Risk of Stroke in Type 2 Diabetes Estimated by the UK Prospective Diabetes Study Risk Engine

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Background and Purpose—People with type 2 diabetes are at elevated risk of stroke compared with those without diabetes. Relative risks have been examined in earlier work, but there is no readily available method for predicting the absolute risk of stroke in a diabetic individual. We developed mathematical models to estimate the risk of a first stroke using data from 4549 newly diagnosed type 2 diabetic patients enrolled in the UK Prospective Diabetes Study.

Methods—During 30 700 person-years of follow-up, 188 first strokes (52 fatal) occurred. Model fitting was carried out by maximum likelihood estimation using the Newton-Raphson method. Diagnostic plots were used to compare survival probabilities calculated by the model with those calculated using nonparametric methods.

Results—Variables included in the final model were duration of diabetes, age, sex, smoking, systolic blood pressure, total cholesterol to high-density lipoprotein cholesterol ratio and presence of atrial fibrillation. Not included in the model were body mass index, hemoglobin A1c, ethnicity, and ex-smoking status. The use of the model is illustrated with a hypothetical study power calculation.

Conclusions—This model forecasts the absolute risk of a first stroke in people with type 2 diabetes using variables readily available in routine clinical practice. (Stroke. 2002;33:1776-1781.)

Key Words: blood pressure ■ cholesterol ■ diabetes mellitus ■ statistics ■ stroke

Materials and Methods

Study Subjects

The UKPDS has been described elsewhere. Briefly, between 1977 and 1991, general practitioners in the catchment areas of 23 participating UKPDS hospitals were asked to refer all patients age 25 to 65 years presenting with newly diagnosed diabetes. There were 5102 patients recruited to the study, who met inclusion criteria listed previously. Patients with a myocardial infarction within the last year, or with more than 1 vascular episode, were excluded. For this analysis, data from 4549 patients of white, Afro-Caribbean, or Asian-Indian ethnic groups were included. Excluded were 39 patients of other ethnic groups; 37 with stroke before...
TABLE 1. Characteristics of Subjects: Mean±sd, or n (Percentage)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>51.5±8.8</td>
<td>52.6±8.8</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2171 (81%)</td>
<td>1583 (84%)</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>198 (7%)</td>
<td>153 (8%)</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>302 (11%)</td>
<td>142 (8%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>908 (34%)</td>
<td>471 (25%)</td>
</tr>
<tr>
<td>AF</td>
<td>18 (0.7%)</td>
<td>10 (0.5%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±5.0</td>
<td>28.8±6.0</td>
</tr>
</tbody>
</table>

Mean values taken 1 and 2 years after diagnosis of diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%)</td>
<td>6.6±1.4</td>
<td>6.9±1.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±18</td>
<td>139±21</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.2±1.0</td>
<td>5.7±1.1</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.06±0.23</td>
<td>1.18±0.26</td>
</tr>
<tr>
<td>T:H</td>
<td>5.2±1.4</td>
<td>5.1±1.5</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; T:H, ratio of total:HDL cholesterol.

TABLE 2. Variables Considered for Inclusion in the Model

<table>
<thead>
<tr>
<th></th>
<th>Age in years at diagnosis of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1 for female; 0 for male</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>1 for Afro-Caribbean; 0 for white or Asian-Indian</td>
</tr>
<tr>
<td>Asian-Indian</td>
<td>1 for Asian-Indian; 0 for white or Afro-Caribbean</td>
</tr>
<tr>
<td>Smoking</td>
<td>1 for a current smoker at diagnosis of diabetes; 0 otherwise</td>
</tr>
<tr>
<td>Ex-smoking</td>
<td>1 for a former smoker at diagnosis of diabetes; 0 if a current or nonsmoker</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index (kg/m²) at diagnosis of diabetes</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation, detected by electrocardiography, at diagnosis of diabetes (1 for yes, 0 for no)</td>
</tr>
<tr>
<td>HbA₁c</td>
<td>HbA₁c (%), mean of values measured 1 and 2 years after diagnosis</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure (mm Hg), mean of values measured 1 and 2 years after diagnosis</td>
</tr>
<tr>
<td>T:H</td>
<td>Mean of values measured 1 and 2 years after diagnosis</td>
</tr>
<tr>
<td>T</td>
<td>Duration of diabetes (years)</td>
</tr>
</tbody>
</table>

T:H indicates ratio of total:HDL cholesterol.

with log-cumulative hazard plots (data not shown). For AF, there were too few cases for a reliable log-cumulative hazard plot.

To improve model stability, SBP, total cholesterol, HDL cholesterol, and HbA₁c were each taken to be the mean of values taken 1 and 2 years after diagnosis of diabetes, as in our previous article. Model fitting was carried out by maximum likelihood estimation, using the Newton-Raphson method as implemented in the Numerical Algorithms Group C Library.

In a supplementary analysis, we fitted alternative models in which the ratio T:H was replaced with each of the following: total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and the ratio LDL:HDL cholesterol.

External validity of the model was examined by comparison with the rates of fatal stroke reported in 1370 patients of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) older-onset cohort, who were followed for an average of 8.3 years. The risk equation of this article was used to calculate 8.3-year risk of stroke in smoking and nonsmoking men and women with type 2 diabetes and characteristics as reported by WESDR. Because the blood pressure and cholesterol values taken are the mean of a large number, correction for regression dilution was incorporated. These risk estimates were then combined in a weighted average, reflecting the male-to-female mix and the prevalence of smoking in the WESDR cohort, to give an estimate of the overall risk of stroke, for comparison with the rates of fatal stroke reported by WESDR. Rates of nonfatal stroke were not reported by WESDR.

End Points
Stroke in the UKPDS is defined as a neurological deficit with symptoms or signs lasting 1 month or more. No distinction was made between ischemic, embolic, and hemorrhagic strokes. In patients with multiple strokes, only the first stroke is considered here. The model treats death from causes other than stroke as censored.

Statistical Model and Methods
The mathematical form of the model and its derivation have been described elsewhere. Model building then proceeded stepwise using likelihood ratio tests for significance. The following well-validated risk factors for stroke were tested for inclusion at a significance level of 0.05: sex, age at diagnosis of diabetes, SBP, atrial fibrillation, smoking, and ratio of total:HDL cholesterol. The following additional possible risk factors were tested at a significance level of 0.005, to reduce the danger of a type I error (erroneous inclusion) occurring: HbA₁c, Afro-Caribbean ethnicity, Asian-Indian ethnicity, body mass index (BMI), and duration of diagnosed diabetes. Proportional-hazards assumptions were verified.
TABLE 3. Parameters Included in Model Equation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.00186</td>
<td>0.000999–0.00271</td>
<td></td>
</tr>
<tr>
<td>Duration of diagnosed diabetes, per year</td>
<td>1.145</td>
<td>1.094–1.196</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at diagnosis of diabetes, per year</td>
<td>1.092</td>
<td>1.067–1.117</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.700</td>
<td>0.486–0.914</td>
<td>0.021</td>
</tr>
<tr>
<td>Smoking at diagnosis of diabetes</td>
<td>1.547</td>
<td>1.082–2.011</td>
<td>0.0052</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.554</td>
<td>2.744–14.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, per 10 mm Hg</td>
<td>1.122</td>
<td>1.040–1.204</td>
<td>0.0025</td>
</tr>
<tr>
<td>Lipid ratio, T:H</td>
<td>1.138</td>
<td>1.034–1.242</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

T:H indicates ratio of total:HDL cholesterol.

(P>0.5) and Asian-Indian (P>0.5) ethnicity, and ex-smoking status (P>0.25). BMI achieved conventional significance (P=0.0085) but did not meet our criteria for inclusion in the model.

In a patient who has had no stroke in the first T years of diagnosed diabetes, the probability of a stroke in the next t years is

\[ R(t) = \exp[-q \cdot 1.145^7 \cdot (1-1.145)/(1-1.145)] \]

where

\[ q = 0.00186 \times 1.092^{10.255} \times 1.122^{147} \times 1135^{0.11} - 531 \times 1.138^{10.5} \times 10^{1.0} \times 1.138^{5} \times 10^{1.1} \times 0.00212, \]

and hence

\[ R(t) = \exp[-0.00212 \times 1.145^{12} \times (1-1.145)/(1-1.145)] = 0.069, \]

so that such a patient has a 6.9% probability of a stroke within the next 5 years, conditional on not dying from causes other than stroke. For a patient who smokes, the probability is 10.5%. Assuming a 30% smoking prevalence, the average 5-year risk in the population is (0.3×10.5%)+(0.7×6.9%)=8.0%. To have 80% power to detect an effect of a therapy that lowers risk by 15%, a 5-year trial would need \(=15,000 \) patients. These event rates are likely to be overestimates for the whole population, because not all patients will remain in the study for 5 years, as a result of deaths from cardiac and other causes as well as loss to follow-up. A more thorough analysis would correct also for regression dilution and account for the variation in risk factors across the population rather than use mean values.

Validation

Figure 1 shows that survival rates predicted by the model lie close to the rates observed in the UKPDS. Observed and

Example

Consider a power calculation for a hypothetical trial of lipid-lowering therapy in primary prevention of stroke, among white men with type 2 diabetes. Based on data from WESDR, assume a cohort with mean SBP 147 mm Hg, total cholesterol 5.65 mmol/L, HDL cholesterol 1.11 mmol/L, age 55 years at diagnosis of diabetes, and with 12 years of diagnosed diabetes.55,56 For a nonsmoking man, with characteristics as above and assuming no AF, calculations are as follows:

\[ q = 0.00186 \times 1.092^{10.255} \times 1.122^{147} \times 1135^{0.11} - 531 \times 1.138^{10.5} \times 10^{1.0} \times 1.138^{5} \times 10^{1.1} \times 0.00212, \]

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Validation

Figure 1 shows that survival rates predicted by the model lie close to the rates observed in the UKPDS. Observed and
modeled survival rates are shown in Figure 2a and 2b, split by SBP and by the ratio T:H, confirming the ability of the model to adjust for these risk factors.

For the WESDR cohort, in which 59 deaths from stroke were observed, the equation derived here predicts a 13.2% risk of fatal and nonfatal stroke in 8.3 years, corresponding to 197 strokes in 1370 patients. Previous studies have reported stroke fatality rates between 23% and 30% in diabetes. Applying a 26.5% fatality rate to our prediction of 197 strokes gives 52 fatal strokes. For comparison, the Framingham equations for mortality predict 33 fatal strokes in the same cohort.41

**Discussion**

To our knowledge, this is the first time a model has been developed to predict the risk of stroke specifically in a population with type 2 diabetes. Because our equations are based on a cohort identified at diagnosis of diabetes and without previous stroke, the model predicts risk of stroke as a primary event. The inputs required by the model are all readily measured in clinical practice, and routinely reported in research, for maximum applicability. The model has been incorporated in the UKPDS Risk Engine software, which is available to noncommercial users without charge from our website.42

Several limitations arise from the use of clinical trial rather than epidemiologic data, although we have attempted to correct for the impact of trial selection criteria, as described above. For time periods <4 years or >20 years after diagnosis of diabetes, or for ages >65 at diagnosis of diabetes, predictions from this model are extrapolations. Our definition of nonfatal stroke is more stringent than is sometimes used, requiring signs or symptoms to persist for more than a month. Our model does not distinguish between fatal and nonfatal strokes or between ischemic and hemorrhagic strokes. It would be ideal to test for any effect of antihypertensive and other therapies, but this is not practical because many patients took many different therapies over the years of UKPDS follow-up.43 Certain limitations are generic to all modeling exercises. Users should be aware that the risk ratio between individuals at 2 levels of a risk factor is not necessarily equal to the risk reduction obtainable for a single individual by changing levels of the risk factor. For tight blood pressure control, the risk reduction obtained in the UKPDS was greater than the risk ratio in an observational model would suggest.3 The current version of the model does not provide for estimation when data are missing. HbA1c was not found to be significant in this analysis, as it was in a previous UKPDS analysis that used more person-years of data and a more informative variable, updated mean HbA1c.4 BMI achieved conventional significance (P<0.05) but did not meet our inclusion criteria, which were designed to protect the generalizability of the risk equation. A risk equation including BMI might not generalize well, because previous studies have found that BMI is not a risk factor for stroke in type 2 diabetes or have even reported a possible protective effect of obesity.44,47

The comparison with stroke death rates in WESDR suggests that the model may generalize well to other populations. Although our derived figure, 52 fatal strokes, is lower than the 59 fatal strokes, this is to be expected because we model first stroke only. There are few other published models for the risk of stroke, and none specific to diabetes. The best-known previously published risk equations for stroke are derived from the Framingham cohort,20,41 and have been used in guidelines for clinical practice49 and in health economic modeling in the general population49 and in diabetes.21–23 The 5734 individuals in Framingham were older than in the UKPDS, (mean age 66 years) and experienced a higher event rate, 472 strokes in 10 years, but fewer than 10% had diabetes. The Framingham profile adjusts for left ventricular hypertrophy. Exclusion of the latter from the present paper gives our equations greater applicability, at the cost of some discriminatory power. The British Regional Heart Study model for risk of stroke does not adjust for presence of diabetes,50 and a recent cardiovascular risk score provides only relative risk in the case of stroke.51

Although guidelines for primary prevention often use risk of coronary heart disease as a surrogate for risk of cardiovascular disease,48,52 accurate estimation of stroke as well as coronary risk is preferable, for example, in hypertension management17 and for patients of African origin.15 The model here is suitable for use in a clinical setting.

Risk estimators also have a role to play in research and in policy formulation. The example in the Results section has demonstrated the use of the model in a power calculation, indicating that in primary prevention the large numbers needed to establish a lipid-lowering effect on stroke may require large-scale meta-analyses.53,54 The literature applying the Framingham equation to cost-effectiveness analyses in diabetes demonstrates a role for a diabetes-specific risk estimator.22,23,55 We hope that the present article will be of use to researchers, planners, and clinicians in the management of cerebrovascular risk in diabetes.

**Appendix: Regression Dilution**

The term regression dilution describes the behavior of parameter estimates in regression and in survival analysis when a predictor variable is subject to biovariability or assay variability.56 The risk equations reported in this article is recommended for use with estimates of blood pressure, and of total and HDL cholesterol, of similar precision to those with which the model was built, that is, the mean of 6 measurements of blood pressure, the mean of 2 measurements of total cholesterol, and the mean of 2 measurements of HDL cholesterol.

Adjustment for regression dilution is appropriate if the available data are not subject to biovariability, for example, if the blood pressure and cholesterol levels are the means over very large populations. Based on a maximum likelihood method,57 the following corrections are appropriate. For blood pressure, replace the parameter estimate 1.122 with 1.122/1.153. For lipid ratio, replace the parameter estimate 1.138 with 1.138×1.181. Because variables are centered around their means in the model equation (for example, blood pressure is used as SBP–135.5), no adjustment is necessary to the intercept parameter.

We use a method reported previously56 to estimate the adjustment necessary if the input data are of greater biovariability than ours. If the available blood pressure is the mean of just 3 measurements, replace 1.122 with 1.101. If blood pressure is a single measurement, replace 1.122 with 1.060. If the lipid ratio is based on single measurements of HDL and total cholesterol, replace the parameter 1.138 with 1.111.
Acknowledgments

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References


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