Impact of Completeness of Ascertainment of Minor Stroke on Stroke Incidence
Implications for Ideal Study Methods

Yannick Béjot, MD, PhD; Ziyah Mehta, DPhil; Maurice Giroud, MD, PhD; Peter M. Rothwell, MD, PhD, FRCP, FMedSci

Background and Purpose—Reliable comparisons of stroke incidence are important. To determine the impact of systematic assessment of patients referred with transient ischemic attack on the measured incidence and severity of stroke, we compared 2 population-based studies.

Methods—Patients with first-ever stroke ascertained during 2006 through 2010 from the Dijon Stroke Registry and the Oxford Vascular (OXVASC) Study were studied. Both studies comply with the criteria for ideal incidence studies, but the OXVASC Study also systematically assessed all patients referred with transient ischemic attack. Stroke severity was measured by the National Institutes of Health Stroke Scale.

Results—Among 902 incident strokes in Dijon and 748 cases in the OXVASC Study, age and gender distribution were comparable, but severity was lower in the OXVASC Study (median National Institutes of Health Stroke Scale, 2 versus 6; P<0.001). Although overall incidence of ischemic stroke was higher in the OXVASC Study (157 versus 98 of 100000/y; incidence rate ratio, 1.59; 95% confidence interval, 1.24–2.05; P<0.001), this was accounted for by a 3-fold excess incidence of stroke with National Institutes of Health Stroke Scale ≤2 in the OXVASC Study (90 versus 29/100000/y; P<0.001), with no difference in incidence of more severe ischemic stroke (incidence rate ratio, 0.95; 95% confidence interval, 0.68–1.33). Of all 660 incident ischemic strokes in the OXVASC Study, 375 (56.8%) cases had an National Institutes of Health Stroke Scale ≤2, of which 232 had been ascertained in the transient ischemic attack clinic. Of these 232 minor strokes, only 71 cases had a diagnosis of definite stroke documented in the medical records by the referring physician.

Conclusions—Reliance on routine clinical coding underestimates the incidence of minor stroke. To improve comparability of incidence studies, researchers should assess patients referred with transient ischemic attack, and all studies should stratify incidence rates by stroke severity. (Stroke. 2013;44:1796-1802.)

Key Words: epidemiology ■ incidence ■ NIHSS score ■ registry ■ stroke ■ stroke severity

Reliable data of the clinical burden of minor stroke are important given the high risk of recurrent stroke,¹ the impact on cognitive function,² fatigue and depression,³ and the implications for clinical service provision. Reliable and comparable ascertainment of minor stroke is also important in geographica and temporal comparisons of incidence and severity of stroke. However, relatively little is known about the population-based epidemiology of minor stroke. Reliable data should come from stroke incidence studies that meet the ideal criteria for methodology,⁴,⁵ including complete prospective case ascertainment in a well-defined population based on multiple overlapping source of information, a standard World Health Organization definition of stroke,⁶ and presentation of rates by age and sex, but achieving complete case ascertainment is difficult in patients with minor stroke who are usually less likely to seek medical attention urgently and who are often coded as transient ischemic attack (TIA) in administrative databases.⁷,⁸

Although differences between stroke incidence studies in the underlying health care system and patients’ attitude toward seeking medical attention could result in discrepancies in reported incidence of minor stroke, the systematic assessment of all patients coded as TIA could be a major determinant of completeness of ascertainment. To test this hypothesis, we compared incidence of stroke, stratified by severity, in 2 similar high-quality population-based registries (Dijon Stroke
Registry and the Oxford Vascular [OXVASC] Study); only 1 of which included systematic face-to-face clinic assessment of all patients coded as TIA.

Methods

Case Ascertainment and Stroke/TIA Adjudication Procedures

The Dijon Stroke Registry is a population-based study of the epidemiology of stroke and TIA among the residents of the city of Dijon, France (151,000 inhabitants), since 1985.4 The OXVASC Study has been conducted since 2002. The population of the OXVASC Study comprises all patients (n=93,000) who are registered with 63 family physicians in 9 primary healthcare centers in Oxfordshire, United Kingdom.10 Both studies comply with the recommendation for running ideal stroke incidence studies.4,5 Case-collection procedures are summarized in Table 1 and have been detailed elsewhere.3,5 The 2 studies share some common procedures: (1) review of hospital admission and emergency department registers; (2) review of computerized hospital discharge diagnostic codes; (3) review of the medical records of patients identified from a computer-generated list of all requests for brain and cerebral vascular imaging, and of all referrals for carotid Doppler ultrasound; and (4) review of all death certificates to identify deaths out of hospital.

In addition to these procedures, other sources of ascertainment are used in OXVASC: a direct collaboration with family doctors who report TIA or stroke cases to the study, which provides a dedicated TIA/minor stroke daily hospital clinic for the purpose of both research and routine clinical care, and a monthly search of the primary care practice computer systems for all patients coded with a cerebrovascular diagnosis.

Some other differences between studies in data collection exist. In Dijon, most of patients (86%) are managed at the University Teaching Hospital, where the Dijon Stroke Registry is located. These patients are systematically referred to a trained neurologist who is responsible for stroke care and data collection. Patients hospitalized in the clinical departments of the 3 private hospitals of the city and its suburbs (10%) are seen by a neurologist working in these establishments. Medical records are then transmitted to and reviewed by the investigators of the Dijon Stroke Registry (Y.B. and M.G.). For out-of-hospital patients (4%), study investigators are responsible for contacting practitioners in charge of patients’ care to obtain clinical information. In the OXVASC Study, the vast majority of patients are assessed face to face by a study clinician as soon as possible after the stroke/TIA, either in hospital (daily visits to the acute medical admissions unit, acute stroke unit, neurology wards, and stroke rehabilitation wards), in a daily dedicated clinic, or at home. For out-of-hospital deaths, clinical information is obtained from the patients’ primary care physician and from the coroner, including all postmortem reports. A detailed history is obtained from each patient with a standardized questionnaire.

All cases are subsequently reviewed by the study senior neurologist (P.M.R.) and classified as stroke, TIA, or other condition using standard definitions to ensure consistent diagnostic practice. Finally, in both studies, when it is necessary to resolve disagreements between adjudicators, stroke/TIA adjudication is based on regular meetings of study investigators.

For the present study, only patients included from January 1, 2006, to December 31, 2010, were analyzed.

Stroke Definition and Assessment

Stroke was defined in both studies according to the World Health Organization diagnostic criteria as rapidly developing clinical signs of focal (at time global) disturbance of cerebral function lasting ≥24 hours or leading to death with no apparent cause other than that of vascular origin.5 Only first-ever symptomatic stroke in a lifetime was considered for this study and was classified as ischemic stroke, spontaneous intracerebral hemorrhage, or undetermined stroke. Ischemic stroke subtypes were defined as lacunar stroke, cardioembolic stroke, and nonlacunar noncardioembolic stroke. Stroke severity was quantified by the means of the National Institutes of Health Stroke Scale (NIHSS) score obtained at the first clinical examination. In a small number of cases, in which patients presented late or were assessed elsewhere for events occurring on vacation, NIHSS score was estimated on the basis of the review of the clinical history and medical records. Such a retrospective evaluation of the NIHSS score has been reported to be valid.11 For this study, minor was defined as a stroke with an NIHSS score of 0 to 2.

Review of Other Population-Based Studies

To identify population-based studies that previously reported the distribution of stroke patients according to NIHSS scores, we searched Medline/PubMed from 1989 to April 2012 with the following keywords: stroke, cerebrovascular, ischemic, hemorrhagic, population-based, epidemiology, registry, register, incidence study, stroke severity, and NIHSS. Only studies from reliable population-based registries that complied with the criteria for incidence studies were eligible. Authors were contacted to obtain additional data about the distribution of NIHSS scores.

Statistical Analysis

Proportions, means, and median values of baseline characteristics were compared between the 2 populations using the χ² test and the Wilcoxon test when appropriate. Incidence rates were calculated for the period 2006 to 2010 using the average population of Dijon (n=151,460) and OXVASC (n=93,091) as denominators. These rates were age and sex adjusted by the direct method to the 2006 European population,12 and stratifications by stroke subtype and NIHSS scores were performed. Confidence intervals (CIs) for a Poisson distribution were calculated. Poisson regression models were used to calculate

| Table 1. Stroke Ascertainment Procedures in Dijon, OXVASC, Melbourne, Örebro, and Basel Studies |
|---------------------------------|---|---|---|---|---|
|                                | Dijon | OXVASC | Melbourne | Örebro | Basel |
| Standard WHO diagnostic criteria | √ | √ | √ | √ | √ |
| Classification of pathological types of stroke | √ | √ | √ | √ | √ |
| Review of medical records of hospitalized patients | √ | √ | √ | √ | √ |
| Review of computerized hospital diagnostic codes | √ | √ | √ | √ | √ |
| Notification of cases by general practitioners | √ | √ | √ | √ | √ |
| Computer-generated list of all requests brain imaging | √ | √ | X | √ | X |
| Computer-generated list of all requests brain vascular imaging | √ | √ | X | X | X |
| Death certificates | √ | √ | √ | √ | √ |
| TIA/minor stroke clinic service | X | √ | X | X | X |
| Search of general practitioners’ computer systems | X | √ | X | X | X |
incidence rate ratios (IRR) and their CIs for OXVASC versus Dijon. Significance was set at \( P < 0.05 \). Statistical analysis was performed with STATA 10.0 software (StataCorp LP, College Station, TX).

**Ethics**

The Dijon Stroke Registry was approved by the National Ethics Committee and the French Institute for Public Health Surveillance. The OXVASC Study was approved by the Oxfordshire Research Ethics Committee.

**Results**

During the 5-year study period, 902 patients with a first-ever stroke were recorded in Dijon and 748 were collected in OXVASC. Baseline characteristics are shown in Table 2. Mean age of patients was not statistically different at conventional levels (\( P = 0.07 \)). OXVASC had a slightly greater proportion of men with stroke, a greater proportion of ischemic strokes (88.3% versus 84.6%), and a lower proportion of lacunar stroke.

Data on NIHSS were available in 890 (98.7%) patients in Dijon and 739 (98.8%) patients in OXVASC. Of these, 14% in Dijon and 10% in OXVASC were assessed retrospectively. NIHSS scores were higher in Dijon: median (interquartile range [IQR]), 6 (2–12) versus 2 (1–7); mean (SD), 8.7 (7.8) versus 5.6 (7.7; both \( P < 0.001 \); Table 2). This difference in severity was present for ischemic stroke (Table 2) and was consistent across pathogenetic subtypes of ischemic stroke, sex, and age groups (Figures I–III in the online-only Data Supplement; http://stroke.ahajournals.org). In contrast, no significant difference in severity (\( P = 0.53 \)) was noted in intracerebral hemorrhage patients: median (IQR) NIHSS, 10 (4–22) versus 10 (3–20). Further analyses stratified by time from stroke onset to assessment of NIHSS were consistent with these overall findings (data not shown).

The annual crude incidence of stroke was 119 of 100 000 (95% CI, 102–137) in Dijon and 161 of 100 000 (95% CI, 135–187) in OXVASC. Standardized incidence rate according to European population was significantly higher in OXVASC than in Dijon (177 versus 117 of 100 000/y; IRR, 1.52; 95% CI, 1.20–1.91; \( P < 0.001 \)). The observed difference was mainly attributable to a higher incidence of ischemic stroke in OXVASC (157 versus 98 of 100 000/y; IRR, 1.59; 95% CI, 1.24–2.05; \( P < 0.001 \)), contrasting with similar rates for intracerebral hemorrhage (IRR, 1.04; 95% CI, 0.52–2.05; \( P = 0.92 \)).

Stratification of incidence rates by stroke severity revealed that most of the discrepancies between the studies were in the incidence of minor ischemic stroke (Figure 1). Incidence of ischemic stroke with an NIHSS score \( \leq 2 \) in OXVASC was 3-fold that observed in Dijon (90 versus 29 of 100 000/y; IRR, 3.07; 95% CI, 2.02–4.66; \( P < 0.001 \)). This excess was consistent in men (89 versus 31 of 100 000/y; IRR, 2.87; 95% CI, 1.91–4.31; \( P < 0.001 \)) and in women (89 versus 28 of 100 000/y; IRR, 3.14; 95% CI, 2.06–4.80; \( P < 0.001 \)). For more severe ischemic stroke, incidence rates were similar, except for a nonsignificant excess incidence of very severe (NIHSS score, \( \geq 20 \)) ischemic stroke in Dijon (12 versus 6.5 of 100 000/y; IRR, 0.54; 95% CI, 0.21–1.41; \( P = 0.21 \)). The excess incidence of stroke with an NIHSS score \( \leq 2 \) in OXVASC was greater for nonlacunar ischemic stroke than for lacunar stroke (Table 3).

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No difference in incidence rates of intracerebral hemorrhage was noted between Dijon and OXVASC, whatever the severity, although the numbers of patients with minor intracerebral hemorrhage were small (Table 3).
Of all 660 incident ischemic strokes in OXVASC, 375 (56.8%) had an NIHSS score ≤2, of which 232 (61.9%) had been ascertained in the TIA clinic. Of these 232 minor ischemic strokes, only 71 (30.5%) had a diagnosis of definite stroke documented in the medical records by the referring physician in primary care or in the emergency department. Other documented diagnoses included TIA (n=62), TIA or stroke (n=12), and cerebrovascular disease (n=12) and in 58 cases, no diagnosis was specified. Of note, when excluding these minor ischemic strokes ascertained in the TIA clinic, there was no longer a difference in the incidence of ischemic stroke with NIHSS score ≤2 between OXVASC and Dijon (standardized incidence rate 34 versus 29 of 100,000/y; IRR, 1.16; 95% CI, 0.71–1.90; P=0.55).

To make sure that discrepancies in the reported incidence between Dijon and OXVASC were not related to differences in the threshold for clinical diagnosis of minor ischemic strokes by study teams, the investigator responsible for the validation of cases in Dijon (Y.B.) assessed the case records on 100 clinic-referred cases from the OXVASC Study in which a diagnosis of stroke with NIHSS score ≤2 had been made. This investigator agreed with the diagnoses of OXVASC investigators in 90 cases and was uncertain in the remainder. To exclude the possibility of a shift from the diagnosis of TIA toward that of minor stroke in OXVASC, we also compared the incidence of TIA between Dijon and OXVASC studies during the same period. The incidence of TIA was also higher in OXVASC than in Dijon, consistent with the difference in rates of minor ischemic stroke (standardized incidence rate 114 versus 47 of 100,000/y; IRR, 2.40; 95% CI, 1.71–3.36; P<0.001). When considering incidence of both TIA and ischemic stroke with NIHSS score ≤2, similar differences were observed (standardized incidence rate 201 versus 75 of 100,000/y; IRR, 2.67; 95% CI, 2.05–2.48; P<0.001).

**Comparisons With Other Population-Based Studies**

We identified 3 other population-based stroke incidence studies in which the authors reported the distribution of NIHSS scores among patients with stroke who met our selection criteria. Stroke ascertainment procedures of these studies are described in Table 1. In the study conducted in Melbourne, Australia, from 1996 to 1999, data about NIHSS scores were available in 77% of hospitalized patients only.13 In Örebro, Sweden, in 1999, NIHSS scores were available in all patients.14 In the study from Basel, Switzerland, only ischemic strokes were included from June 2002 to May 2003, and NIHSS
scores were available in 91.4% of patients. The median NIHSS score in patients with ischemic stroke was 6 (IQR, 2–14) in Melbourne, 5 (IQR, 3–12) in Örebro, and 5 (IQR, 3–9) in Basel. The distribution of severity was similar between Melbourne, Örebro, Basel, and Dijon studies (Figure 2). In contrast, in OXV ASC, a greater proportion of patients with ischemic stroke with an NIHSS score $\leq 2$ was noted.

**Discussion**

This study demonstrated differences in the distribution of stroke severity between the OXVASC study population and the Dijon population, and the 3 previously reported studies, attributable mainly to a major disparity in the reported incidence of minor ischemic stroke. Despite the use of multiple overlapping sources of case ascertainment in all 5 studies, in strict accordance with the published core criteria for conducting ideal stroke incidence studies, residual differences in ascertainment procedures probably contributed to the divergent findings (Table 1). First, some cases of minor stroke not hospitalized and not referred to the research teams may have been missed in the other studies, none of which had access to primary care computer systems to systematically identify all patients coded with a cerebrovascular diagnosis. However, only 4% of cases of ischemic stroke with an NIHSS score $\leq 2$ in OXVASC were identified by such searches alone. Second, and more important, the provision of a dedicated TIA clinic for the OXVASC study population identified the majority of minor ischemic strokes.

It has been reported previously that $\leq 25\%$ of patients initially referred by general practitioners to TIA clinics have evidence of neurological deficits on the neurologist’s assessment and symptoms persisting $>24$ hours. Assessment in TIA clinic also allows the identification of those with persistent discrete symptoms without signs that are coded in the NIHSS score. The high proportion of patients with ischemic stroke with an NIHSS score of 0 in OXVASC (22.1% versus 4.5% in Dijon) would be consistent with this hypothesis, although many patients with TIA and minor stroke do also present late, after clinical signs have resolved. Encouraging referral to a research clinic of all patients with possible TIA or minor stroke, who would perhaps not have been referred to conventional clinical services, might also have an effect on ascertainment. Moreover, the fact that the incidence of TIA was also higher in OXVASC than in Dijon argues against the hypothesis according to which

![Figure 2. Distribution of National Institutes of Health Stroke Scale (NIHSS) scores among patients with ischemic stroke in Melbourne (n=833), Örebro (n=333), Basel (n=246), Dijon (n=763), and Oxford Vascular (OXVASC; n=656) studies.](image-url)
minor strokes were misclassified as TIAs in Dijon. Although we cannot totally exclude a real higher incidence of both TIA and minor ischemic stroke in OXVASC, the magnitude of the observed differences allows us to rather assume that TIA/minor stroke clinics lead to better ascertainment of both TIA and minor strokes.

Some limitations of our study must be acknowledged. First, the evaluation of the NIHSS score was made by different study doctors from 2 distinct teams, with a potential risk of heterogeneity in the way of coding and, in some cases, a retrospective estimation was performed from information obtained in medical records. However, given the small numbers of cases involved and the good interrater reliability,17 and validity of the retrospective assessment with this scale,11 it can be assumed that this limitation did not significantly influence our results. Second, we did not find a difference between the studies in the incidence of minor intracerebral hemorrhage. This perhaps reflects the fact that diagnosis requires brain imaging, and that both studies reviewed all requests for brain imaging, or simply the fact that the numbers of cases were small. Third, it could be argued that our findings are attributable to the fact that the proportion of minor strokes ascertained in the Dijon study was unusually low. However, in the European Registers of Stroke Study, several proxies were used to compare stroke study was unusually low. However, in the European Registers of Stroke Study, several proxies were used to compare stroke incidence studies is important to consider in assessing the clinical burden of cerebrovascular disease, given the high risk of recurrent stroke,1 the impact on cognitive function,2 fatigue and depression,3 and the implications for clinical service provision.

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Disclosures

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Supplemental Figure:

Supplemental figure S1: Box plot of stroke severity among etiological subtypes of ischemic stroke patients in Dijon and OXVASC.
**Supplemental figure S2:** Box plot of stroke severity among ischemic stroke patients in Dijon and OXVASC stratified by gender.

**Supplemental figure S3:** Box plot of stroke severity among ischemic stroke patients in Dijon and OXVASC stratified by age groups.