Risk prediction of cardiovascular disease in type 2 diabetes: A risk equation from the Swedish National Diabetes Register (NDR)

Jan Cederholm, MD, PhD ¹, Katarina Eeg-Olofsson, MD ², Björn Eliasson, MD, PhD ², Björn Zethelius, MD, PhD ³, Peter M Nilsson, MD, PhD ⁴; Soffia Gudbjörnsdottir, MD, PhD ², on behalf of the Swedish National Diabetes Register

¹ Department of Public Health and Caring Sciences, Family Medicine and Clinical Epidemiology, Uppsala University, Uppsala, Sweden
² Department of Medicine, Sahlgrenska University Hospital, Gothenburg University, Gothenburg, Sweden
³ Department of Public Health and Caring Sciences, Geriatrics, Uppsala University, Uppsala, Sweden
⁴ Department of Clinical Sciences, University Hospital, Malmö, Lund University, Sweden

Corresponding author:
Jan Cederholm, MD, PhD
E-mail: jan.cederholm@pubcare.uu.se

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Objective – Risk prediction models obtained in samples from the general population do not perform well in type 2 diabetic patients. Recently, 5-year risk estimates were proposed as more accurate than 10-year risk estimates. This study presents a diabetes-specific equation for estimation of the absolute 5-year risk of first incident fatal/nonfatal cardiovascular disease (CVD) in type 2 diabetic patients with use of HbA1c and clinical characteristics.

Research Design and Methods - The study was based on 11,646 female and male patients from the Swedish National Diabetes Register (NDR), age 18-70 years, with 1,482 first incident CVD events, 58,342 person-years, mean follow-up 5.64 years.

Results - This risk equation incorporates HbA1c, as in the UKPDS risk engine, and several clinical characteristics: onset age of diabetes, diabetes duration, sex, BMI, smoking, systolic blood pressure, antihypertensive and lipid-reducing drugs. All included predictors were associated with the outcome (p <0.0001, except for BMI p=0.0016) at Cox regression analysis. Calibration was excellent, when assessed by comparing observed and predicted risk. Discrimination was sufficient, with a receiver operator curve statistic of 0.70. Mean 5-year risk of CVD in all patients was 12.0±7.5%, while 54% of the patients had a 5-year risk ≥10%.

Conclusion - This more simplified risk equation enables 5-year risk prediction of CVD based on easily available non-laboratory predictors in clinical practice and HbA1c, elaborated in a large observational study obtained from the normal patient population with age up to 70 years.
Estimates of the risk for cardiovascular disease (CVD) can be used as prognostic information and support for the choice of therapeutic strategies for individual patients. Several risk models have been developed in recent years. The Framingham (1), SCORE (2) and DECODE (3) risk models, where type 2 diabetic patients are represented as subgroups of the populations studies, do not include HbA1c and diabetes duration as continuous risk factor variables. Furthermore, these models did not provide quite reliable risk estimates of fatal CVD in type 2 diabetic patients, as demonstrated in a recent review (4).

Risk models optimised for type 2 diabetes are of special importance, as these patients run 2-4 times higher CVD risk compared with the nondiabetic population (5). The UKPDS risk engine is a diabetes-specific model for estimation of the absolute 10-year risk of myocardial infarction (6), stroke (7) and CVD (8) in newly detected type 2 diabetic patients with onset age up to 65 years, and includes HbA1c and diabetes duration as risk factor variables, as well as systolic blood pressure, smoking, total cholesterol and HDL-cholesterol. However, as also stated by the UKPDS, there is a need for risk prediction models, easy to use in daily clinical practice, and based on large surveys obtained from the general type 2 diabetic population, reflecting the normal patient clientele with various diabetes duration. Recently, 5-year estimates of risk were proposed as more accurate than 10-year risk estimates (9).

The aim of this study was to analyse the association between several baseline predictor variables and first incident fatal or nonfatal CVD in type 2 diabetic patients. Data from the Swedish National Diabetes Register (NDR) were used, linked with the Swedish Cause of Death and Hospital Discharge Registers to identify CVD events. We also intended to present a new risk equation for estimation of the absolute 5-year risk of CVD, based on HbA1c and several non-laboratory clinical characteristics within the NDR as predictors.

RESEARCH DESIGN AND METHODS

The Swedish NDR was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or via clinical records databases, with information collected during patient visits at hospital outpatient clinics and primary health care centres nationwide. All included patients have agreed by informed consent to register before inclusion. The present study was approved by the Regional Ethics Committee at the University of Gothenburg. Reports concerning trends in risk factor control in the NDR, with a more detailed description of the NDR and Swedish diabetes care, have been published previously (10-14).

Subjects: This observational study consists of 11,646 female and male type 2 diabetic patients from the NDR, with age span 18-70 years and no previous CVD. All subjects with data available for analysed variables at baseline were included, and were followed prospectively from 1998 to 2003, for an analysis of the association between nine baseline risk predictors and first incident fatal or nonfatal CVD. The definition of type 2 diabetes was treatment with: (a) diet only, (b) oral hypoglycemic agents only, or (c) insulin only or combined with oral agents, and onset age of diabetes ≥40 years. Only 1% and 3% had an onset age <30 years and <40 years, respectively.

Another sample of 3,068 type 2 diabetic patients was also included (age 18-70 years and no previous CVD), comprising all patients newly registered in the NDR 1999, with 4 years follow-up to 2003.
Examinations at baseline: Clinical characteristics at baseline were: type of hypoglycemic treatment, age, diabetes duration, sex, weight, height, smoking, systolic blood pressures, use of antihypertensive and lipid-lowering drugs. Body mass index, BMI (kg/m²), was calculated as weight/height². The Swedish standard for blood pressure recording, used in the NDR, is the mean value of two supine readings (Korotkoff 1–5) with a cuff of appropriate size. A smoker was defined as a patient smoking one or more cigarettes per day, or smoking tobacco using a pipe, or who had stopped smoking within the past three months.

Laboratory analyses of HbA1c were carried out at local laboratories, and are quality assured nationwide by regular calibration with the HPLC Mono-S method. In this study, all HbA1c values were converted to the DCCT standard values using the formula: HbA1c(DCCT) = 0.923 x HbA1c(MonoS) + 1.345; R² = 0.998 (15).

Follow-up, definition of endpoint: All patients, free of CVD at baseline, were followed from 1998 to 2003, until the first incident CVD event, death, or 31st December 2003. The endpoint was fatal or nonfatal CVD, defined as coronary heart disease (CHD) or stroke, whichever came first. Fatal CHD was defined as fatal ischemic heart disease (ICD10 codes I20-I25) or sudden cardiac death (ICD10 codes R96.0-1). Nonfatal CHD was defined as nonfatal myocardial infarction (ICD10 code I21), unstable angina (ICD10 code I20.0), percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG). Stroke was defined as fatal or nonfatal stroke (ICD10 codes I61, I63, I64, I67.9).

All CVD endpoints were retrieved by data linkage with the Swedish Cause of Death Register and the Hospital Discharge Register (National Board of Health and Welfare, Sweden), which is an efficient validated alternative to revised hospital discharge notes and death certificates (16, 17). In total, 1,482 first incident fatal/nonfatal CVD events occurred, based on 58,342 person-years during mean 5.64 years of follow-up.

Statistical methods: Cox regression analysis was used to estimate hazard ratios with 95% confidence intervals (CI) for nine predictors of CVD, adjusted for each other. Forward, backward and score selection showed best model fit with all nine predictors included. Maximum likelihood estimation showed no interaction between the predictors. The proportional hazard assumption was confirmed for all predictors with the Kolmogorov-type Supremum Test, and with Test of all time-dependent covariates simultaneously. The hazard ratios were used as coefficients (β1-β9) for modelling a risk equation. The baseline hazard for year 5 (q5) was also assessed, when all nine covariates were given the value 0.

Survival analysis was used to calculate the observed survival probability rate of CVD for years 1-5, with 95% CI (Figure 1). Calibration of the risk equation was estimated with the ratio of observed survival rate / predicted rate, and with the Hosmer-Lemeshow test assessing goodness-of-fit. Discriminating capacity of the risk equation was estimated with the receiver operator curve statistic (c statistic), and with sensitivity and specificity according to cutoff levels of risk.

The accuracy of the risk equation was also tested in two randomly selected subgroups A and B, with 5,823 patients in each subgroup. A 5-year risk equation was generated in subgroup A, according to hazard ratios for the nine predictors. This equation was used in subgroup B to estimate predicted survival rate, for comparison with observed rate.

Furthermore in all patients, the nine predictor hazard ratios and baseline hazard for year 4 (q4) were used to generate an equation for 4-year CVD risk. This equation
was applied in patients newly registered in the NDR 1999, and calibration (observed 4-year CVD rate/predicted risk) and discrimination (c statistic) were estimated.

All statistical analyses were performed with SAS, version 9.1 (SAS Institute, Cary, NC). A p-value <0.5 was considered significant.

RESULTS
Clinical characteristics at baseline are shown in Table 1, presented as mean values ± SD or proportions, also giving values for the nine predictors used in the risk equation as described in the text.

The adjusted hazard ratios for nine predictors of fatal/nonfatal CVD at Cox regression analysis were all statistically significant (p <0.0001, except for BMI p=0.0016). These hazard ratios (β1-β9) with 95% CI were: 1.066 (1.057 - 1.075) for one year increase in onset age, 1.538 (1.381 – 1.712) for male sex, 1.087 (1.076 - 1.097) for one year increase in diabetes duration, 1.117 (1.074 - 1.161) for one % increase in HbA1c, 1.017 (1.006 – 1.028) for one unit increase in BMI, 1.278 (1.143 - 1.428) for antihypertensive drugs, 1.007 (1.004 – 1.010) for one mmHg increase in systolic BP, 1.314 (1.146 – 1.507) for lipid-lowering drugs, and 1.492 (1.314 - 1.694) for smoking. The baseline hazard (q5) was 0.00013 (0.00003 - 0.00022).

A risk equation was created for estimation of the 5-year risk of CVD, using q and the hazard ratios for the nine predictors (β1 - β9):

$$5\text{-year risk (CVD)} = (1 - \text{Exp}(- q_5 x \beta_1^{-\text{age-duration}} x \beta_2^{-\text{sex}} x \beta_3^{-\text{duration}} x \beta_4^{-\text{HbA1c}} x \beta_5^{-\text{BMI}} x \beta_6^{-\text{antihypertensive drugs}} x \beta_7^{-\text{systolic blood pressure}} x \beta_8^{-\text{lipid-lowering drugs}} x \beta_9^{-\text{smoker}})) x 100$$

β1 expresses the hazard ratio for age at onset of diabetes (age minus duration, in years). Values of the nine predictors were applied to the equation as described in Table 1: 1 for men and 0 for women; 1 for presence of antihypertensive drugs, lipid-lowering drugs and smoker and 0 otherwise.

Figure 1 shows the observed survival probability rate for fatal/nonfatal CVD during five years in all patients. The modelled survival rate for CVD is also shown, estimated with the NDR risk equation. The modelled survival rate is lying very close to observed rate, well within its 95% confidence intervals, and the ratio of observed/predicted rate was 0.999. The Hosmer-Lemeshow test, comparing observed and predicted risk within ten risk deciles, demonstrated excellent goodness-of-fit with a non-significant chi-square statistic 4.29 (p=0.83).

Furthermore, after dividing all patients into subgroups with predicted risk <5%, 5-9.9%, 10-14.9%, 15-19.9%, 20-24.9% and 25-29.9%, predicted survival rates were very close to observed rates in all subgroups, and well within their 95% CI (mean ratio of observed/predicted rate 0.999, range 0.983 - 1.011). Discrimination according to the c statistic was 0.70. The proportion of patients with CVD on follow-up who had predicted risk ≥10% was 78% (sensitivity), and the proportion without CVD events below risk 15% was 75% (specificity).

The modelled survival rate for CVD in subgroup B (randomly selected half part), estimated with the risk equation created in subgroup A, was also found to lie close to the observed survival rate in subgroup B, and within its 95% CI. The modelled 5-year survival rate in subgroup B was 87.7%, and the observed rate (95% CI) was 87.6 (86.7-88.4) %, with a ratio of 0.998. The c statistic in subgroup B was 0.69.

To illustrate the use of the NDR risk equation, consider a male type 2 diabetic patient at age 58 years, with diabetes
duration 5 years, HbA1c 8.0%, BMI 32 kg/m², systolic blood pressure 150 mmHg, treated with antihypertensives, not treated with lipid-lowering drugs, and non-smoker: 5-year risk (CVD) = (1 - Exp( - (0.00013 x 1.066^{58-5} x 1.538^1 x 1.087^5 x 1.117^{32} x 1.278^1 x 1.007^{150} x 1.314^0 x 1.492^0 ))) x 100 = 12.7%

Table 2 shows the 5-year risk of fatal/nonfatal CVD estimated with the NDR risk equation in the study sample, free from previous CVD. In all patients with age 18-70 years, mean 5-year risk of CVD was 12.0%, and the percentage with risk ≥10% and ≥15% was 54% and 29%. In subgroups with age 41-50, 51-60, 61-65 and 66-70 years, percentages with risk ≥10% were 4.2%, 36.8%, 77.3% and 94.3%, respectively.

Application of an equation for 4-year risk of CVD from the study sample (using all predictor hazard ratios together with baseline hazard q₄ = 0.00010) in another sample of 3,068 type 2 diabetic patients from the NDR (newly registered in 1999, followed during 4 years, 11,879 person-years, 261 CVD events, no previous CVD) demonstrated good calibration: ratio of observed CVD rate/predicted risk 0.96 in all patients, and 0.91-1.02-0.98-0.92 in subgroups with risk from <5% to ≥15%, all predicted risks well within 95% CI of observed rates (Table 2). The c statistic was 0.69 in all patients.

DISCUSSION

This study presents a new diabetes-specific risk equation for estimation of the absolute 5-year risk of first incident fatal or nonfatal CVD, developed with use of a large sample of type 2 diabetic patients from the normal patient population nationwide. This NDR risk equation includes as predictors eight easily estimated non-laboratory clinical characteristics and one necessary non-fasting blood sample, HbA1c, enabling quickly performed calculations of the 5-year CVD risk at patient visits in daily clinical practice.

Calibration of this risk equation was found to be excellent when assessed as the ratio of observed/predicted survival rates, and the modelled survival rate was found to lie very close to the observed survival rate (Figure 1). The Hosmer-Lemeshow test, comparing observed and predicted risk, demonstrated excellent goodness-of-fit. The discriminative capacity of the model was also sufficient, with a c statistic of 0.70. Discrimination was further verified by a sensitivity of 78% with predicted risk ≥10%, and a specificity of 75% with risk <15%.

As underlined in a recent review (18), both calibration and discrimination can never be perfect when assessing risk equations, and calibration is more valuable and important for the accurate assessment of risk than the c statistic. Discrimination would be perfect if all cases had e.g. risk 11% and all non-cases had risk 10%, but would not be helpful for treatment decisions based on risk assessment. With an average risk and a spread of the distribution as in this sample, the maximum c statistic might in fact be around 0.75 (18). Most important for a risk equation is its ability to accurately stratify subjects into higher or lower risk categories of importance for clinical treatment (18). We found accurate calibration in subgroups with 5-year CVD risk intervals from <5% up to 25-30%, with excellent match between predicted and observed rate. The accuracy of the model was further verified when a risk equation with the same predictors was modelled in a randomly selected half part of the sample, and then applied in the remaining half part with excellent calibration regarding observed and modelled survival rates.

The data regarding type of hypoglycemic treatment, diabetes duration, HbA1c, BMI, blood pressure, antihypertensive and lipid-lowering drugs
were considered reliable in this study. Smoking might be somewhat biased due to under-reporting by patients or examiners. CVD events retrieved from the National Cause of Death and Hospital Discharge Registers were also reliable, according to previous validations of reporting to these registers (16, 17). The upper age of included patients was limited to 70 years, in order to avoid the risk of less precise end-point diagnosis in old patients. The definition of type 2 diabetes used here should exclude most of the younger patients with possible LADA (Late Autoimmune Disease of the Adult), as only 1% had onset age <30 years, and 3% had <40 years. The large numbers of person-years and CVD events constitute a major strength of the study. The fact that patients were collected from the general Swedish diabetes population, by experienced physicians and nurses according to NDR guidelines for data reporting, at more than one-fourth of all primary care centres and more than three-fourths of all hospital diabetes clinics nationwide, with reported patients ranging up to 200 and 300 patients per unit, should make the study sample reasonably representative. There were no exclusions due to presence or absence of risk factors or co-morbidities, as often present in randomised controlled trials with limitations due to strict inclusion and exclusion criteria that may limit their applicability to the common patient populations.

What does this new NDR risk equation in type 2 diabetic patients add, as compared to the previously derived UKPDS risk engine? The UKPDS risk equations estimate the 10-year risks of myocardial infarction, stroke and CVD, developed from a randomised controlled trial with baseline 1977-91, in around 4,000 newly detected type 2 diabetic patients with age 25-65 years, using several blood tests: HbA1c as well as total and HDL cholesterol (6-8).

Other previous risk models, using several blood tests as predictors, have also presented 10-year estimates of CVD risk (2-4). Comparatively, this NDR risk equation is based on a later sample in 1998-2003, and large enough to allow the use of a 5-year estimate of risk, which is probably more accurate than 10-year estimates of risk regarding the interval from baseline data, and more useful from a patient treatment perspective than events in the far future, as underlined in a recent review (9).

Although this study was observational, it should reflect the normal type 2 diabetic patient population in general care, also allowing the inclusion of patients with various diabetes duration and age up to age 70 years. Other recent risk scores have chosen to estimate CVD risk (1-3, 8), but estimating CVD by combining CHD and stroke in this NDR model also allowed for the inclusion of patients with acute coronary syndromes and patients nowadays increasingly treated with PCI or CABG procedures before the occurrence of manifest myocardial infarction. Antihypertensive and lipid-lowering drugs were included as risk markers of hypertension and dyslipidemia. Although ideally blood lipids might be included, this model allows quick risk estimation with use of non-laboratory clinical characteristics easily available in daily practice, and only one non-fasting blood test needed, HbA1c. The inclusion of BMI in the NDR risk equation should also be of value, as many diabetic patients are overweight or obese, and the trend is increasing. Furthermore, elevated BMI values should fairly well reflect dyslipidaemia, and should also serve as a surrogate marker for increased insulin resistance. Similarly, a recently developed more simple risk model from the Framingham Heart Study used BMI instead of total and HDL cholesterol, and found that this model could predict CVD risk.
reasonably well (19). Overweight and obesity were recently found to be strong independent determinants of CHD in a meta-analysis of more than 300,000 subjects (20), and this finding has also been verified in a recent study of type 2 diabetic patients in the NDR (Eeg-Olofsson et al, 2008, unpublished).

A target level of 15% for the 10-year risk of MI has been suggested by the British National Institute of Clinical Guidance, NICE (21), and SCORE has recommended a level of 5% for the 10-year risk of fatal CVD (2). We have chosen a 5-year risk $\geq 10\%$ for fatal/nonfatal CVD as target level, with sensitivity 78% at this level, and 54% of all patients were above this level in this study. As expected, age had a strong influence, as only 4% with age below 50 years were above this target. One-third of patients with age 51-60 years had a risk $\geq 10\%$, underlining the need for more aggressive multifactorial treatment in these patients, as indicated in the STENO-2 study in this age interval (22). Seventy-seven percent of patients aged 61-65 years had a risk $\geq 10\%$, strongly indicating a need for intensified multifactorial treatment in this age group.

Application of a 4-year risk equation from the study sample in another later separate NDR sample followed during 4 years confirms the accuracy of the NDR risk equation, with good calibration according to the ratio of observed CVD rate/predicted risk.

In conclusion, the NDR risk equation has been elaborated as a more simplified and easily applied tool in daily practice, also allowing for the use of BMI as a marker of lifestyle. It was derived from a large observational prospective study, obtained from the normal patient population with age span 18-70 years. Estimate of 5-year risk of CVD might be preferable to 10-year risk, and the estimated risk also includes patients with acute coronary syndromes and those treated with PCI or CABG. This new risk model should preferably be evaluated in other cohorts.

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**Conflicts of interest:** None.
References


**Table 1.** Baseline characteristics in 11,646 type 2 diabetic patients aged 18-70 years, used as predictors of CVD in the NDR risk equation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=11,646)</th>
<th>Men (n=6,628)</th>
<th>Women (n=5,018)</th>
<th>Values used in the risk equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of diabetes</td>
<td>50.7±9.8</td>
<td>50.3±9.4</td>
<td>51.3±10.3</td>
<td>age – duration: years</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>7.5±6.6</td>
<td>7.5±6.6</td>
<td>7.5±6.7</td>
<td>years</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6±1.4</td>
<td>7.6±1.3</td>
<td>7.7±1.4</td>
<td>%</td>
</tr>
<tr>
<td>Body mass index, BMI</td>
<td>29.2±5.1</td>
<td>28.7±4.5</td>
<td>29.8±5.8</td>
<td>kg/m²</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>144.5±18.1</td>
<td>143.9±17.4</td>
<td>145.2±19.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>Male/female sex, %</td>
<td>56.9/43.1</td>
<td>-</td>
<td>-</td>
<td>1 for men, 0 for women</td>
</tr>
<tr>
<td>Antihypertensive drugs, %</td>
<td>44.7</td>
<td>44.0</td>
<td>45.7</td>
<td>1 for drug presence, 0 otherwise</td>
</tr>
<tr>
<td>Lipid-lowering drugs, %</td>
<td>13.0</td>
<td>13.1</td>
<td>12.8</td>
<td>1 for drug presence, 0 otherwise</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>17.8</td>
<td>18.5</td>
<td>16.8</td>
<td>1 for current smoker, 0 otherwise</td>
</tr>
</tbody>
</table>

Data are means ± SD, or proportions (%).
Table 2. Predicted 5-year fatal/nonfatal CVD risk in study patients with baseline 1998, and predicted 4-year CVD risk with observed CVD rate in a separate sample from the NDR with baseline 1999 and followed during 4 years, estimated with the NDR risk equation.

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>5-year risk</th>
<th>4-year risk</th>
<th>Observed rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean±SD</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>All</td>
<td>11,646</td>
<td>12.0±7.5</td>
<td>53.6</td>
<td>28.8</td>
</tr>
<tr>
<td>Men</td>
<td>6,628</td>
<td>13.5±8.1</td>
<td>60.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Women</td>
<td>5,018</td>
<td>10.1±6.2</td>
<td>44.8</td>
<td>18.9</td>
</tr>
<tr>
<td>Age groups:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-50 years</td>
<td>1,449</td>
<td>4.8±2.4</td>
<td>4.2</td>
<td>0.5</td>
</tr>
<tr>
<td>51-60 years</td>
<td>4,327</td>
<td>9.4±4.3</td>
<td>36.8</td>
<td>10.6</td>
</tr>
<tr>
<td>61-65 years</td>
<td>2,571</td>
<td>14.6±5.8</td>
<td>77.3</td>
<td>40.2</td>
</tr>
<tr>
<td>66-70 years</td>
<td>2,756</td>
<td>19.4±7.4</td>
<td>94.3</td>
<td>67.5</td>
</tr>
</tbody>
</table>

CI: confidence interval of observed CVD rate. a Ratio: observed 4-year CVD rate / predicted 4-year CVD risk.

b Intervals of 4-year risk of first incident fatal/nonfatal CVD. This risk was estimated with the same predictor hazard ratios as for 5-year risk, in a separate later NDR sample with baseline 1999 and followed-up during 4 years.
Figure 1. Observed survival probability rate with 95% confidence intervals, and modelled survival rate, for fatal/nonfatal CVD in 11,646 type 2 diabetic patients.