Risk Factors for Myocardial Infarction Case Fatality and Stroke Case Fatality in Type 2 Diabetes

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OBJECTIVE — Patients with diabetes have a higher case fatality rate in myocardial infarction (MI) or stroke than those without diabetes: that is, MI and stroke are more often fatal if diabetes is present. We investigated whether the risk of MI or stroke being fatal in type 2 diabetes can be estimated using information available around the time diabetes is diagnosed.

RESEARCH DESIGN AND METHODS — Analyses were based on 674 cases of MI (351 fatal) that occurred in 597 of 5,102 U.K. Prospective Diabetes Study (UKPDS) patients for whom covariate data were available during a median follow-up of 7 years. Multivariate logistic regression was used to examine differences in risk factors, measured within 2 years of diagnosis of diabetes, between fatal and nonfatal MI. Similar analyses were performed for 234 strokes (48 fatal) that occurred in 199 patients.

RESULTS — Patients with fatal MI had higher HbA1c than those with nonfatal MI (odds ratio 1.17 per 1% HbA1c, \( P = 0.014 \)). Patients with fatal stroke had higher HbA1c than those with nonfatal stroke (odds ratio 1.37 per 1% HbA1c, \( P = 0.007 \)). Other risk factors for MI case fatality included increased age, blood pressure, and urine albumin level.

CONCLUSIONS — The risk of MI or stroke being fatal in type 2 diabetes is associated with risk factors, including HbA1c, measured many years before onset of MI or stroke. Equations have been added to the UKPDS Risk Engine to estimate likely case fatality rates in MI and stroke.

Diabetes Care 27:201–207, 2004

Myocardial infarction (MI) and stroke are more common among people with diabetes than those without (1–3). Diabetes is also a risk factor for MI case fatality: that is, MI is more often fatal in people with diabetes compared with MI in those without diabetes (4–7). Hyperglycemia has been shown to be a risk factor for MI case fatality in people with and without diabetes (4,8–11), but studies have been limited mainly to risk factor measurements taken after admission to hospital for MI (4,8–10). Some authors have regarded hyperglycemia as a metabolic consequence of severe MI rather than a cause (12–14), and it is known that insulin therapy to reduce blood glucose levels can improve prognosis after MI in patients with diabetes (15).

We have used data from the U.K. Prospective Diabetes Study (UKPDS) to examine differences in risk factors measured during the first 2 years after diagnosis of diabetes between those with fatal MI and those with nonfatal MI. We also examine differences between those with fatal stroke and nonfatal stroke. The prospective design of the UKPDS allows this analysis to include all cases of MI and stroke, not just those surviving to reach hospital, and permits the assessment of risk factors measured many years before the MI or stroke occurs.

The UKPDS Risk Engine is a risk calculator specific to type 2 diabetes that can be used to estimate the risk of MI (16) or stroke (17) occurring within a given time period. The present analysis adds to the risk engine equations for MI and stroke case fatality to enable estimation of the probability of fatal coronary heart disease (CHD) and fatal stroke within the UKPDS Risk Engine or other computer models.
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months of the event; stroke was similarly defined.

Statistical analysis
Model fitting for MI case fatality was carried out on 674 MI events that occurred in 597 patients. A further 206 events occurred in 148 patients for whom not all covariate data were available or for whom the MI occurred before the measurement of covariates. Model fitting for stroke case fatality was carried out on 234 stroke events that occurred in 199 patients. A further 69 strokes occurred in 60 patients for whom not all covariate data were available or for whom the stroke occurred before the measurement of covariates.

Multivariate logistic regression was used to compare levels of potential risk factors (listed in Table 1) between those with fatal MI and those with nonfatal MI and, similarly, between those with fatal stroke and those with nonfatal stroke. Potential risk factors were measured at diagnosis of diabetes with the following exceptions. For each individual, HbA1c, systolic blood pressure (sBP), lipid ratio (total/HDL cholesterol), BMI, urinary albumin, and triglycerides were defined as the mean of values taken 1 and 2 years after diagnosis of diabetes. These mean values can have a strong predictive value as discussed in our previous studies (16,17). To minimize confounding, we entered time to event (from diagnosis of diabetes) into the model as a continuous variable. We also tested whether a second MI or stroke event was more likely to be fatal than a first event by entering into the logistic regression a variable coded 0 for a first event and 1 for a second event. For patients with three or more MIs, the first two MIs were included. We also used permutation testing, carried out in S-plus (Insightful Corporation, Seattle, WA), to verify that the P values from logistic regression were not materially affected by this dependence (26). Details are available from the corresponding author on request.

UKPDS risk engine equations
Risk equations for coronary and stroke case fatality that would be suitable for inclusion in the UKPDS Risk Engine (16,17) were developed. These used logistic regression models as above but differed in two ways. First, for compatibility with the existing risk engine equations, variables were constrained to age at diagnosis of diabetes, time to event, sex, ethnic group, smoking, HbA1c, sBP, and lipid ratio (total cholesterol:HDL cholesterol). Second, to minimize the risk of type I error, variables were tested at the 0.5% rather than 5% significance level, except where the literature already strongly supported a variable as a case fatality risk factor: for MI, age (5,27–29), and previous MI (30,31) and for stroke, age (32–37), sex (37,38–41), and previous stroke (39,40). Tests were carried out for interactions between all variables that were found significant. To verify that the data excluded because of missing variables were comparable with the data used, an internal validation exercise was carried out as follows: model predictions were calculated using the excluded data where possible and compared with observed outcomes.

RESULTS — Of the 674 MI events used in model fitting, 52% were fatal (n = 351). Of the 234 strokes used in model fitting, 21% were fatal (n = 48).

MI model
The multivariate MI model identified increased age at diagnosis of diabetes, time from diagnosis of diabetes to event, HbA1c, sBP, and urinary albumin as significant risk factors for MI case fatality at the 5% level of significance. That is, each of these risk factors was elevated in those with fatal MI compared with those with nonfatal MI. No significant difference was found between the case fatality rate in first MIs (51%, 304 fatal of 597 first MIs) and second MIs (61%, 47 of 77) with P = 0.15 in the multivariate analysis. Time to event was significant with greater MI case fatality in events occurring later after diagnosis of diabetes.

Odds ratios and P values are listed in Table 2. The effect size for time to event from diagnosis of diabetes is greater than the effect size for age at diagnosis of diabetes (P = 0.008 in a likelihood ratio test). Other variables tested had no effect, with all P values >0.2 except for a family history of MI (P = 0.054), white blood cell count (P = 0.063), and plasma creatinine (P = 0.0875). The Hosmer and Lemeshow (25) procedure indicated the logistic link function to be a good fit (P = 0.966). In a supplementary analysis, adjusting for all variables included in the MI model, current sulfonylurea therapy had no effect (P = 0.68) on MI case fatality with 51% (142/277) of patients taking a sulfonylurea having a fatal MI compared with 53% (209/397) of those not taking a sulfonylurea. The calendar year in which MI took place was not associated with case fatality (P = 0.51).

When the ratio of case subjects to control subjects is high, odds ratios cannot be interpreted as approximate risk ratios: in this data, the ratio of fatal to nonfatal MIs is close to 1. For example, in a group of patients with average 50% case fatality rate, the odds ratio of 1.05 per year of age implies that a group of patients 10 years older would have 62% case fatality rate. For the same group, a 1% increment in HbA1c would imply a 54% case fatality rate and a 10-mmHg increment in sBP or a doubling of urinary albumin would imply a 53% case fatality rate.

Stroke model
The multivariate stroke model identified sex (with higher stroke case fatality in women), increased HbA1c, sBP, white blood cell count, and previous stroke as significant risk factors for stroke case fatality at the 5% level of significance. First strokes were less likely to be fatal than subsequent strokes: 18% (36 fatal of 199
Table 1—Variables used in fitting MI and stroke case fatality models and their values in UKPDS patients who experienced an MI or stroke.

<table>
<thead>
<tr>
<th>First MI fatal</th>
<th>First MI not fatal</th>
<th>First stroke fatal</th>
<th>First stroke not fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At diagnosis of diabetes</strong></td>
<td><strong>n</strong> 304 293 36 163</td>
<td><strong>n</strong> 304 293 36 163</td>
<td><strong>n</strong> 304 293 36 163</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>58 (53–62)</td>
<td>55 (49–60)</td>
<td>57 (55–61)</td>
</tr>
<tr>
<td><strong>Race (Caucasian/Afro-Caribbean/Asian) (%)</strong></td>
<td>92/2/6</td>
<td>86/2/12</td>
<td>94/0/6</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>65</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td><strong>Smoker (current/ex/never) (%)</strong></td>
<td>38/35/28</td>
<td>39/36/25</td>
<td>31/36/33</td>
</tr>
<tr>
<td><strong>Fitness level (sedentary/moderately active/active/fit) (%)</strong></td>
<td>22/39/37/2</td>
<td>23/33/38/5</td>
<td>22/39/36/3</td>
</tr>
<tr>
<td><strong>Exercise (1 h per week) (%)</strong></td>
<td>12</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td><strong>Alcohol (none to light/regular/heavy/previous) (%)</strong></td>
<td>79/15/3/2</td>
<td>79/17/2/2</td>
<td>81/8/3/8</td>
</tr>
<tr>
<td><strong>White blood cell count (×10^9/l) mean (range)</strong></td>
<td>7.15 (6.00–8.70)</td>
<td>6.90 (5.70–8.50)</td>
<td>6.35 (5.43–7.13)</td>
</tr>
<tr>
<td><strong>Plasma creatinine (μmol/l) mean (range)</strong></td>
<td>84 (72–95)</td>
<td>83 (72–92)</td>
<td>78 (71–95)</td>
</tr>
<tr>
<td><strong>Family history of myocardial infarction (%)</strong></td>
<td>37</td>
<td>43</td>
<td>—</td>
</tr>
<tr>
<td><strong>Family history of hypertension (%)</strong></td>
<td>22</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td><strong>Atrial fibrillation (%)</strong></td>
<td>—</td>
<td>—</td>
<td>84</td>
</tr>
<tr>
<td><strong>HbA1c (%) mean (range)</strong></td>
<td>6.70 (6.00–7.71)</td>
<td>6.45 (5.90–7.55)</td>
<td>6.78 (6.25–7.94)</td>
</tr>
<tr>
<td><strong>sBP (mmHg) mean (range)</strong></td>
<td>140 (129–156)</td>
<td>135 (125–150)</td>
<td>152 (140–165)</td>
</tr>
<tr>
<td><strong>Lipid ratio (total/HDL cholesterol) mean (range)</strong></td>
<td>5.6 (4.7–6.6)</td>
<td>5.6 (4.9–6.7)</td>
<td>5.2 (4.6–6.1)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) mean (range)</strong></td>
<td>26.2 (24.1–29.7)</td>
<td>26.4 (23.8–29.7)</td>
<td>27.6 (25.1–30.9)</td>
</tr>
<tr>
<td><strong>Urinary albumin (mg/l)† mean (range)</strong></td>
<td>13.0 (6.0–32.6)</td>
<td>9.5 (4.0–20.5)</td>
<td>11.7 (5.4–62.5)</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)† mean (range)</strong></td>
<td>1.66 (1.29–2.47)</td>
<td>1.73 (1.30–2.39)</td>
<td>1.98 (1.31–2.78)</td>
</tr>
<tr>
<td><strong>Time to event (years)</strong></td>
<td>7.59 (4.96–10.64)</td>
<td>6.61 (4.08–8.79)</td>
<td>8.95 (5.51–11.78)</td>
</tr>
</tbody>
</table>

Data are mean (interquartile range) or percentage, and divided by survival status at first MI or stroke. There were no patients who had both MI and stroke. Variables not entered into model—variances not corrected and all others entered.

Individual HbA1c was taken to be the mean of values recorded 1 and 2 years after diagnosis of diabetes (amplitude for all variables in the subheading)†. The values were log transformed before entry into the model.

*For each individual, HbA1c was taken to be the mean of values recorded 1 and 2 years after diagnosis of diabetes (similarly for all variables in this subheading).

†, this variable was log transformed before entry into the model.
first strokes) compared with 60% (12 of 20), respectively ($P < 0.0001$). Time to event was not significant ($P = 0.21$) nor was calendar year of stroke ($P = 0.96$). Odds ratios and $P$ values are shown in Table 2. The other variables tested had no effect with all $P$ values $>0.2$ except for family history of hypertension ($P = 0.11$), atrial fibrillation ($P = 0.13$), and Afro-Caribbean ethnicity ($P = 0.17$). The Hosmer and Lemeshow (25) procedure indicated the logistic link function to be a good fit ($P = 0.248$).

**UKPDS risk engine equations**

The risk engine equation for MI case fatality is:

Probability that a MI is fatal (conditional on MI occurring) = $1/1$
\[
+ \exp[0.713 - 0.048 \times (\text{age} - 55)]
- 0.178 \times (\text{HbA}_1c - 6.86) - 0.141
\times (\text{SBP} - 141)/10 - 0.104 \times \text{time to event}]}

No significant interaction terms were found ($P > 0.1$ in all case subjects). A total of 206 occurrences (in 148 patients) of MI were excluded from model fitting because of missing covariate data. In the 82 occurrences (74 patients) who had the data required for the above equation, predicted MI case fatality rate was 50.1% (95% CI 44.6–55.6%) compared with an observed rate of 50.0% (41 fatal cases).

The risk engine model for stroke case fatality is:

Probability that a stroke is fatal (conditional on a stroke occurring) = $1/1$
\[
+ \exp[1.684 - 0.249 \times (\text{SBP} - 144)/10 - 2.210 \times \text{previous stroke}]}

HbA$_1c$ achieved conventional significance ($P = 0.017$) but did not meet our strict criteria for inclusion in the model. Sex approached significance ($P = 0.0615$) with men having a lower stroke case fatality rate.

The case fatality equations can be combined with risk equations for MI or stroke to give risk estimates for fatal MI or fatal stroke. Suitable risk equations include those from the UKPDS Risk Engine (16, 17) or the Framingham study (42). There are at least three methods for combining a risk equation with a case fatality equation. A simple approximation is to take

Risk of fatal MI in $t$ years $\approx$ (risk of MI over $t$ years) $\times$ (case fatality at year $t/2$)

This approximation is best when $t$ is not too large; for example, $t = 10$ years or less. The exact method is to take the sum over time of the product of risk and case fatality as follows:

\[
\text{Risk of fatal MI in } t \text{ years} = \sum_{i=1}^{t} (\text{risk of MI in year } i) \times (\text{MI case fatality in year } i)
\]
in which $\Sigma$ denotes summation. To make this exact method easily accessible, it is incorporated in the UKPDS Risk Engine software, which may be downloaded free of charge from http://www.dtu.ox.ac.uk/riskengine/. A third method is to use both a risk equation and a case fatality equation in a simulation model. In simple cases (particularly, where competing risks are not considered), this is equivalent to the summation method.

**CONCLUSIONS** — This analysis found that in type 2 diabetes, HbA$_1c$, measured close to diagnosis of diabetes is a risk factor for MI case fatality: that is, those with fatal MI had had higher HbA$_1c$ in previous years than those with nonfatal MI. Whereas glycaemia following a MI is a known risk factor for death, most studies have concluded that hyperglycaemia at the time MI occurs either contributes to the severity of the event or is induced by the event (11, 12, 43, 44). Previous studies designed to resolve this have been small and produced conflicting results (44, 45). Our data show for the first time that increased MI case fatality is associated with increased HbA$_1c$ levels years before onset of MI. Also new here is an association between increased stroke case fatality and previously recorded increased HbA$_1c$ levels. Other studies have reported no effect of HbA$_1c$ levels after a stroke (46–50), but the possible effect of HbA$_1c$ levels many years before stroke has not been studied.

Some studies in the general population have reported a higher case fatality rate in second MIs compared with first MIs, but our analysis has not confirmed this for the diabetic population (30, 31). It may be that treatment differences (for example, medication recommended for secondary prevention of CHD) partly or wholly offset any damage done by the previous MI. Smoking did not appear to be associated with MI case fatality, as has been found in previous studies in both diabetes and the general population (28, 29). The apparent paradox, that some studies of patients admitted to hospital with MI have found smoking to be protective, can be explained by a survivor effect (28, 51). For sex differences in MI case fatality, some studies have suggested that diabetic women had higher MI case fatality rates than diabetic men in the 1970s and early 1980s (5, 32) but similar rates since the mid-1980s (29, 32). As the UKPDS observed only 37 MI events prior

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**Table 2—Risk factors for MI and stroke case fatality found to be significant in multivariate models**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of diabetes (per year)</td>
<td>1.05 (1.03–1.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA$_1c$ (per 1%)</td>
<td>1.17 (1.03–1.32)</td>
<td>0.0144</td>
</tr>
<tr>
<td>sBP (per 10 mmHg)</td>
<td>1.13 (1.04–1.23)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Time to event, from diagnosis of diabetes (per year)</td>
<td>1.11 (1.06–1.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary albumin (per doubling of mg/l)</td>
<td>1.13 (1.03–1.23)</td>
<td>0.0050</td>
</tr>
</tbody>
</table>

**For Stroke**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female versus male)</td>
<td>2.33 (1.11–4.91)</td>
<td>0.0253</td>
</tr>
<tr>
<td>HbA$_1c$ (per 1%)</td>
<td>1.37 (1.09–1.72)</td>
<td>0.0071</td>
</tr>
<tr>
<td>sBP (per 10 mmHg)</td>
<td>1.29 (1.04–1.54)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Subsequent stroke versus first stroke</td>
<td>12.6 (4.34–36.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White blood cell count (per 10$^{-9}$/l)</td>
<td>0.82 (0.67–0.97)</td>
<td>0.0218</td>
</tr>
</tbody>
</table>
1985, there was insufficient statistical power to test for such a trend. Our finding that white blood cell count is protective contradicts one previous study, which found white blood cell count to elevate stroke case fatality (47). A possible mechanism is that high white blood cell count is acting as a marker for embolic rather than hemorrhagic stroke, the latter having faster onset and being more often fatal (33,52). However, some data suggest that white blood cell count is most elevated in hemorrhagic stroke (53). Given the large number of variables tested in our analyses of MI and stroke, it is also possible that this is a statistical artifact (type I error).

The design of the UKPDS, as a clinical trial, could confound our analyses. For example, if a glycemic therapy used in the trial had an effect on MI case fatality that was not mediated through glycaemia, then the glycemic effect reported here could be over- or underestimated. No such effects were observed for the main cardiovascular endpoints of the trial with the exception of metformin to which only 39 of the patients in this analysis were allocated. Conversely, it is not appropriate to test for an effect of randomized therapy group on case fatality in the UKPDS, because case fatality was not one of the predefined endpoints of the trial and because confirmation of the novel observational results of this analysis should come from additional studies rather than a reanalysis of the same cohort. The results reported here are associations present in observational data: the present study does not establish causal link between HbA1c and coronary, or stroke, case fatality.

**UKPDS risk engine equations**

New in this study are risk equations for MI and stroke case fatality in type 2 diabetes that are suitable for use in simulation models and other forecasts. Despite a proliferation of risk calculators for coronary and cardiovascular disease, we are aware of no similar risk calculator for case fatality. It has been observed that the Framingham equations do not give accurate predictions of CHD mortality in diabetes, at least when assessed against the UKPDS cohort (54).

The risk equations presented here are not intended to replace existing MI or stroke outcome scores, which are designed for use at the time the event occurs and use contemporaneous indicators of event severity, such as ST-segment elevation (55,56). Our equations are intended for use in simulation models and other health economic projections, for example, estimating the number of deaths from MI or stroke that might be observed over several years in a large cohort of people with diabetes. It is often useful to be able to estimate case fatality rates from data available at the beginning of a time period to undertake sample size calculations for studies or to plan health care interventions more effectively. Software implementing our equations is available from our website (http://www.dtu.ox.ac.uk/riskengine/).

For maximum applicability, the equations developed for inclusion in the UKPDS Risk Engine are restricted to variables that are widely available to clinicians and health planners. The internal validation exercise found no difficulties with the dataset and also suggested that the equations may be robust when applied to other cohorts that use similar definitions of MI and stroke case fatality. Studies that omit sudden cardiac death or include silent MI (detected for example by electrocardiogram) are likely to report lower case fatality rates. Our equation for stroke contains only two risk factors. Given that some variables, including sex and HbA1c, approached or achieved conventional significance without achieving our inclusion criteria and that only 20 subsequent strokes were included, it is likely that a more robust equation could be built from a study with a higher number of strokes, but no such equation has yet been published. The generalizability of our equations needs to be tested further in different cohorts of people with type 2 diabetes.

**Implications**

This study provides equations for MI and stroke case fatality in type 2 diabetes that will be useful to health planners and researchers when used together with risk equations, as indicated in RESULTS. Many of the risk factors identified are already established. Some, such as HbA1c, as a prospective risk factor for MI case fatality, are novel and have potential clinical implications. That diabetic levels of glycaemia confer higher risk for MI case fatality than nondiabetic levels has been reported before (4,5,7,12,28,29,44,57–61), but we have shown that within diabetes, risk rises with HbA1c. It may be that glycaemia should be thought of as a continuous risk factor for MI and stroke case fatality, across the nondiabetic and diabetic ranges, as has already been established for glycemia as a risk factor for MI events (62). For the individual with type 2 diabetes, lower levels of HbA1c are associated with lower risk of MI and lower fatality when MI occurs.

**References**


Acknowledgments — The funding of the UKPDS has been published previously (19). Richard Stevens is supported by a grant from the Healthcare Foundation. The cooperation of the staff and the patients at the centers is much appreciated. We are grateful to Dr. Mike Patefield of the University of Reading for additional statistical advice and to anonymous reviewers for comments that have greatly enhanced the study.
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64:885–888, 1989


