Significance of Large Vessel Intracranial Occlusion Causing Acute Ischemic Stroke and TIA

Wade S. Smith, MD, PhD; Michael H. Lev, MD, FAHA; Joey D. English, MD, PhD; Erica C. Camargo, MD, MMSc; Maggie Chou; S. Claiborne Johnston, MD, PhD; Gilberto Gonzalez, MD, PhD; Pamela W. Schaefer, MD; William P. Dillon, MD; Walter J. Koroshetz, MD; Karen L. Furie, MD, MPH

Background and Purpose—Acute ischemic stroke due to large vessel occlusion (LVO)—vertebral, basilar, carotid terminus, middle and anterior cerebral arteries—likely portends a worse prognosis than stroke unassociated with LVO. Because little prospective angiographic data have been reported on a cohort of unselected patients with stroke and with transient ischemic attack, the clinical impact of LVO has been difficult to quantify.

Methods—The Screening Technology and Outcome Project in Stroke Study is a prospective imaging-based study of stroke outcomes performed at 2 academic medical centers. Patients with suspected acute stroke who presented within 24 hours of symptom onset and who underwent multimodality CT/CT angiography were approached for consent for collection of clinical data and 6-month assessment of outcome. Demographic and clinical variables and 6-month modified Rankin Scale scores were collected and combined with blinded interpretation of the CT angiography data. The OR of each variable, including occlusion of intracranial vascular segment in predicting good outcome and 6-month mortality, was calculated using univariate and multivariate logistic regression.

Results—Over a 33-month period, 735 patients with suspected stroke were enrolled. Of these, 578 were adjudicated as stroke and 97 as transient ischemic attack. Among patients with stroke, 267 (46%) had LVO accounting for the stroke and 13 (13%) of patients with transient ischemic attack had LVO accounting for transient ischemic attack symptoms. LVO predicted 6-month mortality (OR, 4.5; 95% CI, 2.7 to 7.3; \(P < 0.001\)). Six-month good outcome (modified Rankin Scale score \(\leq 2\)) was negatively predicted by LVO (0.33; 0.24 to 0.45; \(P < 0.001\)). Based on multivariate analysis, the presence of basilar and internal carotid terminus occlusions, in addition to National Institutes of Health Stroke Scale and age, independently predicted outcome.

Conclusion—Large vessel intracranial occlusion accounted for nearly half of acute ischemic strokes in unselected patients presenting to academic medical centers. In addition to age and baseline stroke severity, occlusion of either the basilar or internal carotid terminus segment is an independent predictor of outcome at 6 months. (Stroke. 2009;40:3834-3840.)

Key Words: CT angiography ■ prognosis

A clinician treating acute ischemic stroke is best enabled to make clinical decisions if they have good predictive models of clinical outcome considering all data available. Models of clinical outcome after stroke have reported age and stroke severity as independent predictors of clinical outcome.1-3 It is expected, however, that occlusion of large intracranial vessels such as the basilar artery, carotid terminus, and middle cerebral artery is associated with higher mortality and may also be expected to contribute predictive value to models of stroke outcome. Furthermore, large artery occlusion has been associated with a greater risk of stroke after transient ischemic attack (TIA) and minor stroke.4 The advent of noninvasive techniques for cerebral angiography (CT angiography and MR angiography) allows for routine acquisition of angiographic information on patients with acute stroke and provides an opportunity to explore the predictive value of vascular status on prognosis. The Screening Technology and Outcome Project in Stroke (STOP Stroke) study was designed in part to prospectively obtain complete head and neck CT angiography on an unselected consecutive cohort of patients with acute stroke and with TIA to better understand the prognostic significance of large vessel occlusion of the intracranial vessels. In this study, we used this information to determine whether acute angio-
graphic assessment provides significant prognostic information by itself and if this assessment provides additional information beyond that of age and National Institutes of Health Stroke Scale (NIHSS) at the time of patient presentation.

Methods

The STOP Stroke Study is a prospective imaging-based study of stroke outcomes completed at Massachusetts General Hospital and the University of California San Francisco Medical Center. Patients with suspected acute stroke who presented within 24 hours of symptom onset to the institutions’ emergency departments and who underwent multimodality CT/CT angiography (CTA) were approached for consent for 6-month follow-up and collection of clinical data. Patients who were transferred to these institutions or had stroke while hospitalized were excluded from the analysis. Both institutions routinely used CT/CTA technology to image all suspected stroke or TIA during the study period unless contraindications to intravenous contrast existed. Surrogate consent was allowed for patients unable to consent for themselves. Patients consented by surrogate were reconsented for follow-up if they had regained capacity. The Institutional Review Boards of both institutions approved this clinical study.

Research coordinators for both sites extracted demographic data and data regarding the acute presentation and hospital course and data available through the acute hospitalization, including imaging data, at the time of patient presentation. All patients underwent brain CT imaging at 3.25-mm separation, CTA at 1.25-mm increments from the aortic arch through the circle of Willis, and postcontrast CT imaging. CT angiograms were reconstructed as "thick maximum intensity projection" reconstructions. Both thick maximum intensity projection reconstructions and CT source images were reviewed by 2 neuroradiologists blinded to clinical outcome. Cerebrovascular vessels were divided into segments including supraclinoid internal carotid artery (ICA), first division middle cerebral artery (M1), second division middle cerebral artery (M2), first division anterior cerebral artery (A1), second division anterior cerebral artery (A2), basilar artery (BA), intracranial vertebral artery (VA), first division posterior cerebral artery (P1), and second division posterior cerebral artery (P2). A neuroradiologist determined whether any of these vascular segments was occluded. If this analysis showed no vascular occlusion, the patient was documented as having no large vessel occlusion. If one or more vascular segments were occluded, the case history and NIHSS score were reviewed, and if the vascular occlusion was in the appropriate territory to account for the clinical findings, the case was judged as having a large vessel occlusion; otherwise, if the vascular segment occlusion did not explain the clinical symptoms, the case was classified as not having a large vessel occlusion.

Variables tested for prediction of good outcome and mortality included age, gender, ethnicity/race, prior stroke/TIA, hypertension, diabetes, atrial fibrillation, coronary artery disease, peripheral vascular disease, hypercholesterolemia, current tobacco use, and presence of segmental vascular occlusion. Use of intravenous tissue plasminogen activator (tPA) or use of endovascular intervention, including intra-arterial (IA) tPA, was not included in the primary model nor were other therapies given during hospitalization because the goal of the model was to best understand prognosis based on initial presenting signs and symptoms. However, analysis of outcomes with and without use of intravenous tPA was performed in a secondary model.

Variables were analyzed by univariate and then multivariate modeling using Stata, Version 10 (College Station, Texas). Multivariate modeling included any variable found to have P<0.20 in univariate testing with stepwise elimination by highest probability value and variables retained with P<0.05.

Results

Over a 33-month period, 1636 patients were admitted to the study hospitals with presumed stroke or TIA and 741 patients were enrolled in the STOP Stroke study. Of these 741 patients, 5 had missing NIHSS scores, and one was missing a final diagnosis, yielding 735 patients for further analysis (Figure 1). After review of all clinical, laboratory, and clinical data, an independent stroke neurologist determined that 578 patients had stroke (79%), 97 (13%) had TIA, and 60 (8%) did not have either stroke or TIA. Of the 675 patients with stroke/TIA, 6-month modified Rankin Scale scores were available in 607. Demographics, risk factors, and stroke classification for the patients with stroke and those with TIA are shown in Table 1.

Large vessel occlusion was responsible for 267 (46%) strokes, 13 (13%) TIA, and 41% of stroke and TIA combined. The locations of vascular occlusion and mean NIHSS score are shown in Table 2. The overall mean NIHSS was 7.6. Patients with small vessel occlusions had a significantly lower NIHSS score than patients with large vessel occlusion (P<0.0001, Wilcoxon test); the presence of large vessel occlusion was associated with a significant 7.8-point increase in NIHSS score. There was a wide variation in NIHSS scores based on vascular location with carotid terminus and basilar occlusions having the highest NIHSS scores and more distal occlusions (M2, A2, P2) having lower NIHSS scores. Intravenous tPA was given to patients with higher...
NIHSS scores at baseline, but there were no differences in age or vascular distribution in those who did or did not receive intravenous tPA.

NIHSS scores showed considerable overlap between patients without large vessel occlusion and those with one, 2, or 3 intracranial vascular segments occluded (Figure 2). The mean scores between each category of large vessel occlusion (shown as a horizontal bar for each category in Figure 2) were significantly higher than scores from patients with a normal CT angiogram showing large vessel occlusion (LVO). Vascular segments that were significantly associated with outcome include the ICA, M1, M2, and BA; P1 occlusions correlated with good outcome but not mortality. Only one in 4 patients with ICA or BA occlusions had a good clinical outcome, whereas 34% of M1 and 40% of M2 occlusions had a good outcome. BA occlusions were associated with a 50% mortality compared with ICA occlusion (35%) and M1 and M2 occlusions (24% each). Occlusions of the VA, A1, A2, and P2 segments were not associated with either proportion of good clinical outcome or mortality.

To explore the potential independent influence of large vessel occlusion on stroke outcome, all variables available at hospital admission (ie, not including intravenous or IA treatment or intensive care unit-based treatments) with P<0.20 on univariate analysis were tested in a multivariate model to predict good outcome and mortality. These results are shown in Table 3. Younger age, male gender, and lesser
stroke severity were positive predictors of good outcome, but occlusion of any particular intracranial vascular segment was not found to predict good outcome independently. ICA and BA in combination did independently predict proportion of good outcomes with an OR of 0.18 ($P=0.039$). Interaction was identified between baseline NIHSS score and ICA and BA occlusions (but not age or gender) confirming that knowledge of these locations of vascular occlusion is most informative at higher NIHSS scores as suggested by the univariate analysis shown in Figure 2 and Table 2. Age and NIHSS score were strongly predictive of mortality, but no single vascular segment predicted mortality independently when considered in isolation or in combination. Ordinal logistic analysis using 3 modified Rankin Scale outcomes (0 to 2, 3 to 5, 6) found only the presence of LVO predicted outcome (coefficient 2.7, $P=0.006$) and not age or baseline NIHSS considering the most severe strokes (NIHSS $\geq 20$), supporting the findings shown in Figure 3.

The use of intravenous tPA was associated with good outcome when added to the model in Table 3. Specifically, good outcome was best modeled as age (OR $[P]$; 0.97 [<0.001]), NIHSS (0.84 [<0.001]), female (0.56 [0.002]), and intravenous tPA use (2.0 [0.010]). Intravenous tPA use did not influence mortality. If one explores the influence of LVO in patients who did versus did not receive intravenous tPA, occlusion of the BA and ICA vessels was negatively predictive of good outcome for patients who received intravenous tPA but not in those who were left untreated (Table 4). This analysis is likely confounded by marked differences in baseline NIHSS scores (Table 2) so this analysis should be considered cautiously. Use of IA therapies was so infrequent that this variable was not considered in overall models of outcome.

Discussion

Large vessel occlusion accounted for 46% of acute strokes in our study. This proportion is likely a reasonable measure of the true burden of large vessel stroke in an urban multiethnic US population because the data were obtained from 2 geographically separate urban centers. Knowledge that a patient has a LVO on acute presentation appears to be important. We found that presence of LVO was associated with a 4.5-fold increased odds of death and a 3-fold reduction in odds of good outcome. Ordered from worse outcome to best, BA, ICA, M1, and M2 occlusions were significantly associated with patient mortality and decreased probability of good outcome. The presence or absence of LVO likely adds independent information about prognosis, especially among patients with more severe strokes. Therefore, angiographic imaging appears to provide an additional independent variable beyond age and baseline NIHSS score to predict patient outcome when considering all information available to the treating physician at patient presentation.

Nearly half of all patients with acute stroke and those with TIA in our study were found to have occlusion of at least one intracranial vascular segment. Other studies have found a lower rate based on retrospective reviews of consecutive patients; of 865 consecutive patients with stroke and those with TIA imaged with CTA, 239 (28%) had a LVO7 and in 133 patients with suspected posterior circulation stroke, 44 (33%) had BA or VA occlusion using CTA.8 We also observed a LVO rate of 14% for TIA. Patients with TIA with LVO have been found to have a 40% higher rate of second stroke than those with a normal MR angiogram suggesting that these findings on CTA, even for TIA, may be clinically important.

This estimate of 28% to 46% large vessel stroke proportion is important when one considers the growing use of endovascular techniques that specifically target these lesions. To properly triage patients to endovascular therapy, patients with LVO need to be rapidly identified. We found that stroke severity alone as measured by the NIHSS appears to be only a modest predictor of LVO as shown in Figure 2. For any
particular NIHSS score, the ability to predict occlusion of a single or multiple intracranial vascular segments appears limited, suggesting that the proper triage of patients to endovascular intervention should be informed with noninvasive angiography like CTA.

Patient outcomes from large vessel stroke have not been previously measured in a prospective cohort of consecutively imaged patients with standardized assessment of stroke severity and outcome. One retrospective study of 226 consecutive patients undergoing conventional angiography found NIHSS score for various LVO similar to our study in which patients with BA and ICA occlusions had the highest NIHSS scores and M2 occlusions the least.10 We found a striking dependency of mortality and proportion of good outcomes based on the simple presence or absence of a LVO. The location of the vascular occlusion is important in that ICA, BA, M1, and M2 occlusions were significantly correlated with both mortality and good clinical outcome, whereas more distal occlusions (A2, P2 vessels) were not. At least one conventional angiographic series has shown that a normal angiogram portends a good prognosis,11 and another retrospective study of stroke outcomes showed that proximal LVO was associated with a more than 7-fold odds of unfavorable outcome.12 It is well established that BA occlusions are highly morbid as are ICA terminus lesions.13–15 Our analysis shows that the combination of either BA or ICA occlusion was independently associated with clinical outcome in multivariate analysis—likely for strokes with NIHSS score in excess of 19—further suggesting that angiographic status of vessels is informative at the time of hospital presentation. Less information is available about M1 and M2 occlusions, but it has been shown previously that patients with M2 occlusion have lower NIHSS scores than M1 occlusions.10 The relative impact, however, of one vascular segment occlusion compared with another has not been previously reported and the data reported here may be useful to estimate the prognosis of patients presenting with any particular CTA finding.

Previous multivariate models of stroke prognosis that considered variables available at the time of initial evaluation have shown independence of age and baseline neurological examination,2,16 and age, neurological examination, and baseline imaging (without angiography).1 We confirmed the finding that age and NIHSS score overpower other clinical characteristics, including vascular risk factors (Table 4).

However, our data suggest that angiographic status of intracranial vessels at presentation confers additional prognostic information based on several lines of evidence. First, although NIHSS score and angiographic vascular occlusion are highly correlated, there is significant overlap in NIHSS scores in patients with and without LVO (Figure 2). Because LVO by itself is predictive of outcome, angiographic assessment appears to provide additional information to further refine prognosis in patients with similar age and NIHSS score, specifically at higher stroke severity. Second, clinical trials that have selected patient eligibility by angiography have shown wide variation in NIHSS scale scores despite identical vascular segment occlusions.5,6 For example, the NIHSS scores ranged from 4 to 30 in Prolyse in Acute Cerebral Thromboembolism (PROACT-II) despite the fact that all patients had documented M1 or M2 occlusion angiographically.6 Third, we found that the extent of vascular occlusion is related to stroke severity (Figure 2). Lastly, the combination of BA or ICA occlusions alone was found to be an independent predictor of clinical outcome.

The patient data included in this model are reflective of academic, urban hospitals that have comprehensive stroke centers (high emphasis on intravenous tPA use and optional endovascular therapy). How reflective these patients are of stroke treatment in general is unclear. We chose to model our outcomes based on the information available at the time a physician needs to make a decision regarding therapy; this includes demographic information, their NIHSS score, and the CTA findings. This model assumes that patients who are considered eligible for intravenous tPA do receive it and that a minority of patients (5.3% in our cohort) do go on to have endovascular treatment. Our model cannot be used to predict how a population of patients who would have been eligible for intravenous tPA would do if not treated because the underlying data were observational. Our models of stroke outcome derived from these data therefore likely underestimate the impact of stroke because 18.5% of our patients

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**Figure 3.** Influence of LVO within NIHSS strata on probability of good outcome (A) and mortality (B).
received intravenous or IA or combined intravenous/IA treatment with thrombolitics. However, the database used to create this model approximates a population-based study in that patient eligibility was broad (suspected stroke, create this model approximates a population-based study in treatment with thrombolytics. However, the database used to received intravenous or IA or combined intravenous/IA baseline differences between patients who received thrombolytic therapy and those who did not, like time to presentation, age, and baseline NIHSS, analysis dichotomized by intravenous tPA treatment must be considered with caution. Overall, we feel that this patient sample is reasonably representative of patients with stroke in general who present to urban medical centers.

Our data support the use of multimodality imaging of patients with acute stroke and TIA because of the added prognostic significance obtained with the data and the high prevalence of LVO in acute stroke and TIA. Additionally, such protocols likely expedite triage to endovascular therapy and expedite the clinical investigation of the stroke mechanism. Knowledge of the intracranial vascular status provides additional, useful information to the treating physician at the time of patient presentation that may improve decision-making.

Table 3. Univariate and Multivariate Model of Good and Mortal Outcome for Stroke and TIA

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Good Outcome (mRS ≤2)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or N (%)</td>
<td>Univariate OR (P Value)</td>
</tr>
<tr>
<td>All patients</td>
<td>363 (54%)</td>
<td>0.96 (&lt;0.001) 0.97 (&lt;0.001)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65 (15)</td>
<td>0.96 (&lt;0.001) 0.97 (&lt;0.001)</td>
</tr>
<tr>
<td>Female</td>
<td>143 (44%)</td>
<td>0.48 (&lt;0.001) 0.59 (0.002)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>4.7 (4.8)</td>
<td>0.86 (&lt;0.001) 0.86 (&lt;0.001)</td>
</tr>
</tbody>
</table>

Risk factors

- Hypertension: 205 (49%) 0.63 (0.004) 0.86 (0.503) 67 (16%) 1.98 (0.007) 1.40 (0.267)
- Diabetes mellitus: 56 (46%) 0.68 (0.055) 0.73 (0.165) 23 (19%) 1.68 (0.049) 1.74 (0.071)
- Coronary artery disease: 75 (48%) 0.76 (0.126) 0.78 (0.270) 30 (19%) 1.84 (0.013) 1.51 (0.154)
- Congestive heart failure: 13 (28%) 0.31 (0.001) 0.78 (0.520) 16 (25%) 4.00 (<0.001) 1.68 (0.181)
- Peripheral vascular disease: 9 (36%) 0.47 (0.075) 0.59 (0.280) 4 (16%) 1.25 (0.690) 0.83 (0.766)
- Hyperlipidemia: 108 (56%) 1.13 (0.472) 1.23 (0.293) 22 (10%) 0.65 (0.107) 0.83 (0.545)
- Smoking: 131 (63%) 1.75 (0.001) 1.38 (0.101) 21 (10%) 0.65 (0.107) 0.83 (0.545)
- Atrial fibrillation: 57 (39%) 0.47 (<0.001) 0.92 (0.723) 33 (23%) 2.45 (<0.001) 1.10 (0.742)

Vessels

- Any large vessel (N=280): 106 (38%) 0.33 (<0.001) 0.82 (0.364) 65 (23%) 4.47 (<0.001) 1.42 (0.260)
- No large vessel (N=363): 257 (65%) 3.06 (<0.001) 1.21 (0.364) 25 (6.3%) 0.86 (<0.001) 0.71 (0.260)

Risk factors

- Age: 0.97 (<0.001) NIHSS: 0.84 (<0.001) 109
- Gender: 0.48 (<0.001) NIHSS: 1.08 (0.055) 109
- NIHSS: 4.7 (4.8) 0.86 (<0.001) 0.86 (<0.001) 109

*Final model included age, gender, and NIHSS score; values shown for other variables are for the individual variable added alone to the final model.
†Final model included age and NIHSS score; values shown for other variables are for the individual variable added alone to the final model.

mRS indicates modified Rankin Scale; IV, intravenous.

Table 4. Influence of Intravenous tPA on Models of Outcome

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Good Outcome (mRS ≤2)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA: OR (F)</td>
<td>NIHSS: 0.89 (0.005)</td>
<td>NIHSS: 1.08 (0.055)</td>
</tr>
<tr>
<td>BA or ICA: OR (F)</td>
<td>Age: 0.97 (&lt;0.001)</td>
<td>NIHSS: 1.20 (&lt;0.001)</td>
</tr>
<tr>
<td>No IV tPA: OR (F)</td>
<td>Female: 0.57 (0.005)</td>
<td>NIHSS: 0.84 (&lt;0.001)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; IV, intravenous.
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References
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