Favorable Trends in the Incidence and Outcome in Stroke in Nondiabetic and Diabetic Subjects

Findings From the Northern Sweden MONICA Stroke Registry in 1985 to 2003

Aslak Rautio, MD; Mats Eliasson, MD, PhD; Birgitta Stegmayr, PhD

Background and Purpose—Several studies indicate a declining case-fatality and mortality in stroke. Little is known about time trends in stroke for subjects with diabetes. The purpose of this study was to compare time trends in incidence, case-fatality and mortality for stroke patients with or without diabetes.

Methods—This study was based on the Northern Sweden MONICA Project Stroke registry during 1985 to 2003. 15,382 patients, aged 35 to 74 years, were included in the study. 11,605 had a first-ever stroke and 3,777 had a recurrent stroke. In both men and women previously diagnosed diabetes was found in 22.8%.

Results—The incidence of stroke was 5 and 8 times higher in diabetic subjects than in nondiabetics, in men and women, respectively. Incidence of first-ever stroke decreased for nondiabetic men, probability value <0.001, and for diabetic women, probability value =0.012. Recurrent stroke incidence declined highly significant, probability value <0.001, in all but diabetic men. For diabetic women, the decrease in incidence in first and recurrent stroke was significantly greater than in nondiabetic women. Case-fatality and mortality in stroke declined for all groups except diabetic women with first-ever stroke. The time trends in case fatality and mortality did not differ significantly between nondiabetic and diabetic patients.

Conclusion—The incidence of stroke declined in both nondiabetic and diabetic subjects except for diabetic men and for nondiabetic women with first-ever stroke. Case-fatality in first-ever stroke declined for all but diabetic women. This led to a decreased mortality over the 19-year period for both groups. This is the first time that the decline in stroke incidence is reported in this MONICA population. (Stroke. 2008;39:3137-3144.)

Key Words: time trends ■ incidence ■ mortality ■ diabetes ■ stroke

The heavy impact of diabetes mellitus (DM) on the risk of, and for the prognosis in, cardiovascular disease is well established.1 Diabetes is a major risk factor for stroke, and stroke patients with DM have poorer prognosis with higher morbidity and mortality.2–5

The case fatality and mortality in stroke is declining in Western Europe and the United States.6–8 However, the results regarding the incidence of stroke in the Western world have been inconsistent. Previous studies report declining,9,10 as well as, unchanged incidence8 and increasing incidence.11 Decline in stroke severity is described in most studies with a shift toward more patients presenting with mild symptoms.12,13

Little is known if these beneficial time trends in stroke also apply to patients with DM. However, one study from Norway reports a decline of self-reported stroke morbidity and impairment due to other physical diseases in subjects with diabetes.14 A retrospective cohort study from Ontario, Canada, between 1992 and 2000 reported similar reductions in case-fatality rates related to acute myocardial infarction and stroke for diabetic and nondiabetic subjects.15

With increasing incidence in some parts of the world and increasing prevalence almost everywhere, mostly due to an aging population, the impact of diabetes on burden of disease is growing.16,17 However, in Northern Sweden MONICA area no increase in prevalence of known diabetes in subjects 25 to 64 years of age between 1986 and 1999 was seen.18

Several questions need to be answered. First of all, are the results from previous studies, showing favorable time trends in case-fatality and mortality for the whole stroke population, also valid for the diabetic population? It is also important to study how we manage to treat first-ever stroke and prevent recurrent stroke, especially in diabetic subjects? Previous studies describe time trends in first-ever or in all strokes, but trends for recurrent stroke have not been as well described. Recurrent strokes reflect the effects of acute medical treatment and secondary prevention. Therefore, trends in different patient groups, such as diabetics and men and women...
separately, are important to determine whether the healthcare system manages to deliver care in an equal manner.

The aim of this study was to compare time trends in incidence, case-fatality and mortality in first-ever and recurrent stroke in patients with and without diabetes mellitus.

Methods

The WHO MONICA Project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) is an international collaboration developed to study the trends and determinants in cardiovascular disease. Specifically, the project focuses on trends in event rates for validated fatal and nonfatal coronary heart attacks, sudden death and strokes, and on trends in cardiovascular risk factors in men and women aged 35 to 74 in a defined population. The Northern Sweden MONICA Project is ongoing in Västerbotten and Norrbotten counties since 1985 and covers the 2 most northerly counties of Sweden, with a total population of around half a million inhabitants. The population and age structure in the area have been stable during these 19 years.

The diagnosis of diabetes was based on WHO diabetes definition. Because our aim was to study the impact of previously diagnosed diabetes, the subjects diagnosed with diabetes during the event were not included in the analysis. The estimation of the prevalence of diabetes in the background population was based on the 5 MONICA population surveys in the same area from between 1986 and 2004.

In this study all strokes, including events occurring outside hospitals in subjects 35 to 74 years old, were registered from January 1, 1985 to December 31, 2003 in the MONICA Stroke event registry. All patients with subarachnoidal hemorrhage were excluded because the impact of diabetes as a risk factor for subarachnoidal hemorrhage is more uncertain than it is for brain infarction or for intracranial hemorrhage (Figure 1). All events were validated and registered in a standardized way according to the WHO MONICA manual.

The diagnosis of DM was based on medical records. To estimate the incidence of stroke in a diabetic population, the prevalence of DM in the population needs to be known. For this purpose data from the 5 MONICA population surveys in the same area from between 1986 to 2004 were used. The diabetes prevalence was calculated within 10-year age strata. The prevalence of DM 1986 to 2004 was 3.6% in men and 2.5% in women, ages 35 to 64 years. The total prevalence of diabetes in age group 35 to 64 was 3.1%. For the oldest age group 65 to 74 years the diabetes prevalence was 10.2% in men and 9.1% in women based on data from 1994 to 2004. The total prevalence of diabetes in age group 65 to 74 was 9.7%. As no significant time trend in diabetes prevalence was evident, the pooled and age stratified estimate for the time period was used. The corresponding number of subjects with diabetes was calculated from the total population in 10-year age strata.

Definitions

The following definitions were used: mortality is defined as the annual number of fatal events in the population. Case-fatality is defined as the proportion of all stroke events that are fatal within 28 days. Stroke is defined according to The WHO MONICA Project stroke definitions: “Rapidly developing signs of focal (or global) disturbance of cerebral function lasting 24 hours (unless interrupted by surgery or death), with no apparent nonvascular cause.” This definition excluded patients with transient cerebral ischemia.

Statistical Procedures

The incidence of stroke was based on each year’s individual population data in the age range 35 to 74. During the study period the population was stable and ranged between 236,000 and 251,000 inhabitants in this age group. Poisson regression was used to test for time trends in annual number of events, and logistic regression was used to test for time trends in annual incidence rates. Probability values <0.05 were considered as significant. The models were built separately for men and women. As a first step we built separate models for groups with and without diabetes to test for time trends within each group. To test if the difference between trends was statistically significant an interaction term “year*diabetes” was included in the models, where diabetes was a dummy variable for diabetes. A variable for age group was included in all regression models to control for possible different age distributions between the groups. When using Poisson regression we calculated trends in annual rates (ri) with the log-linear model, where log denotes the natural logarithm, t the year, and et the error term of the regression model:

\[ \log r_i = a + b_1 t + b_2 (\text{age group}) + e_i \]

The estimate 100^{[\exp (b_1)−1]} is the average annual percentage change. For small changes, 100\times b_1 can be used as approximated annual percentage change, which is presented in this article. Confidence intervals for b_1 from the regression models were used to estimate confidence intervals for percentage annual change. Similar approximations were done when logistic regression was used. The SAS v.8 software package was used for statistical analysis.

The Northern Sweden MONICA study has been approved by the Research Ethics Committee of Umeå University and data handling procedures by the National Computer Data Inspection Board.

Results

Between 1985 and 2003, 15,382 stroke events were registered for 9487 men and 5895 women in the age group 35 through 74 years. DM was present in 22.8% of both men and women. Patients with DM were slightly older than patients without DM (Table 1), but the age difference between groups remained relatively unchanged during the study period. Mean
age for patients without DM was 64.6 years in men and 65.6 in women. There was no significant change in mean age during the study period. Hypertension was somewhat more common in nondiabetics, but previous myocardial infarction and atrial fibrillation were more frequent in the diabetic population. 22.6% of the events were recurrent in the nondiabetic population and 31.1% were recurrent in the diabetic population (Table 1).

### Trends in Incidence of Stroke in Diabetics and Nondiabetics

At the start of the observation period, the stroke incidence for nondiabetic subjects was for men 358/100,000 and for women 204/100,000 and 183/100,000 respectively. For diabetic subjects the incidence of all stroke at the start of the observation period was for men 1961/100,000 and for women 1921/100,000. At the end of the observation period, the incidence had declined for diabetic men and women 1815/100,000 and 1176/100,000 respectively. For diabetic subjects the incidence of all stroke at the end of the observation period was for men 1921/100,000 and for women 1921/100,000. At the end of the observation period, the incidence had declined for diabetic men and women 1815/100,000 and 1176/100,000 respectively.

The incidence of stroke was about 5-fold higher among diabetic men as compared with nondiabetic men. In women this increased stroke incidence was even more pronounced with a 7- to 9-fold higher stroke incidence for diabetic women as compared with nondiabetic women. In men this difference in incidence remained unchanged from 1986 through 2003. In women there was a significant decline from an approximately 18/100,000 in first-ever stroke and 16/100,000 in recurrent stroke to 6-fold higher incidence at the end of the study period.

#### Table 1. Description of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic (7328)</th>
<th>Diabetic (2159)</th>
<th>Nondiabetic (4549)</th>
<th>Diabetic (1346)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (9487)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>64.6 (8.1)</td>
<td>66.0 (7.1)</td>
<td>65.6 (8.2)</td>
<td>67.6 (6.3)</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>33.0%</td>
<td>27.7%</td>
<td>31.2%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>15.2%</td>
<td>25.2%</td>
<td>7.9%</td>
<td>13.7%</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>13.5%</td>
<td>16.1%</td>
<td>13.8%</td>
<td>18.0%</td>
</tr>
<tr>
<td>First stroke</td>
<td>5 612</td>
<td>1 480</td>
<td>3 578</td>
<td>935</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1 716</td>
<td>679</td>
<td>971</td>
<td>411</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.

#### Table 2. Trends in Age-Adjusted Incidence of First and Recurrent Stroke According to Gender and Presence of Diabetes, 1985–2003

<table>
<thead>
<tr>
<th>Sex</th>
<th>First-Ever Stroke</th>
<th>Recurrent Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yearly Change (%)</td>
<td>Yearly Change (%)</td>
</tr>
<tr>
<td></td>
<td>With 95% CI</td>
<td>With 95% CI</td>
</tr>
<tr>
<td></td>
<td>Difference in Trend Between the Groups, P Value</td>
<td>Difference in Trend Between the Groups, P Value</td>
</tr>
</tbody>
</table>

For first-ever stroke, a significant declining trend of 0.8% per year (95 CI, 0.3; 1.3) was seen in nondiabetic men, and a smaller insignificant decline, 0.1%, was seen among diabetic men (Table 2). Diabetic women had a significantly more favorable trend than nondiabetic women with a yearly decrease in incidence of 1.5% (CI 0.3; 2.7), whereas first-ever stroke did not change at all in women without diabetes (Table 2, Figure 2a and 2b).

For recurrent stroke, the decline in incidence was significant for all but diabetic men (Table 3). The greatest decline, 5.4%/yr (CI 3.6; 7.2), was seen in diabetic women whereas nondiabetic women showed only a −2.7% yearly trend (CI 1.5; 3.8, Table 2, Figure 2c and 2d).

### Trends in Stroke Case-Fatality in Diabetics and Nondiabetics

At the start of the observation period, the case-fatality for nondiabetic subjects was 15.3% in first-ever stroke and 17.8% in recurrent stroke. For diabetic subjects the case fatalities were 18% and 26.2%, respectively. All groups except diabetic women with first-ever stroke had a significant decline in case-fatality over time (Table 3). Trends between nondiabetics and diabetics did not differ significantly (Figure 3). The yearly decline was higher in recurrent stroke than in first-ever stroke.

#### Trends in Stroke Mortality Rates in Diabetics and Nondiabetics

At the start of the observation period, the mortality for nondiabetic men and women, was 38/100,000 and 25/100,000 respectively in first-ever stroke and 16/100,000 and...
9/100 000 respectively in recurrent stroke. At the end of the observation period, the mortality had declined for nondiabetic men and women to 22/100 000 and 14/100 000 respectively in first-ever stroke and 5/100 000 and 2/100 000 respectively in recurrent stroke. For the diabetic subjects the mortality in first-ever stroke was at the start of the observation period 211/100 000 and 241/100 000 for men and women respectively and 163/100 000 and 168/100 000 respectively in recurrent stroke. At the end of the observation period, the mortality had declined for diabetic men and women to 110/100 000 and 148/100 000 respectively in first-ever stroke and 72/100 000 and 31/100 000 respectively in recurrent stroke (Figure 4a–b).

Trends in mortality in first and recurrent stroke were similar to those for case fatality with declining mortality in all groups except diabetic women with first-ever stroke (Table 4).

Discussion

Our study showed declining incidence in stroke for nondiabetic men, both for first and recurrent stroke and in recurrent

Table 3. Trends in Age-Adjusted Case-Fatality in First and Recurrent Stroke According to Gender and Presence of Diabetes, 1985–2003

<table>
<thead>
<tr>
<th></th>
<th>First-Ever Stroke</th>
<th>Recurrent Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yearly Change (%)</td>
<td>Yearly Change (%)</td>
</tr>
<tr>
<td></td>
<td>Within the Group</td>
<td>Within the Group</td>
</tr>
<tr>
<td></td>
<td>With 95% CI</td>
<td>With 95% CI</td>
</tr>
<tr>
<td></td>
<td>Difference in Trend Between</td>
<td>Difference in Trend Between</td>
</tr>
<tr>
<td></td>
<td>the Groups, P Value</td>
<td>the Groups, P Value</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>−3.6* (−5.2 to −2.0)</td>
<td>−6.7* (−9.3 to −4.1)</td>
</tr>
<tr>
<td></td>
<td>P value &lt; 0.001</td>
<td>P value &lt; 0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−4.1* (−7.0 to −1.3)</td>
<td>−4.2* (−8.0 to −0.5)</td>
</tr>
<tr>
<td></td>
<td>P value = 0.005</td>
<td>P value = 0.028</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>−4.6* (−6.5 to −2.7)</td>
<td>−8.7* (−12.5 to −5.1)</td>
</tr>
<tr>
<td></td>
<td>P value &lt; 0.001</td>
<td>P value &lt; 0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−1.3 (−4.5 to 2.0)</td>
<td>−5.8* (−10.6 to −1.1)</td>
</tr>
<tr>
<td></td>
<td>P value = 0.451</td>
<td>P value = 0.017</td>
</tr>
</tbody>
</table>

*Statistically significant decrease within the group.
†Statistically significant difference in trend between subjects with DM and without DM.

Figure 2. a and b, Incidence of first-ever stroke according to gender and presences of diabetes. c and d, Incidence of recurrent stroke according to gender and presences of diabetes.
stroke also for nondiabetic women. For diabetic individuals beneficial time trends in incidence were shown only for women. There is no apparent explanation for this gender difference. A previous American study did not find any gender differences in care adherence between men patients and women patients with diabetes.26 Furthermore, a Swedish study showed that there is no gender difference in the level of glycemic control, although diabetic women visit outpatient clinics more frequently than diabetic men.27 At least in the Swedish population the women with first-ever stroke are older than men28 and this age difference was evident also in our study. The gender differences observed in this study may, therefore, partially be explained by the upper age limit of 74 years.

Patients with diabetes and stroke had similar positive, though less evident, time trends as nondiabetic subjects in mortality and case-fatality. This is particularly true considering recurrent stroke which indicates a successful secondary prevention. On the other hand, we found more recurrent events among diabetic subjects than nondiabetic subjects. This indicates a need for even more intensive secondary prevention for diabetic patients.

In this study we can, for the first time, report declining stroke incidence in Northern Sweden. The fact that patients with diabetes to a great extent had similar favorable time trends as nondiabetic patients is particularly interesting considering that the diabetic patients with myocardial infarction from the same population did not have any positive time trends.29 The question thus raised is why a diabetic population has a different time trend in myocardial infarction as compared with stroke? Hypertension, as a risk factor, has a greater impact in stroke than in coronary heart disease.30 This is probably part of the explanation why there is a difference in time trends in myocardial infarction for diabetic and for nondiabetic subjects but not in stroke. After UKPDS31 the impact of hypertension for diabetic patients has been more in focus, and hypertension may now be more intensively treated in diabetic patients.

The decline in smoking32 and large decreases in cholesterol levels33 in the population during the study period also have contributed to the declining incidence in both diabetic and non diabetic subjects.

Previous studies in stroke epidemiology indicate declining case-fatality7,11,13,34 and declining stroke incidence5,6,8,35,36 at least in the Western world. Declining incidence combined with declining case-fatality results a decrease in total stroke-mortality. This study confirms declining case-fatality and mortality due to stroke in Northern Sweden MONICA stroke population. Under the study period specialized stroke units had been introduced and established widely in Northern Sweden, providing more accurate management of stroke patients and thus reducing acute stroke case fatality. The fact that stroke units save lives has been shown in a previous meta-analysis.37

The strength in our study is the adherence to the MONICA procedures during event registration. The quality and internal validity in the WHO MONICA Project is well recognized.38 This study has truly population-based data and includes all stroke events not only subjects admitted to hospital.

There are some potential limitations to our study. Firstly, a considerable proportion of patients with stroke may have undiagnosed diabetes or have an impaired glucose tolerance.59 Our aim was to mirror the impact of stroke in subjects with previously clinically diagnosed diabetes and to determine how well the healthcare system has managed to give these subjects treatment to alleviate the burden of stroke disease.

Secondly, the results for trends in incidence among people with diabetes in the population rely heavily on the estimates of the number of diabetic men and women in the background population and are based on the assumption that the number of diabetic people remained stable over time. Over the years...
the background population has been very stable and the prevalence of known diabetes has been relatively unchanged. In addition, the proportion of DM diagnosed with oral glucose tolerance test (OGTT) was stable over time in the background population between 1986 and 2004 as based on the data from the 5 MONICA population surveys in the same area and population. For the age group 65 to 74 years, prevalence of known diabetes is available from 3 surveys,

**Figure 4.** a and b, Number of fatal cases/100 000 with first-ever and recurrent stroke in northern Sweden according to gender and presence of diabetes.

<table>
<thead>
<tr>
<th></th>
<th>First-Ever Stroke</th>
<th>Recurrent Stroke</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Yearly Change (%)</td>
<td>Difference in Trend Between the Groups, P value</td>
</tr>
<tr>
<td>Sex</td>
<td>Within the Group</td>
<td>With 95% CI</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>$-3.7^* (-5.2$ to $-2.3)$</td>
<td>$P$ value $&lt;0.001$</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$-3.3^* (-5.9$ to $-0.7)$</td>
<td>$P$ value $=0.014$</td>
</tr>
<tr>
<td>Women</td>
<td>$0.419$</td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>$-3.8^* (-5.6$ to $-2.0)$</td>
<td>$P$ value $&lt;0.001$</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$-2.4 (-5.4$ to $0.6)$</td>
<td>$P$ value $=0.126$</td>
</tr>
</tbody>
</table>

*Statistically significant decrease within the group.
**Statistically significant difference in trend between subjects with DM and without DM.
1994 to 2004, and OGTT from 1994 and 2004. Therefore, we believe our estimates on incidence of stroke among the diabetic population are as valid as would be possible to achieve. Thirdly, the MONICA Stroke Registry only covers ages up to 75 years and thus an important segment of the stroke population has not been included. However, we have no reason to believe that the results differ among the eldest. An ongoing study within the registry will address the incidence of stroke in all ages. As discussed previously, this age limit may partially explain the gender differences observed in this study. A limitation for the generalizability of our study is the lack of increase in diabetes prevalence observed in other communities. On the other hand, 2 previous Swedish studies have also reported unchanged diabetes incidence. In the county of Skaraborg diabetes incidence was unchanged between years 1991 to 199541 and in the Laxå municipality both the diabetes incidence and prevalence was unchanged between years 1988 to 2001.22

Our findings are supported by a preliminary report from the Swedish Board of Health and Welfare describing decreasing mortality rates among diabetic subjects between 1980 and 2004.28 In men the improved survival paralleled that of nondiabetic men keeping relative mortality for diabetic men stable at double that of nondiabetic men. In diabetic women, both absolute and relative mortality improved.

We have described favorable time trends in stroke for subjects with diabetes and have confirmed previous results showing large risk increases for stroke among people with diabetes.5 The prevalence of patients with known diabetes in the stroke registry was almost 23% as compared with 5% to 7% known diabetic subjects in the actual population in the same age range. We need to intensify our primary prevention of cardiovascular disease in the diabetic population. There were more recurrent events among diabetic subjects than among nondiabetic subjects. Therefore, secondary prevention for the diabetic patient with established cardiovascular disease must be intensified with prevention against all traditional cardiovascular risk factors. Treatment of hypertension and hyperlipidemia are instrumental to this aim.

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Disclosures

None.

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