

Effect of diabetes on stroke symptoms and mortality: Lessons from a recent large population-based cohort study

Diabetes is rapidly increasing worldwide. In 2011, approximately 366 million people had diabetes, with a prevalence of approximately 8.3%, according to a report by the International Diabetes Federation. Approximately half of the diabetic population is concentrated in Asian countries, and there has been a particularly rapid increase in China and India, where diabetes is a major public health burden. As diabetes-related mortality rapidly increases from the age of 40 years onwards, to maintain quality of life, it is important to prevent not only microvascular complications, but also macrovascular complications from the early stage. Needless to say, it is important to prevent cardiovascular events in diabetics, and this is particularly so for Asian populations in whom the prevalence of stroke is higher than in Western populations. Many epidemiological studies have shown that diabetic patients have an approximately two to threefold higher risk of incident stroke compared with non-diabetic subjects. Prevention of stroke will raise quality of life and promote longevity. For clinicians, an in depth knowledge of the relationship between diabetes and stroke is very important from the aspect of preventive medicine.

Recently, two highly interesting studies on an association between diabetes and stroke have been published in *Diabetes Care*, the journal of the American Diabetes Association^{1,2}. One of them, a cross-sectional analysis of baseline data from the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study, a prospective population-based cohort

study, evaluated an association between prediabetes, and diabetes and stroke symptoms in American adults aged 45 years or older without a history of stroke or transient ischemic attack (TIA)¹. Data were collected by means of telephone interviews, self-administered questionnaires and in-home examinations. Stroke symptoms were assessed through telephone interviews using Questionnaire for Verifying Stroke-Free Status, a validated questionnaire consisting of eight questions that identified stroke free status in the general population. The first two questions inquired about physician diagnosis of stroke or TIA, and the other six questions inquired about stroke symptoms that had suddenly occurred. The six stroke symptoms were unilateral weakness, unilateral numbness, vision loss in one or both eyes, half-vision loss, lost ability to understand people and lost ability to express self verbally or in writing. Of the 25,696 participants in this study, 23.6% had diabetes, 15.6% had prediabetes and 60.8% had normal glycemia. Participants with diabetes had the highest prevalence of any stroke symptom (22.7%), followed by participants with prediabetes (15.6%) or normal glycemia (14.9%). Furthermore, diabetic participants had a higher prevalence of any stroke symptom and individual stroke symptom compared with participants with prediabetes or normal glycemia. Diabetes was associated with any stroke symptom (prevalence odds ratios [PORs] 1.28; 95% confidence interval [CI] 1.18–1.39) and two or more stroke symptoms (1.26 [1.12–1.43]) compared with normal glycemia using multiple logistic regression models (Table 1). In contrast, prediabetes was not associated with any stroke symptom, or two or more stroke symptoms. These findings

have clinical implications for stroke prevention, and suggest that screening for stroke symptoms in diabetes might be warranted.

One of the limitations of this research was that the duration of diabetes was not evaluated. The recently published Northern Manhattan Study found that duration of diabetes was an independent risk factor for future ischemic stroke, and that if the duration of diabetes exceeded 10 years, the risk of ischemic stroke was threefold greater in diabetics than in non-diabetics³. If the duration of diabetes is long-term, the effects of therapeutic interventions to prevent macrovascular complications would be attenuated, therefore it is important to evaluate the duration of diabetes by examining an association between diabetes and the risk of incident stroke. Furthermore, a recent meta-analysis has also reported that prediabetes, which is defined by impaired glucose tolerance (IGT) or both impaired fasting glycemia (IFG) and IGT, is independently associated with future stroke risk⁴. The REGARDS study¹ did not show an association between prediabetes and the prevalence of stroke symptoms. A diagnosis of diabetes and prediabetes was determined using a single fasting or random glucose measurement, and therefore it was likely to be misclassified among participants with prediabetes. However, the finding that diabetes was independently associated with stroke symptoms in a large population-based cohort study is highly valuable, because it reminds us that it is important for the physician treating diabetic patients to examine potential stroke symptoms and to carry out early pharmaceutical interventions.

The other research was a 5-year cohort study using claims data from a statutory health insurance fund in Germany, which

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Table 1 | Prevalence odds ratios and 95% confidence intervals for stroke symptoms associated with prediabetes and diabetes among Reasons for Geographic And Racial Differences in Stroke study participants

	POR (95% CI)		
	Normal glycemia (n = 15,615)	Prediabetes (n = 4,011)	Diabetes (n = 6,070)
Any stroke symptom	1.0 (ref)	0.98 (0.89–1.08)	1.28 (1.18–1.39)***+++
Individual stroke symptoms			
Sudden weakness (unilateral)	1.0 (ref)	0.88 (0.75–1.04)	1.10 (0.97–1.26)†
Sudden numbness (unilateral)	1.0 (ref)	1.04 (0.91–1.19)	1.15 (1.03–1.29)*
Sudden painless loss of vision in one or both eyes	1.0 (ref)	1.09 (0.91–1.31)	1.52 (1.31–1.76)***+++
Sudden loss of half-vision	1.0 (ref)	0.94 (0.74–1.19)	1.54 (1.30–1.84)***+++
Suddenly lost ability to understand people	1.0 (ref)	0.98 (0.77–1.25)	1.34 (1.12–1.61)***
Suddenly lost ability to express self verbally or in writing	1.0 (ref)	0.81 (0.65–1.00)	1.10 (0.93–1.29)††
Any two or more stroke symptoms	1.0 (ref)	0.94 (0.81–1.10)	1.26 (1.12–1.43)***+++

CI, confidence interval; POR, prevalence odds ratio. Adjusted for age, race, sex, income, education, health insurance, geographic region, urban/rural residence, systolic blood pressure, antihypertensive medication use, body mass index, smoking status, alcohol consumption, atrial fibrillation, left ventricular hypertrophy and history of cardiovascular disease. **P* < 0.05 compared with normal glycemia. ***P* < 0.01 compared with normal glycemia. ****P* < 0.001 compared with normal glycemia. †*P* < 0.05 compared with prediabetes. ††*P* < 0.01 compared with prediabetes. †††*P* < 0.001 compared with prediabetes. Adapted from Carson *et al.*¹ with permission.

assessed the survival rates in diabetic and non-diabetic individuals after the first stroke event, for men and women separately.² Among 5,757 patients with a first-ever stroke between 2005 and 2007, mortality was evaluated during follow up until 2009. Stroke subtypes included cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage and stroke of uncertain cause, which were defined following the World Health Organization definition, using specific International Classification of Diseases-10 codes of hospital admission. Diabetes status was assessed according to a previously established algorithm based on claims data of German statutory health insurance funds. From the baseline data, the average age was 68.1 years, and cerebral infarction accounted for 73.7% of all stroke subtypes. For both sexes, diabetic patients were older than non-diabetic individuals, and had more ischemic strokes compared with non-diabetic participants. Patients with diabetes had an approximately two-fold higher intake of antihypertensive

drugs, such as β-blockers, angiotensin-converting enzyme inhibitors and calcium antagonists. The mean observation time was 2.66 years, and 1,828 patients died during the 5-year study period. When analyzed by sex using Kaplan–Meier curves and log–log survival plots, the following results were obtained (Figure 1). In men, mortality was significantly lower in diabetic compared with non-diabetic individuals in the first 30 days after incident stroke; but thereafter, mortality risk tended to increase in diabetics. Diabetic individuals had a higher mortality than non-diabetic individuals at 3 months after stroke; but after 3 years, the mortality risk tended to become equal. Although a similar pattern was observed in women, there was no statistically significant time dependency. Age, renal failure (men only), level of care dependency, number of prescribed drugs and hemorrhagic stroke were significantly associated with mortality; however, the association between diabetes and mortality remained after adjusting for these factors. In the 3–5 years after stroke,

there was no longer a difference in mortality between individuals with and without diabetes in both sexes. The findings might be due to a lack of power resulting from small case numbers. The fact that mortality in the first 30 days after stroke was lower in diabetic men is explained by the following hypothesis. In Germany, nationwide disease management programs for diabetics have been carried out since 2003, under which there has been aggressive management of cardiovascular risk factors. Diabetic women with a stroke event are older than men, and more likely to be in long-term care; hence, they might be less likely to be included in a disease management program. These findings suggest that it would be possible to reduce stroke mortality through intensive multifactorial intervention including blood pressure control and lipid-lowering management before any stroke event occurred among patients with diabetes. Furthermore, diabetic patients had a high incidence of ischemic stroke, and based on previously published data, within 30 days the mortality rate for patients suffering ischemic strokes is lower than that for those with hemorrhagic strokes; whereas after 30 days, mortality was higher after ischemic stroke.

A limitation of this study² was that brain imaging was not available. Cerebral infarction in diabetic patients is characterized by the high prevalence of small-vessel disease, as well as large-vessel disease. Although the association between diabetes and small-vessel disease still remains controversial, it has been reported that diabetes is associated with the prevalence and progression of cerebral small-vessel disease, including silent brain infarction and white matter lesions. We have previously suggested that progression of small-vessel disease is associated with future stroke events or cognitive impairment in type 2 diabetes^{5–7}, therefore the serial evaluation of brain magnetic resonance imaging is important in future studies. Recently, Jia *et al.*⁸ investigated the association between diabetes and outcomes of acute ischemic stroke in the China National Stroke Registry. According to this research, diabetes was identified in

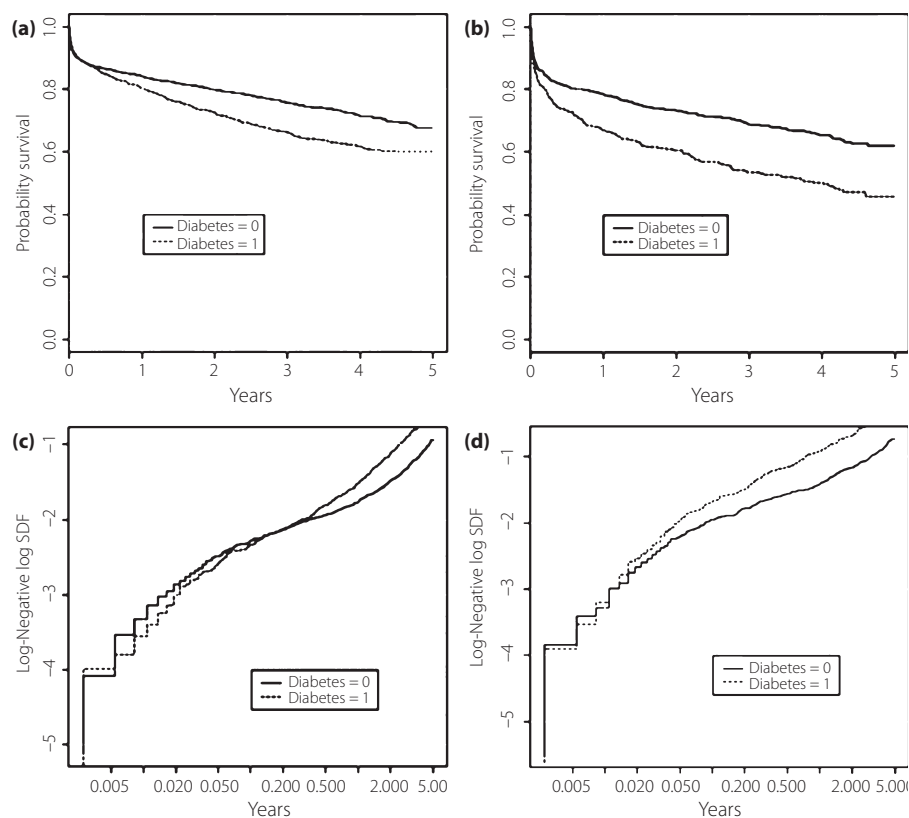


Figure 1 | (a) Kaplan–Meier estimates of crude survival after first incident stroke for male Gmünder ErsatzKasse (GEK) insurants, Germany, 2005–2007. (b) Kaplan–Meier estimates of crude survival after first incident stroke for female GEK insurants, Germany, 2005–2007. (c) Crude log–log survival curves after first incident stroke for male GEK insurants, Germany, 2005–2007. (d) Crude log–log survival curves after first incident stroke for female GEK insurants, Germany, 2005–2007. SDF, survival distribution function. Reprinted from Icks *et al.*², Copyright 2012, with permission from American Diabetes Association.

3,483 (27.0%) of stroke patients. Compared with stroke patients without diabetes, those with diabetes had a significantly higher incidence of poor outcomes at 3 and 6 months after stroke onset. Diabetes was an independent risk factor for death or dependency at 6 months (OR 1.23 [95% CI 1.10–1.37]). There has been other prospective study on an association between diabetes and mortality after stroke; however, the findings still remain controversial. Data from the German cohort study² provide new findings that the impact of diabetes on mortality after stroke onset was time dependent in men, but not in women.

We have gained new insights into an association between diabetes and

stroke symptoms, and mortality from two large population-based cohort studies^{1,2}. Although tight glucose control is naturally very important, we should reconsider the clinical significance of taking early action in dealing with the appearance of any neurological symptoms and prevention of incident stroke. Notable findings of the two studies have potential implications for future clinical practice and research.

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