Risk Prediction of Cardiovascular Disease in Type 2 Diabetes

A risk equation from the Swedish National Diabetes Register

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

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 being 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 A1C and clinical characteristics.

RESEARCH DESIGN AND METHODS — The study was based on 11,646 female and male patients, aged 18–70 years, from the Swedish National Diabetes Register with 1,482 first incident CVD events based on 58,342 person-years with mean follow-up of 5.64 years.

RESULTS — This risk equation incorporates A1C, as in the UK Prospective Diabetes Study risk engine, and several clinical characteristics: onset age of diabetes, diabetes duration, sex, BMI, smoking, systolic blood pressure, and antihypertensive and lipid-reducing drugs. All predictors included were associated with the outcome ($P < 0.0001$, except for BMI $P = 0.0016$) with 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 $12.0 \pm 7.5\%$, whereas 54% of the patients had a 5-year risk $\geq 10\%$.

CONCLUSIONS — This more simplified risk equation enables 5-year risk prediction of CVD based on easily available nonlaboratory predictors in clinical practice and A1C and was elaborated in a large observational study obtained from the normal patient population aged up to 70 years.

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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), Systematic Coronary Risk Evaluation (SCORE) (2), and Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) (3) risk models, in which type 2 diabetic patients are represented as subgroups of the populations studies, do not include A1C and diabetes duration as continuous risk factor variables. Furthermore, these models did not provide reliable risk estimates of fatal CVD in type 2 diabetic patients, as demonstrated in a recent review (4).

Risk models optimized for type 2 diabetic patients are of special importance, as type 2 diabetic patients have a two to four times higher CVD risk than the nondiabetic population (5). The UK Prospective Diabetes Study (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 patients with newly detected type 2 diabetes with onset age up to 65 years and includes A1C 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 that are easy to use in daily clinical practice and are based on large surveys obtained from the general type 2 diabetic population, reflecting the normal patient clientele with various durations of diabetes. Recently, 5-year estimates of risk were proposed as being more accurate than 10-year risk estimates (9).

The aim of this study was to analyze 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 A1C and several nonlaboratory 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 centers nationwide. All patients included 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,

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with a more detailed description of the NDR and Swedish diabetes care, were published previously (10–14).

This observational study consists of 11,646 female and male type 2 diabetic patients from the NDR, with an age span of 18 to 70 years and no previous CVD. All subjects with data available for analyzed 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 *1*) diet only, *2*) oral hypoglycemic agents only, or *3*) insulin only or combined with oral agents, and onset age of diabetes ≥40 years. Only 1 and 3%, respectively, had onset age <30 years and <40 years. Another sample of 3,068 type 2 diabetic patients was also included (aged 18–70 years and no previous CVD), comprising all patients newly registered in the NDR 1999, with 4 years of 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, and use of antihypertensive and lipid-lowering drugs. BMI was calculated as weight in kilograms divided by the square of height in meters. 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, an individual who smoked tobacco using a pipe, or an individual who had stopped smoking within the past 3 months.

Laboratory analyses of A1C were performed at local laboratories, and nationwide quality assurance is assessed by regular calibration with the high-performance liquid chromatography Mono-S method. In this study, all A1C values were converted to the Diabetes Control and Complication Trial (DCCT) standard values using the following formula: A1C (DCCT) = 0.923 × A1C (MonoS) + 1.345; R^2 = 0.998 (15).

Follow-up and definition of end point
All patients, who were free of CVD at baseline, were followed from 1998 to 2003, until the first incident CVD event, death, or 31 December 2003. The end
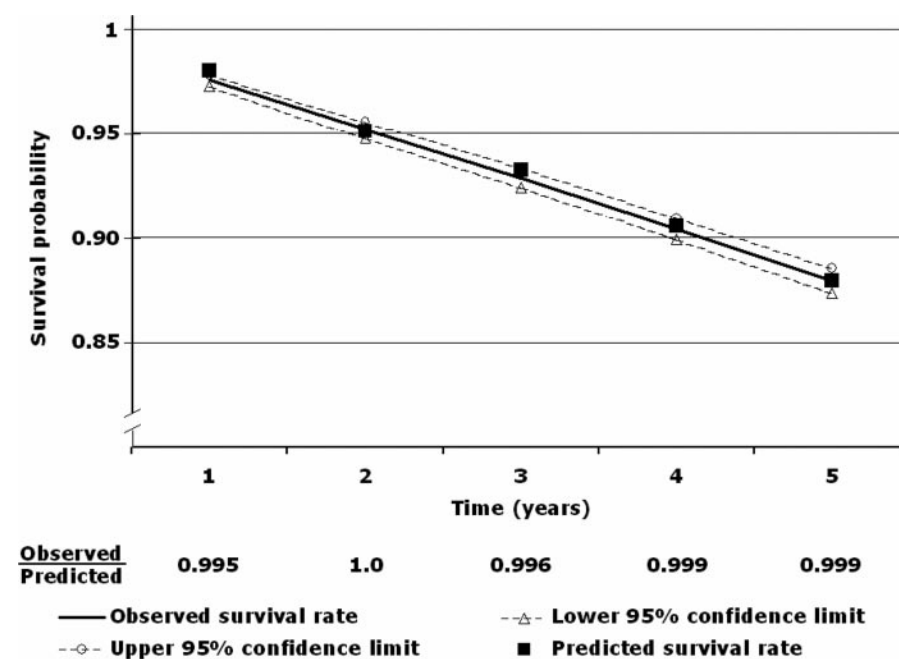

Figure 1—*Observed survival probability rate with 95% CIs and modeled survival rate for fatal/nonfatal CVD in 11,646 type 2 diabetic patients.*

point 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 (ICD-10 codes I20–I25) or sudden cardiac death (ICD-10 codes R96.0–1). Nonfatal CHD was defined as nonfatal myocardial infarction (ICD-10 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, and I67.9).

All CVD end points 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 (HRs) with 95% 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 the test of all time-dependent covariates simultaneously. HRs were used as coefficients (β_1–β_9) for modeling a risk equation. The baseline hazard for year 5 (q_5) 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 (Fig. 1). Calibration of the risk equation was estimated with the ratio of observed survival rate to 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 HRs 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 HRs and baseline hazard for year 4 (q_4) 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 to

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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

	All patients	Men	Women	Values used in the risk equation
n	11,646	6,628	5,018	
Age at onset of diabetes	50.7 ± 9.8	50.3 ± 9.4	51.3 ± 10.3	Age $-$ duration: years
Duration of diabetes	7.5 ± 6.6	7.5 ± 6.6	7.5 ± 6.7	Years
A1C	7.6 ± 1.4	7.6 ± 1.3	7.7 ± 1.4	%
BMI	29.2 ± 5.1	28.7 ± 4.5	29.8 ± 5.8	kg/m^2
Systolic blood pressure	144.5 ± 18.1	143.9 ± 17.4	145.2 ± 19.0	mmHg
Male/female sex (%)	56.9/43.1	—	—	1 for men, 0 for women
Antihypertensive drugs (%)	44.7	44.0	45.7	1 for drug presence, 0 otherwise
Lipid-lowering drugs (%)	13.0	13.1	12.8	1 for drug presence, 0 otherwise
Smokers (%)	17.8	18.5	16.8	1 for current smoker, 0 otherwise

Data are means $\pm$ SD or proportions.

predicted risk) and discrimination (c statistic) were estimated.

All statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC). $P < 0.5$ was considered significant.

RESULTS — Clinical characteristics at baseline, presented as mean values $\pm$ SD or proportions, are shown in Table 1, which also gives values for the nine predictors used in the risk equation as described in the text. The adjusted HRs for nine predictors of fatal/nonfatal CVD with Cox regression analysis were all statistically significant ($P < 0.0001$, except for BMI $P = 0.0016$). These HRs (β_1–β_9) with 95% CI were 1.066 (1.057–1.075) for a 1-year increase in onset age, 1.538 (1.381–1.712) for male sex, 1.087 (1.076–1.097) for a 1-year increase in diabetes duration, 1.117 (1.074–1.161) for a 1% increase in A1C, 1.017 (1.006–1.028) for a 1-unit increase in BMI, 1.278 (1.143–1.428) for antihypertensive drugs, 1.007 (1.004–1.010) for a 1-mmHg increase in systolic blood pressure, 1.314 (1.146–1.507) for lipid-lowering drugs, and 1.492 (1.314–1.694) for smoking. The baseline hazard (q_5) 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 HRs for the nine predictors (β_1–β_9):

$$5\text{-year risk (CVD)} = (1 - \exp[-\{q_5$$
$$\times \beta_1{}^{\text{age}-\text{duration}} \times \beta_2{}^{\text{sex}} \times \beta_3{}^{\text{duration}}$$
$$\times \beta_4{}^{\text{A1C}} \times \beta_5{}^{\text{BMI}} \times \beta_6{}^{\text{antihypertensive drugs}}$$
$$\times \beta_7{}^{\text{systolic blood pressure}} \times \beta_8{}^{\text{lipid-lowering drugs}}$$
$$\times \beta_9{}^{\text{smoker}}\}]) \times 100$$

β_1 expresses the HR 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 5 years in all patients. The modeled survival rate for CVD is also shown, estimated with the NDR risk equation. The modeled survival rate is lying very close to the observed rate, well within its 95% CI, and the ratio of observed to predicted rate was 0.999. The Hosmer-Lemeshow test, comparing observed and predicted risk within 10 risk deciles, demonstrated excellent goodness of fit with a nonsignificant χ^2 statistic of 4.29 ($P = 0.83$).

Furthermore, after we divided 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% CIs (mean ratio of observed to 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 $\geq$10% was 78% (sensitivity), and the proportion without CVD events with a risk <15% was 75% (specificity).

The modeled 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 modeled 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 of 5 years, A1C of 8.0%, BMI of 32 kg/m^2, and systolic blood pressure 150 mmHg, who was being treated with antihypertensives and not with lipid-lowering drugs and was a nonsmoker:

$$5\text{-year risk (CVD)} = (1 - \exp[-\{0.00013$$
$$\times 1.066^{58-5} \times 1.538^1 \times 1.087^5$$
$$\times 1.117^8 \times 1.017^{32} \times 1.278^1$$
$$\times 1.007^{150} \times 1.314^0 \times 1.4920\}])$$
$$\times 100 = 12.7\%$$

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 aged 18–70 years, the mean 5-year risk of CVD was 12.0%, and the percentages with risks $\geq$10 and $\geq$15%, respectively, were 54 and 29%. In subgroups aged 41–50, 51–60, 61–65, and 66–70 years, percentages with risk $\geq$10% were, respectively, 4.2, 36.8, 77.3, and 94.3%.

Application of an equation for 4-year risk of CVD from the study sample (using all predictor HRs together with baseline hazard $q_4 = 0.00010$) to another sample of 3,068 type 2 diabetic patients from the NDR (newly registered in 1999, followed during 4 years based on 11,879 person-years, 261 CVD events, and no previous CVD) demonstrated good calibration: ratio of observed CVD rate to predicted risk 0.96 in all patients and 0.91–1.02 to 0.98–0.92 in subgroups with risk from <5% to $\geq$15%; all predicted risks were well within the 95% CIs of observed rates (Table 2). The C statistic was 0.69 in all patients.

CONCLUSIONS — This study presents a new diabetes-specific risk equation for estimation of the absolute 5-year

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*

5-year risk	n	5-year risk mean ± SD	≥10% (%)	≥15% (%)	4-year risk	n	4-year risk mean ± SD	Observed rate % (95% CI*)	Ratio†
Category					Category				
All	11,646	12.0 ± 7.5	53.6	28.8	All	3,068	8.8 ± 6.1	8.5 (7.5–9.5)	0.96
Men	6,628	13.5 ± 8.1	60.3	36.3	Men	1,791	10.0 ± 6.6	9.8 (8.5–11.2)	0.98
Women	5,018	10.1 ± 6.2	44.8	18.9	Women	1,277	7.2 ± 5.0	6.7 (5.3–8.0)	0.92
Age-groups (years)					Intervals‡				
41–50	1,449	4.8 ± 2.4	4.2	0.5	<5.0%	945	3.0 ± 1.2	2.8 (1.7–3.8)	0.91
51–60	4,327	9.4 ± 4.3	36.8	10.6	5–9.9%	1,066	7.3 ± 1.4	7.4 (5.8–9.0)	1.02
61–65	2,571	14.6 ± 5.8	77.3	40.2	10–14.9%	606	12.3 ± 1.4	12.0 (9.4–14.7)	0.98
66–70	2,756	19.4 ± 7.4	94.3	67.5	≥15.0%	451	20.1 ± 5.1	18.4 (14.8–22.0)	0.92

*CI of observed CVD rate. †Ratio: observed 4-year CVD rate to predicted 4-year CVD risk. ‡Intervals of 4-year risk of first incident fatal/nonfatal CVD. This risk was estimated with the same predictor HRs as for the 5-year risk, in a separate later NDR sample with baseline 1999 and followed up during 4 years.

risk of first incident fatal or nonfatal CVD that was 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 nonlaboratory clinical characteristics and one necessary nonfasting blood sample, A1C, 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 to predicted survival rates, and the modeled survival rate was found to lie very close to the observed survival rate (Fig. 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 of ≥10% and a specificity of 75% with risk of <15%.

As emphasized in a recent review (18), both calibration and discrimination can never be perfect when one is 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 patients had, e.g., risk of 11%, and all nonpatients had risk of 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 ~0.75 (18). The most important aspect 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 an excellent match between predicted and observed rate. The accuracy of the model was further verified when a risk equation with the same predictors was modeled in a randomly selected half-part of the sample and then applied in the remaining half-part with excellent calibration regarding observed and modeled survival rates.

The data for type of hypoglycemic treatment, diabetes duration, A1C, BMI, blood pressure, and antihypertensive and lipid-lowering drugs were considered reliable in this study. The data for smoking might be somewhat biased because of 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 patients included was limited to 70 years to avoid the risk of less precise end point diagnosis in older patients. The definition of type 2 diabetes used here should exclude most of the younger patients with possible late autoimmune disease of the adult, as only 1% had onset age <30 years and 3% had onset age <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 centers 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 rea-

sonably representative. There were no exclusions attributable to the presence or absence of risk factors or comorbidities, as is often present in randomized controlled trials with limitations owing 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, compared with the previously derived UKPDS risk engine? The UKPDS risk equations estimate the 10-year risks of myocardial infarction, stroke, and CVD and were developed from a randomized controlled trial with baseline 1977–1991, in ~4,000 patients aged 25–65 years with newly detected type 2 diabetes, using several blood tests: A1C and 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, which is large enough to allow the use of a 5-year estimate of risk and is probably more accurate than 10-year estimates of risk for the interval from baseline data and more useful from a patient treatment perspective than events in the far future, as emphasized 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 durations of diabetes and age up to 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 pa-

tients 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 the use of nonlaboratory clinical characteristics easily available in daily practice, and only one nonfasting blood test, A1C, was needed. The inclusion of BMI in the NDR risk equation should also be of value, as many diabetic patients are overweight or obese, and this trend is increasing. Furthermore, elevated BMI values should fairly well reflect dyslipidemia 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 showed 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 >300,000 subjects (20), and this finding has also been verified in a recent study of type 2 diabetic patients in the NDR (K.E.-O. et al., 2008, unpublished observations).

A target level of 15% for the 10-year risk of myocardial infarction has been suggested by the British National Institute of Clinical Guidance (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 ≥10% for fatal/nonfatal CVD as the target level, with sensitivity of 78% at this level, and values for 54% of all patients were greater than this level in this study. As expected, age had a strong influence, as only 4% aged <50 years had values greater than this target. One-third of patients aged 51–60 years had risk ≥10%, emphasizing the need for more aggressive multifactorial treatment in these patients, as indicated in the STENO-2 study in this age interval (22). Of patients aged 61–65 years, 77% had risk ≥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 a later separate NDR sample followed during 4 years confirmed the accuracy of the NDR risk equation, with good calibration according to the ratio of observed CVD rate/predicted risk.

In summary, 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 an age span of 18 to 70 years. The estimate of 5-year risk of CVD might be preferable to that of 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.

References

1. Anderson KM, Odell PM, Wilson PWF, Kannel WB: Cardiovascular disease risk profiles. *Am Heart J* 121:293–298, 1991
2. Conroy RM, Pyörälä K, De Backer G, De Bacquer D, Wilhelmsen L, Graham IM, SCORE Project Group: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 24:987–1003, 2003
3. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyorala K, DECODE Study Group, European Diabetes Epidemiology Group: Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor: the DECODE Study. *Diabetologia* 47:2118–2128, 2004
4. Coleman RL, Stevens RJ, Retnakaran R, Holman RR: Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 30:1292–1294, 2007
5. Gu K, Cowie C, Harris M: Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971–1993. *Diabetes Care* 21:1138–1145, 1998
6. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR: The UKPDS Risk Engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci* 101:671–679, 2001
7. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, Holman RR, UK Prospective Diabetes Study Group: UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 33:1776–1781, 2002
8. Coleman RL, Stevens RJ, Holman RR: Estimating cardiovascular disease risk for individuals with type 2 diabetes: the new UKPDS risk engine. *Diabet Med* 24 (Suppl. 1):56, 2007
9. Jackson R: Cardiovascular risk prediction: are we there yet? *Heart* 94:1–3, 2008
10. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B: The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. *Diabetes Care* 26:1270–1276, 2003
11. Cederholm J, Eliasson B, Nilsson PM, Weiss L, Gudbjörnsdottir S, Swedish National Diabetes Register: Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. *Diabetes Res Clin Pract* 67:258–266, 2005
12. Eliasson B, Cederholm J, Nilsson P, Gudbjörnsdottir S, Swedish National Diabetes Register: The gap between guidelines and reality: type 2 diabetes in a national diabetes register 1996–2003. *Diabet Med* 22:1420–1426, 2005
13. Nilsson PM, Cederholm J, Gudbjörnsdottir S, Eliasson B, Steering Committee of the Swedish National Diabetes Register: Predictors of successful long-term blood pressure control in patients with diabetes: data from the Swedish National Diabetes Register (NDR). *J Hypertens* 23:2305–2311, 2005
14. Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjörnsdottir S, Eliasson B, the Steering Committee of the Swedish National Diabetes Register: Glycemic and risk factor control in type 1 diabetes: results from 13,612 patients in a national diabetes register. *Diabetes Care* 30:496–502, 2007
15. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, IFCC Working Group on A1C Standardization: IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. *Clin Chem* 1:166–174, 2004
16. Merlo J, Lindblad U, Pessah-Rasmussen H, Hedblad B, Rastam J, Isacsson SO: Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. *Eur J Epidemiol* 16:235–243, 2000
17. Tunstall-Pedoe H, Kuulasmaa K,

Amouyel P, Arveiler D, Rajakangas AM, Pajak A: Myocardial infarction and coronary deaths in the World Health Organization MONICA project: registration procedures, events rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 90:583–612, 1994

18. Cook NR: Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 115:928–935, 2007

19. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Massaro JM, Kannel WB: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 117:743–753, 2008

20. Bogers RP, Bemelmans WJE, Hoogenveen RT, Boshuizen HC, Woodward Knekt P, Shipley MJ, BMI-CHD Collaboration Investigators: Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 167:1720–1728, 2007

21. National Institute of Clinical Excellence (NICE): *Management of Type 2 diabetes: Management of Blood Pressure and Blood Lipids (Guideline H)*. London, NICE, 2002

22. Gaede P, Lund-Andersen H, Parving HH, Pedersen O: Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 358:580–591, 2008