Different Risk Factor Profiles for Ischemic and Hemorrhagic Stroke in Type 1 Diabetes Mellitus

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Background and Purpose—Despite the fact that patients with type 1 diabetes mellitus have a markedly increased risk of experiencing a stroke, independent risk factors for stroke and its subtypes in these patients have remained unclear.

Methods—A total of 4083 patients with type 1 diabetes mellitus from the Finnish Diabetic Nephropathy (FinnDiane) Study, without a history of stroke at baseline, were included. Strokes were classified based on medical files and brain imaging. At baseline, mean age was 37.4±11.8 years, duration of diabetes mellitus was 20.0 (11.0–30.0) years, and 51% were men. During 9.0±2.7 years (36680 patient-years) of follow-up, 105 patients experienced an ischemic stroke and 44 a hemorrhagic stroke. Cox proportional hazards analyses were performed to determine independent risk factors.

Results—Independent risk factors for ischemic stroke were duration of diabetes mellitus, presence of diabetic nephropathy, higher hemoglobin A1c, higher systolic blood pressure, insulin resistance, and history of smoking, whereas sex, lipids, high-sensitivity C-reactive protein, and the metabolic syndrome were not associated with an increased risk. Diabetic nephropathy, severe diabetic retinopathy, higher systolic blood pressure, and lower body mass index were independently associated with hemorrhagic stroke.

Conclusions—The risk factor profile for ischemic stroke seems partly different from that of hemorrhagic stroke in patients with type 1 diabetes mellitus. (Stroke. 2014;45:00-00.)

Key Words: diabetes mellitus, type 1 □ risk factors □ stroke
infarction, and hemorrhagic stroke, in a large study population of patients with type 1 diabetes mellitus.

Methods
All patients were part of the Finnish Diabetic Nephropathy (FinnDiane) Study, a nationwide multicenter study, with the aim to uncover risk factors for microvascular and macrovascular complications of type 1 diabetes mellitus. The study design is an observational follow-up study, and a detailed description of the research design and population has previously been reported. At baseline, both the attending physicians and the patients themselves completed questionnaires regarding the patient’s medical condition, medical history, and lifestyle. For the present study, we included all the 4083 patients with type 1 diabetes mellitus in the FinnDiane database without a history of stroke at baseline, as well as with complete information on stroke during follow-up available. Patients with unclear information on stroke were excluded (n=15). In addition, we excluded 2 patients with subdural hemorrhages, 1 with traumatic cerebral hemorrhage, and 1 with perinatal cerebral hemorrhage. The local ethics committee of each center approved the study protocol, and the study was performed in accordance with the Declaration of Helsinki. Each participating patient signed a written informed consent.

Diabetes Mellitus and Diabetic Complications
Type 1 diabetes mellitus was defined as diabetes mellitus diagnosis before 40 years of age and insulin medication commenced within 1 year after diagnosis. At baseline, mean age was 37.4±11.8 years, mean duration of diabetes mellitus was 20.0 (11.0–30.0) years, and 51% of the patients were men. Serum samples were analyzed for lipids, lipoproteins, hemoglobin A1c (HbA1c), and high-sensitivity C-reactive protein. Each patient collected timed urine samples for the measurement of urinary albumin excretion rate. Kidney status was defined based on the urinary albumin excretion rate measured from 2 of 3 overnight or 24-hour urine collections. DN was defined as urinary albumin excretion rate ≥200 µg/min or ≥300 mg/24 h, the patient being on dialysis, or having received a kidney transplant. SDR was defined as retinal laser treatment. Estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Coronary heart disease was defined as a history of myocardial infarction or coronary artery revascularization or treatment with long-acting nitrroglycerin.

Anthropometric Measurements
Waist circumference was measured midway of the lowest rib and the iliac crest. Blood pressure was measured twice in the sitting position after a 10-minute rest, and the mean values for both the systolic blood pressure (SBP) and the diastolic blood pressure were used. Antihypertensive medication was defined as use of any antihypertensive agent. Aspirin medication was defined as use of low-dose acetyl-salicylic acid for primary or secondary prevention of vascular events.

The metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III, as well as the Joint Statement criteria. The glucose criterion in both definitions was considered to be fulfilled for all patients. Patients were classified as current smokers if they smoked ≥1 cigarette per day, whereas history of smoking was defined as current smoking or smoking cessation. Insulin resistance was assessed by calculation of the estimated glucose disposal rate.

Results
Table 1 presents the baseline characteristics based on the type of incident stroke compared with no stroke.

Ischemic Stroke
The risk factor profile for ischemic stroke is shown in Table 2. The risk factors, as shown in the model, were longer duration of diabetes mellitus, higher HbA1c, higher SBP, presence of DN, and history of smoking. In a separate model, a lower estimated glucose disposal rate, indicating insulin resistance, also proved to be an independent risk factor (hazard ratio, 0.78 [0.69–0.88]; P<0.001; Table I in the online-only Data Supplement). Sex, waist circumference, triglycerides, and low-density lipoprotein and HDL cholesterol were not associated with an increased risk of ischemic stroke in any of the models (Table 2) as were not high-sensitivity C-reactive protein, the metabolic syndrome, or estimated glomerular filtration rate (data not shown).

Hemorrhagic Stroke
The risk factor profiles for any stroke, as well as for lacunar infarction, were similar to that of ischemic stroke (Tables III and IV in the online-only Data Supplement).
SBP, and presence of DN and SDR, as shown in Table 3. Duration of diabetes mellitus, triglycerides, and history of smoking were not associated with an increased risk of this subtype of stroke (Table 3) as were not estimated glucose disposal rate (data not shown) or antihypertensive medication (Table II in the online-only Data Supplement).

After observing that DN is a strong risk factor for stroke, we performed similar univariate and multivariate analyses for the patients with normal urinary albumin excretion rate (n=2482). The independent risk factors for any stroke in the multivariate analyses were male sex (2.79 [1.20–6.44]; P=0.017), longer duration of diabetes mellitus (1.04 [1.01–1.08]; P=0.026), SDR (3.09 [1.28–7.49]; P=0.012), and coronary heart disease (3.54 [1.24–10.1]; P=0.018).

**Discussion**

In this large study consisting of 4083 patients with type 1 diabetes mellitus, we show that the risk factor profile for ischemic stroke partly differs from that of hemorrhagic stroke. Longer duration of diabetes mellitus, presence of DN, poor glycemic control, higher SBP, history of smoking, and insulin resistance all independently increased the risk of ischemic stroke. The risk factor profile for hemorrhagic stroke included presence of DN and SDR, higher SBP, and, in addition, lower BMI.

Only 1 single study has previously assessed the independent risk factors for stroke (n=31) and that study showed that duration of diabetes mellitus, SBP, and non-HDL cholesterol independently increased the risk of ischemic stroke (n=21) in patients with type 1 diabetes mellitus. However,
independent association between HbA1c and the risk of stroke. As far as we know, this is the first study to show an increased risk of ischemic stroke. This was also the case in the present study in which higher HbA1c levels independently increased the risk of ischemic stroke and hypertension, a well-known risk factor for both any stroke and ischemic stroke in the general population, was surprisingly not significant after adjustment for overt nephropathy, which proved to be one of the strongest independent risk factors for ischemic stroke with a hazard ratio of 4.37 (1.54–12.4). In our study, both duration of diabetes mellitus and SBP remained in the model even after adjustment for DN. Dyslipidemia, a traditional risk factor for cardiovascular disease, was associated with an increased risk of ischemic stroke in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study but did not appear as a risk factor in any model in our study. As a matter of fact, in the general population, non-HDL cholesterol has been shown to be the only lipid variable associated with increased risk of ischemic stroke, and the association is far weaker than that for coronary heart disease. In our study, none of the lipid variables, including non-HDL cholesterol (data not shown), were independently associated with any type of stroke.

Studies on the effect of glycemic control on the risk of diabetic complications in patients with type 1 diabetes mellitus have shown a strong association between hyperglycemia and the microvascular complications DN, retinopathy, and neuropathy. The impact of hyperglycemia on the risk of macrovascular complications such as cardiovascular disease and stroke has been somewhat contradictory. However, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed rather continuously that poor glycemic control also increases the risk of macrovascular disease, defined as a combined cardiovascular and cerebrovascular end point. This was also the case in the present study in which higher HbA1c levels independently increased the risk of ischemic stroke. As far as we know, this is the first study to show an independent association between HbA1c and the risk of stroke in type 1 diabetes mellitus.

Table 2. Risk Factors for Ischemic Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>1.06 (1.04–1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.81 (1.75–4.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.93 (1.23–3.02)</td>
<td>0.004</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>1.23 (1.06–1.41)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Model also included sex, waist circumference, diastolic blood pressure, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, coronary heart disease, and severe diabetic retinopathy. CI indicates confidence interval; and HbA1c, hemoglobin A1c.

A new finding was that SBP, despite having DN in the model, was an independent risk factor for both ischemic and hemorrhagic stroke. Although SBP is strongly associated with an increased risk of stroke and its subtypes in the general population, no such associations have been found in patients with type 1 diabetes mellitus after adjusting for DN. This is probably because of the fact that DN is strongly associated with blood pressure and may, therefore, diminish its effect on the risk of ischemic stroke in multivariate analyses.

Although the risk factors for any stroke, ischemic stroke, and lacunar infarction were similar, the risk factors for hemorrhagic stroke differed from the other subtypes of stroke. This could partly be explained by the smaller number of cases in this subgroup, leading to lower power in the analyses. Furthermore, the cause of hemorrhagic stroke differs from that of the ischemic subtypes. This was also observed in the risk factor profile of our study in which duration of diabetes mellitus, poor glycemic control, and insulin resistance were no longer independent risk factors for hemorrhagic stroke. Lower BMI, however, increased the risk of hemorrhagic stroke. The same phenomenon has also been shown in the general population in which the role of BMI as a risk factor for stroke is J-shaped, meaning that both low and very high BMI are associated with an increased risk of hemorrhagic stroke. It is of note that patients with DN also have more end-stage renal disease, are more cachectic, and are therefore more likely to experience hemorrhages.

In our study, the majority (50%) of patients who experienced a hemorrhagic stroke had end-stage renal disease.

The strength of our study is the well-characterized patient population in which the same methodology has been used for all patients. To this date, this study is also the largest one on risk factors for stroke in patients with type 1 diabetes mellitus, and the number of cases is large enough for performing multivariate analyses also on the subtypes of stroke. The present study also has some limitations. We could only study such risk factors that we had available data on. Therefore, we cannot rule out that there could have been other significant risk factors as well. Furthermore, strokes in patients with type 1 diabetes mellitus are sometimes asymptomatic. We can, therefore, not exclude that the patients without a stroke could have experienced a stroke without our knowledge. However, we are rather sure that all patients with an incident stroke experienced a stroke, because the medical files and brain images were reviewed by 2 stroke neurologists, with the help of a neuroradiologist, who then classified all strokes. We had to, however, use a purely clinical definition for lacunar infarction and could not reliably apply a more specific subtype classification, because the patients were treated in a diversity of hospitals all over Finland during a period of 14 years and the study setting did not allow standardization of the diagnostic procedures. Another limitation is that both intracerebral and subarachnoid hemorrhages were included in hemorrhagic stroke. The cause of these 2 subtypes of hemorrhagic stroke may differ, and therefore, the risk factors for each subtype may also differ. However, in contrast to the general population, most of the subarachnoid hemorrhages in our patients were nonaneurysmal with a suspected microvascular cause. Because of the limited number of events, comparison of risk factors in these 2 subtypes of hemorrhagic stroke could not be performed.

Table 3. Risk Factors for Hemorrhagic Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>0.89 (0.81–0.98)</td>
<td>0.016</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.77 (1.20–6.42)</td>
<td>0.017</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.02 (1.00–1.03)</td>
<td>0.019</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.99 (1.18–7.55)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Model also included duration of diabetes, triglycerides, diastolic blood pressure, and history of smoking. BMI indicates body mass index; and CI, confidence interval.
Conclusions
The risk factor profile for ischemic stroke seems to partly differ from that of hemorrhagic stroke in patients with type 1 diabetes mellitus. Patients who experienced an incident stroke were, in general, of poorer health and had more DN and SDR. However, several modifiable risk factors for stroke were identified, including smoking, poor glycemic control, and high blood pressure. Intensive treatment of glucose control and blood pressure before any changes develop in the target organs is, thus, of outmost importance, in that this may diminish the risk of stroke in patients with type 1 diabetes mellitus.

Acknowledgments
We acknowledge all the physicians and nurses at each center participating in the collection of the patient data (Appendix in the online-only Data Supplement). We are indebted to Olli Salonen, MD, DMSc, Department of Radiology, Helsinki University Central Hospital, for the help in neuroradiological evaluation.

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Disclosures
Dr Tätäsmäki has served on scientific advisory boards for Boehringer Ingelheim and Mitsubishi Pharma; he has received speaker’s bureau honorariums from the Boehringer Ingelheim and Mitsubishi Pharma; he has received speaker’s bureau honorariums from the Boehringer Ingelheim, Cebix, Eli Lilly, and Finnish Neurological Association. Dr Groop has received speaker’s bureau honorariums from the Boehringer Ingelheim and Mitsubishi Pharma; he has received speaker’s bureau honorariums from the Boehringer Ingelheim, Cebix, Eli Lilly, and Finnish Neurological Association. Dr Tatlisumak has served on scientific advisory boards for Boehringer Ingelheim and Mitsubishi Pharma; he has received speaker’s bureau honorariums from the Boehringer Ingelheim, Cebix, Eli Lilly, and Finnish Neurological Association. Dr Groop has received speaker’s bureau honorariums from the Boehringer Ingelheim, Cebix, Eli Lilly, and Finnish Neurological Association.

References
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**SUPPLEMENTAL TABLE I. Risk factors for ischemic stroke.**

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<tr>
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<th>Model 2</th>
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<tr>
<td>Duration of diabetes (years)</td>
<td>1.06 (1.03-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.56 (1.59-4.13)</td>
<td>&lt;0.001</td>
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<tr>
<td>History of smoking (yes/no)</td>
<td>1.74 (1.12-2.72)</td>
<td>0.014</td>
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<tr>
<td>eGDR (mg/kg/min)</td>
<td>0.78 (0.69-0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.05 (1.03-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>1.89 (1.13-3.16)</td>
<td>0.015</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.91 (1.21-3.00)</td>
<td>0.005</td>
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<tr>
<td>HbA1c (%)</td>
<td>1.21 (1.05-1.40)</td>
<td>0.008</td>
</tr>
<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td>2.53 (1.31-4.89)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are presented as hazard ratio with 95% confidence interval. Model 2=Main model with HbA1c, waist circumference, systolic and diastolic blood pressure excluded, and with eGDR included. Model 3=Main model with anti-hypertensive medication, lipid-lowering medication, and aspirin medication included. eGDR=estimated glucose disposal rate.
**SUPPLEMENTAL TABLE II. Risk factors for hemorrhagic stroke.**

<table>
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</thead>
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<tr>
<td>BMI (kg/m²)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.012</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.027</td>
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<td>Severe diabetic retinopathy (yes/no)</td>
<td>3.18 (1.29-7.82)</td>
<td>0.012</td>
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<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
<td>0.004</td>
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</table>

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.49 (1.06-5.81)</td>
<td>0.036</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.036</td>
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<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.89 (1.14-7.30)</td>
<td>0.025</td>
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<tr>
<td>Lipid-lowering medication (yes/no)</td>
<td>2.38 (1.14-4.74)</td>
<td>0.021</td>
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</table>

Data are presented as hazard ratio with 95% confidence interval. Model 2=Main model with duration of diabetes excluded and with eGFR included. Model 3=Main model with anti-hypertensive medication, lipid-lowering medication, and aspirin medication included. eGFR=estimated glomerular filtration rate.
### SUPPLEMENTAL TABLE III. Risk factors for any stroke.

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</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.28 (1.46-3.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.17 (1.04-1.32)</td>
<td>0.010</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.90 (1.15-3.13)</td>
<td>0.012</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.58 (1.10-2.29)</td>
<td>0.015</td>
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<table>
<thead>
<tr>
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<td></td>
<td><strong>P</strong></td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.30 (1.49-3.55)</td>
<td>&lt;0.001</td>
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<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.80 (1.09-2.99)</td>
<td>0.022</td>
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<tr>
<td>History of smoking (yes/no)</td>
<td>1.50 (1.04-2.16)</td>
<td>0.031</td>
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<td>eGDR (mg/kg/min)</td>
<td>0.83 (0.75-0.92)</td>
<td>&lt;0.001</td>
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<td><strong>P</strong></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.15 (1.02-1.30)</td>
<td>0.020</td>
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<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.74 (1.70-4.41)</td>
<td>&lt;0.001</td>
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<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
<td>&lt;0.001</td>
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<table>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>1.73 (1.09-2.74)</td>
<td>0.020</td>
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<tr>
<td>HbA1c (%)</td>
<td>1.16 (1.03-1.31)</td>
<td>0.016</td>
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<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.65 (1.09-2.71)</td>
<td>0.046</td>
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<tr>
<td>History of smoking (yes/no)</td>
<td>1.56 (1.07-2.25)</td>
<td>0.019</td>
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<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td>2.18 (1.25-3.78)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are presented as hazard ratio with 95% confidence interval. Main model also included sex, waist circumference, diastolic blood pressure, triglycerides, LDL cholesterol, and coronary heart disease. Model 2=Main model with HbA1c, waist circumference, systolic and diastolic blood pressure excluded, and with eGDR included. Model 3=Main model with sex and duration of diabetes excluded, and with eGFR included. Model 4=Main model with anti-hypertensive medication, lipid-lowering medication, and aspirin medication included. eGDR=estimated glucose disposal rate, eGFR=estimated glomerular filtration rate.
## Online Supplement

**Supplemental Table IV. Risk factors for lacunar infarction.**

<table>
<thead>
<tr>
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<th>Main model</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
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<tbody>
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<td></td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.05 (1.02-1.08)</td>
<td>1.05 (1.02-1.08)</td>
<td>1.02 (1.01-1.03)</td>
<td>1.04 (1.01-1.07)</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.72 (1.45-5.10)</td>
<td>2.26 (1.21-4.24)</td>
<td>2.89 (1.37-6.08)</td>
<td>2.99 (1.27-7.07)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>2.60 (1.45-4.69)</td>
<td>3.12 (1.59-6.15)</td>
<td>1.90 (1.22-2.94)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.22 (1.01-1.47)</td>
<td>0.76 (0.65-0.88)</td>
<td>0.99 (0.98-0.99)</td>
<td>0.99 (0.98-0.99)</td>
</tr>
</tbody>
</table>

Data are presented as hazard ratio with 95% confidence interval. Main model also included sex, waist circumference, diastolic blood pressure, triglycerides, LDL cholesterol, HDL cholesterol, coronary heart disease, severe diabetic retinopathy, and history of smoking. Model 2=Main model with HbA1c, waist circumference, systolic and diastolic blood pressure excluded, and with eGDR included. Model 3=Main model with sex and duration of diabetes excluded, and with eGFR included. Model 4=Main model with anti-hypertensive medication, lipid-lowering medication, and aspirin medication included. eGDR=estimated glucose disposal rate, eGFR=estimated glomerular filtration rate.
APPENDIX

The Finnish Diabetic Nephropathy Study Centers

Anjalankoski Health Center
Central Finland Central Hospital, Jyväskylä

Central Hospital of Åland Islands, Mariehamn
Central Hospital of Kanta-Häme, Hämeenlinna
Central Hospital of Kymenlaakso, Kotka
Central Hospital of Länsi-Pohja, Kemi
Central Ostrobothnian Hospital District, Kokkola

City of Espoo Health Center:
Espoonlahti
Tapiola
Samaria
Viherlaakso

City of Helsinki Health Center:
Puistola
Suutarila
Toölö

City of Hyvinkää Health Center

City of Vantaa Health Center:
Korso
Länsimäki
Martinlaakso
Myyrmäki
Rekola
Tikkurila

Heinola Health Center
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology

Herttoniemi Hospital, Helsinki
Hospital of Lounais-Häme, Forssa

S.Koivula, T.Uggeldahl
M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
R.Paldanius, M.Riihelä, L.Rytsy
H.Laukkanen, P.Nyländen, A.Sademies
S.Anderson, B.Asplund, U.Byskata, P.Liedes, M.Kuusela, T.Virkkala
A.Nikkola, E.Ritola
M.Niska, H.Saarinen
E.Oukko-Ruponen, T.Virtanen
A.Lyytinen
A.Kaprio, J.Kärkkäinen, B.Rantaeskola
P.Kääriäinen, J.Haaga, A-L.Pietiläinen
S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere
R.Toivonen, H.Virtanen
R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
M.Laine, T.Pellonpää, R.Puranen
A.Airas, J.Laakso, K.Rautavaara
M.Erola, E.Jatkola
R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
P.Hentunen, J.Lagerstam
A.Ahola, M.Feodoroff, O.Heikkilä, K.Hietala, J.Kytö,
S.Lindh, K.Pettersson-Fernholm, M.Rosengård-Bärlund, L.Salovaara, A.Sandelin, M.Sarasteimo,
A.Soro-Paavonen, N.Tolonen, J.Tuomikangas,
T.Vesisenaho, J.Wadén
V.Sipilä
T.Kalliomäki, J.Koskelainen, R.Nikkanen,
N.Savolainen, H.Sulonen, E.Valtonen
Hyvinkää Hospital  
Iisalmi Hospital  
Jokilaakso Hospital, Jämsä  
Jorvi Hospital, Helsinki University Central Hospital  
Jyväskylä Health Center, Kyllö  
Kainuu Central Hospital, Kajaani  
Kerava Health Center  
Kirkkonummi Health Center  
Kivelä Hospital, Helsinki  
Koskela Hospital, Helsinki  
Kotka Health Center  
Kouvolä Health Center  
Kuopio University Hospital  
Kuusamo Health Center  
Kuusankoski Hospital  
Laakso Hospital, Helsinki  
Lahti City Hospital  
Lapland Central Hospital, Rovaniemi  
Lappeenranta Health Center  
Lohja Hospital  
Länsi-Uusimaa Hospital, Tammisaari  
Loimaa Health Center  
Malmi Hospital, Helsinki  
Mikkeli Central Hospital  
Mänttä Regional Hospital  
North Karelian Hospital, Joensuu  
Nurmijärvi Health Center  
Oulaskangas Hospital, Oulainen  
Oulu Health Center  
Oulu University Hospital  
Päijät-Häme Central Hospital  

L. Norvio, A. Hämäläinen  
E. Toivanen  
A. Parta, I. Pirrtiniemi  
S. Aranko, S. Ervasti, R. Kauppinen-Mäkelä  
A. Kuusisto, T. Leppälä, K. Nikkilä, L. Pekkonen  
K. Nuorva, M. Tihonen  
S. Jokelainen, P. Kemppainen, A-M. Mankinen, M. Sankari  
H. Stuckey, P. Suominen  
A. Lappalainen, M. Liimatainen, J. Santaholma  
A. Aimolahti, E. Huovinen  
V. Ilkka, M. Lehtimäki  
E. Päälkki-Kontinen, A. Vanhanen  
E. Koskinen, T. Siitonen  
T. Kääriäinen, E. Isopoussi  
E. Kilikki, I. Koskinen, L. Riihelä  
T. Meriläinen, P. Poukka, R. Savolainen, N. Uhlenius  
A. Mäkelä, M. Tanner  
L. Hyvärinen, K. Lampela, S. Pöykkö, T. Rompasaari, S. Severinkangas, T. Tulokas  
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I.-M. Jousmaa, J. Rinne  
A. Mäkelä, P. Eloranta  
H. Lanki, S. Moinilan, M. Tilly-Kiesi  
A. Gynther, R. Manninen, P. Nironen, M. Salminen, T. Vänttinen  
I. Pirrtiniemi, A-M. Hänninen  
U-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen, M. Voutilainen  
A. Burgos, K. Urtamo  
E. Jokelainen, P.-L. Jylkkä, E. Kaarlela, J. Vuolaspuro  
L. Hiltunen, R. Häkkinen, S. Keinänen-Kiukaanniemi  
R. Iläheimo  
H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Acknowledgment Permission Form

Journal: Stroke
Manuscript No.
First author: Hogg Stephanie
Title of work: Risk factors for stroke
Type 1 diabetes

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