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The disparity in long-term survival after a first stroke in patients with and without diabetes persists: the Northern Sweden MONICA Study

Cover title: Long-term survival after stroke in diabetes

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Abstract

Background Diabetes is an established risk factor for stroke. Compared to non-diabetic patients, diabetic patients also have an increased risk of new vascular events and death after stroke. We analyzed how differences in long-term survival between diabetic and non-diabetic stroke patients have changed over time, and if differences varied with respect to sex and age.

Methods This population based study included 12 375 first-ever stroke patients, 25-74 years old, who were registered in the Northern Sweden MONICA Stroke Registry 1985-2005.

Uniform diagnosis criteria for stroke case ascertainment were used throughout the study period. The diagnosis of diabetes was based on medical records or diabetes diagnosed during the acute stroke event. Patients were separated into four cohorts according to year of stroke and followed for survival until August 30, 2008.

Results The diabetes prevalence at stroke onset was 21%, similar in men and women, and remained stable throughout the study period. The diabetic patients were an average of 2 years older, more often non-smokers and more likely to have antihypertensive treatment, antithrombotics, atrial fibrillation, and a history of myocardial infarction or TIA than the non-diabetic patients. The total follow-up time was 86 086 patient-years during which a total 1930 (75.7%) of the diabetic patients and 5744 (58.5%) of the non-diabetic patients died ($P<0.001$). Median survival was 60 months (95% CI: 57-64) in diabetic patients and 117 months (113-120) in the non-diabetic patients. The survival improved significantly in both groups ($P<0.001$). A Cox regression, adjusting for possible confounders (age, sex, antihypertensive medication, antithrombotics or other thrombolytic agents, history of myocardial infarction, type of stroke, diabetes, cohort and the diabetes-by-sex, diabetes-by-age and diabetes-by-cohort interactions), showed a hazard ratio of 1.67 (1.58-1.76) comparing survival in diabetic vs. non-diabetic patients. The reduced survival in diabetic stroke patients was more

pronounced in women ($P=0.02$) and younger patients ($P<0.001$). There was a tendency that the difference in survival decreased between the earlier cohorts and the 2000-2005 cohort, but the test for interaction did not reach statistical significance ($P=0.08$).

Conclusion Long-term survival after a first stroke has improved in both diabetic and non-diabetic patients. Survival is markedly lower in diabetics, especially in women and younger patients, and the disparity persisted over 24 years. Decreasing the disparity in stroke survival is a challenge for stroke and diabetes care. New treatment methods in combination with intense secondary prevention in diabetic patients, especially in younger women, are needed.

INTRODUCTION

Patients with diabetes have a two to threefold increased risk of stroke, and diabetes is present in 15-27% of all incident strokes in the US [1,2]. Although ischemic and recurrent strokes are more common in persons with diabetes than in those without diabetes, transient ischemic attacks and hemorrhagic stroke are less common. Around 40% of ischemic strokes are due to diabetes [3]. In Sweden, diabetes was present among 12% of the patients dying due to stroke during the period 1997-2010, and there has been no decrease or increase over time in that percentage [4].

Most studies agree that fatality up to one year after a stroke is increased in diabetic patients [5-8] and that diabetes increases the risk of cardiovascular events and death within 2 years after ischemic stroke [9]. Meanwhile, data on long-term survival is scant. Two recent Danish studies found that diabetes is associated with much lower survival at 10-12 years' follow-up [5,10]. In a Veteran Study, restricted to men suffering an ischemic stroke during 1990 to 1997, long-term mortality was lower in patients with diabetes, although much improved compared to earlier studies [11].

We wished to assess the impact of intensified primary and secondary prevention, including surgery for carotid stenosis and dedicated stroke units, on mortality among diabetic patients after a first stroke. Towards this goal, survival data over periods much longer than one year are needed to describe the secular trends over a period that includes the introduction of evidence-based cardiovascular diabetology [1]. In addition, data should include patients not treated in hospital or deceased before reaching the hospital.

Using population based data, our objectives were to compare long-term survival after a first stroke between diabetic and non-diabetic patients, to assess if possible differences in survival

have changed over time 1985-2005, and to determine if differences vary with respect to sex and age.

METHOD

This study was based on the Northern Sweden MONICA Stroke Registry. The registry is population-based, and details of the event-registration procedure have been described previously [12]. The registry includes all acute stroke events in the age range 25-74 years in the two northernmost counties of Sweden, Norrbotten and Västerbotten, and the average total population in the target group aged 25-74 years was 313 800 during 1985-2005. Suspected acute stroke events were identified through reports from hospitals and general practitioners, hospital discharge registers and death certificates. Suspected acute strokes were validated by a research nurse according to the WHO criteria as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours, with no apparent cause other than vascular origin” throughout the time period [13,14].

This study included intra-cerebral hemorrhages (ICH), ischemic strokes, and unspecified strokes (ICD-10: I61, I63 and I64) occurring between January 1, 1985 and December 31 2005. Patients were excluded from the study if they had experienced a previous stroke event (according to the register or medical records). The diagnosis of diabetes was based on medical records or diabetes diagnosed during the acute stroke event.

The endpoint studied was death from any cause and stroke patients were followed-up using the Swedish Cause of Death Registry (National Board of Health and Welfare) as of August 30, 2008. Patients not identified in the register were assumed to be alive at that date.

The patients were separated into four cohorts according to year of stroke: 1985-1989, 1990-1994, 1995-1999, and 2000-2005.

The Northern Sweden MONICA Study was approved by the regional ethical review board in Umeå. Patients or relatives to non-survivors gave written consent.

Statistical analyses

Differences in baseline characteristics between diabetic and non-diabetic stroke patients were tested using chi-square test for categorical variables and t-test for continuous variables.

The median survival time from stroke onset was presented for subgroups of patients. The log rank test was used for univariate comparisons of time to event between patient groups.

Multiple Cox proportional hazard regression was used to analyze time to event, adjusting for potential confounders. The model included the independent variables age, sex, antihypertensive medication at onset, antithrombotics at onset (anticoagulants, acetylsalicylates, platelet anitaggregants, other thrombolytic agents), history of myocardial infarction, type of stroke (ICH/other), diabetes (yes/no), cohort (1985-1989, 1990-1994, 1995-1999, and 2000-2005) and the diabetes-by-sex, diabetes-by-age and diabetes-by-cohort interactions. The smoking parameter contained a large amount of missing values (53%) and was therefore excluded from the multiple regression. Patients who were still alive at the end of study, August 30, 2008, were censored at that time point. Kaplan-Meier survival curves were examined to identify deviations from the proportional hazard's assumption. Outcome was presented by hazard ratios (HR) with 95% confidence intervals (95% CI). IBM SPSS Statistics 19 was used for statistical analysis.

RESULTS

Between 1985 and 2005, 12 477 18-74 year old stroke patients with a first stroke were registred. Personal identification numbes were missing for seven patients, and therefore those seven were lost to follow-up. Eleven patients had negative survival times, which suggest clerical errors, and those eleven were excluded from the analysis. Of the remaining patients,

84 lacked information on diabetes. Hence, complete data regarding diabetes and follow-up were available for 12 375 patients.

Of the stroke patients, 2549 (20.6%) had diabetes of which 101 (4.0%) had type 1 diabetes, 2092 (82.1%) type 2 diabetes, 253 (9.9%) had unspecified diabetes, and 103 (0.8%) were diagnosed with diabetes during the event. The proportion of men in diabetic (61.6%) and the non-diabetic groups (61.0%) were similar.

Patients with diabetes were on average 2 years older (66.2 vs. 64.2, $P<0.001$), were less likely to smoke (32.2% vs. 37.7%, $P=0.001$), and had more often antihypertensive treatment (71.3% vs. 44.8%, $P<0.001$) or antithrombotics (32.2% vs. 20.1%, $P<0.001$) at stroke onset. Patients with diabetes had atrial fibrillation (17.1% vs. 13.2%, $P<0.001$), history of myocardial infarction (20.7% vs. 12.3%, $P<0.001$), and previous TIA (5.7% vs. 4.2%, $P=0.036$) more often than nondiabetic patients. Diabetic patients were more often fully conscious at hospital arrival (90.5% vs. 87.6%, $P=0.006$), and less likely to have ICH (7.4% vs. 15.4%, $P<0.001$). The prevalence of diabetes, the proportion of men, and the mean age remained stable during the four time periods.

Patients were followed for a median time of 6.1 years (74 months) and maximum of 23.7 years (284 months). The total follow-up time was 86 086 patient-years during which a total 1930 (75.7%) of the diabetic patients and 5744 (58.5%) of the non-diabetic patients died ($P<0.001$). The median survival was 5.0 years (95% CI: 4.7-5.4) in the diabetic and 9.7 years (95% CI: 9.4-10.0) in the non-diabetic stroke patients. The mortality rates in diabetic (non-diabetic) patients were 15% (12%) at 28 days, 25% (18%) at 1 year, 38% (25%) at 3 years, 50% (32%) at 5 years, and 73% (51%) at 10 years after stroke. For each of the successive cohorts, mortality rates decreased both for diabetic and non-diabetic patients (**Fel! Hittar inte referenskölla.**). The reduced survival in diabetic, as compared to non-diabetic, patients was

evident in both men and women in all time periods ($P<0.001$ using log rank tests for each cohort (Table 2).

A multiple Cox regression confirmed the disparity in survival between diabetics and non-diabetics, HR= 1.67 (95% CI: 1.58-1.76). Other factors associated with increased mortality were higher age, male sex, antihypertensive medication at onset, atrial fibrillation, history of myocardial infarction, and hemorrhagic stroke (Table 3). Including interactions in the regression showed that the relative difference between diabetic and non-diabetic patients was smaller in men (diabetes-by-sex interaction HR=0.88, $P=0.025$) and decreased with higher age (diabetes-by-age interaction HR=0.98, $P<0.001$), Table 3 and **Fel! Hittar inte referenskölla..** There was also a tendency toward decreased difference during 2000-2005 as compared to earlier years (Figure 1), but the diabetes-by-cohort interaction effect did not reach statistical significance ($P=0.08$).

DISCUSSION

Long-term survival after a first stroke has improved, and the improvement has been at least as good in diabetic patients as in non-diabetic patients. However, the survival of a diabetic patient suffering a stroke after 2000 was similar to the survival of a patient without diabetes who had his stroke in the late eighties. The markedly lower survival in stroke patients with diabetes, as compared to patients without diabetes, persisted between 1985 and 2005. The reduced survival after stroke in patients with diabetes was even more pronounced in women and younger patients.

This study included stroke patients during a period of 21 years, and followed them for up to 23 years. Both stroke patients treated in hospital and patients who died outside of hospital were captured. A previous validation of the MONICA stroke registry using the National Patient Register (National Board of Health and Welfare) showed that MONICA has almost

complete coverage in the selected age interval (unpublished data). During the extensive time period of this study, diagnostic methods have developed in clinical praxis. The increased use of MRI and CT enables detection of strokes with very minor neurological symptoms, which may partly explain improved survival in both groups. A major strength of this study is the uniform methods and strict diagnosis criteria for stroke case ascertainment throughout the study period. This minimizes the effect of changes in clinical stroke diagnosis. The prevalence of diabetes has also remained at a stable level in the study population [15].

This study was limited to patients under 75 years with a first stroke, which excluded approximately half of all stroke patients. We observed a smaller difference in survival between diabetic and non-diabetic patients in the older age group 65-74 years as compared to younger patients, and it is possible that other factors than diabetes influence survival more in the elderly. However, one should be cautious to extrapolate the findings of our study to more advanced age groups.

Stroke severity is an established predictor of outcome after stroke [5,16] and we used level of consciousness as a proxy. The impact of stroke severity has been shown to be weaker for long-term survival [5], and during the latter part of this study, where level of consciousness was registered, diabetic patients were slightly less often unconscious at presentation. Hence stroke severity was unlikely to explain the observed difference in survival between patients with and without diabetes.

Improved long-term survival after stroke has been observed in previous Swedish studies [17-19]. The present observed difference in survival between diabetic and non-diabetic stroke patients (HR= 1.66) was consistent with the difference reported from a Danish cohort study (HR=1.74) [10]. The similar improvement, but persisting difference in long-term survival between diabetic and non-diabetic stroke patients, is in agreement with the development in 1-

year case-fatality observed in Finnish ischemic stroke patients with and without type 2 diabetes [8]. A large cohort study from the UK using the General Practice Research Database showed that the increased relative risk of stroke in patients with type 2 diabetes compared to patients without diabetes was highest in women and decreased with age [20]. In the Finnish study, the highest excess 28-day stroke case fatality caused by diabetes was in younger women. We observed a similar pattern when it came to long-term survival after stroke, where the relative risk for patients with diabetes was more elevated in women and in younger patients. Hence, in addition to a higher risk of stroke, younger women with diabetes seem to have a worse prognosis after stroke. Interestingly, a recent study showed almost identical trends and disparities in long-term survival after a first myocardial infarction among diabetic subjects within the Northern Sweden MONICA Study [21] implying common pathways not reversed by traditional risk factor treatment.

A recent population based study showed increased use of lipid-lowering agents and antihypertensive drugs, and substantial improvements in cardiovascular risk factors (blood pressure, smoking, cholesterol levels and education) in northern Sweden between 1986 and 2009 [15]. Life style changes, improved secondary prevention, more patients being treated in stroke units and the use of stroke thrombolysis have probably all contributed to the increased survival after stroke in the general population. The recently noted improved blood pressure control among Swedish patients with type 2 diabetes will reduce both risks of stroke and of mortality after a stroke [22]. While no increase in stroke patients with diabetes was observed in our study, an increasing proportion of stroke patients with diabetes have been observed in the United States [23].

Another study from the United States found quality of care to be comparable in patients with and without diabetes in most aspects with the exception that diabetic patients are less likely to receive stroke thrombolysis [24] a difference that has also been seen in the Swedish stroke

register [25]. Despite a probable treatment difference in thrombolysis, the difference in survival between diabetic and non-diabetic patients did not increase during the last period during which thrombolysis for acute ischemic stroke was introduced in Sweden. The SPARCL study showed no difference in the effect of statin treatment to prevent recurrent stroke in patients with or without type 2 diabetes, but patients with diabetes still had an increased risk of recurrent stroke or cardiovascular disease [26].

The worse survival in diabetic patients remained after adjustments for differences in risk factors. However, there may be other unmeasured confounders. Differences in socio-economic status and other differences in case-mix might partially explain the observed differences.

The similar favorable trend in survival in diabetic and non-diabetic patients suggests that acute stroke care and secondary prevention have been successful both in patients with and without diabetes. However, the treatment has not decreased the gap in long-term survival. The reason for the gap remains unclear, and decreasing the disparity in stroke survival is a challenge for stroke and diabetes care. New treatment methods in combination with intense secondary prevention in diabetic patients, especially in younger women, are needed.

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The northern Sweden MONICA study has received grants from Norrbotten and Västerbotten County Councils, the Swedish Research Council (MFR), the Joint Committee of Northern Sweden Health Care Region (Visare Norr), the Heart and Chest Foundation, the Stroke fund, King Gustaf V's and Queen Victoria's Foundation, the Vårdal Foundation, and the Social Sciences Research Council.

Conflicts of interest

The authors declare that they have no conflict of interest in relation to this study.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier survival curves of diabetic (black) and non-diabetic (grey) stroke patients for men and women in different time periods of stroke onset.

Figure 2. Kaplan-Meier survival curves of diabetic (black) and non-diabetic (grey) stroke patients for men and women in different age groups (25-64 years and 65-74 years).

TABLES

Table 1. Baseline characteristics (mean or proportion) for diabetic and non-diabetic patients in each time period. P-values for overall comparisons of patient groups (1985-2005) were calculated using t-test for age and chi-square test for other variables.

		Cohort				All years	
		1985-1989	1990-1994	1995-1999	2000-2005	1985-2005	P
No. of stroke patients	Non-diabetic	2360	2530	2536	2400	9826	
	Diabetic	651	628	642	628	2549	
Diabetes (%)		21.6	19.9	21.2	20.7	20.6	
Mean age (years)	Non-diabetic	64.5	64.7	63.6	63.8	64.2	<0.001
	Diabetic	66.2	66.5	66.4	65.8	66.2	
Men (%)	Non-diabetic	62.9	60.2	60.9	60.0	61.0	0.610
	Diabetes	58.2	61.5	63.7	62.9	61.6	
Regular smoking (%)	Non-diabetic	43.8	36.2	38.5	34.1	37.7	0.001
	Diabetic	36.8	28.0	30.7	35.0	32.2	
Fully conscious at hospital arrival*	Non-diabetic	-	-	88.0	87.2	87.6	0.006
	Diabetic	-	-	90.9	90.1	90.5	
Antihypertensive medication at onset (%)	Non-diabetic	44.8	42.0	45.6	46.9	44.8	<0.001
	Diabetic	71.8	62.3	73.8	77.3	71.3	
Antithrombotics at onset (%)	Non-diabetic	8.1	15.3	26.4	30.1	20.1	<0.001
	Diabetic	10.4	26.1	41.8	51.2	32.2	
Atrial fibrillation (%)	Non-diabetic	9.4	13.4	14.7	15.1	13.2	<0.001
	Diabetic	15.3	18.8	16.9	17.7	17.1	
History of TIA*	Non-diabetic	-	-	4.3	4.0	4.2	0.036

	Diabetic	-	-	5.9	5.6	5.7	
History of myocardial infarction (%)	Non-diabetic	15.8	13.6	12.2	7.7	12.3	<0.001
	Diabetic	25.5	21.9	19.1	16.1	20.7	
Hemorrhagic stroke (%)	Non-diabetic	13.8	15.2	16.4	16.0	15.4	<0.001
	Diabetic	6.1	5.9	7.2	10.5	7.4	

*) was not measured 1985-1994

Table 2. Median survival (months) with 95% confidence intervals for men and women in diabetic and non-diabetic stroke patients.

	1985-1989	1990-1994	1995-1999	2000-2005	1985-2005
Women					
Non-diabetics	97 (84-110)	116 (106-126)	146 (.-.)	. (.-.)	127 (121-133)
Diabetics	38 (30-46)	56 (45-66)	80 (63-96)	92 (71-112)	61 (54-68)
Men					
Non-diabetics	87 (81-94)	97 (89-105)	136 (127-145)	. (.-.)	111 (107-115)
Diabetics	40 (32-48)	51 (40-62)	69 (59-79)	102 (83-122)	60 (56-65)
All					
Non-diabetics	91 (85-96)	104 (98-110)	141 (133-149)	. (.-.)	117 (113-120)
Diabetics	39 (34-45)	54 (46-63)	73 (63-82)	97 (86-108)	60 (57-64)

(.-.) – confidence intervals could not be calculated

Table 3. Multiple Cox regression of survival in diabetic vs. non-diabetic stroke patients.

Hazard ratio (HR) with 95% confidence intervals (CI). ICH = intra-cerebral hemorrhages

	Main effects model			
	P	HR	95% CI for HR	
			Lower	Upper
Main effects:				
Cohort	0.000			
(ref: 1985-1989)				
1990-1994	0.000	0.832	0.785	0.881
1995-1999	0.000	0.628	0.587	0.671
2000-2005	0.000	0.530	0.487	0.577
Age (1 year)	0.000	1.063	1.059	1.067
Male sex	0.000	1.188	1.132	1.247
Antihypertensive	0.000	1.116	1.062	1.174
medication at onset				
Antithrombotics at	0.106	1.053	0.989	1.120
onset				
Atrial fibrillation	0.000	1.259	1.180	1.343
History of myocardial	0.000	1.422	1.334	1.516
infarction				
ICH	0.000	1.430	1.335	1.532
Diabetes	0.000	1.667	1.578	1.761

Figure 1

Figure 2.