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
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 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 I 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,

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**Table 1. Baseline Characteristics of Patients With No Stroke, Any Stroke, Ischemic Stroke, Lacunar Infarction, and Hemorrhagic Stroke During Follow-Up**

<table>
<thead>
<tr>
<th>Baseline Data</th>
<th>No Stroke</th>
<th>Any Stroke</th>
<th>Ischemic Stroke</th>
<th>Lacunar Infarction</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3,934</td>
<td>149</td>
<td>105</td>
<td>58</td>
<td>44</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>51</td>
<td>65*</td>
<td>66*</td>
<td>69*</td>
<td>64</td>
</tr>
<tr>
<td>Age, y</td>
<td>37.1±11.8</td>
<td>45.5±9.3*</td>
<td>46.1±9.8*</td>
<td>45.1±8.8*</td>
<td>44.0±8.1*</td>
</tr>
<tr>
<td>Age at onset of diabetes mellitus, y</td>
<td>15.8±9.0</td>
<td>15.0±9.3</td>
<td>15.3±9.6</td>
<td>14.6±9.2</td>
<td>14.4±8.8</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>21.0 (11.0–30.0)</td>
<td>31.0 (24.0–36.0)*</td>
<td>31.0 (24.0–37.5)*</td>
<td>31.5 (24.0–36.0)*</td>
<td>29.0 (24.0–35.5)*</td>
</tr>
<tr>
<td>Age at stroke, y</td>
<td>...</td>
<td>50.5±8.1</td>
<td>51.2±9.6</td>
<td>50.3±8.9</td>
<td>48.7±7.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0±3.6</td>
<td>24.9±3.7</td>
<td>25.3±3.8</td>
<td>25.5±3.9</td>
<td>23.9±3.2*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>84.0 (77.0–92.0)</td>
<td>88.0 (80.0–97.0)*</td>
<td>88.5 (81.0–98.0)*</td>
<td>88.0 (80.3–97.8)*</td>
<td>86.0 (78.5–92.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±18</td>
<td>151±24*</td>
<td>152±23*</td>
<td>151±22*</td>
<td>148±25*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±10</td>
<td>84±12*</td>
<td>84±11*</td>
<td>84±12*</td>
<td>84±12*</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>1.77 (1.07–3.22)</td>
<td>2.19 (1.25–3.86)*</td>
<td>2.28 (1.25–4.01)*</td>
<td>2.29 (1.21–3.89)</td>
<td>1.99 (1.16–2.98)</td>
</tr>
</tbody>
</table>

**Lipids and lipoproteins**

| Total cholesterol, mmol/L | 4.9±1.0 | 5.3±1.1* | 5.3±1.1* | 5.2±0.9* | 5.4±1.3* |
| LDL cholesterol, mmol/L | 3.0±0.9 | 3.4±1.0* | 3.4±1.0* | 3.4±0.8* | 3.3±1.1 |
| HDL cholesterol, mmol/L | 1.3±0.4 | 1.3±0.4 | 1.3±0.4* | 1.2±0.3* | 1.3±0.4 |

**Triglycerides, mmol/L**

| 1.02 (0.77–1.46) | 1.30 (0.96–1.71)* | 1.27 (0.96–1.67)* | 1.30 (1.05–1.62)* | 1.32 (0.92–1.88)* |

**Glycemic control and insulin resistance**

| HbA₁c, % | 8.4±1.5 | 8.9±1.3* | 9.0±1.3* | 8.9±1.1* | 8.7±1.3 |
| eGDR, mg/kg per minute | 6.23 (4.39–8.45) | 4.13 (2.95–5.19)* | 3.89 (2.94–4.82)* | 3.89 (2.98–4.89)* | 4.44 (2.94–5.80)* |

**Metabolic syndrome NCEP/JS, %**

| 33/48 | 53*66/ | 55*69/ | 56*70/ | 46/61 |

**Micro- and macrovascular complications**

| eGFR, mL/min per 1.73 m² | 101 (82–115) | 65 (36–98)* | 66 (40–98)* | 66 (42–98)* | 60 (31–100)* |
| Severe diabetic retinopathy, % | 32 | 77* | 76* | 76* | 80* |
| Coronary heart disease, % | 5 | 15* | 18* | 18* | 7 |
| Antihypertensive medication, % | 36 | 82* | 83* | 81* | 82* |
| Lipid-lowering medication, % | 11 | 25* | 23* | 21* | 30* |
| Aspirin, % | 12 | 31* | 31* | 26* | 32* |
| Warfarin, % | 1 | 1 | 1 | 0 | 0 |
| Current smoking, % | 24 | 29 | 28 | 33 | 32 |
| History of smoking, % | 46 | 63* | 66* | 62* | 56 |

Data are presented as means±SD, median with interquartile range, or number of cases (%). BMI indicates body mass index; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; HbA₁c, hemoglobin A₁c; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; JS, Joint Statement criteria; LDL, low-density lipoprotein; and NCEP, National Cholesterol Education Program Adult Treatment Panel III criteria.

*P<0.05 compared with no stroke.
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.\textsuperscript{16} 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.\textsuperscript{17} The impact of hyperglycemia on the risk of macrovascular complications such as cardiovascular disease and stroke has been somewhat contradictory.\textsuperscript{18,19} 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.\textsuperscript{20} This was also the case in the present study in which higher HbA\textsubscript{1c} levels independently increased the risk of ischemic stroke. As far as we know, this is the first study to show an independent association between HbA\textsubscript{1c} and the risk of stroke in type 1 diabetes mellitus.

### Table 2. Risk Factors for Ischemic Stroke

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.81 (1.75–4.51)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.02 (1.01–1.03)</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.93 (1.23–3.02)</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}, %</td>
<td>1.23 (1.06–1.41)</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 HbA\textsubscript{1c}, hemoglobin A\textsubscript{1c}.

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,\textsuperscript{21–24} 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.\textsuperscript{25} 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.\textsuperscript{26} 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 could have experienced a stroke without our knowledge. However, we are rather sure that all patients with an incident stroke could have experienced a stroke without our knowledge. However, we are rather sure that all patients with an incident stroke could have experienced a stroke without our knowledge.
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

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 Oili Salonen, MD, DMSc, Department of Radiology, Helsinki University Central Hospital, for the help in neuroradiological evaluation.

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Disclosures

Dr Tatlisumak has served on scientific advisory boards for Boehringer Ingelheim, Cebix, Eli Lilly, 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.

References

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on behalf of the FinnDiane Study Group

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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</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</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.
### ONLINE SUPPLEMENT

**SUPPLEMENTAL TABLE II. Risk factors for hemorrhagic stroke.**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model 2 Hazard Ratio (95% CI)</th>
<th>Model 3 Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.88 (0.80-0.97)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>2.49 (1.06-5.81)</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>3.18 (1.29-7.82)</td>
<td>2.89 (1.14-7.30)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
<td>2.38 (1.14-4.74)</td>
</tr>
</tbody>
</table>

| **Model 3**                        |                               |                               |
| BMI (kg/m²)                        | 0.88 (0.80-0.97)              | 0.88 (0.80-0.97)              |
| Diabetic nephropathy (yes/no)      | 2.49 (1.06-5.81)              | 2.49 (1.06-5.81)              |
| Systolic blood pressure (mmHg)     | 1.02 (1.00-1.03)              | 1.02 (1.00-1.03)              |
| Severe diabetic retinopathy (yes/no) | 2.89 (1.14-7.30)            | 2.89 (1.14-7.30)             |
| Lipid-lowering medication (yes/no) | 2.38 (1.14-4.74)             | 2.38 (1.14-4.74)             |

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>P</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

**Model 2**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.02-1.06)</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.30 (1.49-3.55)</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.80 (1.09-2.99)</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.50 (1.04-2.16)</td>
</tr>
<tr>
<td>eGDR (mg/kg/min)</td>
<td>0.83 (0.75-0.92)</td>
</tr>
</tbody>
</table>

**Model 3**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.15 (1.02-1.30)</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.74 (1.70-4.41)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
</tr>
</tbody>
</table>

**Model 4**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</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>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>1.73 (1.09-2.74)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.16 (1.03-1.31)</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>1.65 (1.09-2.71)</td>
</tr>
<tr>
<td>History of smoking (yes/no)</td>
<td>1.56 (1.07-2.25)</td>
</tr>
<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td>2.18 (1.25-3.78)</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>
<th></th>
<th>Main model</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>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.72 (1.45-5.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.013</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.22 (1.01-1.47)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.05 (1.02-1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy (yes/no)</td>
<td>2.26 (1.21-4.24)</td>
<td>0.011</td>
</tr>
<tr>
<td>eGDR (mg/kg/min)</td>
<td>0.76 (0.65-0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.01-1.03)</td>
<td>0.006</td>
</tr>
<tr>
<td>Severe diabetic retinopathy (yes/no)</td>
<td>2.89 (1.37-6.08)</td>
<td>0.005</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.99 (0.98-0.99)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.04 (1.01-1.07)</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00-1.03)</td>
<td>0.036</td>
</tr>
<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td>2.99 (1.27-7.07)</td>
<td>0.013</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
Viheraa

City of Helsinki Health Center:
Puistola
Suutarila
Toööö

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
T.Forslund, A.Halonen, A.Koistinen, P.Koskiaho,
M.Laukkanen, J.Saltevo, M.Tiihonen
M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
R.Paldanius, M.Riihelä, L.Ryysy
H.Laukkonen, 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
H.Kari, T.Simonen
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.Jatokka
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.Saraheimo,
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
Isalmi Hospital
Jokilaakso Hospital, Jämäs
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
Kouvola 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-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä, L. Peikonen
K. Nuorva, M. Tiitonen
S. Jokelaßen, 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. Päälkkö-Kontinen, A. Vanhanen
E. Koskinen, T. Siitonen
T. Kääriäinen, E. Isopoussu
E. Kilkki, 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
P. Erola, P. Linkola, T. Pekkanen, I. Pulli, E. Repo
I.-M. Jousmaa, J. Rinne
A. Mäkelä, P. Eloranta
H. Lanki, S. Moilanen, 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. Jokelaßen, P.-L. Jylkkä, E. Kaarlela, J. Vuolaspuro
L. Hiltunen, R. Häkkinnen, S. Keinänen-Kuukaanniemi
R. Ikäheimo
H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Palokka Health Center  P.Sopanen, L.Welling
Pieksämäki Hospital  V.Javtsenko, M.Tamminen
Pietarsaari Hospital  M.L.Holmbäck, B.Isomaa, L.Sarelin
Pori City Hospital  P.Ahonen, P.Merisalo, E. Muurinen, K.Sävelä
Porvoo Hospital  M.Kallio, B.Rask, S.Rämö
Raahe Hospital  A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää
Rauma Hospital  K.Laine, K.Saarinen, T.Salminen
Riihimäki Hospital  P.Aalto, E.Immonen, L.Juurinen
Salo Hospital  A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen
Satakunta Central Hospital, Pori  M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki,
P.Pääkkönen, M.Rautavirta
Savonlinna Central Hospital  T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, T.
Tuominen, H.Valtonen, A.Varti, S.-L. Viitanen
Seinäjoki Central Hospital  E.Korpi-Hyövälti, T.Latvala, E.Leijala
South Karelia Central Hospital, Lappeenranta  T.Ensala, E.Hussi, R.Härkönen, U.Nyholm,
J.Toivanen
Tampere Health Center  A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius,
T.Niskanen, T.Kaitala, T.Vatanen
Tampere University Hospital  I.Ala-Houhala, T.Kuningas, P.Lampinen, M.Määttä,
H.Oksala, T.Oksanen, K.Salonen, H.Tauriainen, S.Tulokas
Tiirismaa Health Center, Hollola  T.Kivelä, L.Petlin, L.Savolainen
Turku Health Center  A. Artukka, I.Hämäläinen, H.Virtamo, M.Vähätalo
Turku University Central Hospital  K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä,
P.Saarinen, R.Tuominen, S.Äyräpää
Vaajakoski Health Center  K.Mäkinen, P.Sopanen
Valkeakoski Regional Hospital  S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen,
T.Immonen
Vammala Regional Hospital  I.Isomäki, R.Kroneld, L. Mustaniemi, M.Tapiolinna-Mäkelä
Vasa Central Hospital  S.Bergkulla, U.Hautamäki, V.-A.Myllyniemi, I.Rusk
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Manuscript No.
First author Hogg Stephanie
Title of work Risk factors for stroke in type 1 diabetes

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Signature
Date 4/18/2014

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Signature
Date

Printed Name
Signature
Date

Printed Name
Signature
Date