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 (36,680 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;45:2558-2562.)

Key Words: diabetes mellitus, type 1 ■ risk factors ■ stroke

Worldwide, cerebrovascular disease is the second leading cause of death not only in high-income but also in low-income countries. Patients with type 1 diabetes mellitus have a markedly increased risk of stroke compared with non-diabetic subjects,1 and it is of note that these patients are at a high risk of stroke 10 to 15 years earlier than non-diabetic subjects.2

Age, hypertension, atrial fibrillation, smoking, and diabetes mellitus are well-known risk factors for stroke in the general population.2–4 In patients with type 2 diabetes mellitus, similar risk factors have been observed.4 Furthermore, the metabolic syndrome and its components have also been shown to increase the risk of stroke, especially in patients with type 2 diabetes mellitus.5

Although the risk factors for stroke in patients with type 2 diabetes mellitus have been assessed in several studies, few studies on the risk factors for stroke and stroke subtypes in patients with type 1 diabetes mellitus exist. No sex difference has been observed for the risk of stroke in type 1 diabetes mellitus, which is in contrast to the general population in which premenopausal women are protected from cardiovascular disease and stroke.1,2 Stroke is usually divided into 2 subgroups: ischemic stroke and hemorrhagic stroke. Ischemic stroke can be further subgrouped into lacunar and non-lacunar infarction, whereas hemorrhagic stroke includes intracerebral and subarachnoid hemorrhage. We have earlier shown that both the severity of diabetic nephropathy (DN) and the presence of severe diabetic retinopathy (SDR) increase the risk of any stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke.4 However, comprehensive studies on independent risk factors for each subtype of stroke are still missing.

Therefore, we aimed to study the independent risk factors for stroke, and also for the subtypes ischemic stroke, lacunar

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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 of stroke 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 ≥300 mg/24 h, 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 nitroglycerin.

**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 acetylsalicylic 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.

**Stroke**

A detailed description of the identification and classification of the strokes has previously been reported. In short, patients who experienced a stroke during follow-up were identified from the FinnDiane questionnaires, death certificates, and the National Hospital Discharge Register. Medical records, computed tomographic images, and magnetic resonance images on each of these patients were ordered from the hospitals in which the patient had been treated. Based on these data, 2 stroke neurologists (J.P. and R.L.), with the help from a neuroradiologist, classified all strokes with clinical symptoms into either hemorrhagic or ischemic stroke. Ischemic strokes were further classified into nonlacunar or lacunar infarctions, based on one of the known lacunar syndromes. Follow-up time was calculated from the baseline visit until the last date the patients were known to be free of stroke or until the date of the first stroke for those who experienced a stroke. Of the 4083 eligible patients, 149 (4%) experienced an incident stroke. Of these, 105 (70%) were ischemic strokes and 44 (30%) hemorrhagic strokes. Of the ischemic strokes, 58 (55%) were lacunar infarctions.

**Statistical Analyses**

Parametric continuous variables were analyzed with the t test, and results are presented as means with SD. Nonparametric variables were analyzed with the Mann-Whitney U test, and results are presented as medians with interquartile range. The difference in categorical variables between groups was tested with the χ² test. Cox proportional hazards analyses with forward stepwise variable entry and removal were performed to determine the independent risk factors for the different end points. Variables that were univariately associated with stroke were included in the multivariate analyses. Because of the well-known collinearity, some of the variables could not be tested in the same model. The main model for ischemic stroke consisted of sex, duration of diabetes mellitus, waist circumference, SBP, diastolic blood pressure, triglycerides, low-density lipoprotein and high-density lipoprotein (HDL) cholesterol, HbA1c, coronary heart disease, DN, SDR, and history of smoking. In a separate model, we also included estimated glucose disposal rate, but excluded HbA1c, waist circumference, SBP, and diastolic blood pressure because of collinearity (Table 1 in the online-only Data Supplement). Similar models were built for any stroke and lacunar infarction (Tables III and IV in the online-only Data Supplement).

The main model for hemorrhagic stroke included duration of diabetes mellitus, body mass index (BMI), SBP, diastolic blood pressure, triglycerides, DN, SDR, and history of smoking. The results are presented as hazard ratio with 95% confidence interval. P<0.05 was considered statistically significant. All analyses were performed with the SPSS Statistical software 19.0 (IBM Corporation, Armonk, NY).

**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).

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).

**Hemorrhagic Stroke**

The variables that were independently associated with an increased risk of hemorrhagic stroke were lower BMI, higher
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.15 However,
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 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.

### 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 utmost importance, in that this may diminish the risk of stroke in patients with type 1 diabetes mellitus.

Acknowledgments

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Disclosures

Dr Tatlisumak has served on scientific advisory boards for Boehringer Ingelheim and Mitsubishi Pharma; he has received speaker’s bureau from the Professio Finland, University of Helsinki, Finnish Medical Association, University of Donau (Austria), Genzyme Oy, and Finnish Neurological Association. Dr Groop has received speaker honorariums from the Boehringer Ingelheim, Cebix, Eli Lilly, Genzyme Oy, Medscape, MSD, Novartis, and Novo Nordisk and is an advisory board member of Boehringer Ingelheim, Cebix, Medscape, and Novartis. The other authors report no conflicts.

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/07/22/STROKEAHA.114.005724.DC1


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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model 2 Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.74 (1.12-2.72)</td>
<td>0.014</td>
</tr>
<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>Risk Factor</th>
<th>Model 3 Hazard Ratio (95% CI)</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>
</tr>
<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>
<thead>
<tr>
<th></th>
<th>Model 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.012</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.027</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>3.18 (1.29-7.82)</td>
<td>0.012</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 3</th>
<th>P</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.036</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.89 (1.14-7.30)</td>
<td>0.025</td>
</tr>
<tr>
<td>Lipid-lowering medication (yes/no)</td>
<td>2.38 (1.14-4.74)</td>
<td>0.021</td>
</tr>
</tbody>
</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.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Main model</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>1.04 (1.02-1.06)</td>
<td>1.02 (1.01-1.03)</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.02-1.06)</td>
<td>1.04 (1.02-1.06)</td>
<td>1.04 (1.02-1.06)</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.28 (1.46-3.54)</td>
<td>2.30 (1.49-3.55)</td>
<td>2.74 (1.70-4.41)</td>
<td>1.73 (1.09-2.74)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.17 (1.04-1.32)</td>
<td>2.30 (1.49-3.55)</td>
<td>1.50 (1.04-2.16)</td>
<td>1.16 (1.03-1.31)</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.90 (1.15-3.13)</td>
<td>1.80 (1.09-2.99)</td>
<td>2.74 (1.70-4.41)</td>
<td>1.65 (1.09-2.71)</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.58 (1.10-2.29)</td>
<td>1.50 (1.04-2.16)</td>
<td>0.99 (0.98-0.99)</td>
<td>1.56 (1.07-2.25)</td>
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<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td></td>
<td></td>
<td></td>
<td>2.18 (1.25-3.78)</td>
</tr>
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</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>
<th></th>
<th>Main model</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
<th>Model 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.05 (1.02-1.08)</td>
<td>&lt;0.001</td>
<td>1.05 (1.02-1.08)</td>
<td>0.001</td>
<td>1.02 (1.01-1.03)</td>
<td>0.006</td>
<td>1.04 (1.01-1.07)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.72 (1.45-5.10)</td>
<td>0.002</td>
<td>2.26 (1.21-4.24)</td>
<td>0.011</td>
<td>2.89 (1.37-6.08)</td>
<td>0.005</td>
<td>2.99 (1.27-7.07)</td>
<td>0.013</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.013</td>
<td>0.76 (0.65-0.88)</td>
<td>&lt;0.001</td>
<td>0.99 (0.98-0.99)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.22 (1.01-1.47)</td>
<td>0.042</td>
<td></td>
<td></td>
<td></td>
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</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.Riheittä, L.Ryysy
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.Saarin
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.Toironen, H.Virtanen
R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
M.Laine, T.Pellonpää, R.Purane
A.Airas, J.Laakso, K.Rautavaara
M.Erola, E.Jatkola
R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
P.Hentunen, J.Lagerstam

V.Sipilä
T.Kalliomiäki, J.Koskelainen, R.Nikkanen, N.Savalainen, H.Sulonen, E.Valtonen
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Journal Stroke
Manuscript No.
First author Hogg Stephanie
Title of work Risk factors for stroke in type 1 diabetes

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