Good Outcome Rate of 35% in IV-tPA–Treated Patients With Computed Tomography Angiography Confirmed Severe Anterior Circulation Occlusive Stroke

R. Gilberto González, MD, PhD; Karen L. Furie, MD; Gregory V. Goldmacher, MD, PhD; Wade S. Smith, MD, PhD; Shervin Kamalian, MD; Seyedmehdi Payabvash, MD; Gordon J. Harris, PhD; Elkan F. Halpern, PhD; Walter J. Koroshetz, MD; Erica C.S. Camargo, MD, PhD; William P. Dillon, MD; Michael H. Lev, MD

Background and Purpose—To determine the effect of intravenous tissue plasminogen activator (IV-tPA) on outcomes in patients with severe major anterior circulation ischemic stroke.

Methods—Prospectively, 649 patients with acute stroke had admission National Institutes of Health stroke scale (NIHSS) scores, noncontrast computed tomography (CT), CT angiography (CTA), and 6-month outcome assessed using modified Rankin scale. IV-tPA treatment decisions were made before CTA, at the time of noncontrast CT scanning, as per routine clinical protocol. Severe symptoms were defined as NIHSS>10. Poor outcome was defined as modified Rankin scale >2. Major occlusions were identified on CTA. Univariate and multivariate stepwise-forward logistic regression analyses of the full cohort were performed.

Results—Of 649 patients, 188 (29%) patients presented with NIHSS>10, and 64 out of 188 (34%) patients received IV-tPA. Admission NIHSS, large artery occlusion, and IV-tPA all independently predicted good outcomes; however, a significant interaction existed between IV-tPA and occlusion (P<0.001). Of the patients who presented with NIHSS>10 with anterior circulation occlusion, twice the percentage had good outcomes if they received IV-tPA (17 out of 49 patients, 35%) than if they did not (13 out of 77 patients, 17%; P=0.031). The number needed to treat was 7 (95% confidence interval, 3–60).

Conclusions—IV-tPA treatment resulted in significantly better outcomes in patients with severely symptomatic stroke with major anterior circulation occlusions. The 35% good outcome rate was similar to rates found in endovascular therapy trials. Vascular imaging may help in patient selection and stratification for trials of IV-thrombolytic and endovascular therapies. (Stroke. 2013;44:3109-3113.)

Key Words: computed tomography angiography ■ ischemic stroke ■ thrombolysis ■ tissue plasminogen activator ■ treatment outcome

Intravenous tissue plasminogen activator (IV-tPA) is an effective treatment for acute ischemic stroke. However, the relationships between arterial occlusion, IV-tPA administration, and outcomes in patients with severe stroke symptoms are largely unknown. The Screening Technology and Outcomes Project in Stroke (STOPStroke) was undertaken to assess the value of computed tomography (CT) technology including CT angiography (CTA) in patients with acute ischemic stroke. The study has shown that combining CTA information with neurological examination provides superior prognostic information than either alone. Because =1 in 6 patients who were recruited into the STOPStroke study received IV-tPA, it was possible to investigate outcomes in patients with specific arterial occlusions. We tested the hypothesis that the efficacy of IV-tPA treatment in patients with severe symptoms depends on the presence of a major anterior circulation artery occlusion that is detectable by CTA.

Methods

Patient Cohort

We reviewed the records of 742 consecutive patients who were prospectively enrolled in the STOPStroke between March 2003 and January 2006. The STOPStroke study was completed at the Massachusetts General Hospital and at the University of California...
San Francisco Medical Center as a prospective image-based outcome study. All patients with suspected acute ischemic stroke who presented within 24 hours of symptom onset and had multimodal CT examination (ie, unenhanced head CT and arch-to-vertex head and neck CTA) were consented for data collection and 6-month follow-up. Exclusion criteria included intracranial hemorrhage, contraindication to iodinated contrast agent, and having a stroke while in hospital. During the study period, all patients with suspected stroke or transient ischemic attack had multimodal CT examination as part of their routine clinical care in both institutions, except those with a contraindication to intravenous contrast. Surrogate consent was obtained when the patient was unable to communicate. The study received Institutional Review Board approval from both institutions and was Health Insurance Portability and Accountability Act compliant.

Patients were managed according to our routine clinical workflow, which specifies that the decision to treat with IV-tPA be made immediately at the time of CT scanning, before the CTA acquisition. Contraindications to IV-tPA included any hemorrhage on CT and last known normal >3 hours; large CT hypodensity (more than one third middle cerebral artery territory) was considered a relative contraindication.

Demographic data, past medical history, and National Institutes of Health stroke scale (NIHSS) scores were obtained at admission. Modified Rankin scale (mRS) scores were obtained at 6 months. Favorable outcome was defined as mRS 2. Patients were excluded if reliable mRS or NIHSS scores were not obtained. Study staff certified by the NIHSS training programs of the American Stroke Association obtained the mRS and NIHSS scores.

Scanning Procedures
Noncontrast computed tomography and arch-to-vertex CTA were performed according to standard protocols with multidetector CT scanners (LightSpeed; GE Healthcare, Chalfont St. Giles, UK). Representative noncontrast computed tomography parameters were the following: 120 to 140 kVp, 170 mA, 2-second scan time, and 5-mm section thickness. Biphasic helical CT scanning, at the same head tilt, was performed immediately afterward, with 100 to 140 mL of contrast (исоvue; Bracco Diagnostics, Princeton, NJ) at 3 mL/s and a 25-second delay (40 seconds for patients in atrial fibrillation). Parameters were 140 kVp, 220 to 250 mA, 0.8 to 1.0-second rotation, 2.5-mm section thickness, 1.25-mm reconstruction interval, 3.75-mm/rotation table speed, and 0.75:1 pitch. Source images were reconstructed into standardized maximum intensity projections of the intracranial and extracranial vasculature.

Image Review
Image review was independently performed on a workstation (Impax; Agfa Technical Imaging Systems, Richfield Park, NJ) by neuroradiologists or neurologists (M.H.L., E.C., and W.J.K.) as previously described. Reviewers had information on patient age, sex, and presenting clinical symptoms but were blinded to all information after the initial emergency evaluation. Noncontrast computed tomography images were reviewed first, followed by CTA. Disagreements were resolved by consensus. The reviewers recorded both major intracranial arterial occlusions and brain areas with hypodensity considered to have resulted from acute ischemia. A major anterior circulation occlusion was defined as occlusion of the terminal internal carotid artery and proximal middle cerebral artery (M1, M2) segments.

Statistical Analysis
Comparisons were tested for statistical significance using \( \chi^2 \) 2x4 contingency tables, Fisher exact tests, or \( \chi \) tests, as appropriate, with significance defined as \( P \leq 0.05 \) (all \( P \) values 2-tailed unless noted otherwise). Multivariate binary logistic regression, both with and without stepwise-forward likelihood ratio variable entry, was performed by using dichotomized outcome (mRS>2 poor versus mRS=2 good). Input variables, adjusted for time-to-CTA by forced entry, included admission NIHSS, major vessel occlusion, IV-tPA therapy, and the interaction terms between NIHSS×tPA and occlusion×tPA. All statistical results were calculated using SPSS (SPSS Inc, version 20.0, Chicago, IL).

Results
A total of 742 patients were enrolled in STOPStroke; in which, 90 patients were excluded for lack of a reliable mRS at 6 months, and 3 patients were excluded for lack of reliable NIHSS scores at admission. Thus, 649 patients formed the analyzed cohort and, of these, 101 patients (15.6%) received IV-tPA within 3 hours of stroke onset (86 patients received IV-tPA only, and 15 patients received both IV-tPA and endovascular therapy). For all patients who received IV-tPA, mean time from symptom onset to administration was 124.5±37.1 (SD) minutes. In patients with NIHSS>10 who received IV-tPA (n=64/188), mean time from symptom onset to administration was 126.5±36.1 (SD) minutes. The majority of patients who did not receive IV-tPA (~80%, 125 out of 158 patients) were imaged beyond the 3-hour time window for thrombolysis. Tables 1 and 2 show patient demographics, comorbidities, and endovascular (intra-arterial) treatment of both the entire (Table 1) and NIHSS>10 (Table 2) cohorts, stratified by IV-tPA treatment. Of the 101 patients who received IV-tPA, 50 patients had good outcomes (50/101, 50%). This good outcome rate was significantly lower than that of the 346 out of 548 (63%) similar patients who did not receive IV-tPA (P=0.010). However, 342 of these untreated patients had mild clinical symptoms (NIHSS≤5) as compared with 10 in the IV-tPA–treated group. If these subsets were removed, there were better outcomes in those receiving (43/91, 47%) versus not receiving IV-tPA (70/206, 34%; P=0.04).

Multivariate binary logistic stepwise-forward regression modeling was performed on the entire STOPStroke cohort, both including (n=649) and excluding (n=618) patients who received endovascular-only treatment. In the model with forward regression and interaction terms, for both groups, only (1) admission NIHSS and (2) the interaction term between major vessel occlusion and IV-tPA therapy were significant (P<0.001), supporting that the effects of IV-tPA on outcome vary with the presence or absence of major vessel occlusion. In the binary logistic model without forward regression or interaction terms entered, NIHSS, occlusion, and IV-tPA were all highly significant outcome predictors (P<0.004). When time-to-CTA was adjusted for by forced entry into the models, these results were unchanged.

The effect of IV-tPA on good outcome rates for the entire STOPStroke cohort, stratified by admission NIHSS score, is shown in Table 3. For patients with admission NIHSS>5 treated with IV-tPA, the reduction of risk for poor outcome was similar for each of the different subgroups shown in Table 3 (the number needed to harm in the NIHSS≤5 group was 10 [95% confidence interval, 18% to 39%; P=NS]). The 2 groups of patients that most strongly benefited from IV-tPA were those with (1) NIHSS of 6 to 10, and (2) NIHSS>10 with major anterior occlusion documented by CTA. Stratification by occlusion did not significantly change the results for the NIHSS 6 to 10 group. The numbers needed to treat in these 2 classes were 5 (95% confidence interval, 2–53) and 7 (95% confidence interval, 3–60), respectively.

A beneficial effect of IV-tPA treatment in patients presenting with severe neurological symptoms (NIHSS>10) is observed...
when patients are stratified by the presence of a major anterior circulation occlusion. \(\chi^2\) 2x4 contingency table analysis of good versus poor outcomes in patients with NIHSS>10 without posterior circulation involvement (n=175, with/without occlusion and with/without IV-tPA administration) disclosed highly significant differences (\(P<0.001\)). Patients with NIHSS>10 with major anterior circulation occlusions who received IV-tPA had significantly better outcomes (17/49, 35%) than similar patients who did not receive IV-tPA (11/36, 31%), this did not reach significance (\(P=0.031\)). Although there was a trend toward better outcomes in patients with NIHSS>10 without major occlusions who received IV-tPA (6/13, 46%) compared with those who did not receive IV-tPA (11/36, 31%), this did not reach significance (\(P=0.331\), likely because of the small cohort size.

These results were essentially identical when the entire cohort of patients with NIHSS>10, including those with both posterior fossa involvement (n=13) and endovascular treatment (n=29), were analyzed (Table 2). In this cohort (n=188), the good outcome rate for those with occlusion was 33% (17 out of 51 patients) IV-treated versus 17% (14 out of 84 patients; \(P=0.034\)) non-IV-treated, compared with 46% (6 out of 13 patients) IV-treated versus 33% (13 out of 40 patients; \(P=0.507\)) non-IV-treated for those without occlusion. These percentage-good outcome rates were similarly unchanged when the patients with anterior circulation stroke with endovascular treatment were excluded (n=151; 104 with occlusion; \(P=0.07\) 1-sided).

Moreover, when patients with admission CT Alberta Stroke Program Early Computed Tomography Score (ASPECTS)\(\leq\)7 were excluded from the full NIHSS>10 cohort (ie, excluding patients with a relative contraindication to IV-lytic therapy based on admission hypodensity lesion size), the proportion of good outcomes for those with occlusion was 40% treated versus 17% untreated (\(P=0.05\)), compared with 50% treated versus 33% untreated (\(P=0.50\)) for those without occlusion.

### Discussion

Outcomes of patients with ischemic stroke with documented cerebral artery occlusions treated with IV-tPA are not well studied and are poorly understood. The imperative to treat promptly supersedes other considerations, and imaging for vascular occlusion is typically not performed. Patients in the STOPStroke study were unusual in that they underwent CTA as part of their initial stroke evaluation after the decision to administer IV-tPA based on the unenhanced CT findings, and these data have revealed new information on the efficacy of IV-tPA. Most importantly, the STOPStroke study indicates that in patients presenting with
severe stroke symptoms caused by major anterior circulation artery occlusions, IV-tPA improves outcomes with an efficacy comparable with those found in endovascular therapy trials of like cohorts.11,12 The >30% good outcome rate produced by IV-tPA is a threshold that is considered successful for endovascular therapy. Indeed, according to recent benchmarks agreed on by 8 professional societies, “intra-arterial treatment for stroke should … result in a good outcome in ≥30% of patients.”13 Notably, this benefit was found to be statistically significant in a small number of patients: 49 with NIHSS>10 and anterior circulation occlusion that we observed in the STOPStroke cohort comes. Although the possibility of selection bias exists because CTA, regardless of symptom severity, unless specifically contraindicated. It is also noteworthy that despite the observational nature of our study and lack of randomization, differences in outcome between the treated and untreated groups are unlikely to be biased by the presence or absence of large vessel occlusion because the decision to administer IV-tPA was made immediately after the unenhanced CT before and independent of the CTA results. Moreover, because admission infarct size is another possible source of bias, we performed a subgroup analysis excluding patients with low admission ASPECTS scores (≤7), which resulted in similar good outcome rates as our primary analysis. There are other potential limitations to our study. The confidence intervals for the number needed to treat and number needed to harm analyses are wide and underpowered. Also, data are unavailable concerning the number and specific reasons for nonenrollment, although our ability to obtain surrogate consent may have, in part, mitigated any potential bias toward enrolling less severe strokes. Indeed, although our cohort was treated before European Cooperative Acute Stroke Study III (ECASS III), standardization of statins in acute stroke management, and widespread acceptance of the more aggressive use of IV-tPA in patients with relative contraindications, it is striking that our percentage of good outcomes, even in patients who

### Table 3. Effect of IV-tPA on Good Outcome rates (n, %) in the Entire STOPStroke Cohort, Stratified by Admission NIHSS score

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Good</th>
<th>Poor</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N=649)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=548)</td>
<td>63% (346/548)</td>
<td>37% (202/548)</td>
<td>0.007</td>
</tr>
<tr>
<td>IV-tPA (n=101)</td>
<td>50% (50/101)</td>
<td>50% (51/101)</td>
<td></td>
</tr>
<tr>
<td>NIHSS≥5 patients (n=297)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=206)</td>
<td>34% (70/206)</td>
<td>66% (136/206)</td>
<td>0.021</td>
</tr>
<tr>
<td>IV-tPA (n=91)</td>
<td>47% (43/91)</td>
<td>53% (48/91)</td>
<td></td>
</tr>
<tr>
<td>NIHSS 0–5 patients (n=352)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=234)</td>
<td>81% (276/342)</td>
<td>19% (66/342)</td>
<td>0.31</td>
</tr>
<tr>
<td>IV-tPA (n=10)</td>
<td>70% (7/10)</td>
<td>30% (3/10)</td>
<td></td>
</tr>
<tr>
<td>NIHSS 6–10 patients (n=109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=82)</td>
<td>52% (43/82)</td>
<td>48% (39/82)</td>
<td>0.038</td>
</tr>
<tr>
<td>IV-tPA (n=27)</td>
<td>74% (20/27)</td>
<td>26% (7/27)</td>
<td></td>
</tr>
<tr>
<td>NIHSS 11–15 patients (n=79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=55)</td>
<td>35% (19/55)</td>
<td>65% (36/55)</td>
<td>0.15</td>
</tr>
<tr>
<td>IV-tPA (n=24)</td>
<td>50% (12/24)</td>
<td>50% (12/24)</td>
<td></td>
</tr>
<tr>
<td>NIHSS≥16 patients (n=109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IV-tPA (n=69)</td>
<td>12% (8/69)</td>
<td>88% (61/69)</td>
<td>0.034</td>
</tr>
<tr>
<td>IV-tPA (n=40)</td>
<td>27.5% (11/40)</td>
<td>72.5% (29/40)</td>
<td></td>
</tr>
</tbody>
</table>

All P values Fisher exact (1-tailed). IV-tPA indicates intravenous tissue plasminogen activator; NIHSS, National Institutes of Health stroke scale score; and STOPStroke, Screening Technology and Outcomes Project in Stroke.
were severely symptomatic (NIHSS>10), were IV-tPA–treated, and had large vessel occlusion, so closely matches that of more recent trials of both IV and intra-arterial therapy in similarly symptomatic patients.\textsuperscript{11,12} The value of IV-tPA in such severely symptomatic patients with CTA proven large vessel occlusion has not previously been emphasized.

In summary, STOPStroke has revealed that treatment with IV-tPA results in better outcomes in patients with severe stroke symptoms with major anterior circulation occlusions than in similar patients that did not receive IV-tPA. Treatment using targeted vascular imaging such as CTA may be important for patient selection and stratification in clinical trials of ischemic stroke, including direct comparisons between IV-thrombolytic and endovascular approaches.

Acknowledgments
We thank all STOPStroke research coordinators and fellows for assistance in data gathering and patient enrollment.

Sources of Funding
This work was supported by the National Institutes of Health Agency for Health Care Policy and Research (AHCPR), R01 HS11392-01A1. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures
Dr Kamalian reports GE Healthcare research support. Dr Lev reports research support from GE Healthcare, Department of Defense through Center for Integration of Medicine and Innovative Technology, and is Consultant to Millennium Pharmaceuticals.

References
Good Outcome Rate of 35% in IV-tPA–Treated Patients With Computed Tomography Angiography Confirmed Severe Anterior Circulation Occlusive Stroke


Stroke. 2013;44:3109-3113; originally published online September 3, 2013; doi: 10.1161/STROKEAHA.113.001938

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/11/3109

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/