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%). (Stroke. 2003;34:919-924.)

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

Minimal Adjusted-for-TIA-Duration 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 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.

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-MR selected Cornell TIA series.

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 available series reporting data was used. 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 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.
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 neuronal dropout and other evidence of brain parenchymal injury even when late MRIs are unremarkable. 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 (yearly increase), and multiplying by 6. The Williams incidence rate of 821 181 for traditionally defined stroke incidence. A new stroke/pH11015/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 per 100 000 was then calculated (292 per 100 000) and applied to the actual 2000 and 1990 census bureau head counts, dividing by 10 (yearly increase), and multiplying by 6. The Williams incidence rate per 100 000 was then calculated (292 per 100 000) and applied to the 2000 US (~281 million) population, resulting in an adjusted figure of 821 181 for traditionally defined stroke incidence. A new stroke incidence estimate based on a tissue-based definition was then calculated.

Results

The literature search identified 13 US population-based studies of TIA incidence published in the last 25 years (Table 1). The median value used as the best TIA incidence rate estimate was 64 per 100 000 and, based on the 2000 US population of 281 million, came to 179 840.

Five studies11,12,19,21,22 of the frequency of diffusion MR abnormalities in TIA patients were identified (Table 2). Collectively, these studies found that among 202 imaged TIA patients, 44% exhibited diffusion abnormalities.

Table 3 displays the adjusted DWI positivity rates for each individual duration period, ie, duration-adjusted TIA MR diffusion positivity rates (Table 3, column 3), the sum of which resulted in an overall TIA-duration-adjusted MR diffusion positivity rate of 33% (Table 3, row 9).

Under the best-estimate model for the year 2000, 43 per 100 000 traditionally defined TIA would remain TIAs under a tissue-based classification, but 21 per 100 000 would be redefined as strokes (Table 4). This would result in a decrease in the annual incidence of TIAs 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 TIAs 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 TIAs. If the best model is applied to the alternative estimate of traditional TIA incidence available from the Seattle study, the number of TIAs remaining classified as TIAs is 25 per 100 000, and the number of TIAs 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 TIAs remaining classified as TIAs is 72 per 100 000, and the number of TIAs requiring reclassification as strokes is 35 per 100 000. As such, the range of annual tissue-defined TIAs would run from 25 to 72 per 100 000, and the number of TIAs 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>
<thead>
<tr>
<th>TABLE 1. United States TIA Estimates From Different Population-Based Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Seattle, Washington</td>
</tr>
<tr>
<td>Wichita, Kansas</td>
</tr>
<tr>
<td>State of Kansas</td>
</tr>
<tr>
<td>Greater Kansas City</td>
</tr>
<tr>
<td>Area, Kansas</td>
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<tr>
<td>Minneapolis, Minnesota</td>
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<tr>
<td>St. Paul, Minnesota</td>
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<tr>
<td>State of Wisconsin</td>
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<tr>
<td>State of Missouri</td>
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<tr>
<td>St. Louis, Missouri</td>
</tr>
<tr>
<td>State of Illinois</td>
</tr>
<tr>
<td>Rochester, Minnesota</td>
</tr>
<tr>
<td>United States</td>
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<tr>
<td>United States</td>
</tr>
</tbody>
</table>

*Based on 2000 US census (281 million).

TABLE 2. Frequency of Diffusion Positive TIAs Across 5 Reported Series

<table>
<thead>
<tr>
<th>Series 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>Bisschops</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>

†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 TIAs of Indicated Duration</th>
<th>Frequency of Episodes of Indicated Duration Among All TIAs†</th>
<th>Duration-Specific Adjusted Rate of DWI Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5 m</td>
<td>0.24</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>6–30 m</td>
<td>0.33</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>31–60 m</td>
<td>0.36</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>61–180 m</td>
<td>0.33</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>181–360 m</td>
<td>0.55</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>6–12 h</td>
<td>0.5</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>12–24 h</td>
<td>0.71</td>
<td>0.078</td>
<td></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 TIs. 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 cerebral 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

Serum biomarkers are attractive candidate measures of brain injury during transient cerebral ischemia. Release into the serum of end-organ–specific proteins provides an easily ascertainable index of the presence and extent of end-organ injury. Serum biomarkers have long been integral to the definitions of myocardial infarction and myocardial ischemia without infarction (angina). In the most recent revision of the diagnosis of myocardial infarction, the American College of Cardiology recognized a newer, more sensitive serum biomarker (troponin) as an authoritative indicator of MI.20 As a result, many cases of myocardial ischemia that previously would have been classified as angina are now classified as myocardial infarction. The S-100 protein, neuron-specific enolase, and additional candidate markers of brain injury may in the future prove helpful in distinguishing TIA without brain injury from stroke with rapidly transient clinical signs. However, no study has yet systematically applied these serum biomarkers to patients with well-defined clinical TIs. Alternatively, it is possible that all clinical TIs will be associated with elevated serum biomarkers.

Brain imaging is a longstanding critical tool in the diagnosis of cerebral infarction. Numerous CT and MR studies have demonstrated the ability of conventional CT and MR to demonstrate ischemic lesions in TIA patients. Among pa-

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### TABLE 4. Model Results for Tissue-Defined TIA (Based on Median Traditional TIA Value of 179,840)

<table>
<thead>
<tr>
<th>Models</th>
<th>% of Traditional TIA With DWI-Positive TIA Values</th>
<th>Tissue-Based Definition TIA Incidence*</th>
<th>Tissue-Based Definition TIA Incidence/100,000</th>
<th>Tissue-Based Definition Stroke Incidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal direct</td>
<td>44</td>
<td>79,130</td>
<td>100,710</td>
<td>36</td>
</tr>
<tr>
<td>Minimal direct</td>
<td>25</td>
<td>44,313</td>
<td>135,527</td>
<td>48</td>
</tr>
<tr>
<td>Maximal adjusted-for-TIA duration</td>
<td>33</td>
<td>59,347</td>
<td>120,493</td>
<td>43</td>
</tr>
<tr>
<td>Minimal adjusted-for-TIA duration</td>
<td>19</td>
<td>33,234</td>
<td>146,606</td>
<td>52</td>
</tr>
</tbody>
</table>

*Based on maximal adjusted-for-TIA-duration estimate.
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 lesions. For both these reasons, diffusion MRI is an attractive diagnostic test 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 MRI abnormalities show evidence on delayed imaging 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.23 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 asymptomatic strokes (including stroke associated with rapidly transient clinical symptoms) occur with an annual incidence of 313 per 100 000.

References

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