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Small-vessel occlusion versus large-artery atherosclerotic strokes in diabetics: Patient characteristics, outcomes, and predictors of stroke mechanism

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Abstract

Introduction: Diabetes mellitus exerts a detrimental effect on cerebral vasculature affecting both macrovasculature and microvasculature. However, although ischaemic stroke is typically included among macrovascular diabetic complications, it is frequently omitted from microvascular diabetic complications. We aimed to compare the proportion of large-artery atherosclerotic and small-vessel occlusion strokes among diabetic stroke patients, explore their differences and outcomes, and assess potential mechanisms which may determine why some diabetic patients suffer large-artery atherosclerotic stroke whereas others suffer small-vessel occlusion stroke.

Methods: We pooled data of diabetic patients from four prospective ischaemic stroke registries (Acute Stroke Registry and Analysis of Lausanne (ASTRAL), Athens, Austrian, and Helsinki Stroke Thrombolysis Registries). Stroke severity and prognosis were assessed with National Institutes of Health Stroke Scale (NIHSS) and ASTRAL scores, respectively; functional outcome with three-month modified Rankin score (0–2 considered as favourable outcome). Logistic-regression analysis identified independent predictors of large-artery atherosclerotic stroke.

Results: Among 5412 patients, 1069 (19.8%) were diabetics; of them, 232 (21.7%) had large-artery atherosclerotic and 205 (19.2%) small-vessel occlusion strokes. Large-artery atherosclerotic stroke had higher severity than small-vessel occlusion stroke (median NIHSS: 6 vs. 3, $p < 0.001$), worse prognosis (median ASTRAL score: 23 vs. 19, $p < 0.001$), and worse three-month outcome (60.3% vs. 83.4% with favourable outcome, $p < 0.001$). In logistic-regression analysis, peripheral artery disease (odds ratio: 4.013, 95% confidence interval: 1.667–9.665, $p < 0.01$) and smoking (odds ratio: 1.706, 95% confidence interval: 1.087–2.675, $p < 0.05$) were independently associated with large-artery atherosclerotic strokes.

Conclusion: In the diabetic stroke population, small-vessel occlusion and large-artery atherosclerotic strokes occur with similar frequency. Large-artery atherosclerotic strokes are more severe and have worse outcome than small-vessel occlusion strokes. The presence of peripheral artery disease and smoking independently predicted large-artery atherosclerotic stroke.

Keywords

Ischaemic stroke, diabetic complications, microvascular, macrovascular, large-artery atherosclerotic, small-vessel occlusion

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Introduction

Diabetes mellitus (DM) exerts a detrimental effect on cerebral vasculature affecting both macrovasculature (via atherosclerotic changes)[1] and microvasculature (via lipohyalinosis).[2–5] However, although ischaemic stroke is typically included among macrovascular diabetic complications (along with coronary artery disease and peripheral artery disease), it is frequently omitted from microvascular diabetic complications (along with retinopathy, neuropathy, and nephropathy) even by classic medical textbooks[6–8] and health care organisations.[9,10]

Also, there are only limited data about the proportions of macrovascular (i.e. large-artery atherosclerotic (LAA)) and microvascular (small-vessel occlusion (SVO)) strokes in the diabetic stroke population, as well as about their characteristics like severity, prognosis, and outcome. Finally, it is not clear why some diabetics develop LAA strokes whereas others develop SVO strokes.

The aim of the present study was to analyse a large multicentre population of diabetic patients with ischaemic stroke, compare the proportions of LAA and SVO strokes, and explore their differences with regards to baseline characteristics, prognosis, and outcome. Also, we sought to identify the potential mechanisms which may explain why some diabetic patients develop LAA stroke while others develop SVO.

Methods

We pooled data from four prospective stroke registries, i.e. the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) registry,[11] the Athens Stroke Registry,[12] the Austrian Stroke Registry,[13] and the Helsinki Stroke Thrombolysis Registry.[14] Stroke was defined as a new syndrome of rapidly developing clinical symptoms and/or signs of focal disturbance of cerebral function lasting longer than 24 h with no apparent cause other than vascular origin, regardless of whether infarction was evident on cerebral imaging.[15] Stroke pathophysiologic mechanism was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[16] Stroke severity was evaluated at admission with the National Institutes of Health Stroke Scale (NIHSS) score. Stroke prognosis was evaluated with the ASTRAL score.[17] Favourable functional outcome was defined as modified Rankin scale (mRS) score ≤ 2 at 3 months and at 12 months (for the two registries in which 12-month functional outcome was available, i.e. ASTRAL registry and Athens Stroke Registry). DM was defined as fasting plasma glucose >126 mg/dl (7.0 mmol/l), a 2-h value in the oral glucose tolerance test >200 mg/dl (11.1 mmol/l), a random plasma glucose concentration >200 mg/dl (11.1 mmol/l) in the presence of symptoms, or when already on oral antidiabetics or insulin treatment.[18] In order to distinguish between poststroke hyperglycaemia and newly diagnosed hyperglycaemia, we used the HbA1c during hospitalisation as a criterion. If HbA1c $\geq 6.5\%$, the patient was considered as previously diabetic. If HbA1c $< 6.5\%$, a diagnosis of poststroke hyperglycaemia was reached.[10] Small vessel disease was diagnosed with either CT or MRI. Inclusion criteria included previously independent patients presenting within 24 h after stroke onset (or last proof of well-being in case of stroke of unknown onset). Patients with missing data about the presence of diabetes, TOAST type, NIHSS score, ASTRAL score, or functional outcome at three months were excluded from the analysis.

The scientific use of each registry was approved by appropriate authorities according to national and institutional legislation.

Statistical analysis

Variables are summarised as median (interquartile range (IQR)) or absolute number and percentage. Categorical variables were compared with the Pearson χ^2 test and continuous with the Mann–Whitney U test for two independent groups or the Kruskal–Wallis one-way analysis of variance for more than two independent groups.

Logistic regression analysis was performed in the subpopulation of diabetic patients with LAA stroke or SVO to identify which parameters can independently predict LAA strokes. We included all relevant parameters which were available in the registries, i.e. age, sex, and the main cardiovascular risk factors, i.e. hypertension, dyslipidaemia, active or ex-smoking, coronary artery disease, peripheral artery disease, previous stroke, and previous transient ischaemic attack. Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All reported p values were based on two-sided tests; level of statistical significance was set at 10% for the univariate analysis (to prevent type II errors, i.e. false-negative associations) and at 5% for all other tests. The Statistical Package for Social Sciences (SPSS Inc. version 16.0 for Windows) was used for all statistical analyses.

Results

Our dataset comprised four prospective stroke registries including 7022 patients. Among them, 1610 (22.9%) had incomplete data and were excluded from the analysis. Among the 5412 (77.1%) patients (mean age 68.7 ± 13.9 years) who were finally included in the analysis, 3178 (58.7%) were males, and mean NIHSS was 9.0 ± 7.8. The baseline characteristics of the

Table 1. Basic characteristics of the included stroke registries (diabetic patients only).

	Period of patient registration	*N*	Female	Age (years)	SVO stroke	LAA stroke
ASTRAL	2003–2013	413	151 (36.7%)	72.8 (63.3–79.8)	67 (16.2%)	75 (18.2%)
Athens	2000–2011	414	153 (37.0%)	71.0 (64.0–77.0)	93 (22.5%)	91 (22.0%)
Austrian	2007–2012	105	40 (38.1%)	72.0 (62.0–80.5)	32 (30.5%)	21 (20.0%)
Helsinki	1995–2010	137	52 (38.0%)	71.0 (64.0–77.0)	13 (9.5%)	45 (32.8%)
Total		1069	396 (37.0%)	71.9 (63.6–78.0)	205 (19.2%)	232 (21.7%)

SVO: small-vessel occlusion; LAA: large-artery atherosclerotic

excluded patients were similar to those of included patients (58.8% males, mean age 66.9 ± 13.6, and mean NIHSS of 9.3 ± 6.9). There were no significant differences among the four stroke registries with regards to the patients' age and sex distribution (Table 1). The nondiabetic population ($n = 4343$, 80.2%) had similar gender (42.3% females) and age distribution (median age: 71 years) with the diabetic population.

The baseline characteristics of the diabetic patients ($n = 1069$, 19.8%) are summarised in Table 2. Among them, there were 232 (21.7%) LAA strokes and 205 (19.2%) SVO strokes (Table 1). LAA strokes were more severe than SVO strokes (median NIHSS: 6 (IQR: 3–13) vs. 3 (IQR: 2–6), $p < 0.001$) and had a less favourable prognosis (median ASTRAL score: 23 (IQR: 19–30) vs. 19 (IQR: 17–22), $p < 0.001$). Among the 232 LAA stroke patients, 21 (9.1%) underwent carotid endarterectomy.

At 3 and 12 months follow-up, favourable functional outcome was less frequent in patients with LAA stroke compared to patients with SVO stroke (58.9 vs. 83.4%, OR: 0.303 (95%CI: 0.192–0.476), $p < 0.001$) and (62.3 vs. 86.8%, OR: 0.272 (95%CI: 0.155–0.478), $p < 0.001$), respectively. Similarly, mortality at 3 and 12 months was lower in patients with SVO stroke compared to patients with LAA stroke (1.5 vs. 9.9%, OR: 0.367 (95%CI: 0.200–0.676), $p = 0.001$) and (2.5 vs. 11.9%, OR: 0.436 (95%CI: 0.251–0.757), $p < 0.01$), respectively. In the three of the four included registries (Helsinki registry excluded), the rate of stroke recurrence was 9.5% in patients with SVO stroke and 13.3% in patients with LAA stroke (OR: 0.83, 95%CI: 0.44–1.58, $p = 0.58$).

In the logistic regression analysis, peripheral artery disease (OR: 4.013, 95%CI: 1.667–9.665, $p < 0.01$) and smoking (OR: 1.706, 95%CI: 1.087–2.675, $p < 0.05$) were independently associated with LAA strokes.

Discussion

The present study shows that in a diabetic ischaemic stroke population, SVO and LAA strokes occur with similar frequency. LAA strokes are more severe and have worse outcome than SVO. The presence of peripheral artery disease and smoking are associated with higher risk that a diabetic will develop LAA stroke.

Similar results can be identified in previous studies from different ethnic populations. In a prospective ischaemic stroke registry in Spain, the proportion of diabetic patients with LAA and SVO stroke was 41.2 and 35.1%, respectively.[19] Similarly, in the Nurses' Health Study which was performed in the USA, the incidence of patients with LAA stroke and SVO stroke was 12 and 13 per 100,000 person-years, respectively, in female diabetic patients.[20] Also, in a subanalysis of the Young Cerebral Infarction Study in China, the proportion of diabetic patients—which may be up to 10% of all young strokes[21]—with LAA and SVO stroke was 40.8 and 36.0%, respectively.[22]

The classic concept of ischaemic stroke as a macrovascular complication is based on the profound atherogenic effect of diabetes, which is mediated by endothelial dysfunction and inflammation, dyslipidemia, increased oxidation and glycosylation, and triglyceride enrichment of lipoproteins.[23] However, diabetes exerts a detrimental effect on microvasculature as well, which is mediated by direct glucose-mediated endothelial damage, oxidative stress due to superoxide overproduction, and production of advanced glycation end-products and sorbitol, and leads to impaired endothelial permeability and extravascular protein deposition.[24] Obviously, the pathophysiologic derangements affecting the micro- and macrovasculature run in parallel and explain why ischaemic stroke in diabetics can be either a micro- or a macrovascular complication, as suggested by the present study and others.[25] Moreover, the strong association between smoking and atherosclerosis[26] explain our finding that smoking increases the risk that a diabetic smoker will develop a LAA stroke rather than a SVO stroke. Similarly, our finding that patients with peripheral artery disease have a higher risk for LAA stroke (rather than SVO) is related to the widespread nature of atherosclerotic lesions in these patients. Of course, we need to keep in mind that like in the general population, ischaemic stroke in

Table 2. Baseline characteristics of diabetic stroke patients.

Characteristics	All strokes ($n = 1069$)	SVO strokes ($n = 205$)	LAA strokes ($n = 232$)	p-value
Demographics				
Age (years)	71.9 (63.6–78.0)	69.1 (62.0–75.0)	69.0 (61.5–75.9)	0.802
Female gender	396 (37.0%)	61 (29.8%)	71 (30.6%)	0.874
Clinical and laboratory values on admission				
NIHSS	6 (3–14)	3 (2–6)	6 (3–13)	<0.001
SBP (mmHg)	160 (140–177)	160 (148–180)	160 (142–180)	0.507
Glucose (mmol/L)	9.0 (6.9–11.9)	9.2 (7.0–12.6)	9.4 (7.3–12.2)	0.774
ASTRAL score	23 (19–32)	19 (17–22)	23 (19–30)	<0.001
Risk factors				
Hypertension	885 (82.9%)	163 (79.9%)	191 (82.3%)	0.518
Atrial fibrillation	316 (29.6%)	7 (3.4%)	0 (0.0%)	N/A
Smoking	250 (27.1%)	50 (26.3%)	73 (39.2%)	0.008
Dyslipidemia	679 (63.7%)	138 (67.6%)	155 (67.1%)	0.903
Coronary artery disease	1003 (18.6%)	34 (16.7%)	59 (25.4%)	0.028
Peripheral artery disease	276 (5.2%)	8 (3.9%)	29 (12.8%)	0.001
Imaging				
Brain MRI	154 (35.2%)	89 (43.4%)	65 (28.0%)	0.001
Outcome at 3 months				
mRS = 0–2	637 (59.6%)	171 (83.4%)	140 (60.3%)	<0.001
mRS = 3–5	295 (27.6%)	31 (15.1%)	69 (29.7%)	
Death	137 (12.8%)	3 (1.5%)	23 (9.9%)	
Outcome at 12 months				
mRS = 0–2	486 (60.5%)	138 (86.8%)	102 (64.2%)	<0.001
mRS = 3–5	170 (21.2%)	17 (10.7%)	38 (23.9%)	
Death	147 (18.3%)	4 (2.5%)	19 (11.9%)	
Treatment				
Intravenous thrombolysis	254 (23.8%)	27 (13.2%)	66 (28.6%)	<0.001
No specific thrombolytic treatment	804 (75.4%)	177 (86.3%)	163 (71.2%)	
TOAST classification				
Large artery atherosclerosis	232 (21.7%)	N/A	232 (100%)	N/A
Cardioembolic	345 (32.3%)	N/A	N/A	N/A
SVO	205 (19.2%)	205 (100%)	N/A	N/A
Rare causes	15 (1.4%)	N/A	N/A	N/A
Undetermined	272 (25.4%)	N/A	N/A	N/A

SVO: small-vessel occlusion; LAA: large-artery atherosclerotic; SBP: systolic blood pressure; mRS: modified Rankin scale; N/A: not applicable

diabetic patients may have different causes such as cardioembolism, atherosclerosis of large arteries, small vessel disease, and other rare causes. The fact that diabetic patients have increased risk for LAA strokes and small-vessel disease infarcts compared to the general population should not be received as that these patients may not have strokes of other aetiologies.

The strengths of this study include the multicentre nature of the study involving different populations (i.e. from central, northern, and southern Europe), the large dataset, the common definitions used to describe stroke characteristics (e.g. NIHSS score to describe stroke severity and TOAST classification to classify stroke aetiology) as well as the prospective registration of consecutive patients in the included registries which minimises the possibility of selection bias. However, one could argue that there is heterogeneity among studies given that the proportions of SVO and LAA strokes in the Helsinki Stroke Thrombolysis Registry deviate from the mean values of the overall dataset, i.e. the proportion of SVO is almost half and the proportion of LAA is almost 50% higher than the

corresponding averages in the overall dataset. A plausible explanation for this finding is apparently that the Helsinki registry includes only patients who were treated with thrombolysis; SVO strokes are generally mild and, very frequently, their NIHSS is lower than 4 which is frequently used as a lower threshold for thrombolysis[11,27] or due to mild symptoms they arrive later than the thrombolysis time window. Therefore, it seems logical that many SVO strokes were not treated with thrombolysis and therefore were not included in the Helsinki Stroke Thrombolysis Registry leading to under-representation of SVO strokes in this registry. These considerations strengthen further our conclusions that SVO and LAA strokes occur with similar frequency in the diabetic population given that the true proportion of SVO strokes may be even higher.

On the other hand, this study is limited by the lack of data about parameters which are related to the severity of the underlying stroke risk factors (e.g. number of pack-years of smoking, glycosylated haemoglobin, left ventricular hypertrophy documented by echocardiography or electrocardiography, evidence of retinopathy, proteinuria, white matter changes in brain MRI, carotid plaque, and intima-media thickness assessment) which could provide additional insight in the underlying pathophysiology and shed more light to the question why some diabetics develop SVO whereas others suffer LAA stroke. It would be of interest to see whether the results apply to both type I and type II diabetic patients; however, relevant information was not available in this dataset. Also, we had a relatively large proportion of patient with missing data due to our methodological approach to work on a complete dataset in order to avoid any imputation of missing data. This may have introduced selection bias in the analysis; however, the baseline characteristics of the excluded patients were similar to those of the included patients. In addition, data about stroke recurrence were not available for all databases. Finally, small vessel disease was diagnosed with CT or MRI together with clinical evaluation including elements such as lack of cortical symptoms, presence of typical lacunar syndromes, and the TOAST classification. CT imaging together with clinical judgment for distinguishing SVD from other causes is a standard approach. Still, this may have introduced bias given that the two methods have different accuracy.

In conclusion, the present study shows that in the diabetic stroke population, SVO and LAA strokes occur with similar frequency. LAA strokes are more severe and have worse outcome than SVO. The presence of peripheral artery and smoking are associated with higher risk that a diabetic will develop LAA stroke.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The scientific use of each registry was approved by appropriate authorities according to national and institutional legislation.

Informed consent

Not applicable.

Guarantor

G Ntaios

Trial registration

Not applicable

Contributorship

Study concept: Dr. Ntaios. Data acquisition: Dr. Curtze, Dr. Ferrari, Dr. Makaritsis, Dr. Michel, Dr. Strbian, Dr. Tatlisumak, and Dr. Vemmos. Statistical analysis: Dr Milionis, Dr. Ntaios, and Dr. Papavasileiou. Preparation of the initial draft: Dr. Ntaios. Critical revision of the manuscript: all authors. Study supervision: Dr. Ntaios.

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