Response to Intra-Arterial and Combined Intravenous and Intra-Arterial Thrombolytic Therapy in Patients With Distal Internal Carotid Artery Occlusion

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Background and Purpose—The objective of this study was to determine the clinical features, angiographic findings, and response to treatment with thrombolytic therapy in patients with ischemic stroke caused by acute occlusion of the distal internal carotid artery.

Methods—This is a retrospective case series from a prospectively collected stroke database for patients with acute internal carotid occlusion presenting within 6 hours of stroke onset to evaluate safety, feasibility, and response to thrombolytic therapy. The University Hospital–based brain attack database was reviewed over a 5-year period. Demographics, clinical features, stroke mechanisms, severity, imaging findings, type of thrombolysis, treatment responses, mortality, and long-term outcome using modified Rankin Scale and Barthel Index were determined. The short-term outcome was assessed using the National Institutes of Health Stroke Scale (NIHSS). Acute thrombolytic therapy was administered using recombinant tissue plasminogen activator or urokinase given intra-arterially or in combination with intravenous (IV) routes.

Results—Two hundred seven patients treated with thrombolysis between 1995 and 2000 were reviewed, and of these, 101 were studied with cerebral angiography. Eighteen patients were identified with acute ischemic stroke and ipsilateral occlusion of the distal internal carotid artery. Time to treatment was the most powerful predictor of response to thrombolytic therapy ($P\leq0.001$). The response to therapy also correlated well with the severity of the initial clinical deficit as judged by the NIHSS ($P\leq0.001$). There was no difference in recanalization rate, symptomatic hemorrhage, and NIHSS for IV/intra-arterial (IA) versus IA alone ($P=NS$). Complete angiographic recanalization was accomplished in 80% of those who received combined IV/IA thrombolysis and in 62% of those who received IA therapy ($P=NS$). Those with distal occlusions extending to the middle and anterior cerebral arteries were the least likely to respond to thrombolysis. Symptomatic intracerebral hemorrhage occurred in 20% of the patients receiving IV/IA therapy, and in 15% of the IA only ($P=NS$). At 24 hours, the NIHSS dropped by 3 points in the IA group and 4 points in the IV/IA group ($P=NS$). Mild disability with independence was found in 77% of the survivors at 3-month follow-up. The mortality rate was 50% in this group despite thrombolysis.

Conclusions—Thrombolytic therapy using a combination of IV and IA routes and using the IA-only route may be effective in improving outcome for the patients suffering from occlusion of the distal internal carotid artery. Shorter intervals between onset and treatment seem to be correlated with higher rate of recanalization and improved outcome. (Stroke. 2002;33:1821-1827.)

Key Words: angiography ■ atherosclerosis ■ carotid arteries ■ occlusion ■ stroke, ischemic ■ thrombolysis ■ tissue plasminogen activator

The use of cerebral angiography as an adjunct to intra-arterial (IA) delivery of thrombolytic agents has allowed precise identification of the site of vascular occlusion in acute ischemic stroke.1,2 The size of the clot and the precise site of occlusion may influence outcome and response to thrombolytic therapy. Prior studies using IV and local IA thrombolysis (IAT) indicate that the response to acute stroke therapy is correlated with the severity of clinical deficits and with imaging findings using computerized head tomography or MRI at the time of initial presentation.3,4 The latter is
thought to be related to the site of occlusion, the size of the clot, and the presence or absence of enough collateral. The IV recombinant tissue plasminogen activator study (National Institute of Neurological Disorders and Stroke) did not correlate the outcome with the type of stroke or the presumed occlusion sites.

In the Prolyse in Acute Cerebral Thromboembolism II study, IA recombinant pro-urokinase administered within 6 hours of symptom onset in patients with angiographically proven proximal middle cerebral artery occlusion was found to improve outcome in 40% of treated patients versus 25% of the control group using a modified Rankin scale (mRs). The study was restricted to the horizontal portion of the middle cerebral artery and did not treat other types of occlusion. The combined studies using both IV followed by IA thrombolytic agents are promising but are too small in size to reach a conclusion about the response to therapy in relation to the location.

Acute occlusion of the distal internal carotid artery (ICA) is a very challenging dilemma to treating physicians due to the dismal neurological outcome and resistance to thrombolysis. Different anecdotal techniques and modes of intervention have been used to overcome this challenge. Only few scattered cases in the literature discuss the outcome and the pros and cons of the currently available potential therapeutic intervention.

**Methods**

**Patient Selection**

Over the period from 1995 through 2000, 842 patients presenting to University Hospitals of Cleveland within presumed 6 hours of ischemic stroke onset were evaluated by one of the authors and underwent emergent cranial computerized tomography (CT) scanning without contrast. A total of 219 patients underwent immediate cerebral angiography. Patients who were eligible for thrombolytic therapy and had documented carotid terminus clot were evaluated for the purpose of this study. We used the following criteria to judge eligibility for thrombolytic therapy.

**Inclusion Criteria**

Inclusion criteria were the following: (1) National Institutes of Health Stroke Scale (NIHSS) score of ≤4, (2) age >18 and <80 years, and (3) angiographic evidence of distal ICA occlusion.

**Exclusion Criteria**

Exclusion criteria were the following: (1) cerebral hemorrhage, presence of clear hypodensity, or definite mass effect on the CT scan; (2) questionable diagnosis (seizure disorder, preexisting encephalomalacia in the symptomatic arterial territory, cerebral neoplasm, or dementia requiring custodial care); (3) high risk for hemorrhage (prothrombin time >15; platelets <100 000; history of gastrointestinal or genitourinary bleeding in previous 21 days; history of cardiopulmonary resuscitation, trauma, or surgery within 14 days; arterial puncture at a noncompressible site within 7 days; lumbar puncture within 7 days; pregnancy or delivery within 14 days; or history of cerebral hemorrhage); (4) systolic blood pressure >180 mm Hg and diastolic blood pressure >110 mm Hg despite the use of IV nitroprusside or labetalol; (5) clinical improvement before treatment initiation; and (6) data from patients with clot present not only at the distal ICA.

**Thrombolytic Therapy**

Patients presenting 3 hours or more after the clinical onset were considered candidates for IA therapy and underwent immediate cerebral angiography. Angiography was performed via femoral artery approach. We used rapid Transit or Prowler-14 microcatheters (Cordis) and Mach 16 select, Transcend 14, and Fast Dasher 14 wires (Target Therapeutics). Heparin at a dose of 500 U/hour was continuously infused to keep the introducer sheath open and stopped immediately after completion of the procedure. The femoral introducer sheath was kept in place overnight, while the patient was in the neuroscience intensive care unit, and removed 12 to 24 hours after use. IA urokinase (UK) was used with an initial dose of 250 000 U diluted in 3 cm³ of a saline solution, administered over 5 minutes in close proximity to the clot. A second dose of 250 000 U was diluted in 20 cm³ of a saline solution and infused over 20 minutes proximal to the clot. Repeat doses of 250 000 U in 20 cm³ over 20 minutes were given to achieve recanalization with total dose limited to 1.5 million units. The recombinant tissue plasminogen activator (rtPA) replaced UK as the IA agent after withdrawal of the latter from the market.

Patients presenting with acute ischemic stroke before 3 hours had elapsed were given sequential IV and IA rtPA therapy if they did not show any sign of neurological improvement after the IV therapy. The IV rtPA dose was 0.6 mg/kg delivered over 30 minutes. The dose of IA rtPA was given in increments of 5 mg over 10 minutes diluted in 10 cm³ normal saline until complete resolution of the clot or maximum total dose of 0.9 mg/kg was given (including the IV dose of 0.6 mg/kg).

In all instances, mechanical disruption of clot with the microwire and microcatheter was attempted before and after administration of the thrombolytic agent. The use of IV heparin was not allowed for the first 24 hours after IA UK or rtPA regardless of the CT scanning appearance. Our Institutional Review Board approved our treatment protocol, and all patients or their legal representatives signed informed written consent before treatment initiation.

**Neuroradiological Evaluation**

Oclusions were classified into one of 3 types. Type I occlusions extended from the carotid artery above the origin of the ophthalmic artery and involved both A1 and M1 segment (T-shaped clot). Type
II clots extended from the origin of the ophthalmic artery to either M1 or A1, but not both. Type III occlusions originated proximal to the ophthalmic artery but distal to the carotid bifurcation. The recanalization findings after thrombolytic therapy were classified as no, partial, or complete recanalization. Restoration of flow was defined as passage of contrast with complete filling and clearance to patent distal vessels. However, if the rate of clearance was slower compared with normal arteries, the restoration of flow was classified as partial. All patients underwent head CT scanning immediately after thrombolytic therapy. CT scanning was classified as without abnormality, with early signs of infarction, with hemorrhagic infarction, or with parenchymal hematoma. In those images obtained after thrombolytic therapy administration, increased density could reflect contrast enhancement due to contrast extravasation during angiography (if >50% of the hyperdensity area resolved on the 24-hour follow-up CT study, it would be considered contrast extravasation), hemorrhage, or both. Hemorrhagic infarction was defined as areas of increased density with an indistinct border within the vascular territory for which the patient was treated. A parenchymal hematoma was defined as a homogenous, hyperdense area, with well-defined border with or without surrounding edema. Symptomatic intracranial hemorrhage was defined as neurological worsening ≥4 points in NIHSS and attributable to the presence of the clot.

### Outcome Measures
The NIHSS was obtained on arrival, after IAT, and 24 and 120 hours after onset. Neurological improvement was defined as a 4-point decrement in the NIHSS in the initial 24 hours after symptom onset. A Barthel Index was obtained 90 days after the onset of ischemia. Scores of 95 or 100 were considered to indicate favorable outcome. The mRs was also used to measure the disability secondary to stroke. Scores of 2 or less to define good outcome in other stroke studies, a score of 3 or less was considered a relatively good outcome in this lethal disease. An examiner unaware of the precise nature of treatment obtained Barthel Index and mRs. In-hospital and 90-day mortality rates were also recorded.

### Statistical Analysis
The Fisher exact test or t test was used to analyze differences between survivors and nonsurvivors. The Wilcoxon signed rank sum test was used to analyze the NIHSS. P<0.05 was considered significant. All values are presented as means±SD or as medians.

### Results
In the period between 1995 and 2000, 842 patients were evaluated for possible brain attack on the basis of the initial evaluation by the emergency medical services or emergency department staff. After further screening by the brain attack team, only 207 eventually received thrombolytic therapy. Of
these, 101 patients received IA therapy, and the precise site of vascular occlusion could be identified accurately via cerebral angiography. Eighteen of the 101 patients undergoing angiography were found to have distal occlusion of the ICA; the majority were distal to the origin of the ophthalmic artery.

**Demographics**
Most patients were female (61%) and white (80%). The mean age was 69 years, and hypertension was the most common risk factor (80%) (demographic data presented in Table 1). Cardiac disease was present in 67% of patients. The most common cardiac abnormality was atrial fibrillation (50%).

The main clinical, laboratory, and neuroimaging features of the patients are summarized in Table 2 with a comparison between survivors and nonsurvivors.

**Cerebral Angiography Results**
Type I (T-shaped clot) was the most common class of occlusions. Type I was found in 10 patients, type II in 6, and type III in 2 (Table 3). There was good evidence of collateral blood flow derived from the contralateral circulation in 50% of patients. The collateral blood supply was more evident for type III and II than for type I. Collateral circulation was mainly via leptomeningeal, communicating arteries and in type III occlusion via the external carotid artery and ophthalmic artery. A conventional cerebral angiogram demonstrating T-shaped clot before and after treatment with IV/IA rtPA thrombolysis is shown in the Figure.

**Thrombolysis**
Thirteen patients received IAT with UK and the remaining 5 patients received a combination of IV and IA (IV/IA) therapy with rtPA (Table 4). The rate of any angiographic recanalization was 80% for the patients receiving IV/IA as compared with 62% for IAT only (P=NS). A T-shaped distal ICA clot (type I) angiographic occlusion was associated with 50% recanalization rate (5/10), whereas 6 patients with type II had angiographic recanalization, and 1 of 2 patients with type III.

**Outcome**
The total mortality rate in the whole group was 50% (9/18). The severity of the clinical deficit as judged by the NIHSS correlated with the in-hospital mortality (P<0.00002). Twenty-four hours after clinical onset, the initial NIHSS had dropped by an average of 3 points in the IAT group and by >4 points in the IV/IA group. Mortality was closely related to the initial cranial CT findings. The initial cranial CT was interpreted by a Board-certified neuroradiologist as normal in 6 out of the survivors, and in 1 of the nonsurvivors. The initial cranial CT was abnormal in 3 of the survivors, as compared with 8 nonsurvivors (P=0.05). The incidence of symptomatic intracerebral hemorrhage (ICH) within the first 24 hours was 20% for the IV/IA group (1/5), and 15% for the IA group (2/13). All of the patients with symptomatic ICH died. Of the 3 patients who developed ICH, 2 had been treated with IA therapy, and 1 with IV/IA therapy. Five other patients died from malignant cerebral edema, and 1 patient died from a combination of cerebral edema and cardiac causes (myocardial infarction and congestive heart failure). Of the 5 patients who died with cerebral edema, the decision had been made with the family to withdraw life support measures in 2 patients, 1 with right hemispheric and 1 with left hemispheric stroke, who were on mechanical ventilation and had increasing cerebral edema with herniation on cranial CT scan.

**Long-Term Outcome**
At 3 months, evaluation of patients surviving the initial hospitalization with mRs showed 77% (7 patients) of survivors with mild disability (scale of 3 or less) and 23% with moderate to severe disability (Table 4). Four of the 6 survivors who had occlusion of the left ICA had mRs of 0 to 1 with near-complete resolution of their aphasia.

Evaluation with the Barthe Index disclosed a score of 95 to 100 in 50% of the survivors. Initial NIHSS, CT findings, and response to thrombolysis were the strongest predictors of mortality (Table 2). The type of angiographic occlusion had some utility as a predictor of response to thrombolytic therapy and outcome. In particular, a T-shaped, type I occlusion was associated with poor recanalization rate and increased mortality despite the use of thrombolytic therapy.

**Discussion**
Acute distal ICA occlusion is associated with dismal outcome and high mortality rate. Severe disability with dependency is
common in those who survive. The implementation of the combined IV/IA and local IAT with the use of cerebral angiography within the first 6 hours after clinical onset of stroke allowed an accurate identification and precise localization of the vascular occlusion. Consequently, new knowledge and insight into the response of this type of clot to available treatment and its clinical course are being acquired. In this case series we are presenting and analyzing a clinical course of treatment of the distal carotid artery occlusion.

In most of the previously reported cases of acute distal ICA occlusion, the underlying mechanism has been thought to be embolism, and the source of the embolus had been most commonly cardiac.11 Of the 18 patients, only 1 had carotid artery stenosis/ipsilateral to the distal ICA occlusion. Thus, the source of the embolus in the remaining 17 patients is unlikely to be the carotid bifurcation. A cardiac origin for the embolus seems especially likely in the 8 patients (44%) with a history of coronary artery disease and the 7 patients (39%) with atrial fibrillation.

Type I was the most commonly encountered class of occlusion (10/18). Seven patients in this group had clinical evidence of risk for cardiac embolization, making the cardio-genic source the most frequent one for type I carotid occlusion.

It has been suggested that distal ICA occlusion is the real mechanism of stroke in patients described as suffering from the "malignant MCA [middle cerebral artery] syndrome."11 In several reported series, the mortality in patients with main trunk MCA and distal ICA occlusion ranged between 60% and 87%,11–13 versus 50% in this group of thrombolysis-treated patients (P<0.05). The severity of the clinical course probably reflects the pattern and severity of ischemia caused by distal ICA occlusion. In instances of T-shaped clots extending into the proximal anterior cerebral artery and MCA, there is immediate loss of direct arterial perfusion. Tissue may only survive if there is sufficient collateral supply via leptomeningeal arteries derived from the posterior cerebral artery.

The reported rates of recanalization of distal ICA occlusion with IV or IAT therapy vary with the type and precise site of occlusion, time to treatment, and techniques used.1,4,14–19 The findings in the present series are compared with those in the

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<th>TABLE 4. Comparison Between IA-UK and IV/IA rtPA</th>
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<td>Number of patients</td>
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<td>Mortality</td>
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<td>Outcome (mRs at 3 months)</td>
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<td>Symptomatic intracerebral hemorrhage</td>
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<td>Recanalization</td>
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<th>TABLE 5. Summary of the Reported Recanalization Rates After Different Type and Route of Thrombolytic Therapy for Acute Distal Carotid Artery Occlusion: Number of Patients (%)</th>
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<tbody>
<tr>
<td>Reference</td>
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<td>Ernst et al8</td>
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<td>Current series (any recanalization)</td>
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*Hours:minutes.

Total number of responders in all groups was 36/125 (29%).
literature in Table 5. In the current series (IA and IV/IA), the proportion of treated patients with any angiographic recanalization was 67% versus 15% in the historic IV therapy (P<0.05). The frequency of any angiographic recanalization was 80% in the IV/IA group; it may be pertinent that therapy was initiated earlier in this group than in those with IA therapy only (4 hours versus 2 hours and 23 minutes, P<0.001). The complete recanalization rate was 50% in all patients; this is higher than in most of the previous studies, as mentioned in Table 5. A total of 125 cases of distal ICA disease were treated with various types of thrombolytic therapy. Of those patients, only 36 (29%) had some reconstitution of blood flow, as compared with 50% in this study. The other studies mentioned in Table 5 did not include or specify the exact location of the clot. The relatively poor outcome in the previously reported patients may reflect the fact that many were treated with IV therapy only, and fewer were treated with IA or the combination of IV/IA routes. Given the above limitations and the small number of patients in the previously reported cases, it is difficult to reach any firm conclusions or generalization.

Despite applying the current available management strategies, the clinical and angiographic response to therapy remains limited. The reasons for the low rate of recanalization in distal ICA occlusion are uncertain. It is likely that the original size of the clot is larger in distal ICA than in those that end up in the MCA. It is also possible that the stiffness (or extent of organization) of the clot is greater in those that lodge in the distal ICA as compared with those that can pass farther to the MCA.

Because of the small sample size, our results are preliminary and preclude us from reaching completely generalizable conclusions. However, patients who received therapy earlier after clinical onset tended to have a better response. It is unclear whether combined therapy (IV/IA) is more efficacious than IA alone despite a minor trend in favor of IV/IA. Future larger studies with a control group are needed.

Acknowledgments
We thank the neurology and neurosurgery residents and emergency room staff who participated in the brain attack program at University Hospitals of Cleveland.

References
Despite the substantial clinical benefit associated with intravenous (IV) rtPA administration in acute stroke, the majority of patients remain unaffected by treatment. Acute carotid occlusions can be particularly difficult to manage, because they tend to cause more severe brain injury, and the natural history of such strokes is reported to be poor. Thus, any means to improve outcome in these patients warrants investigation.

In this study, the authors retrospectively review their experience with both IA and a combination of IA and IV (IA/IV) therapy in carotid occlusion. They report better recanalization rates than in prior series and speculate that such aggressive treatment may be superior to IV treatment alone in these patients. Unfortunately, the current study adds little new information to the debate. Although the authors suggest improved recanalization and possibly better treatment outcomes with IA and IA/IV treatment compared with historical series, it is inappropriate to perform such comparisons, given the retrospective and uncontrolled nature of these analyses. In addition, it is unclear how successful IV rtPA alone may be in these patients since only those individuals who had persistent clot after IV treatment were included in the study. This likely underestimates the effectiveness of IV treatment alone, since those patients who were successfully recanalized by IV treatment would be excluded from this analysis. Only randomized controlled trials with adequate statistical power can ever hope to answer these questions. Given the substantial added expense, limited availability, and significant time delay associated with IA treatment, IV rtPA should still be considered the mainstay of acute stroke treatment in most patients, particularly within the <3-h time window, except in the setting of an investigational study.

However, based on the limited data available in this study, some observations can be made regarding IA- and IA/IV-treated patients. First, time to treatment was the factor most strongly correlated with outcome. This is consistent with other recent studies of both IA1 and IV rtPA2–3 that also found a strong correlation between early treatment and good outcome. These data emphasize the need to treat acute stroke patients as rapidly as possible, regardless of treatment modality. Similarly, an abnormal CT on admission and extensive occlusion on angiogram significantly reduce the probability of both survival and good outcome, consistent with current hypotheses. However, it is important to note that although mortality was reduced by IA/IV treatment, there was no significant difference in the final Rankin scores between IA- and IA/IV-treated patients. This is concerning, and it could indicate that even if aggressive treatment improves survival in these patients, it may be at the expense of increased morbidity, an outcome of uncertain overall benefit.

Nevertheless, both IA and IA/IV therapy remain extremely attractive therapeutic options at centers that can perform the procedures. Moreover, in the future, combination of IA treatment with other nonthrombolytic technologies such as lasers, catheter-based retrieval devices, and even intracatheter ultrasound,4 remain exciting possibilities. Similarly, the combination of IA therapy with neuroprotection or antithrombotic agents has many theoretical advantages. In addition, the use of neuroimaging such as perfusion- and diffusion-weighted MRI or CT perfusion5 as a means to determine tissue viability may also aid in improving the efficacy of therapy. However, all of these theoretically superior approaches need to be rigorously tested to confirm their effectiveness before they may be adopted into routine clinical practice. It is only in this way that we can clearly identify those treatments that are most beneficial to our patients.

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References
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Stroke. 2002;33:1821-1827
doi: 10.1161/01.STR.0000020363.23725.67
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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