Incidence of Transient Ischemic Attack and Early Stroke Risk
Validation of the ABCD2 Score in an Italian Population-Based Study

Iacopo Cancelli, MD; Francesco Janes, MD; Gian Luigi Gigli, MD; Anna Perelli, MD; Barbara Zanchettin, PhD; Giessica Canal, MD; Lucio D’Anna, MD; Valentina Russo, MD; Fabio Barbone, MD; Mariarosaria Valente, MD

Background and Purpose—The importance of transient ischemic attack (TIA) lies on the short-term risk of stroke, and the ABCD2 score may improve early stroke risk prediction. However, population-based studies are still needed. We aimed to provide data on TIA incidence and to evaluate the ABCD2 predictive ability for early recurrent stroke in a population-based study.

Methods—This study is part of a 2-year prospective community-based registry of all cerebrovascular events in the district of Udine (153 312 inhabitants), Friuli Venezia Giulia region, northeast of Italy, between April 1, 2007 and March 31, 2009. Multiple overlapping sources for finding cases were used, combining hot and cold pursuit.

Results—We identified 178 TIA, 161 (90.4%) of which were incident. The crude overall annual TIA incidence rate per 1000 residents was 0.52 (95% confidence interval [CI], 0.45–0.61). Incidence rate was 0.45 (95% CI, 0.31–0.65) when standardized to the 2007 Italian population and 0.25 (95% CI, 0.16–0.39) when standardized to the European standard population. Estimates of stroke risk after the index TIA within 2, 7, 30, and 90 days were, respectively, 2.5% (95% CI, 0.7–6.2), 5.6% (95% CI, 2.6–10.3), 6.2% (95% CI, 3.0–11.1), and 11.2% (95% CI, 6.8–17.1). ABCD2 score was strongly associated with stroke occurrence after index TIA: the areas under the receiver operating characteristic curve at 2, 7, 30, and 90 days were, respectively, 0.85 (95% CI, 0.72–0.97), 0.69 (95% CI, 0.56–0.82), 0.69 (95% CI, 0.56–0.85), and 0.76 (95% CI, 0.67–0.86). No patients with an ABCD2 score <4 had a stroke within the 90-day follow-up period.

Conclusions—This study adds new data on TIA incidence and prognosis and it further validates the ability of the ABCD2 score to identify patients at early risk for stroke. (Stroke. 2011;42:2751-2757.)

Key Words: cerebrovascular accident • epidemiology • outcome • transient ischemic attack

There is mounting emphasis on creating dedicated services for transient ischemic attack (TIA) patients.¹ Measures of TIA incidence are needed to improve appropriate allocation of health resources.¹

The importance of TIA lies in the short-term risk of stroke. Ten to 15% of TIA patients have a stroke within 3 months, with half occurring within 48 hours.²–⁴ Urgent assessment and management of patients in a dedicated TIA clinic may decrease the 90-day stroke risk by almost 80%.⁵,⁶ Patients with TIA are a heterogeneous group of patients; although most TIA patients will experience no acute consequence, a significant minority will experience a potentially disabling stroke.¹ Early identifications of individuals at high risk for stroke in the early phase after TIA is expected to improve patients outcome and health care costs.² Clinical prediction tools such as the ABCD/ABCD2 scores (age, blood pressure, clinical features, duration, diabetes) have been developed to identify TIA subgroups at higher short-term risk for stroke.⁷ A recent meta-analysis of 11 validation studies of the ABCD/ABCD2 system has reported a good predictive ability.³ However, concerns persist about the external validity of the ABCD2 score in clinical practice.⁸ A recent study documented that the ABCD2 score has predictive utility in patients with TIA suspected by nonspecialists.⁸ In contrast, the predictive ability of the ABCD2 score was no better than chance in TIA cases confirmed by stroke specialists.⁸ The need for further population-based validation studies has been advocated.⁸

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Patients visiting Udine who were not residents were excluded. They had an event while temporarily away from the Udine district. Before March 31, 2009. Case ascertainment included patients who presented late with a stroke or a TIA that might have occurred on or continuing for 3 months after March 31, 2009, to identify patients of 1 month to improve the case finding process. Ascertainment Before the start of the formal ascertainment, we completed a test run and TIA occurring between April 1, 2007 and March 31, 2009. We attempted to ascertain all cases of incident or recurrent strokes Cases Ascertainment Study Population

The Udine district includes the city of Udine and 8 small municipalities (Corno di Udine, Martignacco, Pagnacco, Pasian di Prato, Pavia di Udine, Pradamano, Pozzuolo del Friuli, Tavagnacco). The population of the Udine district includes 153,312 residents (data based on the 2007 census; 80,349 women and 72,963 men). All residents are served by 1 university hospital, 1 small private hospital, and 128 general practitioners (GP). The private hospital has no neurological and no emergency department. Almost all stroke and TIA patients are referred to the Udine University Hospital. Cases Ascertainment

We attempted to ascertain all cases of incident or recurrent strokes and TIA occurring between April 1, 2007 and March 31, 2009. Before the start of the formal ascertainment, we completed a test run of 1 month to improve the case finding process. Ascertainment continued for 3 months after March 31, 2009, to identify patients presenting late with a stroke or a TIA that might have occurred on or before March 31, 2009. Case ascertainment included patients who had an event while temporarily away from the Udine district. Patients visiting Udine who were not residents were excluded. Before the study start, all GP were contacted by telephone and e-mail to explain the study purpose and to invite them to refer all stroke and TIA cases or to give information about patients evaluated at home or in nursing homes. Multiple overlapping sources for finding cases were used, combining hot and cold pursuit. Hot pursuit included: daily review of hospital and emergency department admission registers; daily review of all patients referred to neurology, neurology, and neurosurgery services; daily assessment of admission to cardiology, emergency, medicine, neurology, ophthalmology, stroke, and vascular surgery wards; and GP referrals of all possible TIA and strokes to the 24-hour open-access outpatient clinic for neurological emergency of our department. Cold pursuit included: monthly review of hospital discharge records; monthly contacts with rehabilitation services; quarterly telephone contacts with GP; and reviews of death certificates every 6 months.

Definitions

The World Health Organization definition of stroke was used. TIA was defined as an acute loss of focal cerebral or ocular function lasting <24 hours presumed, after adequate investigation, to be attributable to embolic or thrombotic vascular disease. Both incident and recurrent TIA occurring during the study period were recorded. Incident TIA was defined as a first ever in a lifetime TIA occurring within the study period. TIA that the patient had not brought to a doctor’s attention was ignored. The following cases were excluded: patients with isolated vertigo, diplopia, bilateral blindness, drop attacks, dysarthria, confusion, dysphagia; patients with only nonfocal symptoms such as loss of consciousness; patients with features suggesting migraine, epilepsy, transient global amnesia; patients who had a stroke before the index event; and patients who had a TIA but did not seek medical advice until after a stroke had occurred. Only incident cases were used for the calculation of ABCD2 score. The first recorded blood pressure after index TIA was used for ABCD2 calculation. High blood pressure was defined as systolic pressure $\geq 140$ mm Hg and/or diastolic pressure $\geq 90$ mm Hg, and/or use of antihypertensive medication, and/or being told at least twice by a physician or other health professional that high blood pressure was the diagnosis. Atrial fibrillation was diagnosed if patient had atrial fibrillation in ECG recording before stroke and/or during hospitalization. Carotid stenosis was defined according to TOAST criteria as narrowing of the internal carotid artery lumen of $>50\%$ on carotid duplex ultrasound or angiography. Diabetes mellitus was defined as history of diabetes that was confirmed in medical records, and/or use of insulin/oral hypoglycemic agents, and/or random nonfasting blood glucose concentration $\geq 11.1$ mmol/L. Hypercholesterolemia was defined as fasting total cholesterol serum level $\geq 5.18$ mmol/L (200 mg/dL), and/or fasting low-density lipoprotein cholesterol serum level of $\geq 4.14$ mmol/L (160 mg/dL), and/or use of lipid-lowering medications. Coronary heart disease was defined as a history of acute myocardial infarction, or angina pectoris, or coronary artery bypass graft, or percutaneous coronary intervention. Patients were defined as smokers if they were current smokers or they had stopped smoking $<3$ months before the index stroke/TIA.

Patient Evaluation and Follow-Up

Patients were assessed as soon as possible by a study neurologist in the hospital or at home. All participants signed an informed consent at the time of the interview. If needed, the principal caregiver of the patient enrolled in the study signed the informed consent. Data collection concerned event characteristics, demographic issue, risk factors, and diseases. The patients were asked to report any use of prescription drugs. Hospital and outpatients records were reviewed to obtain a confirmation of the self-reported diagnosis and of the drug prescriptions. For patients who were dysphasic or died before assessment, information was obtained by relatives, GP, and/or hospital records. All patients were followed-up by a face-to-face interview with a study neurologist at 2, 30, and 90 days after the TIA onset.
Statistical Analysis
TIA were categorized as incident or recurrent. Only incident TIA was included in the analysis. Incidence is reported as crude rates and age rates standardized to the 2007 Italian population and to the European standard population. The denominator for the calculation of incidence was calculated approximately by multiplying the average size of the study population by the length of the study period. The 95% confidence intervals (CI) were calculated assuming a Poisson distribution for the number of events. Poisson regression was used to calculate relative incidence for men versus women. The Kaplan-Meyer product limit method was performed to determine the cumulative probability of recurrent stroke at 2, 7, 30, and 90 days after the index TIA, with censoring of patients who died before having a stroke. The log-rank test was used for comparison of event-free survival between groups. The discriminative ability of ABCD2 score was evaluated by receiver-operating characteristic curves analysis and the predictive value was expressed as the area under the receiver operating characteristic curve. All probability values are 2-tailed. A significance level of P < 0.05 was used for hypothesis testing.

Results
During the study period, 1150 patients were referred by their GP or presented to a hospital with transitory neurological symptoms. After our assessment, 175 were included as having a definite TIA. Nineteen hundred thirty-three patients were excluded because their conditions were in a number of other diagnostic categories (see Supplemental Materials I, http://stroke.ahajournals.org). Forty-one patients were excluded because their conditions were not definite TIA. Nine hundred thirty-three patients included in the study population by the length of the study period. The 95% confidence intervals (CI) were calculated assuming a Poisson distribution for the number of events. Poisson regression was used to calculate relative incidence for men versus women, the difference in TIA incidence between men and women became statistically significant (relative incidence, 1.79; 95% CI, 1.4–89.7; P=0.02). When we adjusted the Poisson regression for the age structures of the 2 populations, the difference in TIA incidence between men and women became statistically significant (relative incidence, 1.79; 95% CI, 1.32–2.44; P<0.001). Those considered middle-aged had increased TIA incidence that was different between the sexes in the 55- to 64 year-old group (relative incidence, 11.2% [95% CI, 6.8–17.1]; P=0.02).

Overall, 161 (90.4%) patients with incident TIA and 17 (9.6%) with recurrent TIA were included. The median time from symptoms onset to assessment by either a general physician or an emergency department physician was 1 day (88.2% within 24 hours, 94.4% within 48 hours, and 98.3% within 7 days). The median time from symptoms onset to a “study” neurologist assessment was 2 days (7.2% within 24 hours, 51.7% within 48 hours, and 80.3% within 7 days). A brain CT scan was performed in 169 (95%) patients, in 61.5% of them within 24 hours and in 86.7% within 48 hours. Ninety-two (50%) patients were hospitalized. ABCD2 score was higher in hospitalized patients than in nonhospitalized patients (median, 5 versus 4; Mann-Whitney P=0.001), but no statistically significant difference was observed concerning age, sex, and recurrent stroke (data not shown).

Baseline characteristics of patients included in the study are listed in Table 1. Age-specific and sex-specific incidence rates with 95% CI are shown in Table 2. The crude overall incidence rate per 1000 population was 0.56 for men and 0.49 for women (relative incidence, 1.14; 95% CI, 0.84–1.55; P=0.4). When we adjusted the Poisson regression for the age structures of the 2 populations, the difference in TIA incidence between men and women became statistically significant (relative incidence, 1.79; 95% CI, 1.32–2.44; P<0.001). Those considered middle-aged had increased TIA incidence that was different between the sexes (Table 2). In particular, the difference was statistically significant in the 55- to 64 year-old group (relative incidence, 11.4; 95% CI, 1.4–89.7; P=0.02).

Follow-up status was determined for all patients at 90 days. Five (3.1%) patients died, 3 of them subsequently because of a recurrent stroke. Overall, 18 (11.2%) patients had a recurrent stroke. Seventeen (94.4%) recurrent strokes were ischemic and 1 was hemorrhagic. All patients with stroke recurrences had a brain CT scan performed.

Kaplan-Meier estimates of stroke risk after the index TIA within 2, 7, 30, and 90 days were, respectively, 2.5% (95% CI, 0.7–6.2), 5.6% (95% CI, 2.6–10.3), 6.2% (95% CI, 3.0–11.1), and 11.2% (95% CI, 6.8–17.1). Atrial fibrillation
and symptomatic internal carotid stenosis (>50%) were not found to be predictive of stroke risk at 90 days after TIA (atrial fibrillation: 7.1% versus 12.6%, log-rank test, \(P = 0.33\); carotid stenosis: 13.6% versus 10.3%, log-rank test, \(P = 0.63\)).

ABCD2 score was calculated for 152 patients (94.4%). We were not able to calculate the score for 9 patients because no blood pressure measure was taken after the index TIA. One of these patients had a stroke 82 days after the index TIA. This patient had an ABCD2 score of 4, regardless of blood pressure assessment.

Forty-seven (29.9%) patients had low ABCD2 scores (0–3), 71 (44.1%) had intermediate ABCD2 scores (4–5), and 34 (21.1%) had high ABCD2 scores (6–7). We found a strong association between ABCD2 score and recurrent stroke. No patients with an ABCD2 score <4 had a recurrent stroke within 90 days. Higher 90-day stroke risk was observed in the group with high scores compared with groups with intermediate and low scores (24.0% versus 12.7% versus 0%; log-rank \(P = 0.004\)). Estimates of stroke risk according to ABCD2 scores at 2, 7, 30, and 90 days are reported in Table 3.

ABCD2 score was highly predictive of the 2-day risk of stroke (area under the receiver-operator characteristic curve = 0.85; 95% CI, 0.72–0.97). An ABCD2 score threshold of 4 had 100% sensitivity and 42% specificity to identify stroke recurrence 2 days after TIA. The area under the receiver-operator characteristic curve for 7-day stroke was 0.69 (95% CI, 0.56–0.82), 0.69 (95% CI, 0.56–0.85) for the 30-day risk of stroke, and 0.76 (95% CI, 0.67–0.86) for the 90-day risk of stroke (Figure 2).

### Discussion

A study of TIA epidemiology involves several technical hitches. In fact, TIA diagnosis is sometimes difficult and even experienced neurologists may disagree. Several patients with TIA do not seek medical advice and several others are not hospitalized. To overcome these shortcomings, we used multiple sources of case finding (hospitals, outpatient clinics, GP, death certificates), and we provide a rigorous and standardized definition of incident TIA to include cases at an early and uniform point of the natural history of the disease. TIA and stroke cases were assessed simultaneously to reduce the possibility of a misclassification. Standard criteria for stroke incidence study were used: prospective study design; large, well-defined, and stable population (allowing at least 100 000 person-years of observation); brain imaging in at least 80% of patients; and follow-up of patients for at least 1 month. The main limitation of our study is the small sample size to validate the ABCD2 score. However, our study has a number of strengths to reduce the impact of this limitation: population-based design; large, well-defined, and stable population (allowing at least 100 000 person-years of observation); brain imaging in at least 80% of patients; and follow-up of patients for at least 1 month.

### Table 2. Age-Specific and Sex-Specific Annual Incidence Per 1000 Population for Transient Ischemic Attack in Udine District, Italy, April 1, 2007 to March 31, 2009

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Total Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–44</td>
<td>3 153 586</td>
<td>1 75 260</td>
</tr>
<tr>
<td>45–54</td>
<td>7 42 158</td>
<td>1 21 420</td>
</tr>
<tr>
<td>55–64</td>
<td>11 41 550</td>
<td>1 22 218</td>
</tr>
<tr>
<td>65–74</td>
<td>29 35 562</td>
<td>14 19 622</td>
</tr>
<tr>
<td>75–84</td>
<td>75 24 654</td>
<td>39 15 498</td>
</tr>
<tr>
<td>85 or older</td>
<td>36 9114</td>
<td>23 6680</td>
</tr>
</tbody>
</table>

### Table 3. Kaplan-Meier Estimates of Risk and 95% Confidence Intervals of Stroke After Index Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Days</th>
<th>ABCD2 0–3</th>
<th>ABCD2 4–5</th>
<th>ABCD2 6–7</th>
<th>All TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0 0 ...</td>
<td>1 1.4</td>
<td>3 8.8</td>
<td>4 2.5</td>
</tr>
<tr>
<td>7</td>
<td>0 0 ...</td>
<td>6 8.4</td>
<td>3 8.8</td>
<td>9 5.6</td>
</tr>
<tr>
<td>30</td>
<td>0 0 ...</td>
<td>7 9.9</td>
<td>3 8.8</td>
<td>10 6.2</td>
</tr>
<tr>
<td>90</td>
<td>0 0 ...</td>
<td>9 12.7</td>
<td>8 23.9</td>
<td>18 11.2</td>
</tr>
</tbody>
</table>
think that our findings are plausible for the following reasons. In our population, TIA incidence increases with age in both sexes but tended to be higher in men than in women, especially in the middle-aged patients. These findings have been reported in previous studies. Early stroke risk was quite similar to that previously reported. We detected a high proportion of TIA patients who have not been admitted to hospital (50%). This proportion is higher than that reported in most studies, suggesting that case ascertainment was efficient for outpatients. Finally, a report from the WHO MONICA project suggested that stroke incidence may be lower in Udine than in other European populations. 

Table 4. Incidence Rate per 1000 per Person-Years

<table>
<thead>
<tr>
<th>Study</th>
<th>Crude Incidence</th>
<th>ASRE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segovia</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>Udine</td>
<td>0.52</td>
<td>0.25</td>
</tr>
<tr>
<td>Dijon</td>
<td>0.36</td>
<td>0.27</td>
</tr>
<tr>
<td>Novosibirsk</td>
<td>0.29</td>
<td>0.31</td>
</tr>
<tr>
<td>OCSP</td>
<td>0.35</td>
<td>0.36</td>
</tr>
<tr>
<td>Portugal (Porto)</td>
<td>0.61</td>
<td>0.40</td>
</tr>
<tr>
<td>Umbria</td>
<td>0.64</td>
<td>0.41</td>
</tr>
<tr>
<td>Belluno</td>
<td>0.80</td>
<td>0.58</td>
</tr>
<tr>
<td>Rochester</td>
<td>1.34</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Studies are ordered by increased incidence. ASRE indicates age rate standardized to European population; OCSP, Oxfordshire Community Stroke Project.

In our study, early risk of stroke at 2, 7, 30, and 90 days after TIA (2.5%, 5.6%, 6.2%, 11.2%, respectively) was quite similar to that found in 2 recent meta-analysis. The first meta-analysis showed an overall risk of stroke at 2 days after TIA of 3.1 (95% CI, 2.0–4.1) and 5.2% (95% CI, 3.9–6.5) at 7 days, but with significant heterogeneity between studies. Heterogeneity between studies was almost fully explained by study method, setting, and treatment. Three population-based studies used methods quite similar to ours, such as multiple means of ascertainment, prospective identification of TIA patients from a well-defined population, and assessment and follow-up of all patients in person by a neurologist. In these 3 studies, the pooled risk of stroke after TIA was higher than that in our study: 6.7 (95% CI, 3.6–9.7) at 2 days and 10.4 (95% CI, 8.1–12.6) at 7 days. However, each of these studies included patients who had a stroke after a TIA, but before they sought medical attention. In our study, the exclusion of these patients may have decreased the measured risk.

The second meta-analysis showed an overall risk of stroke at 2, 30, and 90 days after TIA of 3.5 (95% CI, 2.1–5.0), 8.0 (95% CI, 5.7–10.2), 9.2 (95% CI, 6.8–11.5), respectively. Heterogeneity between studies was associated with methods of outcome ascertainment. Three studies used an active method of case ascertainment, as we did. In our study, the exclusion of these patients may have decreased the measured risk.
In conclusion, we think that our study provides further information about TIA incidence and prognosis. It further validates the ability of the ABCD2 score to identify patients at early risk for stroke and supplies useful data to design dedicated services for TIA patients in Italy.

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Disclosures
None.

References
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/10/2751

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/08/11/STROKEAHA.110.612705.DC1

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1. Patients referred with transient neurological symptoms and excluded after our assessment.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Isolated Vertigo</td>
<td>297</td>
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<tr>
<td>Syncope</td>
<td>199</td>
</tr>
<tr>
<td>Migraine</td>
<td>61</td>
</tr>
<tr>
<td>Confusion / non focal symptoms</td>
<td>55</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>55</td>
</tr>
<tr>
<td>Transient Global Amnesia</td>
<td>52</td>
</tr>
<tr>
<td>Possible TIA *</td>
<td>48</td>
</tr>
<tr>
<td>After Stroke TIA</td>
<td>41</td>
</tr>
<tr>
<td>Lone Bilateral Blindness</td>
<td>23</td>
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<tr>
<td>Drop Attack</td>
<td>16</td>
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<tr>
<td>Isolated Diplopia</td>
<td>11</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>117</td>
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</table>

* Possible TIA: applied to patients with transient focal neurological symptoms in whom clinical features were not sufficiently clear to make diagnosis of definitive TIA. [ref.: Dennis MS, Bamford JM, Sandercock PAG, Warlow CP. Incidence of transient ischaemic attacks in Oxfordshire, England. Stroke 1989;20:333-339].