parameters, the null hypothesis would be rejected if ±0.10, based on these assumptions and the experience of excellent patient follow-up. IMS I, the fixed sample size was 72 subjects.

The primary analysis of futility was conducted by 1-sample test for binomial proportions using normal approximation. Given the statistical parameters, the null hypothesis would be rejected if ±0.10, based on these assumptions and the experience of excellent patient follow-up. IMS I, the fixed sample size was 72 subjects.

The primary analysis of futility was conducted by 1-sample test for binomial proportions using normal approximation. Given the statistical parameters, the null hypothesis would be rejected if ±0.10, based on these assumptions and the experience of excellent patient follow-up. IMS I, the fixed sample size was 72 subjects.

For the comparison of angiographic outcomes between IMS II subjects and the EKOS catheter and IMS I subjects treated with the standard microcatheter, a χ² test for homogeneity of binomial proportions was conducted.

With the exception of the primary analysis of the proportion of successful outcome (mRS of 0 or 1), interpretation of P for outcome analyses should be made with caution because multiple analyses, considered exploratory, were performed.

Results

IMS II and IMS IIb enrolled a combined total of 81 subjects from a reported 3602 patients screened at 13 clinical sites across North America from January 26, 2003 to February 28, 2006.

Two clinical sites did not submit the requisite exclusion logs to the Clinical Coordinating Center, one because of stated HIPPA concerns by the local Institutional Review Board. IMS II enrolled 73 subjects from January 26, 2003 to April 12, 2005. Seventy-three subjects were enrolled because of a delay by a clinical site in notifying the Clinical Coordination Center of enrollment of subject 72. Subject follow-up was completed by July 18, 2005. Eight additional subjects were then enrolled in the IMS IIb extension, with completion of the last 3-month follow-up on May 25, 2006. All analyses include the 81 subjects in both IMS II and the IMS IIb extension and are hereafter referred to as the IMS II study population.

The subject population consists of 81 individuals (46 males, 35 females; 66 whites, 9 blacks, 6 Asians). The median subject age was 67. Comparison of baseline characteristics between IMS II, IMS I, and NINDS rt-PA Stroke Trial subjects are presented in Table 3.

Subject flow for IMS II is presented in Figure 2. Twenty-six subjects received only IV rt-PA, including one without a treatable clot identified on angiography who experienced a symptomatic ICH. Early access difficulties with EKOS catheter models SV2510 and SV3014 in IMS II required 2 design modifications during the early phase of the study. As a result, only 4 out of 10 EKOS catheter-eligible subjects were treated with the 2 early catheter models. The current SV3014 Primo version of the EKOS micro-infusion catheter was used in 32 out of 35 subjects eligible for Primo. There were three access failures requiring exchange for a standard micro-catheter and three cases in which infusion of rt-PA through the EKOS catheter was not accompanied by ultrasound activation. Considering all 3 models (SV2510, SV3014, and the SV3014 Primo), 33 subjects were treated with an EKOS ultrasound-activated micro-infusion catheter.
The median dose of IV rt-PA administered to IMS II subjects was 46.4 mg and the median dose of IA rt-PA was 12 mg. The total median dose of rt-PA for IMS II subjects (56 mg) was significantly less than the total dose of 67.5 mg administered to subjects in the NINDS rt-PA Stroke Trial and similar to total median dose administered to IMS I subjects (59.95 mg).

The 3-month mortality of 16% (13/81) for IMS II is identical to IMS I and is not significantly lower than subjects in the NINDS rt-PA Stroke Trial with regards to the primary outcome of a mRS of 0 to 1 as well as other outcome measures. However, IMS II subjects had significantly better 3-month outcomes as measured by the Barthel Index and the Global Outcome Test.

The arterial occlusive lesion 3 recanalization rate after 1 hour of treatment for IMS II subjects treated with IA rt-PA and the ultrasound activated EKOS catheter was 36.4% (12 of 33) as compared with 30.4% (7 of 23) in IMS I treated subjects with 1-hour angiograms \( (P=0.9916) \). The grade 2 and 3 recanalization rate for EKOS-treated subjects in IMS II at 1 hour was 45.5% (15 of 33) as compared with 30% (7 of 23) in IMS I-treated subjects \( (P=0.26) \). The rate of recanalization grades 2 and 3 at the specific site of arterial occlusion at the end of the procedure in EKOS-treated subjects was 73% (24 of 33) as compared with subjects treated with standard micro-catheter in IMS I (56%; 33 of 59; \( P=0.11 \)).

Neither M3 nor M4 occlusions were included in this comparison because EKOS® was not used for M3 or M4 occlusions.

Overall, all IMS II subjects treated with IA rt-PA via EKOS or standard micro-catheters had a 4% (2/55) TICI/TIMI 3 and a 60% (33/55) TICI/TIMI 2 and 3 reperfusion grade flow after completion of the intra-arterial procedure as compared with IMS I subjects with an 11% (7/62) and 56% (35/62) grade flow, respectively. Of the 33 subjects with TICI/TIMI 2 to 3 reperfusion at the end of the procedure, 15 (55%) had a 3-month favorable outcome as measured by Rankin of 0 to 2 as compared with 6 (27%) of 22 subjects with TICI/TIMI 0 to 1 \( (P=0.046, \chi^2 \text{ test}) \).

**Discussion**

The IMS II study confirms the findings of the IMS I study,\(^6\) the Emergency Management of Stroke Study,\(^3\) and reported

![Figure 2. IMS II subject flow.](image-url)
case series\textsuperscript{21,22} that a combined IV and IA approach to recanalization, begun within 3 hours of onset, has similar safety as compared with full-dose IV rt-PA as administered during the NINDS rt-PA Stroke Trial. In addition, as compared with placebo-treated subjects of similar baseline severity and age in the NINDS rt-PA Stroke Trial, IMS II subjects were significantly more likely to have an excellent outcome at three months. Consistent trends toward better outcomes were present in IMS II subjects as compared with rt-PA–treated subjects in the NINDS rt-PA Stroke Trial. Based on the IMS II, IMS I, and Emergency Management of Stroke Trials, a randomized controlled trial comparing standard IV rt-PA to the combined IV and IA approach started within 3 hours of onset is warranted. Such a trial, the NINDS-funded IMS III trial, began in late summer of 2006.

IMS II was designed to evaluate the safety and effectiveness of the combined IV/IA approach using the EKOS micro-infusion catheter system. In particular, we were interested in whether recanalization of the occluded artery could be accelerated as compared with IA delivery of rt-PA using a standard micro-catheter. From the standpoint of reperfusion of the entire vascular territory of an occluded vessel as measured by TIMI/TICI 2 or 3 grade flow, the EKOS catheter performed similarly to the standard micro-catheter in IMS I. However, from the standpoint of reopening of the primary arterial occlusive lesion, the EKOS catheter reopened more arteries more completely at the site of the occlusion than subjects treated with the standard micro-catheter in IMS I. For this reason, after issuance of substantial equivalence determination from the Food and Drug Administration in April 2005, the EKOS catheter was included as part of the IMS III trial.

The 90-day mortality of IMS II of 16% is identical to the 90-day mortality in IMS I and nonsignificantly lower than the mortality of subjects treated in the NINDS rt-PA stroke trial of similar stroke severity. The 90-day mortality of IMS II and IMS I subjects (16%) is lower than mortality of subjects in PROACT II (27%)\textsuperscript{11} and Merci Trial (44%)\textsuperscript{23} despite similar rates of reperfusion after completion of IA therapy. The lower mortality in IMS subjects most likely relates to earlier recanalization because IMS II subjects had IV rt-PA initiated within a median time of 2 hours and 20 minutes as compared with median time to start of angiography of 4.3 hours in the Merci Trial and time to randomization of 4.7 hours in the PROACT II Trial. This illustrates the advantage of a combined IV/IA approach in which IV rt-PA can be started as quickly as possible while preparations for IA therapy, either at the same hospital or a tertiary hospital, are underway.

The rate of reperfusion (TIMI 2 to 3) in the IMS II Trial after completion is similar to the rates of reperfusion reported in the PROACT II and Merci Trials.\textsuperscript{11,12,23} One difficulty in comparing overall reperfusion or recanalization rates in IMS II to PROACT II or MERCII, or any IA therapy without previous IV treatment, is that IV t-PA completely recanalizes occluded major intracranial arteries in 13% to 21% of patients during the first 30 to 60 minutes after onset of IV t-PA therapy as measured by transcranial Doppler.\textsuperscript{22,24} Recanalization may include complete reopening or even fragmentation and distal embolization of clots that were initially more proximal. In IMS II, we were treating clots intra-arterially that had yet to respond or had responded incompletely to IV t-PA, but some patients had been already recanalized by IV t-PA and required no additional therapy. Thus, the reperfusion rates reported in the IMS II Study are an underestimate of the true reperfusion rate of the combined IV/IA approach.

The rate of symptomatic ICH and PH2 was slightly higher in IMS II than in IMS I and in NINDS rt-PA–treated subjects in the NINDS rt-PA Stroke Trial. All but one symptomatic ICH occurred in IMS II subjects with an NIHSS of \(\geq 20\) and the one exception had a right hemisphere stroke with an NIHSS of 16, which is equivalent to a baseline NIHSS of 21 for a left hemisphere subject. As first noted in the NINDS rt-PA Stroke Trial, subjects with an NIHSS of \(\geq 20\) have a substantially greater risk of ICH as compared with those with less severe strokes.\textsuperscript{25} However, this population of patients with severe stroke have a poor prognosis, with or without hemorrhagic transformation, and effective recanalization can dramatically improve outcome as compared with patients who are treated with placebo. Thus, it is not surprising that the overall mortality trended lower in IMS I and II.

The rate of asymptomatic ICH in IMS II subjects was not significantly different from IMS I but significantly greater than the rate of hemorrhagic change that was seen in rt-PA–treated subjects in the NINDS rt-PA Stroke Trial.\textsuperscript{25} The increased rate of hemorrhagic change overall in IMS I and II

\begin{table}[h]
\centering
\caption{Three-month and 24-hour Clinical Outcomes}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
& IMS II & NINDS Placebo & OR* (95% CI) & NINDS rt-PA & OR* (95% CI) \\
\hline
nRS 0–1 & 33% & 18% & 2.78 (1.46, 5.31) & 32% & 1.36 (0.72, 2.56) \\
\hline
nRS 0–2 & 46% & 28% & 2.82 (1.54, 5.16) & 39% & 1.74 (0.95, 3.19) \\
\hline
NIHSS \(\leq 1\) & 27% & 15% & 2.84 (1.40, 5.73) & 25% & 1.85 (0.92, 3.70) \\
\hline
NIHSS \(> 1\) & 33% & 20% & 2.66 (1.38, 5.12) & 33% & 1.47 (0.78, 2.77) \\
\hline
BI 95–100 & 53% & 30% & 3.24 (1.80, 5.85) & 42% & 2.29 (1.24, 4.23) \\
\hline
Global Test Statistic & NA & NA & 2.88 (1.66, 4.99) & NA & 1.85 (1.06, 3.23) \\
\hline
NIHSS 0–2 at 24 hours & 19% & 3% & 7.07 (2.54, 19.63) & 14% & 2.27 (0.996, 5.16) \\
\hline
\end{tabular}
\*Adjusted for age, baseline NIHSS, and time to treatment.
\end{table}
studies as compared with the NINDS rt-PA Stroke Trial has several potential explanations including higher resolution CT technology, the presence and effects of residual angiographic contrast in the infarct bed, concomitant use of heparin during IA therapy (forbidden in the NINDS rt-PA Stroke Trial), and more frequent early reperfusion with combined therapy. In addition, the rate of asymptomatic hemorrhage in IMS II is quite similar to rate of asymptomatic hemorrhage in more recent reports of IV thrombolytic and IA thrombolytic trials. The clinical consequences of asymptomatic ICH and symptomatic ICH are quite different and asymptomatic ICH frequently occurs in the setting of clinical improvement and some types of hemorrhagic transformation have been associated with improved outcome in the setting of early recanalization.

The combined IV and IA approach to recanalization is one that allows flexibility in the selection of the appropriate tools to accomplish timely and rapid reopening of the occluded artery. This approach and choice of tools and medications will evolve as new technology is evaluated. IMS II demonstrated that the most recent iteration of the EKOS micro-infusion catheter is a reasonable and easy-to-use tool for re-opening occluded intracranial arteries. Additionally, the delivery of intra-arterial rt-PA or other thrombolytic drugs via a standard micro-catheter remains an excellent option.

The just-initiated randomized IMS III Trial, which compares the combined IV/IA approach to standard IV rt-PA alone, includes not only the EKOS and standard micro-catheters but also the Concentric Merci retriever device as a potential option for clot removal in the IV/IA paradigm. Inclusion of the Merci retriever was based on the results of the Merci and Multi-Merci Trials and subsequent Food and Drug Administration approval.

While the combined IV and IA approach is attractive from a theoretical standpoint and is promising in pilot nonrandomized controlled trials, the next critical step is to compare the combined approach with standard IV rt-PA within 3 hours of onset. Until such a direct comparison is made, we will not know whether a combined approach, or even an IA approach alone, is more effective than IV rt-PA therapy and worth the additional cost, training, and resources. The success of interventional cardiology in acute myocardial infarction suggests a bright future for interventional treatment of acute stroke, but well done rigorous randomized trials are necessary to make sure that the promise of acute stroke therapy is scientifically well-grounded.

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Disclosures
J.P.B. has acted as consultant for Genentech, Inc.

References


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