Recurrent Events in Transient Ischemic Attack and Minor Stroke
What Events Are Happening and to Which Patients?
Shelagh B. Coutts, MD, FRCPC; Michael D. Hill, MD, FRCPC; Cynthia R. Campos, MD; Young B. Choi, MD; Suresh Subramaniam, MD; Jayme C. Kosior, BSc; Andrew M. Demchuk, MD, FRCPC; for the VISION study group

Background and Purpose—The risk of a recurrent stroke after transient ischemic attack (TIA) or minor stroke is high. Clinical trials are needed to assess acute treatment options in these patients. We sought to evaluate the type of recurrent events and to identify which subsets of patients are at risk for recurrent events.

Methods—One hundred and eighty patients with TIA or minor stroke were examined within 12 hours and underwent brain MRI within 24 hours. Any neurological deterioration was recorded, and a combination of clinical and MRI factors were used to create a combined event classification. Subgroups of patients analyzed included classical TIA, patients with NIHSS=0, and patients with NIHSS >0 in ED.

Results—Overall there were 38 events in 36 patients (20% event rate); 20 were symptomatic and 18 were silent (only evident because of the follow up MRI). 18/20 (90%) symptomatic events were associated with progression of presenting symptoms, compared to 2/20 (10%) with a clear recurrent stroke distinct from the original event. We found a low risk of recurrent stroke among classical definition TIA patients (1.1%). Patients with an NIHSS=0 in the ED, had an intermediate event rate (6.6%) between TIA (classical – 1.1%) and NIHSS >0 (14.4%; χ² test for trend, P=0.02). All clinical categories of patient (TIA, stroke, NIHSS=0) accumulated silent lesions on MRI.

Conclusions—Most events were classified as stroke progression or infarct growth rather than a recurrent stroke. A low risk of recurrence was found in patients with classical TIA and those with no neurological deficits on initial assessment.

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Key Words: stroke ■ TIA ■ MRI ■ diffusion weighted imaging

The chance of a subsequent stroke after an acute transient ischemic attack (TIA) or minor stroke is high1–7 with a 90-day risk between 10% and 20%. The prognosis for these patients is often unfavorable. There is a distinct lack of evidence for emergency treatments in these patients and with the majority of events happening in the first 48 to 72 hours after symptom onset, the time window for prevention is short.

Historically there has been a difference between the end points used in acute stroke trials as outcome measures and those in secondary prevention trials after TIA or minor stroke. This has meant that acute stroke trials such as the NINDS tPA trial8 have looked at disability eg, excellent functional outcome defined on the modified Rankin scale. Whereas secondary prevention trials in TIA and minor stroke (which have historically commenced in the non acute setting, even up to 6 months after the event) have used recurrent events as an outcome. The advent of trials such as the FASTER9 trial, an acute prevention trial, has made the choice of which outcome measure to use problematic.

Even the definition of a recurrent stroke event is challenging.10 Because most events occur acutely, it is critical to follow these patients with repeated clinical examination and with imaging. The distinction between a truly new stroke lesion, anatomically remote from the index stroke, and stroke progression attributable to the evolution of the ischemic core into the penumbral tissues is not facile. Because stroke is heterogeneous, recurrent stroke defined as neurological deterioration of vascular origin lasting more than 24 hours causing functional impairment may be caused by varying pathophysiology.11 These include new vessel occlusion, enlargement of the existing infarct, and even hemorrhage.12 Some events, such as recurrent sensory events are low risk and may not represent ischemia at all.13,14
A useful way to assess recurrent stroke is with imaging because it may be less prone to bias than the neurological interpretation of symptoms. Recurrent symptomatic and silent lesions on MRI have been described in acute stroke over the course of the first 90 days from original symptom onset.15,16,17 The pattern of these events may give us insight into mechanisms behind the disease and offer potential therapeutic targets.

We therefore assessed both clinical and MRI end points in a population of minor stroke and TIA patients to evaluate the type of events in minor stroke and TIA in a more detailed manner. We also attempted to identify which subsets of patients are at high and lower risk for recurrent events.

Methods
VISION was a prospective cohort study evaluating modern neurovascular imaging techniques for predicting clinical outcome, recurrent events, and ischemic tissue salvageability in patients presenting to an emergency room with a suspected stroke or TIA. The research protocol was approved by the Institutional Ethics Committee and all participants provided written informed consent. To be eligible, patients had to have been examined within 12 hours of symptom onset by a stroke neurologist who felt that the deficits were consistent with a TIA or minor stroke. The MRI scanner was only available during regular business hours (8 AM to 4 PM Monday to Friday) and so patients were only enrolled in the study if they could have their imaging completed within 24 hours. Patients were enrolled in this substudy if they had a persistent focal neurological deficit with a baseline NIHSS ≤3 or TIA consisting of hemiparesis or aphasia lasting 10 minutes or more and a premorbid mRS ≤1. The “classical definition of TIA” that was used was vascular neurological symptoms lasting less than 24 hours.19 Some of these patients have been previously described.12,14,17 All patients were admitted to hospital for a minimum of 24 hours. Treatment for secondary prevention of stroke was determined by the attending neurologist. However all patients were treated acutely with aspirin (including a 160 mg loading dose if the patient was aspirin naïve). Patients with large artery disease were generally treated acutely with aspirin and clopidogrel (300 mg load and then 75 mg per day). This was before carotid intervention being performed. Patients with atrial fibrillation were treated with heparin while coumadin was commenced or simply started on coumadin. Most patients would be commenced on a statin before discharge.

Imaging
MR imaging was performed as soon as possible (but not emergently) after arrival in the emergency department and within 24 hours of symptom onset. All neuroimaging was assessed by a neuroradiologist who was blind to all clinical data other than symptom side. Baseline MRI parameters have been previously described,12,17 but included DWI, FLAIR, T2, MRA circle of Willis (pre- and postgadolinium), GRE, and Perfusion imaging. The presence of an intracranial vessel occlusion in the anterior or posterior circulation was assessed on the MRA. Follow up MR imaging was completed at 30 days from symptom onset. The 30-day follow-up MRI was rated with the acute MRI scan visible simultaneously. FLAIR and DWI sequences were used to identify any new lesions as compared to the baseline imaging.17 The presence of an acute DWI lesion at baseline is referred to as DWI positive in the results section and the absence of an acute lesion is referred to as DWI negative.

Lesion volumes were measured on the acute DWI sequence by a Stroke Neurologist blind to all clinical data. The final volume of this lesion was measured on the 30-day FLAIR sequence with direct comparison to the baseline scan. If the volume of the follow-up lesion was more than 2 mL larger than the baseline lesion then this was considered lesion growth.18

Clinical Events
Any new clinical strokes were recorded before the 3-month follow-up and the date of the event was recorded. Occurrence of new stroke during follow-up was defined as a functional deterioration in neurological status of vascular origin or a new sudden focal neurological deficit of vascular origin lasting more than 24 hours.3 Patients were also reviewed at 3 months, at which time all clinical and imaging information was reviewed and their final clinical assessment was made. Clinical events were recorded that occurred in the 90 days before final assessment.

Combined Clinical and MRI Outcomes
The clinical and imaging information was reviewed by 2 stroke neurologists independent of the 90-day assessment and each event is defined below. The area of abnormal perfusion was used to help classify events. In some patients more than 1 event occurred (eg, symptomatic infarct growth and new silent infarct). We defined symptomatic events (types 1 through 4) and asymptomatic events (types 5 and 6) as follows:

New Symptomatic Infarct
Infarct outside initial perfusion abnormality with new functional deficit. In the situation where there was no baseline perfusion abnormality seen, then the new infarct must be geographically separate from the original infarct.

New Symptomatic Stroke Without Infarct
New clinical stroke deficits not referable to the initial infarct territory without evidence of a new infarct on imaging. We included this category for completeness, but there were no patients in this population who were found to be in this category.

Symptomatic Infarct Growth
Functional deterioration clinically with evidence of a new infarct within baseline perfusion abnormality or directly extending from initial infarct if no perfusion abnormality was seen on baseline imaging.

Stroke Progression Without Infarct Growth
Functional deterioration without infarct growth.

Silent Infarct Growth
New infarct within baseline perfusion abnormality without functional deterioration. New DWI lesion can be separate from original lesion, if contained within original perfusion abnormality.

New Silent Infarct
New infarct on imaging outside the area of original perfusion abnormality without new functional deficit.

Statistics
Proportions of patients in different clinical and imaging categories having a recurrent stroke (defined previously) and silent events were calculated. We examined event rates in several ways; these groups are all considered separately in the entire population: (1) classical TIA19 versus minor stroke status; (2) NIHSS ≥0 versus NIHSS=0 at the time of evaluation in the ED; (The NIHSS=0 group included both patients who had completely resolved on initial assessment and those that had subtle neurological deficits not picked up by the NIHSS); (3) baseline DWI positive versus negative; and (4) intracranial vessel occlusion versus no intracranial occlusion. Preliminary analysis of event rates in patients with an NIHSS=0 stratified according to DWI lesions status was competed. Risk ratios and risk differences were also calculated with 95% confidence intervals. Functional impairment on the modified Rankin scale at 90 days (mRS ≥2) was considered a poor outcome in the assessment of silent MR lesions as a surrogate marker. Fisher’s exact test was used to assess the relationship of silent events to outcome. All tests were two-sided and conventional levels of significance were used (P<0.05).
Results

Of 180 patients enrolled, 162 (90%) had a 30-day MRI (reasons for no follow-up MRI included pacemaker or heart valve insertion, death, and patient refusal). There were 111 men (62%) and the average age was 65.6 years (95% CI: 63.6 to 67.6). Mean systolic blood pressure was 155 (151 to 159), diastolic BP was 85 (82 to 87), and mean blood glucose was 6.6 mmol/L (6.2 to 6.9).

There were 87 TIA patients (48%) in the cohort when the classical WHO definition of TIA (vascular neurological symptoms lasting less than 24 hours) was used. 8 patients had a final diagnosis that was felt to be not stroke or TIA (migraine, seizure etc). Of the enrolled 180 patients, 76 patients had an NIHSS of 0 when examined by a stroke neurologist in the emergency room and only 4 of these patients had subtle neurological deficits not picked up by the NIHSS. Of the 76 patients with an NIHSS of 0, 57 (75%) were ultimately classified as a TIA.

There was only one recurrent stroke event that occurred after the 30-day MRI was completed. This event is described as a new symptomatic infarct. All other clinical events occurred before the 30-day MRI.

Overall there were 38 events in 36 patients (20%); 20 were symptomatic events and 18 were silent events (asymptomatic but identifiable because of the follow up MRI). There was only 1 symptomatic event among patients with the classical TIA definition (1.1%). Using a real-time definition of TIA, only 1 symptomatic event among patients with the classical but identifiable because of the follow up MRI. There was only one recurrent stroke event that occurred after the 30-day MRI was completed. This event is described as a new symptomatic infarct. All other clinical events occurred before the 30-day MRI.

Overall there were 38 events in 36 patients (20%); 20 were symptomatic events and 18 were silent events (asymptomatic but identifiable because of the follow up MRI). There was only 1 symptomatic event among patients with the classical TIA definition (1.1%). Using a real-time definition of TIA, NIHSS=0 in the emergency room, we found an intermediate event rate (6.6%) between that of TIA (classical definition, 1.1%) and that of those who had ongoing symptoms in the ED (14.4%; χ² test for trend, P=0.02). Out of the 4 patients with an NIHSS=0, but with subtle neurological deficits not picked up by the NIHSS, 1 patient had progression of his symptoms.

Breakdown of event subtype is described in Table 1. There were only 2 (10%) of the symptomatic events classified as a new symptomatic infarct, whereas all other events were associated with infarct growth or progression of presenting symptoms (90%). Proportions of event rates for symptomatic and asymptomatic events are described in Tables 2 and 3. Important results are that the rate of recurrent events in classical TIA patients was low (meaning that patients had to reach 24 hours without deterioration to be described as a classical TIA). Also the difference in event rates between patients with NIHSS=0 and NIHSS >0 on initial assessment by a neurologist was not statistically significant, but showed a trend to greater event rates in patients with persistently abnormal neurological examination. Preliminary analysis on symptomatic events rates in patients with NIHSS=0 in the ED stratified according to DWI lesion status revealed a trend toward DWI lesion status being predictive of recurrent symptomatic events: 14.8% event rate in DWI positive patients and 2% in DWI negative patients (P=0.0509, Risk ratio 7.26 [95% CI: 0.85 to 62]). Table 4 shows the breakdown of events according to the TOAST classification.20

Table 1. Breakdown of Clinical and MRI Events by Category

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall*</th>
<th>TIA Patients Only n=87</th>
<th>Non TIA Patients Only n=93</th>
<th>NIHSS 0 in ED n=76</th>
<th>NIHSS&gt;0 in ED n=104</th>
<th>No Intracranial Vessel Occlusion n=156</th>
<th>Intracranial Vessel Occlusion n=24</th>
<th>DWI Negative Only n=81</th>
<th>DWI Positive Only n=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>New symptomatic infarct</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic infarct growth</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Stroke progression without infarct growth</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Total symptomatic events 20 (11%) 1 (1.1%) 19 (20%) 5 (6.6%) 15 (14%) 9 (5.8%) 11 (46%) 2 (2.5%) 18 (18%)
Silent infarct growth 6 2 4 2 4 3 3 1 5
New silent infarct 12 5 7 5 7 10 2 3 9
Total events (symptomatic and MRI) 38 (21%) 8 (9.2%) 30 (32%) 12 (16%) 26 (25%) 22 (14%) 16 (67%) 6 (7.4%) 32 (32%)

Table 2. Proportion of Clinical Event Rates (Recurrent Stroke) Within 90 Days of Symptom Onset Dependent on Clinical or Imaging Factors at Baseline

<table>
<thead>
<tr>
<th>Patient Subgroups and Recurrent Clinical Stroke Rate Within 90-days</th>
<th>Risk Difference</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Classical TIA</td>
<td></td>
</tr>
<tr>
<td>22.4%*</td>
<td>1.1%</td>
<td>21.3</td>
</tr>
<tr>
<td>NIHSS&gt;0</td>
<td>NIHSS=0†</td>
<td></td>
</tr>
<tr>
<td>14.4%</td>
<td>6.6%</td>
<td>7.8</td>
</tr>
<tr>
<td>Intracranial occlusion</td>
<td>No intracranial occlusion</td>
<td></td>
</tr>
<tr>
<td>45.8%</td>
<td>5.8%</td>
<td>40.1</td>
</tr>
<tr>
<td>DWI positive</td>
<td>DWI negative</td>
<td></td>
</tr>
<tr>
<td>18.2%</td>
<td>2.5%</td>
<td>15.7</td>
</tr>
</tbody>
</table>

*The percentage of stroke patients having a recurrent stroke in Table 2 is different than that of the “non-TIA” patients in Table 1 as the patients with a final nonstroke or TIA diagnosis are not included in the Stroke category in Table 2. NIHSS=0 refers to the neurological examination at baseline by a stroke neurologist that was completed at first assessment (which was within 12 hours of symptom onset).
We found that silent events were common, and that there was no relationship to the clinical presentation—TIA, minor stroke, NIHSS=0. For silent events, we did not find a relationship to functional impairment on the modified Rankin scale at 90 days. ($P = 1.0$, Fisher exact).

Overall there were 99 patients with a DWI lesion at baseline (55%) and 36 outcome events (in 34 patients = 34.3% combined symptomatic and asymptomatic event rate). There were 81 patients without a DWI lesion (45%) who had 2 symptomatic events and 4 asymptomatic events (7.4% combined event rate). Among these DWI negative patients, 1 patient was DWI negative and had a late symptomatic event after the follow up MRI, 1 symptomatic patient was DWI negative at baseline, but at 24 hours had a thalamic lacunar infarction evident on repeat imaging. Another patient with a lacunar syndrome who had resolved clinically, had a pontine lacunar infarct visible on follow up (but not at baseline) that could explain the presenting symptoms. Two patients rated as DWI negative who had silent events had in retrospect small, subtle DWI lesions that were missed on initial radiological review.

### Discussion

This study demonstrates that a high rate of symptomatic and asymptomatic events in minor stroke and TIA patients. The majority of symptomatic events (90%) were rated as progression of the original infarct demonstrating an evolving process over the first few days after the event. We found that recurrent events outside of the initial vascular territory or perfusion defect were rare. Perfusion imaging at the time of any event may help to distinguish between perfusion failure and recurrence and embolism. The identification of a variety of types of outcome events is very likely correlated with the variety of underlying pathophysiology. These results suggest that therapies targeting the mechanism of stroke, such as antithrombotic agents, may be less effective than drugs targeting reduction of final infarct volume in reducing the risk of stroke recurrence in the first few days after TIA or minor stroke. Therapies will need to be directed at the underlying mechanism.

We confirmed that the event rate in TIA and minor stroke patients is high despite urgent best available medical intervention. However, we found that clinical and MRI parameters may be used to predict the event rate. The event rate in TIA patients using the classical 24-hour symptom resolution definition was extremely low with only 1 patient having a recurrent symptomatic event (1.1%). This was true, even though the inclusion criteria for our study selected patients high risk patients with motor and speech symptoms. The reasons for this are not completely clear, however all patients had all proven therapies offered to them early; aspirin, anticoagulation for atrial fibrillation, carotid endarterectomy for internal carotid artery stenosis, and stents. Table 4 shows the high rate of events in patients with large artery disease and highlights the risk in this particular group of patients. Trials are needed to optimize the medical regime in surgical patients and to assess the surgical risk in the hyperacute setting after a TIA or minor stroke.

If we used a more real-time definition such as a NIHSS score of 0 in the ED, the overall event rate fell between that of a classical TIA and that of a minor stroke. However, the risk of worsening in patients with an NIHSS of 0 is not negligible and it is perhaps better to regard all these patients (who have the high risk clinical phenotype required for enrolment into this study) assessed within the first 24 hours as at high risk for a recurrent event, and one option would be to use MRI to stratify risk. The high risk of a recurrent stroke or neurological deterioration in patients who have not resolved on initial assessment (but are mild) has implications for the management of these patients who in many institutions would be sent home. The low clinical event rate in true TIA patients managed emergently has been recently described in 2 European studies demonstrating a stroke event rate of approximately 1%. However, the classical definition of TIA is considered by many experts in the field to be outdated and is impractical because the emergent assessment of these patients happens well before the 24-hour time point required for this arbitrary definition. The clinical implications of our findings are uncertain. We believe they need to be validated in a second study. Perhaps the most important finding is the higher risk in patients who have not completely resolved on first assessment. The preliminary analysis of the use of MRI to further stratify risk in patients who have neurologically resolved in the ED is potentially exciting paradigm.

Table 3. Proportion of Silent MR Events Assessed at 30 days (as Compared to Baseline MRI) Dependent on Clinical or Imaging Factors at Baseline

<table>
<thead>
<tr>
<th>Patient Subgroups and Silent MR Event Rate on 30 Day MR</th>
<th>Risk Difference</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Classical TIA</td>
<td>7.4%</td>
</tr>
<tr>
<td>NIHSS&gt;0</td>
<td>NIHSS=0</td>
<td>9.2%</td>
</tr>
<tr>
<td>Intracranial Occlusion</td>
<td>No Intracranial Occlusion</td>
<td>25%</td>
</tr>
<tr>
<td>DWI positive</td>
<td>DWI negative</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

*NIHSS=0 refers to the neurological examination at baseline by a stroke neurologist that was completed at first assessment (which was within 12 hours of symptom onset).

Table 4. Breakdown of the TOAST Classification Stratified According to Symptomatic and MR Events for the 172 Patients Rated as Stroke or TIA at Final Clinical Assessment

<table>
<thead>
<tr>
<th>Toast Classification</th>
<th>Symptomatic Events</th>
<th>MR Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery disease</td>
<td>8/31 (26%)</td>
<td>6/31 (19%)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>4/36 (11%)</td>
<td>4/36 (11%)</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>3/22 (14%)</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td>Other determined</td>
<td>0/2 (0%)</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>5/81 (6%)</td>
<td>6/81 (7%)</td>
</tr>
</tbody>
</table>
confirmed, MRI could stratify patient risk among those who present early (before 24 hours) even if they are neurologically normal.

MRI detected recurrent silent events in all subtypes of clinical presentation that we assessed. Even patients, who had an extremely low rate of clinically overt events eg, classical TIA patients, were at risk for accumulating silent events. This perhaps suggests that presumably these patients have done well in the short term because the recurrent lesions were in less eloquent areas of brain. We found that the use of MRI outcomes doubled our event rate. This is comparable to previous studies looking at a general population of stroke patients. However, it remains unclear whether MR is an appropriate surrogate outcome because the correlation with 90-day clinical outcomes is less than convincing. Although the importance of these events is undoubtedly marginal in the short term, the accumulation of small subclinical events has a known impact on the future risk of vascular cognitive impairment. A longer term study with neuropsychological outcomes would be required to demonstrate any effect of silent MR lesions after TIA or minor stroke. Such studies need to be done to provide enough evidence to justify MR as a useful surrogate outcome measure.

The limitations of our study are that we only included high risk motor or speech TIA patients, suggesting that the overall rate of symptomatic events in classical definition TIA patients may be even lower than the 1% risk we found in this study. We acknowledge that the use of MRI in assessing these patients has not reached mainstream stroke care. However, for design of stroke trials MRI is the ideal tool to capture the maximal rate of events and better understand drug effect on the different clinical and imaging outcomes seen in this study. With the recent publicity surrounding negative trials in the stroke literature further research into MR as a surrogate outcome measure need to be strongly considered. Another potential limitation is the assumption, on our part, that diffusion-weighted MR imaging represents a gold standard in defining stroke recurrence. Because progression of the initial lesion was the commonest finding, it is possible that our findings reflect the expected evolution of the stroke lesion over time. However, in many cases this correlated with clinical deterioration, suggesting that this may be an important surrogate marker. We also allowed the treating physician to use what secondary prevention measures that they felt were appropriate for each patient. We did not capture this data and this could potentially have an effect on clinical outcomes.

The high proportion of patients who progress from their initial symptoms has not been recognized previously. True recurrent events, in a new location in the brain, after TIA and minor stroke are actually uncommon.

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Disclosures
None.

References


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