Epidemiological Impact in the United States of a Tissue-Based Definition of Transient Ischemic Attack

Bruce Ovbiagele, MD; Chelsea S. Kidwell, MD; Jeffrey L. Saver, MD

Background and Purpose—The traditional definition of transient ischemic attack (TIA), based on an arbitrary time criterion of symptom resolution within 24 hours, is problematic because a large number of patients with traditionally defined TIAs have a relevant cerebral infarction on brain imaging. The objective of this study was to characterize the epidemiological impact of adopting a tissue-based definition of TIA.

Methods—Estimates of the annual US incidence of traditionally defined transient ischemic attacks were abstracted from the literature. Models were then constructed for determining the frequency of brain injury in traditionally defined TIAs, derived from recent human studies of MR diffusion-weighted imaging (DWI) in transient cerebral ischemia.

Results—Traditionally defined US TIA annual incidence rates ranged from 37 to 107 per 100 000 per year. Across 5 series, the raw frequency of DWI positivity in traditionally defined TIAs was 44%. Adjusting for an overrepresentation of longer-duration TIAs in MR series yielded an expected frequency of diffusion MRI positivity of 33% in unselected, traditionally defined TIAs. Applying this model to the US population in the year 2000 showed that adopting a tissue-based definition of TIA would decrease the annual number of events classified as TIAs from 179 840 to 120 493 and increase events classified as strokes from 821 181 to 880 520.

Conclusions—Adopting a tissue-based definition of transient ischemic attack would reduce estimates of the annual incidence of TIA by 33% (sensitivity analysis range, 19% to 44%) and increase estimates of the annual incidence of stroke in the United States by 7% (range, 4% to 10%).

Key Words: cerebral ischemia, transient ■ epidemiology ■ incidence ■ magnetic resonance imaging, diffusion-weighted ■ United States

Transient ischemic attack (TIA) is currently defined as an episode of focal neurological symptoms with abrupt onset and rapid resolution lasting <24 hours that is due to altered circulation to a limited region of the brain. Time-based definitions for TIA first arose in the 1950s as an imprecise means to distinguish between the cerebral ischemic episodes that caused brain injury and those that did not in the absence of imaging or other laboratory measures that could directly determine tissue parenchymal status. Proposed time cutoffs varied widely. A 1958 National Institutes of Health (NIH) committee on classification of cerebrovascular disease suggested that TIAs could last as long as 1 hour. In 1964, Acheson and Hutchinson also used a 1-hour threshold to distinguish TIA from stroke. However, also in 1964, Marshall used a 24-hour limit in defining TIA, although his data showed that symptoms lasted <1 hour in three fourths of his patients. In 1975 second revision of the NIH classification document, a 24-hour limit for TIAs was adopted.

Mounting evidence suggests that this 24-hour operational definition for TIA is clinically misleading. Large-scale studies have clarified our understanding of the typical duration of TIAs, showing that most TIAs resolve within 10 to 60 minutes rather than lasting several hours. CT studies in the 1980s and early 1990s demonstrated that clinical “TIAs” that last >1 hour are often associated with new parenchymal brain injury and represent pathological cerebral infarctions with transient clinical signs rather than episodes of brain ischemia without end-organ injury. Subsequent conventional MRI studies of traditionally defined TIA patients confirmed that lesions consistent with acute infaracts were frequent in patients with clinical TIAs. Most recently, diffusion-weighted imaging (DWI) MRI studies have shown that nearly half of traditionally defined TIA patients will exhibit a DWI lesion consistent with acute ischemic cerebral injury and nearly half of these DWI-positive lesions maintain persistent evidence of infarction on follow-up imaging. Moreover, diffusion MRI studies have demonstrated the untenability of any definition of TIA based solely on clinical manifestations and an arbitrarily assigned time window rather than tissue changes and underlying physiological processes. Although the likelihood of DWI alterations is directly related to the duration of symptoms, some patients with spells as brief as 10 minutes will show parenchymal changes on diffusion imaging and some with spells exceeding 12 hours will show no diffusion alteration. Any conceivable time cutoff for TIA is inaccurate in reflecting end-organ injury.
Accordingly, there is an emerging consensus to adopt a new definition of TIA based on the more objective foundation of the presence or absence of tissue injury rather than time interval. Several groups, including the TIA Working Group and our investigative team, are developing or have advanced proposals for a new tissue-based definition of TIA that is based on this fundamental physiological process that can be indexed by imaging or other laboratory measures rather than an arbitrary time limit. It is important to note that the new definition being advanced for TIA is not dependent on a particular imaging technique. A variety of modalities may be used to identify tissue injury in transient cerebral ischemic episodes, including not only CT and MRI imaging techniques but also serum biomarkers and cerebrospinal fluid biomarkers. The key biological variable is end-organ injury, which can be identified by a variety of neuroimaging and laboratory means.

Any redefinition of TIAs is likely to have substantial epidemiological ramifications. Accurate epidemiological studies are necessary to assess the full extent, natural course, population differences, and etiologic and prognostic factors of cerebrovascular disease, as well as for the successful implementation of therapeutic trials. However, the current 24-hour definition of TIA is overinclusive, misclassifying many patients experiencing true pathologic cerebral infarction as TIA rather than stroke. A tissue-based definition of TIA would result in an increased number of patients classified as having stroke annually and a reduced number classified as having TIA. The objective of the present study was to provide the first quantitative estimates of revised annual TIA and stroke incidence rates in the United States through the use of a tissue-based definition of TIA.

Methods

Identification of US Population-Based Studies of (Traditionally-Defined) TIA Incidence
We performed a computerized literature search for population-based US studies of TIA incidence rates performed over the last 25 years. MEDLINE (1975 to 2001) was searched with the key words TIA, incidence rates, hospital discharges, epidemiology, hospital abstract reports, and population surveys. Potentially relevant citations from identified articles were also retrieved and analyzed.

Inclusion criteria for final analysis were the following: (1) population-based study, (2) US population studied, and (3) TIA incidence identified unambiguously (no overlap with minor stroke, non-disabling stroke, other categories).

Tissue-Based Definition of TIA
We used the following proposed tissue-based definition of TIA: a brief episode of neurological dysfunction caused by focal cerebral ischemia that is not associated with permanent brain injury.

Identification of DWI MR Studies of Traditionally Defined TIA
To project how many traditionally defined TIAs would be reclassified as strokes under the proposed tissue-based definition of TIA, we searched MEDLINE for all reported DWI studies in TIA patients using the key words DWI and TIA. The aggregate incidence of diffusion MR abnormalities in traditionally defined TIAs was computed across all identified studies.

Models for Adjusting Traditional TIA Incidence to Determine Tissue-Based Definition TIA Incidence
Four models for adjusting traditional TIA incidence estimates to project tissue-based definition TIA incidence were generated, with the following model assumptions.

Maximal Direct Estimate
This model assumes that all patients with diffusion MR abnormality experience some end-organ injury and that the frequency of diffusion MR abnormalities in TIA patients who actually underwent MRI in reported series equals the frequency of diffusion MR abnormalities that would be found in the general TIA population if MRI was performed in all.

Minimal Direct Estimate
This model assumes that only TIA patients with persistent imaging abnormality experience some end-organ injury, whereas patients with transient diffusion MR abnormality but no permanent imaging abnormality do not experience end-organ injury. This model also assumes that the frequency of diffusion MR abnormalities in TIA patients who actually underwent MRI in reported series equals the frequency of diffusion MR abnormalities that would be found in the general TIA population if MRI was performed in all.

Maximal Adjusted-for-TIA-Duration Estimate
This model assumes that all patients with diffusion MR abnormality experience some end-organ injury. This model also adjusts for TIA episode duration differences between MR series populations and larger, less selected TIA cohorts when projecting the frequency of diffusion MR abnormalities in the general TIA population.

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The TIA duration-adjusted models were generated because some but not all series have suggested that TIA duration is a critical predictor of the presence of diffusion abnormality and because TIA episodes in populations with MRI have tended to be longer than TIA episodes in earlier, non-MRI series. The overrepresentation of longer TIA episodes in MRI series likely is due to an ascertainment bias, reflecting a greater likelihood of longer-duration-TIA patients presenting at the Emergency Department and undergoing MRI. To adjust for this bias, data from the 2 MR series reporting duration-specific frequencies of diffusion MR abnormalities were adjusted according to the frequencies of TIA episodes of varying duration in the large, non-MRI selected Cornell TIA series.6

The maximum and minimum models were generated because some uncertainty exists as to the frequency with which an acute MR diffusion abnormality in TIA reflects permanent brain injury compared with temporary regional bioenergetic compromise without permanent brain injury. For the minimal estimate models, the frequency (27%) of persistent imaging abnormality observed among initially DWI-positive patients in the 1 available series reporting data was used.11 For the maximal estimate models, all patients showing acute diffusion MRI abnormality were projected to have experienced some degree of permanent brain injury.

Duration-specific TIA MR diffusion positivity rates were abstracted from the studies with salient data. These rates were then multiplied by the frequency of TIAs of each duration category in the larger, broader hospital-based cohort of Levy et al to yield a duration-adjusted TIA MR diffusion positivity rate. The median value from the population-based US studies of TIA incidence was used as the best TIA incidence rate estimate; the low and high values were used in sensitivity analyses.
in the annual incidence of TIs from 64 to 43 per 100 000 and a corresponding increase in the annual number of events classified as strokes per year from 292 to 313 per 100 000. For the year 2000, the estimated annual number of TIs would decrease from 179 840 to 120 493, and the estimated annual number of events classified as strokes would increase from 821 181 to 880 528.

Sensitivity analysis showed that applying the 3 alternative models (Table 5) varied the estimate of the annual incidence of tissue-defined TIs. If the best model is applied to the alternative estimate of traditional TIA incidence available from the Seattle study, the number of TIs remaining classified as TIs is 25 per 100 000, and the number of TIs requiring reclassification as strokes is 12 per 100 000. If the best model is applied to the alternative estimate of traditional TIA incidence available from the Gallup study, the number of TIs remaining classified as TIs is 43 per 100 000, and the number of TIs requiring reclassification as strokes is 35 per 100 000. As such, the range of annual tissue-defined TIs would run from 25 to 72 per 100 000, and the number of TIs being reclassified as strokes would go from 12 to 35 per 100 000.

Discussion

Our analysis suggests that adopting a tissue-based definition of TIA would reduce estimates of the annual incidence of TIA by 19% to 44% and increase estimates of the annual incidence of stroke in the United States by 4% to 10%. In our

### TABLE 1. United States TIA Estimates From Different Population-Based Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Year(s) of Study</th>
<th>Annual TIs per 100 000 Persons</th>
<th>Annual TIA Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Paul, Minnesota</td>
<td>1996</td>
<td>64</td>
<td>179 840</td>
</tr>
<tr>
<td>State of Wisconsin</td>
<td>1996</td>
<td>64</td>
<td>179 840</td>
</tr>
<tr>
<td>State of Missouri</td>
<td>1997</td>
<td>65</td>
<td>182 650</td>
</tr>
<tr>
<td>State of Illinois</td>
<td>1996</td>
<td>67</td>
<td>188 270</td>
</tr>
<tr>
<td>Rochester, Minnesota</td>
<td>1985–1989</td>
<td>68</td>
<td>191 080</td>
</tr>
<tr>
<td>United States</td>
<td>1995</td>
<td>73</td>
<td>205 130</td>
</tr>
<tr>
<td>United States</td>
<td>2000</td>
<td>107</td>
<td>300 000</td>
</tr>
</tbody>
</table>

*Based on 2000 US census (281 million).

The maximal adjusted-for-TIA-duration value was chosen as the best estimate on the basis of the pathological studies in animal models suggesting that most DWI-positive transient ischemic insults are associated with neural dropout and other evidence of brain parenchymal injury even when late MRIs are unrewardable. The other models were used in sensitivity analyses.

To calculate total TIA events in the year 2000, incidence rates were applied to the US Census Bureau nationwide population estimate for 2000 (281 million). We arrived at an estimated year 2000 stroke incidence by using the Williams20 1996 US first-ever or recurrent stroke figure of 783 000. A 1996 US population figure of 268 million was arrived at by obtaining the difference between the actual 2000 and 1990 census bureau head counts, dividing by 10 (yearly increase), and multiplying by 6. The Williams incidence rate of tissue-definedTIAs per 100 000 was then calculated (292 per 100 000) and applied to the alternative estimate of traditional TIA incidence available from the Gallup study, the number of TIs remaining classified as TIs is 25 per 100 000, and the number of TIs requiring reclassification as strokes is 12 per 100 000. If the best model is applied to the alternative estimate of traditional TIA incidence available from the Gallup study, the number of TIs remaining classified as TIs is 43 per 100 000, and the number of TIs requiring reclassification as strokes is 35 per 100 000. As such, the range of annual tissue-defined TIs would run from 25 to 72 per 100 000, and the number of TIs being reclassified as strokes would go from 12 to 35 per 100 000.

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### TABLE 2. Frequency of Diffusion Positive TIs Across 5 Reported Series

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of TIA Patients Imaged</th>
<th>No. of TIA Patients DWI Positive</th>
<th>% of TIA Patients DWI Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidwell</td>
<td>42</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>Engelter</td>
<td>40</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Ay</td>
<td>57</td>
<td>26</td>
<td>46</td>
</tr>
<tr>
<td>Takayama</td>
<td>19</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Bisc Hopkins</td>
<td>44</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>Sum</td>
<td>202</td>
<td>67</td>
<td>44</td>
</tr>
</tbody>
</table>

*Aggregate data from Kidwell and Engelter series.
†Levy data.

### TABLE 3. Calculation of Duration-Specific Rates of DWI Positivity

<table>
<thead>
<tr>
<th>Duration of TIA</th>
<th>Frequency of DWI Positivity* in TIs of Indicated Duration</th>
<th>Frequency of Episodes of Indicated Duration Among All TIs†</th>
<th>Duration-Specific Adjusted Rate of DWI Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5 m</td>
<td>0</td>
<td>0.24</td>
<td>0.000</td>
</tr>
<tr>
<td>6–30 m</td>
<td>0.33</td>
<td>0.26</td>
<td>0.086</td>
</tr>
<tr>
<td>31–60 m</td>
<td>0.36</td>
<td>0.1</td>
<td>0.036</td>
</tr>
<tr>
<td>61–180 m</td>
<td>0.33</td>
<td>0.11</td>
<td>0.036</td>
</tr>
<tr>
<td>181–360 m</td>
<td>0.55</td>
<td>0.1</td>
<td>0.055</td>
</tr>
<tr>
<td>6–12 h</td>
<td>0.5</td>
<td>0.07</td>
<td>0.035</td>
</tr>
<tr>
<td>12–24 h</td>
<td>0.71</td>
<td>0.11</td>
<td>0.078</td>
</tr>
<tr>
<td>Sum</td>
<td>0.326</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Aggregate data from Kidwell and Engelter series.
†Levy data.
core model, in the year 2000 in the United States, the annual incidence of TIA would decrease by 33% to 120,493, and the incidence of stroke would increase by 7% to 880,528.

These projections should be taken as provisional because analyzing the epidemiological impact of adopting a tissue-based definition of TIA poses several challenges. Not least is the sparse number of, and remarkable variation among, existing studies of the annual US incidence of traditionally defined, 24-hour TIA. In our literature review, we were able to identify 13 population-based US studies of TIA incidence within the last 25 years, and incidence estimates among these varied 3-fold. Studies of the epidemiology of traditionally defined TIA have not flourished in part because of the lesser reliability of the diagnosis of TIA. TIA investigations must use information based on patient recall of onset and duration of symptoms, which can be subjective and inaccurate. Considerable differences in methods of case ascertainment have contributed to the wide variation in assessments of traditionally defined TIA incidence. In our models, we took the middle available estimate of traditionally defined TIA incidence as the best estimate. Using the other available estimates in sensitivity analysis altered estimates of tissue-defined TIA incidence downward by 42% or upward by 67%. An additional limitation on our estimates is the lack of data precisely specifying the number of traditionally defined strokes in the year 2000. Our estimates projected forward from 1996 data are intended to be illustrative rather than definitive.

An additional challenge to gauging the epidemiological impact of a tissue definition of TIA is determining the best way to measure brain end-organ injury during an episode of transient clinical symptoms resulting from cerebral ischemia. Candidate measures of brain end-organ injury include neuropathological examination, serum biomarkers, and various brain imaging studies.

The gold standard of neuropathologic examination is itself problematic on both practical and theoretical grounds. From the practical viewpoint, neuropathological examination is not an option for diagnosis in life. Moreover, performing a postmortem study would be impractical because patients rarely come to postmortem examination in the immediate aftermath of a TIA, thus making it difficult to conclude that a particular histopathological lesion identified at a delayed examination is definitely related to a particular, temporally remote symptomatic episode rather than to an intervening, clinically silent insult.22

Table: Sensitivity Analysis

The Table: Sensitivity Analysis provides a comprehensive overview of the impact of different methods of defining TIA on stroke incidence. The table includes data from various sources, including the Seattle and Gallup studies, and demonstrates the variability in results that can arise from different definitions. This variability underscores the importance of standardizing definitions to improve the accuracy and reliability of stroke epidemiology studies.
patients with traditionally defined TIAs, 31% to 39% demonstrate neuroanatomically relevant infarcts on conventional MRI and 2% to 48% on standard CT. However, it is difficult with conventional MRI and CT to determine what proportion of these appropriately localized infarcts occurred at the time of the index TIA and what proportion existed before the presenting event.

DWI MR imaging is more sensitive than conventional MR and CT imaging to acute ischemic changes, and allows differentiation of recent from remote events. For both these reasons, diffusion MRI is an attractive diagnostic tool to use in distinguishing between tissue-defined TIAs and strokes with transient clinical symptoms.

One concern with DWI MRI is that it may be overly sensitive. In serial MR studies in animal models of transient cerebral ischemia and in human TIA patients, brain regions that exhibit diffusion changes acutely may not show MR signatures of permanent injury on follow-up T2-weighted imaging. It is theoretically possible that a transient ischemic insult of a certain degree could produce temporary membrane pump failure and cytotoxic edema, followed by recovery of cellular homeostasis and survival of all neurons initially compromised. The sparse serial MRI data available on human patients with traditionally defined TIA suggest that 56% of patients with acute diffusion MR abnormalities show evidence on delayed reimaging of permanent parenchymal injury (T2-weighted abnormalities), but 44% do not. However, studies in animal models of transient cerebral ischemia suggest that brain regions that show only transient diffusion abnormality and late normalization of MRI still exhibit substantial neuronal loss and gliosis on neuropathological examination, if not frank through-and-through tissue infarction.

By the definition of TIA we used, any occurrence of brain end-organ permanent injury mandates classification of an event as a stroke rather than as a TIA. One reason for adopting this definition is that it avoids the ambiguities of how to distinguish between complete and incomplete infarction, using instead the more straightforward and simply operationalized distinction between presence and absence of end-organ injury. The differentiation between myocardial infarction and angina in cardiology similarly rests on a simple distinction between the presence and absence of end-organ injury. The experimental data from animal models of transient cerebral ischemia suggests that nearly all individuals showing DWI abnormality acutely do suffer some degree of end-organ injury of the cerebrum. Accordingly, in our core model, we reclassify all traditionally defined TIA patients exhibiting acute diffusion abnormality as strokes, regardless of the results of late, delayed imaging. In sensitivity analysis, reclassifying only the proportion of patients showing both acute diffusion MRI and late T2-weighted MRI change as strokes further increased estimates of tissue-defined TIA incidence by another 14% and reduced redefined stroke incidence estimates by 3%.

One additional caveat is that often patients experiencing first neurological symptoms of short duration do not seek medical advice immediately or even ever. As a result, estimates of TIA incidence based on patients receiving an overt diagnosis of TIA, rather than a household-by-household query of individuals for any history of TIA symptoms whether reported to medical authorities or not, are likely to underestimate TIA incidence. The incidence of end-organ tissue injury in TIA-like episodes not reported to medical authorities is likely to be less than in episodes coming to medical attention but unlikely to be nil.

The true annual incidence of tissue-defined TIAs in the United States will best be estimated by prospective studies that systematically obtain tests sensitive to permanent brain injury (DWI MRI, serum biomarkers, etc) in a population-based sample of patients with transient clinical symptoms. While we await these studies, it may be provisionally estimated that currently in the United States, tissue-defined TIAs occur with an annual incidence of 43 per 100,000 and that symptomatic strokes (including stroke associated with rapidly transient clinical symptoms) occur with an annual incidence of 313 per 100,000.

References


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