Short-Term Risk for Stroke Is Doubled in Persons With Newly Treated Type 2 Diabetes Compared With Persons Without Diabetes

A Population-Based Cohort Study

Thomas Jeerakathil, MD, MSc; Jeffrey A. Johnson, PhD; Scot H. Simpson, PharmD, MSc; Sumit R. Majumdar, MD, MPH

Background and Purpose—Cardiovascular risk factors are suboptimally treated in diabetes, possibly because of the impression that there is a long delay between diagnosis and the development of macrovascular complications such as stroke. We determined the incidence of stroke in people newly treated for type 2 diabetes.

Methods—We conducted an inception cohort study with the use of linked administrative databases from Saskatchewan Health. Subjects entered the type 2 diabetes cohort on receipt of their first prescription for an oral antidiabetic drug. We defined incident stroke as any hospital admission with International Classification of Diseases, Ninth Revision, codes 430 to 438 inclusive. Age-standardized incidence rates were compared between the diabetes cohort and the general population.

Results—There were 12 272 subjects in the diabetes cohort, the mean±SD age was 64±13.6 years, and 55% were male. During a mean 5-year follow-up, 9.1% of the diabetes cohort had a stroke. The age-standardized incidence rate for stroke was 642 per 100 000 person-years in subjects with diabetes, compared with 313 per 100 000 person-years in the general population (rate ratio=2.1, 95% CI=1.8 to 2.3). The relative short-term risk for stroke in the diabetes cohort compared with the general population ranged from 1.8 (95% CI=1.6 to 1.9) in persons ≥75 years to 5.6 (95% CI=2.5 to 9.3) in the 30- to 44-year category.

Conclusions—The risk of stroke is high within 5 years of treatment for type 2 diabetes and more than double the rate for the general population. This further supports the need for aggressive early cardiovascular risk factor management in type 2 diabetes. (Stroke. 2007;38:1739-1743.)

Key Words: type 2 diabetes mellitus ■ stroke incidence ■ follow-up study

Type 2 diabetes mellitus is associated with a 2- to 3-fold increase in the risk of stroke.1–6 Some of these observational studies have reported stroke risk for periods of 10 or more years, but there are few data on the absolute or relative stroke risk in the first 4 to 5 years (ie, in the short term) after diagnosis of type 2 diabetes. In fact, the widely cited UKPDS risk model specifically excluded stroke events that occurred during this short-term period.7 In addition, the data for this model were drawn from observations taken from trial participants, rather than a more applicable general diabetic population. Limited data do exist about the prevalence of stroke at the time of diagnosis of type 2 diabetes. The DIADEM study, which examined 5572 persons with newly diagnosed diabetes recruited from primary care offices, reported that the point prevalence of stroke was 1.6% and the prevalence of coronary disease was 6.3%.7 The cross-sectional DICE study reported “prior stroke” to be present in 3% to 5% of persons with diabetes when assessed within 5 years after diagnosis.8 Neither study, however, provided information on the incidence of stroke after the onset of diabetes.

An understanding of the short-term risk for stroke, in both absolute and relative terms, may be relevant, considering the widely documented “care gaps” present in the treatment of cardiovascular risk factors in patients with type 2 diabetes.8–13 It is possible that this undertreatment of atherosclerotic risk may be the result of a prevailing attitude among physicians and patients that the cardiovascular complications of diabetes occur long after diagnosis (ie, 10 to 15 years) or...
that glycemic control (rather than management of blood pressure or high cholesterol) is paramount. Furthermore, early stroke risk may be important for both physicians and patients, given that the general public is more concerned with having a major stroke than with having a myocardial infarction and that patients attach more value to preventing events that occur in the short term. Thus, an understanding of the short-term risk for stroke in people with type 2 diabetes may improve the motivation of both physicians and patients to adhere to proven therapies to lower stroke risk in this group of subjects. Therefore, we investigated the short-term risk for stroke in all patients with newly treated type 2 diabetes from the population of Saskatchewan, Canada.

**Subjects and Methods**

**Setting and Sources of Data**

This study used linkable administrative health databases of the province of Saskatchewan, which has a population of ~1 million people. Health care within the province is publicly funded for all residents, and all are assigned a personal healthcare number. The provincial databases include a population registry with basic demographic data on all registered beneficiaries. The hospital services database contains discharge codes for all hospital separations, as well as information on discharge destination. A vital statistics database captures deaths and causes of death. The pharmacy prescription database records medication name, strength, quantity, and dispensation date for the ~91% of provincial residents who are eligible for prescription drug coverage.

**Diabetes Cohort**

As in previous studies, registered beneficiaries of Saskatchewan Health ≥30 years old were included in the cohort if they had a dispensation claim for a sulfonylurea or metformin during the index period of 1991 to 1996. We defined persons as newly treated type 2 diabetics if there were no other dispensations for antidiabetic prescription drug coverage. We considered only the first stroke-related event that occurred in the short term. Thus, an understanding of the short-term risk for stroke in people with type 2 diabetes may improve the motivation of both physicians and patients to adhere to proven therapies to lower stroke risk in this group of subjects.

**General Population Comparison Group**

The number of stroke hospitalizations (see subsequent section for definition) per year, by age and sex category, for the entire province of Saskatchewan is publicly available from the Canadian Institute for Health Information. Similarly, Statistics Canada reports the population size per year, by age and sex category, for the entire province. This allows population-based stroke rates to be calculated for the province and subsequently, age- and sex-standardized comparisons of stroke rates between the study group and the general population.

**Outcomes**

Information on stroke hospitalizations was available from the hospital services database using International Classification of Diseases, Ninth Revision, codes 430 to 438 inclusive as the primary discharge diagnosis. We considered only the first stroke-related event that occurred in the diabetes cohort in our analyses, although all stroke hospitalizations were included in the population comparator group, including recurrent events. These diagnostic codes have been previously validated for stroke-related events in Saskatchewan.

**Analysis**

We determined the proportion of subjects in the diabetes cohort who had a stroke-related hospitalization. The occurrence of stroke was also expressed as an incidence rate with person-years of follow-up as the denominator. We also produced Kaplan–Meier survival curves for stroke occurrence for our diabetes cohort. We then compared stroke rates in our population-based sample of people with type 2 diabetes with the independently ascertained and published stroke rates from the general population of Saskatchewan. To do so, we determined the population of Saskatchewan as of July 1, 1996, according to published data from Statistics Canada. From the discharge abstracts database, we obtained the number of stroke hospitalizations that occurred in fiscal year 1996 by age category. We age-standardized stroke rates from our cohort to the 1996 general population of Saskatchewan by the direct method and then determined rate ratios for stroke for our cohort compared with the general population. To ensure that our rate ratios remained stable for reference population samples from different years, we also determined rate ratios for stroke between our study sample and the general population of Saskatchewan from the years 1994 and 1999. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

**Results**

There were 12 272 persons in the diabetes cohort. Their mean age was 64 years (range, 30 to 105; SD = 13.6) and 55% were male. There was a mean 5.1 years of follow-up (range, 0 to 9; SD = 2.16), providing a total of 62 808 person-years of follow-up. Antidiabetic medication use during the course of follow-up was as follows: sulfonylurea monotherapy, 4424 (36%); metformin monotherapy, 1547 (12%); metformin and sulfonylurea combination, 4858 (40%); and combination therapy with insulin, 1443 (12%). There were 990 240 persons in the census population of Saskatchewan in 1996 (49% male).

Admission for any stroke-related diagnosis occurred in 9.1% (1122/12 272) of the diabetes cohort, and 21.9% (2688/12 272) died during the 5 years of follow-up (the Table). There were 1122 individuals who had a first admission for a stroke-related diagnosis, yielding a rate of 1786 strokes per 100 000 person-years. This figure compares with 3099 strokes for 990 240 person-years in the general population. After age standardization, the stroke rate was 642 per 100 000 person-years for those with newly treated type 2 diabetes compared with 313 per 100 000 person-years for the general population. The rate ratio (95% CI) for stroke was 2.1 (95% CI = 1.8 to 2.3) for those in the diabetes cohort compared with the general population. Age-standardized stroke rates increased markedly with age and were higher for the diabetes cohort than for the general population (Figure 1). The magnitude of elevated risk for stroke in persons with diabetes compared with the general population was greater for younger subjects than older subjects (the Table 1 and Figure 2). For example, in the 30- to 44-year age category, persons with newly treated diabetes had a rate ratio for stroke of 5.6 (95% CI = 2.5 to 9.3) compared with individuals of similar age in the general population. However, the absolute risk for stroke was much higher in older persons with diabetes (18.7%) compared with younger persons with diabetes (1.0%). We found similar or greater rate ratios for stroke when we age-standardized our cohort to the general population for the year 1994 (rate ratio = 2.0, 95% CI = 1.8 to 2.2) or 1999 (rate ratio = 2.5, 95% CI = 2.3 to 2.8) and compared stroke rates in the diabetes cohort with those of the general population in those years. Hospitalization for stroke occurred...
in a lower proportion of women (8.7%) than men (9.5%); however, women had a slightly higher relative risk for stroke compared with the general population than men (the Table).

The Kaplan–Meier survival curve for persons with diabetes shows that stroke hospitalizations increased steadily in the first 5 years and then more precipitously afterward, with nearly 19% of those remaining in the diabetes cohort having a stroke hospitalization by the 8-year mark (Figure 3).

### Discussion

We found that persons newly treated for type 2 diabetes were at a substantially elevated short-term risk for stroke compared with individuals in the general population, with an almost 10% absolute risk within 5 years. The relative risk of stroke within the diabetes cohort itself was greater for younger persons than for older persons. On the other hand, the absolute risk for stroke increased considerably with age, ranging from ~1% in 5 years for those 30 to 44 years old to almost 20% for those >75 years of age. To our knowledge, ours is the first study to specifically examine stroke-related outcomes soon after the diagnosis of and initiation of treatment for type 2 diabetes. Given the number of evidence-based treatments available for the prevention of stroke, these data should be useful for both patients with new-onset diabetes and their healthcare providers.

The strengths of this study include a large population-based sample with little loss to follow-up, universal healthcare coverage, and databases that have been validated in general and for stroke specifically. Our study also has a number of limitations. First, persons with “diet-controlled”

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Group</th>
<th>No. of Stroke Admissions (% of Total n in Category)</th>
<th>Person-Years of Follow-Up</th>
<th>Stroke Rate per 100 000 Person-Years</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All combined</td>
<td>DM cohort</td>
<td>1122 (9.14)</td>
<td>62 808.06</td>
<td>642.08†</td>
<td>2.1 (1.8, 2.3)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>3099§</td>
<td>990 240</td>
<td>312.95</td>
<td></td>
</tr>
<tr>
<td>Age 30–44 y</td>
<td>DM cohort</td>
<td>12 (0.98)</td>
<td>6749.65</td>
<td>177.79</td>
<td>5.6 (2.5, 9.3)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>72§</td>
<td>226 285</td>
<td>31.82</td>
<td></td>
</tr>
<tr>
<td>Age 45–59 y</td>
<td>DM cohort</td>
<td>110 (3.31)</td>
<td>18 336.14</td>
<td>599.91</td>
<td>3.6 (2.8, 4.5)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>248§</td>
<td>148 400</td>
<td>167.12</td>
<td></td>
</tr>
<tr>
<td>Age 60–74 y</td>
<td>DM cohort</td>
<td>476 (9.67)</td>
<td>26 005.43</td>
<td>1830.39</td>
<td>2.1 (1.9, 2.4)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>993§</td>
<td>115 980</td>
<td>856.18</td>
<td></td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>DM cohort</td>
<td>524 (18.65)</td>
<td>11 709.17</td>
<td>4475.13</td>
<td>1.8 (1.6, 1.9)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>1774§</td>
<td>69 625</td>
<td>2547.94</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>DM cohort</td>
<td>640 (9.45)</td>
<td>34 251.26</td>
<td>635.95‡</td>
<td>1.9 (1.6, 2.2)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>1641§</td>
<td>489 430</td>
<td>335.29</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>DM cohort</td>
<td>482 (8.74)</td>
<td>28 556.8</td>
<td>631.28‡</td>
<td>2.2 (1.8, 2.5)</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>1458§</td>
<td>500 805</td>
<td>291.13</td>
<td></td>
</tr>
</tbody>
</table>

DM (diabetes mellitus) cohort refers to the group of 12 272 persons with newly treated diabetes. GP refers to the general population of the province of Saskatchewan in 1996.

†Age-standardized to the entire control population.

‡Age-standardized to the male or female control population.

§Stroke hospitalizations for the control population were available as population rates with a denominator of person-years; therefore, it was not appropriate or possible to report the percentage of persons with stroke for the control population.
diabetes were not captured. If these individuals are at an earlier stage in their disease process, it is conceivable that they might be at lower risk for stroke than our results would indicate. Conversely, there is evidence that patients with diet-controlled type 2 diabetes may have poorer control of serum glucose and cardiovascular risk factors than those treated with hypoglycemic agents or insulin.23

Second, we were unable to exclude with certainty those patients who had experienced a stroke in the remote past. Recently diagnosed individuals with a history of stroke would be expected to be at a higher risk for recurrence. We do not, however, consider this exclusion to substantially have affected the results for the reasons that follow. The actual prevalence of stroke in newly diagnosed diabetes is low, considering data from the DIADEM and DICE studies.7,8 Even if 2% to 5% of subjects in our cohort had had a previous stroke and were at a higher risk for recurrence, they would be unlikely to substantially have affected the aggregate risk estimates for the entire cohort. Furthermore, persons with a past occurrence of stroke were not excluded from the general population comparator either, so the comparison between the 2 groups should still be valid. Along the same lines, although only the first stroke during the period of surveillance was included for our diabetes cohort, individuals in the general population also could have contributed recurrent stroke events. This difference in case ascertainment would serve to bias our results to the null, increasing the stroke rate in the reference population group.

In summary, this study addressed a gap in the literature and found that the risk of stroke in newly treated persons with type 2 diabetes is 9.1% within the first 5 years. This stroke rate is double that of the general population. An understanding of the high level of short-term risk for stroke, a devastating and disabling condition, will help to dispel the notion that the macrovascular consequences of diabetes occur only in the long term and hopefully will improve the motivation of both patients and providers to aggressively control cardiovascular risk factors soon after diagnosis.

Sources of Funding
The research project was supported by an Alliance for Canadian Health Outcomes Research in Diabetes NET grant; the Canadian Diabetes Association; the Kidney Foundation of Canada; the Canadian Institutes for Health Research (CIHR) Institute of Nutrition, Metabolism, and Diabetes; the Heart and Stroke Foundation of Canada; the CIHR Institute of Circulatory and Respiratory Health; and the Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut. Drs Majumdar and Simpson hold new investigator awards from the CIHR. Dr Majumdar is also a Population Health Investigator with the Alberta Heritage Foundation for Medical Research. Dr Johnson is a Health Scholar with the Alberta Heritage Foundation for Medical Research and holds a Canada Research Chair in Diabetes Health Outcomes.

Disclosures
None.

References
Short-Term Risk for Stroke Is Doubled in Persons With Newly Treated Type 2 Diabetes Compared With Persons Without Diabetes: A Population-Based Cohort Study
Thomas Jeerakathil, Jeffrey A. Johnson, Scot H. Simpson and Sumit R. Majumdar

Stroke. 2007;38:1739-1743; originally published online May 3, 2007;
doi: 10.1161/STROKEAHA.106.481390

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/38/6/1739

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/