Are Patients With Acutely Recovered Cerebral Ischemia More Unstable?

S. Claiborne Johnston, MD, PhD; J. Donald Easton, MD

Background and Purpose—Recent studies suggest that the short-term risk of stroke may be greater after transient ischemic attack (TIA) than after stroke.

Methods—We compared risks of neurological deterioration in those with and without TIA in the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial, a randomized trial of intravenous tPA given within 3 hours of onset of cerebral ischemia, after excluding those with cerebral hemorrhage and those dying before 90 days of causes other than new ischemic stroke. TIA was defined as a National Institutes of Health Stroke Scale (NIHSS) score of zero at 24 hours. We chose subsequent deterioration as our outcome, defined as a worsening on the NIHSS at 90 days compared with 24 hours, so that episodes of new ischemia that may have been attributed to other causes would be included.

Results—Of 498 subjects meeting entry criteria, 40 (8%) had TIA. Subsequent deterioration occurred in 30% of those with TIA and 10% of others (P=0.001, Fisher exact test). In multivariable models with adjustment for age, sex, ethnicity, 24-hour NIHSS score, tPA administration, presumed stroke subtype, and baseline systolic blood pressure, temperature, and glucose, TIA was an independent predictor of subsequent deterioration (odds ratio, 5.0; 95% CI, 2.0 to 12.5; P=0.001). Subsequent deterioration was not associated with tPA treatment, and there was no interaction between tPA administration, TIA, and subsequent deterioration. Lesser degrees of substantial acute recovery were also associated with greater risk of subsequent deterioration.

Conclusions—Patients with TIA may be a greater risk of subsequent neurological deterioration from causes other than hemorrhage. Substantial acute recovery may be an indicator of greater instability more broadly. (Stroke. 2003;34:2446-2452.)

Key Words: cerebral ischemia, transient classification prognosis recovery of function stroke

The short-term risk of ischemic stroke after a transient ischemic attack (TIA) appears to be high, with studies that have included follow-up from the point of symptom onset observing 90-day risks of stroke ranging from 10% to 20%. Studies of ischemic stroke recurrence have generally found lower short-term risks of new stroke after a stroke, with estimates of 3-month risk ranging from 2% to 7%. Although a comparison of these results suggests that short-term risk of stroke may be greater after TIA than after stroke, methodologies in these studies have varied, and therefore direct comparison is problematic.

Three studies have directly compared short-term risk of subsequent ischemic stroke among patients initially presenting with stroke and TIA. In patients with hemispheric ischemia enrolled in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the 90-day risk of stroke was 20.1% in the 603 with index TIA and 2.3% in those with an index ischemic stroke. A population-based study from Rochester, Minn, compared risk of ischemic stroke after TIA and completed stroke and found that short-term risks were greater for TIA than for ischemic stroke. Similarly, an observational study of consecutive patients found greater 6-month risk of recurrence after TIA (29%) than after completed stroke (7%).

If stroke risk is greater after TIA than after stroke, the presence of acute recovery may be the important defining characteristic. Acute recovery probably indicates reversal of ischemia and the presence of tissue still at risk from an unstable atherothrombotic process. Among 50 consecutive patients with acute recovery (which was defined as improvement to a National Institutes of Health Stroke Scale [NIHSS] score of ≤4 within 6 hours of symptom onset), 16% deteriorated within 24 hours, often in association with occlusion or stenosis of a large intracranial blood vessel. If acute recovery is an important predictor of subsequent risk of new ischemia, then the requirement that recovery is complete, as
with the definition of TIA, may be less important than the existence of significant early improvement in neurological function. In support of this, 1 study found that the short-term risk of stroke was identical in those with complete improvement at 24 hours and those with mild residual deficits after improvement.\(^1\) A prior analysis from the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial found that deterioration after improvement occurred in 13% of patients during the first 24 hours, regardless of whether the patient was allocated to tPA or placebo.\(^2\) However, whether deterioration was more frequent after initial improvement compared with those with no improvement was not studied.

To evaluate whether acute recovery (manifest as TIA or as a lesser degree of recovery) is a predictor of greater risk for subsequent deterioration, we analyzed data from the NINDS tPA trial (parts I and II), a randomized trial of intravenous tPA given within 3 hours of onset of an ischemic stroke.\(^3\) Rapidly improving symptoms at the time of enrollment was an exclusion criterion in this study, but some subjects improved after enrollment but within 24 hours of symptom onset. We evaluated whether those with TIA and others who improved substantially within 24 hours were more likely to deteriorate from causes other than intracranial hemorrhage (most likely new ischemia) during 90-day follow-up.

### Subjects and Methods

Neurological impairment was measured with the NIHSS before administration of study drug at 24 hours, at 7 to 10 days, and at 90±14 days after symptom onset.\(^4\) We defined TIA as complete resolution in the deficit on NIHSS at 24 hours; we also evaluated other levels of acute recovery, defined as the percent improvement in the NIHSS score at 24 hours compared with baseline.

We were primarily interested in the risk of deterioration due to new cerebral ischemia. Although investigators in the study attempted to identify instances of new stroke, we were concerned that some episodes could be attributed incorrectly to other causes, such as cerebral edema, or that fluctuation in the initial deficit may not be considered new stroke even if new ischemia were present. Therefore, we defined subsequent deterioration as an increase in the NIHSS score at 90 days compared with 24 hours regardless of whether new ischemic stroke was indicated as the cause; we excluded those with symptomatic intracranial hemorrhage and those who died of causes other than new ischemic stroke. In this way, subsequent deterioration would include all episodes of neurological deterioration attributed to ischemic stroke but would not include new symptomatic hemor-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIA (n=40)</th>
<th>Not TIA (n=458)</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>66.0±9.9</td>
<td>66.0±11.8</td>
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<tr>
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<td>17 (43)</td>
<td>192 (42)</td>
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<tr>
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<tr>
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<td>126 (28)</td>
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<tr>
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<tr>
<td>Asian</td>
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<tr>
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<tr>
<td>NIHSS at 24 hours</td>
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<td>10.7±7.4</td>
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<td>tPA given</td>
<td>33 (83)</td>
<td>217 (47)</td>
<td>&lt;0.0001</td>
</tr>
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<td>159±27</td>
<td>0.87</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<td>Glucose, mg/dL</td>
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<td>147±72</td>
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</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
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</table>

*Mean±SD or n (%). P values were calculated using the Fisher’s exact test or the Wilcoxon rank-sum test.*

the Wilcoxon rank sum test for others. Various cut points for defining substantial acute recovery were evaluated as predictors of subsequent deterioration by calculating OR with cut points at all levels of improvement in the NIHSS and estimating 95% CI by the Taylor series approach.\(^5\) Logistic regression was used to determine whether TIA was an independent predictor of subsequent deterioration after adjustment for age, sex, ethnicity, 24-hour NIHSS score, tPA administration, presumed subtype of stroke, and baseline systolic blood pressure, temperature, and glucose. An interaction term for TIA and tPA administration was tested in the multivariable model. All statistical analyses were performed with the Stata Statistical Package (version 7.0).

### Results

Of 624 enrolled in the trial, 120 died within 90 days of causes other than new ischemic stroke, 7 had nonfatal symptomatic intracranial hemorrhage, and 1 did not have NIHSS measured at 24 hours, leaving 498 meeting inclusion criteria for this analysis. Forty (8.0%) had complete recovery at 24 hours, consistent with the standard definition of TIA. Another 57 (11.4%) had 75% to 99% recovery in the NIHSS at 24 hours, and 84 (16.8%) had 50% to 74% recovery. Those with TIA had lower NIHSS scores at 24 hours (by definition) and were more likely to have received tPA compared with others (Table 1). For those with TIA, NIHSS score improved a mean±SD of 8.0±3.8 points in the first 24 hours compared with an improvement of 3.2±6.4 points for those without TIA (P<0.001). There was no difference in heparin use in patients with TIA and others (no use in TIA patients; 7 others received heparin; P>0.99).

Subsequent neurological deterioration occurred between day 1 and day 90 in 59 (12%), with a mean increase in NIHSS score of 6.2±9.0 in those who deteriorated and a decrease of
ORs for deterioration in NIHSS score between day 1 and day 90 at varying cut points for degree of acute recovery at 24 hours, measured as the percent decrease in NIHSS between baseline and 24 hours (black line). The lower bounds of the 95% CI were calculated by the Taylor-series method (gray line). At greater degrees of acute recovery, the odds of subsequent neurological deterioration not attributed to hemorrhage increased.

5.1 ± 4.1 points in others. Subsequent deterioration was more common in those with TIA compared with others (30% versus 10%; P = 0.001). We also evaluated whether spells of incomplete recovery were also associated with subsequent risk of deterioration by varying the cut point that defined acute recovery (Figure). Deterioration was significantly more frequent in those with acute recovery of ≥27%, with the unadjusted OR for deterioration generally increasing with greater degrees of acute recovery, ranging from OR of 1.8 at 27% recovery to OR of 4.1 at 94% recovery. Age, ethnicity, and NIHSS score at 24 hours were also significant predictors of subsequent deterioration in univariate analysis, but treatment with tPA was not (Table 2).

In multivariable models with adjustment for age, sex, ethnicity, 24-hour NIHSS score, tPA administration, presumed stroke subtype, and baseline systolic blood pressure, temperature, and glucose, TIA was an independent predictor of subsequent deterioration (OR, 5.0; 95% CI, 2.0 to 12.5; P = 0.001). Deterioration was not independently associated with tPA treatment (OR, 1.0; 95% CI, 0.5 to 1.9; P = 0.98). When recovery ≥75% on the NIHSS at 24 hours was tested in the multivariable model instead of TIA, results were similar (OR, 3.0; 95% CI, 1.3 to 6.9; P = 0.008).

Among those receiving tPA (n = 250), subsequent deterioration occurred in 10 (30%) of 33 with TIA and in 24 (11%) of 217 others (P = 0.006). Among those receiving placebo (n = 248), deterioration occurred in 2 (29%) of 7 with TIA and 23 (10%) of 241 without (P = 0.15). In the multivariable model, an interaction term for tPA administration and TIA, representing the possibility that the effect of TIA on risk of deterioration was different in the tPA and placebo groups, was not significant (P = 0.63). Multivariable models were repeated for the groups treated with tPA and placebo. For the tPA group, the risk of deterioration was greater among those with TIA (OR, 5.2; 95% CI, 1.7 to 16.3; P = 0.005). For the placebo group, the OR was similar, but the association between TIA and subsequent deterioration was not significant, and CIs were broad (OR, 5.9; 95% CI, 0.7 to 46.3; P = 0.09). Among those receiving tPA, dose was similar in those with TIA and others (66 versus 69 mg; P = 0.43). Furthermore, tPA dose was similar in those with and without subsequent deterioration among those receiving tPA (68 mg in both groups; P = 0.77).

In a sensitivity analysis, we included all patients in the study except those with symptomatic hemorrhage (leaving 40 with TIA and 554 without TIA). The association between TIA and subsequent deterioration was not significant in this cohort in univariate analysis (risk of deterioration in those with TIA 30% versus 26% in others; P = 0.58). As expected, the 90-day risk of death was greater among those with more severe strokes (27% in those with NIHSS ≥15 at 24 hours versus 9% in others). However, the association was highly significant in multivariable analysis (OR, 6.0; 95% CI, 2.6 to 13.9; P < 0.001). Furthermore, when the cohort was limited to those with less severe strokes (NIHSS score <15), the association between TIA and subsequent deterioration was significant in univariate analysis (risk of deterioration in those with TIA 30% versus 15% in others; P = 0.03).

### Discussion

The NINDS tPA trial provides detailed information about acute changes in neurological condition for a large group of patients presenting with acute cerebral ischemia. In these patients, 8% recovered completely on the NIHSS within 24 hours of symptom onset. The risk of subsequent neurological deterioration attributable to causes other than hemorrhage was greater among those with TIA. The odds of deterioration...
by 90 days were 5-fold greater for those with TIA than for those with lesser degrees of recovery. Lesser degrees of acute recovery produced similar results, with ORs for deterioration tending to increase with greater degrees of acute recovery (Figure). Thus, acute recovery may be best considered as a continuum, generally representing greater instability with greater degrees of initial improvement.

Our results require replication. We combined results for those receiving tPA and others. Although we found no evidence that the impact of initial improvement on risk of subsequent deterioration was different between groups receiving tPA and placebo, the inclusion criteria of the NINDS tPA trial limited the number of patients in the placebo group who had TIA. Neurotoxic effects of tPA could produce delayed deterioration.20 Additionally, partial thrombolysis may be a common occurrence after tPA administration and may be associated with a particularly high risk of repeated thrombosis and neurological deterioration. This pathophysiology may be present in fewer patients who recover spontaneously. However, deterioration was attributed to reocclusion of a vessel in a similar proportion of those receiving tPA and placebo in a prior analysis from the NINDS tPA trial utilizing data from adverse event report forms.21 Furthermore, in 1 study of 50 patients who improved spontaneously within 6 hours of symptom onset, deterioration within 24 hours occurred in 16% and was associated with occlusion and stenosis of intracranial vessels.22 Finally, in our study the association between recovery and subsequent deterioration was as strong in those receiving placebo as in those receiving tPA, although there was a trend toward significance only in the placebo group. Thus, the risk of deterioration appears to be high after substantial acute recovery regardless of whether tPA is given. Still, our findings should be replicated in a larger group of patients who have not received tPA and in patients presenting after a longer delay. Other acute therapy trials provide additional opportunities to confirm the hypothesis that acute recovery is generally associated with greater risk of subsequent cerebral ischemia and neurological deterioration.

Several other studies have shown that the short-term risk of stroke after TIA is high, ranging from 10% to 20% in the first 3 months among studies that followed patients from the time of symptom onset.1–7 The short-term risk of ischemic stroke after a completed ischemic stroke appears to be lower than after TIA, with studies reporting 3-month risks ranging from 2% to 7%.8–20 Among those with TIA in our analysis, the risk of deterioration due to causes other than hemorrhage, likely attributable to new ischemia, was 30%, while the risk of deterioration in those without any improvement was 10% among those surviving to 90 days. The higher risks of deterioration in this analysis may be due to patient selection or to our broader definition of outcome.

Our results suggest that there may be no reason to distinguish TIA from episodes of acute substantial but incomplete recovery, at least on the basis of risk of subsequent neurological deterioration. TIA and episodes with substantial but incomplete recovery appear to share an elevated risk of subsequent ischemic stroke, while this risk may be lower after a completed ischemic stroke. Similarly, in the Northern California TIA study, 181 patients had dramatic acute recovery without documentation of complete resolution of symptoms within 24 hours.1 The 90-day risk of stroke in this group was 10.4%, which was identical to that in those with complete resolution. On the basis of early prognosis, there does not appear to be a clear reason to distinguish TIA from episodes of substantial but incomplete acute recovery: events with acute recovery appear to share a greater risk of deterioration.

The extent of early improvement after presentation with acute cerebral ischemia may be associated with risk of subsequent stroke because rapid recovery may indicate a distinct, unstable pathophysiology in some instances.22,23 Rapid recovery is an indicator of return of normal function in a previously ischemic territory, often due to return in blood flow. The previously ischemic tissue remains at risk. When in situ thrombosis at a ruptured atherosclerotic plaque is responsible for the initial ischemic event, a rapid recovery may signify resolution of the thrombosis. However, the plaque may remain highly thrombogenic, thereby elevating the risk of a subsequent ischemic event. Contrarily, if the ruptured plaque leads to a completed stroke in the distal vascular territory, additional thrombosis will generally be asymptomatic; the situation is more stable, and risk of new stroke is lower. Thus, an elevated risk of deterioration would be anticipated after rapid recovery, suggesting reversal of ischemia, compared with after an ischemic event with no rapid recovery, and complete recovery would not be necessary to distinguish an event.

Brain collateral blood flow may also produce rapid recovery. This situation may again be associated with greater instability and risk of subsequent infarction.30 Collateral blood flow may be inadequate to maintain compensation when the blood pressure is lower or if there is any brain swelling after limited infarction. Even after a cardioembolic event, the presence of substantial early recovery may be associated with greater risk of new symptomatic infarction. New infarction in the presence of an existing stroke may go unnoticed or may be attributed to the deterioration commonly seen after stroke. After substantial recovery, a new deficit may be more obvious, again creating the appearance of greater instability. A new deficit may have a greater overall impact on the patient.

The presence of rapid recovery in an event of acute cerebral ischemia may dictate different treatment strategies. A greater risk of subsequent ischemic stroke may justify more aggressive attempts to reduce risk of new thrombus. For example, atherosclerotic plaque stabilization is theorized to explain early reduction in recurrent cardiac events with statins31 and may also be more effective after rapid brain ischemic recovery, when the distal territory is still at risk. Cerebral infarction is often less extensive when rapid substantial recovery has occurred, and this also may have important implications for treatments. Agents that reduce risk of recurrent ischemia frequently increase the risk of brain hemorrhage, as has been demonstrated for heparin12,23 and aspirin.34 This is particularly problematic in those with more extensive brain infarction. Those with rapidly recovered cerebral ischemia may be at lower risk of brain hemorrhage with some interventions,35 but this has not been tested.

In conclusion, acute recovery of cerebral ischemia appears to be an important predictor of subsequent stroke, may identify a more unstable pathophysiology, and may dictate particular acute treatment strategies. Complete neurological recovery, required for the current definition of TIA, may not be required to identify a distinct entity. Acute infarction is present in a large portion of
patients with complete neurological recovery at 24 hours,36 risk of subsequent stroke is elevated in those with rapid recovery whether complete or incomplete,1 and recovery itself, rather than its completeness, would be expected to be an indicator of tissue still at risk. The presence of recovery that can be attributed to reversal of ischemia is likely to be an important defining characteristic. Since acute recovery may be complete, substantial but incomplete, minor, or absent, it may be more useful to differentiate cerebral ischemic events on a continuum of recovery rather than to attempt to define a distinct clinical entity. There is no obvious cut point for categorization of cerebral ischemic events based on rapid recovery: similar to duration of symptoms, any cut point based on timing and extent of recovery would be arbitrary. Rather, it may be more useful to consider the degree of rapid recovery as another “adjective” with which to describe an event, a descriptor that may provide useful information about prognosis and management even more valuable than symptom duration. Emergent evaluation and treatment may be particularly important in this group at high risk of subsequent neurological deterioration.37

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References
Patients suffering a transient ischemic attack (TIA) are at high risk of stroke in the days and weeks following the index event: the risk even at 2 days is more than 5% in studies from the United States\(^1\) and the United Kingdom.\(^2\)

Johnston and Easton take this concept further and have not only considered those with TIA (as conventionally defined, with no deficit at 24 hours\(^3\)) but have also examined patients who have had a \(\geq 50\%\) improvement in NIHSS scores despite a continuing neurological deficit. Their aim was to identify whether the crucial factor in the increased early risk of stroke with TIA is the reversible, labile nature of the neurological deficit, which could be a marker for an underlying unstable atherosclerotic plaque in the cerebral circulation.

The authors utilized the NINDS tPA dataset\(^4\) to test their hypothesis. One of the exclusion criteria for the NINDS study was “rapidly improving symptoms,” so it is likely that a number of patients with TIA who would otherwise have been eligible for NINDS were excluded, which may account for the small number of TIA patients in the study. NINDS was also restricted to those eligible patients for thrombolysis randomization within 3 hours of symptom onset, which again limits the applicability of the results of this study. Many patients with TIA will not present within this time frame,\(^1,\)\(^2\) but their physicians want to know how aggressive the initial investigation of these patients should be.

The methods used in this study were robust. The authors attempted to include all possible patients who may have had a neurological deterioration (unless due to symptomatic intracranial hemorrhage) after initial improvement by defining deterioration as an increase of 1 point or more on the NIHSS. While this may appear to be trivial, the actual deterioration detected was 6 NIHSS points (mean), which is clinically important. No data were presented on the time course of subsequent deterioration, but other work suggests that half of all patients who will deteriorate will do so within 2 days of the index TIA.\(^1\)

A higher proportion of the TIA group received tPA compared with the non-TIA group (83% versus 47%, \(P<0.0001\)), although there was no difference in tPA administration rates between those who did deteriorate as compared with those who did not. These findings suggest that tPA may be more likely to lead to reversal of the observed deficit, but that it is no more likely to prevent a deterioration over the ensuing 90 days. These 90 days are a window of opportunity for physicians to evaluate potential causes for transient cerebral ischemia and consider other therapies to improve outcome.\(^5\)

The suggested underlying theory of an unstable atherosclerotic plaque undergoing rupture, followed by thrombosis and then resolution, is pathophysiologically attractive. Statins have been shown to play a significant role in plaque stabilization after myocardial infarction and they may fulfill this role in the cerebral vasculature patients as well.\(^6\) Significant early improvement may also be caused by an increase in collateral cerebral blood flow locally, but this effect may be offset by reductions in flow secondary to local infarct related edema.

It is clear from these data that the artificial dichotomy between TIA (as traditionally defined) and stroke that has some spontaneous functional recovery is unnecessary.\(^3\) Even a functional recovery of 30\% to 50\% on the initial NIHSS is associated with up to nearly twice the odds of subsequent deterioration compared with no recovery. All patients with evidence of early functional recovery following a probable ischemic neurological deficit, of \(>10\) minutes’ duration,\(^4\) are at risk of subsequent deterioration and require urgent evaluation. The authors have identified that TIA is an independent predictor of subsequent deterioration and it is likely that as a TIA represents “maximum improvement,” it also gives the potential for most clinically apparent neurological deterioration.

Further studies are required to confirm the data of Johnston and Easton, but their elegant work should prompt us to examine whether the current services provided to patients with unstable cerebral ischemia are appropriate.\(^7\) Many countries and states have fewer neurologists than they should. In the United Kingdom, the specialty of stroke medicine is now established but requires a significant increase in numbers of specialist physicians to provide a uniformly available and effective service.\(^8,\)\(^9\)

Patients with symptoms and signs suggestive of unstable cerebral ischemia should have immediate cerebral imaging, either computed tomography (CT) or magnetic resonance imagine (MRI).\(^5\) While this may be possible in many centers in the United States, the relative lack of radiologists and traditional differences in practice in other countries often delay acute cerebral imaging. While there are accepted standards and guidelines for cranial CT imaging after trauma,\(^10\) radiologists are sometimes reluctant to undertake emergency imaging for patients with cerebral ischemia.

Apart from the issue of imaging, what should the emergency physician or family physician do with patients with acutely recovered cerebral ischemia? Despite national recommendations for rapid-access clinics for patients with TIA,\(^11\) it remains unclear whether these patients would have better outcomes from hospital admission or clinic assessment. It is clear that many patients do not present for some time after the development of symptoms suggestive of cerebral ischemia.\(^12\) Obvious electrolyte abnormalities should be identified and hypoglycemia must be excluded. Atrial fibrillation must be identified and therapy instituted if required. The decision to anticoagulate may be difficult and may require hospital admission for brain imaging and echocardiography. In the absence of a cardioembolic source, the carotid arteries should
be urgently imaged using Doppler ultrasound and if a high-grade stenosis is identified, an urgent vascular surgery referral is required.\textsuperscript{5}

Further collaboration among stroke physicians, neurologists, epidemiologists, family physicians, radiologists, and emergency physicians, for both research and service delivery, is a necessary first step to improve the long-term outcome of patients with unstable cerebral ischemia.

Colin A. Graham, FRCS, Guest Editor
Department of Emergency Medicine
Southern General Hospital
Glasgow, UK

References
Editorial Comment—Transient Cerebral Ischemia Demands Urgent Evaluation
Colin A. Graham

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