Long Term Postischemic Stroke Mortality in Diabetes
A Veteran Cohort Analysis

Masoor Kamalesh, MD, FACC; Jianzhao Shen, MS; George J. Eckert, MAS

Background and Purpose—Recent data on stroke mortality in diabetics in the United States is lacking. We investigated trends in diabetes prevalence and stroke mortality among diabetics in a large veteran cohort.

Methods—The Patient Treatment File was used to identify all patients discharged from any Veterans hospital between October 1990 and September 1997 with a diagnosis of ischemic stroke (ICD-9-CM codes 434, 436) listed as primary diagnosis. Demographic, morbidity, and mortality data were recorded. Chi-square tests were used to examine differences between diabetics and nondiabetics, and t tests were used for continuous variables. Cox proportional hazards regression was used to examine the effects of diabetes (DM) on the survival times controlling for multiple covariates.

Results—Of 48,733 ischemic stroke patients identified, 98% were male and 13,925 (25%) had DM. Mean age was similar between DM and non-DM (67.2 versus 67.5, \( P = \text{NS} \)). Prevalence of DM among stroke subjects increased from 25% to 31%. Charlson index >2 was much higher in DM (68.2% versus 47.9%, \( P < 0.001 \)). Mortality at 60 days and 1 year was similar in both groups (2.9 versus 2.7%, \( P = \text{NS} \); 12.6 versus 13.1, \( P = \text{NS} \)). Kaplan–Meier survival plot showed that DM had shorter long-term survival time (log-rank, \( P < 0.001 \)). Multivariate Cox proportional hazards regression showed a higher risk of death for diabetics (HR = 1.15, 95% CI 1.11 to 1.19, \( P < 0.001 \)).

Conclusion—Despite greater comorbidity, postacute ischemic stroke mortality at 60 days and 1 year is not different between subjects with and without DM. Long-term mortality after stroke is much lower among DM than that reported in older studies. (Stroke. 2008;39:2727-2731.)

Key Words: diabetes ■ stroke ■ mortality

Stoke remains the third leading cause of mortality in the United States and the second leading cause of death worldwide. The incidence of stroke declined steadily from the 50s through the 70s presumably because of improved control of hypertension. From 1991 to 2001 the prevalence of diabetes, hypertension, and hypercholesterolemia has increased among all races, ethnic groups, age, and education groups. Given the rising prevalence of diabetes worldwide, the American Heart Association has focused on reducing vascular complications of diabetes.

Several large studies including the Framingham cohort confirm the excess risk imposed by diabetes on occurrence of ischemic stroke. In the UK prospective diabetes study (UKPDS), for each 1% increase in glycosylated hemoglobin there was a 37% increase in case fatality rate. Because diabetes is a modifiable risk factor, effect of diabetes on short term and long prognosis after stroke remains an important issue. In this study, we report on the trends in prevalence of diabetes among subjects admitted with stroke in the 1990s and their short- and long-term outcomes.

Methods

Study Population
The study was approved by the Institutional Review Board of the Roudebush VA Medical Center (VAMC) and the Indiana University School of Medicine. The study methodology has been described by us previously. The VA’s Patient Treatment File is an administrative database that stores information for all patients discharged from any VAMC in the United States. We queried the Patient Treatment File and identified all veterans discharged between October 1990 and September 1997 with a primary diagnosis of ischemic stroke (ICD-9-CM codes 434 and 436). The validity of this strategy to identify patients with ischemic stroke has been previously established.

For VHA stroke patients with more than 1 admission with an eligible ICD-9-CM code during the study period, the first admission was considered the index admission. Patients who were discharged and readmitted the same day were assumed to have been transferred from one medical center to another (a common practice in the VA medical system) and their admissions were considered to represent a single hospitalization. Patients whose length of stay exceeded 1 year were excluded from the analyses. These patients either had comorbid conditions causing long-term disability or were receiving mental health care and thus had different poststroke courses and health care utilization than those without these conditions.
Demographic data were extracted from the VA’s patient registration system. The patients were grouped as diabetic or nondiabetic as recorded when enrolled in the VA health system.

### Data on Hospitalization, Follow-Up, and Mortality

Data were extracted from the central Veteran’s Affairs administrative data center in Austin, Texas. Clinical data regarding VA inpatient care for the index hospitalizations were extracted from Patient Treatment Files. There is a high agreement between Patient Treatment File data and data extracted from patients’ paper medical charts. Each hospitalization record in the Patient Treatment File contains up to 10 discharge diagnoses. We used discharge diagnoses in positions 2 through 10 from the index admission to identify comorbid conditions, from which we constructed the Charlson index, an indicator of severity of illness used to predict inpatient mortality during an acute hospitalization. The severity of the patient’s acute ischemic stroke and medication profile were not available from the VA’s central databases.

To assess resource utilization, all readmissions and readmissions for cardiovascular reasons (unstable angina-ICD code 411.1, myocardial infarction-ICD codes 410.00 to 410.92, congestive heart failure-ICD code 428.0 and stroke-ICD codes 430 to 432.9, 434, 435, 436) to any VAMC were assessed at 60 days and 1 year after discharge from the index admission. Patients who died before 30 days were excluded from readmission analysis because, for both VA and Medicare administrative purposes, death within 30 days of a hospital discharge is considered an outcome of that hospitalization. For outpatient services, utilization data were extracted from the VA Outpatient Clinic File for visits to primary care, neurology clinic, and emergency units. Regions of the country (Northeast, South, Midwest, West) were based on the 22 geographical locations of the hospital. We excluded VAMCs outside of the continental United States.

To determine mortality, we queried the Beneficiary Information and Resource Locator (BIRLS) file which contains date of death but not cause of death. Hence all-cause mortality was used as the study end point.

### Statistical Analysis

To describe the cohort, means and standard deviations were first computed for all continuous variables and frequencies and proportions for categorical variables.

For categorical variables, χ² tests were used to examine differences between diabetics and nondiabetics, and t tests were used for continuous variables. The prevalence of diabetes was determined in 4 age groups: ≤44, 45 to 64, 65 to 74, and ≥75 years.

Time to death was defined as the number of days between the discharge from the index admission and death. Patients were censored in the analysis if they were still alive as of October 1, 1998. Cox proportional hazards regression was used to examine the effects of diabetes on the survival times controlling for age, gender, ethnicity, chronic conditions, comorbidities, hospital utilization, and regions.

### Results

Between November 1989 and September 1998, a total of 48,733 patients were discharged from any VAMC in the United States with a primary diagnosis of ischemic stroke. Of these, 13,925 (28%) had diabetes. The baseline demographics and clinical characteristics of the sample were presented in the following table:

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics and Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Diabetes</strong></td>
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<tr>
<td>n</td>
</tr>
<tr>
<td>Mean (SD) age</td>
</tr>
<tr>
<td>Gender, % male</td>
</tr>
<tr>
<td>Ethnicity, % white</td>
</tr>
<tr>
<td>Chronic conditions, %</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Mean (SD) # of discharge diagnoses</td>
</tr>
<tr>
<td>Mean (SD) Length of stay</td>
</tr>
<tr>
<td>Charlson Index &gt;2, %</td>
</tr>
<tr>
<td>Post-discharge mortality, %</td>
</tr>
<tr>
<td>60-day mortality</td>
</tr>
<tr>
<td>1-year mortality</td>
</tr>
<tr>
<td>Mean (SD) No. of readmissions</td>
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<tr>
<td>Readmission within 1 year</td>
</tr>
<tr>
<td>CV readmission within 1 year</td>
</tr>
<tr>
<td>Readmission ever</td>
</tr>
<tr>
<td>CV readmission ever</td>
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<tr>
<td>Region</td>
</tr>
<tr>
<td>MW</td>
</tr>
<tr>
<td>NE</td>
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<tr>
<td>S</td>
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<tr>
<td>W</td>
</tr>
</tbody>
</table>
Table 1. Being a veteran cohort, majority of patients (98%) were male.

In general, a similar increasing pattern was reported in the percentage of diabetics admitted for ischemic stroke from 1990 to 1998 compared to the general population (Figure 1). However, the percentage of diabetics admitted for ischemic stroke was much higher than the one in the general population for any age groups (Figure 2). The age group <50 years or less had the lowest prevalence of diabetes consistently over years from 1990 to 1998. The highest prevalence of diabetes occurred in the age group >65 years.

Patients with diabetes had more chronic conditions, higher numbers of discharge diagnosis, and higher numbers of CV readmissions within 1 year or ever. However, neither 60-day postdischarge mortality nor 1-year postdischarge mortality showed a significant difference between diabetics and nondiabetics. Kaplan–Meier survival plot showed that diabetics had shorter long term survival time (log-rank, $P<0.001$; Figure 3). Multivariate Cox proportional hazards regression showed that the hazard of death for diabetics was 15% more than nondiabetics after controlling for other covariates ($HR=1.15, P<0.001$; Table 2).

**Discussion**

Our investigation reveals several findings regarding recent trends in stroke among subjects with diabetes. Not surprisingly, the prevalence of diabetes among subjects admitted with stroke is increasingly reflecting the general trend in rise of diabetes in the population. The greatest increase occurred in the highest age group. Short-term and medium-term (1 year) mortality was similar for diabetics and nondiabetics. Long-term mortality was 15% higher for subjects with diabetes.

**Diabetes Prevalence in Stroke Subjects**

Sprafka and coworkers analyzed trends in diabetes prevalence from the Minnesota Heart Study and showed that between 1970 and 1985, the prevalence of diabetes as listed on the discharge diagnoses among stroke patients increased from 10.5% to 22.5% among men ($P=0.006$). Our study confirms the continuing increase in diabetes prevalence among stroke subjects and is more than 30% in our cohort. Given the recent trends in rising rates of obesity and diabetes in the general population, prevention and control of diabetes will be of paramount importance if its contribution to stroke is to be reduced. In addition, appropriate management of diabetes may have salutary effects on improving outcomes in patients with ischemic stroke. Admission hyperglycemia and poor control of blood glucose has been reported to be associated with worse outcomes in diabetics with stroke.

**Stroke Mortality in Diabetes**

Our results are more in line with the Minnesota Heart Survey where a 2-fold increase in mortality among diabetics subjects with stroke was seen over 5-year follow-up. Similarly, with data collected in the 1990s in the Copenhagen
Heart Study, the odds ratio for mortality among diabetics was 1.8 after stroke compared to nondiabetics.\textsuperscript{23} Diabetes is a prognostic factor of poor outcome during the acute phase of cerebrovascular disease attributable to hyperglycemia or the metabolic disease per se; diabetes is also a predictor of in-hospital mortality even in primary intracerebral hemorrhage.\textsuperscript{24}

Late appearing mortality pattern is probably related to progression of atherosclerotic cardiovascular disease over time, which is known to be much more rapid among diabetics and nondiabetics. Our own prior report\textsuperscript{25} looking at prognosis of myocardial infarctions in veteran population during this same time period shows excess long term mortality in diabetics. In general, as seen here, the cardiovascular risk profile among diabetics is much worse because of higher number of comorbidities and chronic conditions which result in accelerated atherosclerosis.\textsuperscript{26}

The negative association of hypertension and hyperlipidemia with mortality in our multivariate analysis probably reflects treatment effect for these condition.

\textbf{Study Strengths and Limitations}

Our study has several strengths. It is one of the largest studies to date to investigate long-term postischemic stroke mortality. The data were collected from all patients hospitalized with ischemic strokes from all VAMCs throughout the United States, thus giving a homogenous and unbiased population. Hospitals treating the patients included both community hospitals and tertiary care referral centers. There was a good mix of white and black patients, with 21\% of the study cohort being black.

Certain methodological considerations merit discussion. As with all retrospective administrative database studies, the diagnosis of diabetes and stroke was based on ICD9-CM codes. Data on severity of stroke was not available; however, data from the Lausanne Stroke Registry showed no difference in severity of stroke between diabetics and nondiabetics.\textsuperscript{23} Another potential limitation that needs to be considered while comparing with other reports is the differential follow-up time in chronic disease states, which may account for some of the differences in event rates. Data on duration of diabetes, HbA1c levels, and classification of diabetes as type I or type II were not available. Because diagnosis of diabetes was obtained from the discharge diagnoses, validation of diabetes presence was not available. It is possible that some patients in the nondiabetic group had diabetes. Further, patients who have been diagnosed subsequent to their index admission may be misclassified. It is possible that during the period of the study some patients in the group without diabetes may have developed diabetes. This could potentially narrow the mortality difference between the two groups on long-term follow-up. Our study population consisted of predominantly male subjects, as it was a VA study. These patients in general have more comorbid conditions than Medicare patients. Direct application of these conclusions to non-VA populations, especially to women, should be done with caution.

\begin{table}[h]
\centering
\caption{Multivariate Predictors of Mortality (time to death)}
\begin{tabular}{lccc}
\hline
 & Hazard Ratio & 95\% CI & \(P\) Value \\
\hline
Demographics & & & \\
Age & 1.043 & 1.041, 1.045 & <0.001 \\
Gender (male versus female) & 1.289 & 1.142, 1.474 & <0.001 \\
Ethnicity (white versus non-white) & 1.071 & 1.034, 1.110 & <0.001 \\
Chronic conditions & & & \\
Hypertension & 0.844 & 0.818, 0.870 & <0.001 \\
Diabetes & 1.149 & 1.112, 1.188 & <0.001 \\
Coronary artery disease & 0.930 & 0.894, 0.968 & <0.001 \\
Congestive heart failure & 1.324 & 1.259, 1.393 & <0.001 \\
Hyperlipidemia & 0.625 & 0.582, 0.671 & <0.001 \\
Atrial fibrillation & 1.092 & 1.041, 1.145 & <0.001 \\
Comorbidities & & & \\
# of discharge diagnoses & 1.105 & 1.098, 1.113 & <0.001 \\
Charlson Index >2 & 1.154 & 1.114, 1.195 & <0.001 \\
Utilization & & & \\
General medicine follow-up w/in 60 days & 0.847 & 0.807, 0.889 & <0.001 \\
Neurology follow-up w/in 60 days & 0.717 & 0.672, 0.765 & <0.001 \\
Region & & & \\
MW versus S & 0.993 & 0.956, 1.030 & 0.698 \\
NE versus S & 0.838 & 0.800, 0.878 & <0.001 \\
W versus S & 0.930 & 0.890, 0.972 & 0.001 \\
\hline
\end{tabular}
\end{table}
is important because recent studies have shown gender-associated differences in prognosis of subjects with diabetes and cerebral ischemia, although some of the difference could be explained by higher age of women, greater comorbidities, and stroke subtype. Because medication history was not available, it is not possible to comment on differences in treatment modalities between the groups and how they may have influenced the outcomes.

Conclusions
The prevalence of diabetes among stroke subjects continues to rise. Compared to nondiabetic stroke patients, stroke patients who were diabetic (despite having more comorbid conditions) did not have significantly higher mortality rate at 60 days and 1 year after the index stroke. Long-term all cause conditions) did not have significantly higher mortality rate at 60 days and 1 year after the index stroke. Compared to nondiabetic stroke patients, stroke patients who were diabetic (despite having more comorbid conditions) did not have significantly higher mortality rate at 60 days and 1 year after the index stroke. Long-term all cause conditions) did not have significantly higher mortality rate at 60 days and 1 year after the index stroke.

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Disclosures
None.

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