ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Patients with diabetes are at higher risk for death and cardiovascular outcomes than the general population. We investigated whether the excess risk of death and cardiovascular events among patients with type 2 diabetes could be reduced or eliminated.

METHODS

In a cohort study, we included 271,174 patients with type 2 diabetes who were registered in the Swedish National Diabetes Register and matched them with 1,355,870 controls on the basis of age, sex, and county. We assessed patients with diabetes according to age categories and according to the presence of five risk factors (elevated glycated hemoglobin level, elevated low-density lipoprotein cholesterol level, albuminuria, smoking, and elevated blood pressure). Cox regression was used to study the excess risk of outcomes (death, acute myocardial infarction, stroke, and hospitalization for heart failure) associated with smoking and the number of variables outside target ranges. We also examined the relationship between various risk factors and cardiovascular outcomes.

RESULTS

The median follow-up among all the study participants was 5.7 years, during which 175,345 deaths occurred. Among patients with type 2 diabetes, the excess risk of outcomes decreased stepwise for each risk-factor variable within the target range. Among patients with diabetes who had all five variables within target ranges, the hazard ratio for death from any cause, as compared with controls, was 1.06 (95% confidence interval [CI], 1.00 to 1.12), the hazard ratio for acute myocardial infarction was 0.84 (95% CI, 0.75 to 0.93), and the hazard ratio for stroke was 0.95 (95% CI, 0.84 to 1.07). The risk of hospitalization for heart failure was consistently higher among patients with diabetes than among controls (hazard ratio, 1.45; 95% CI, 1.34 to 1.57). In patients with type 2 diabetes, a glycated hemoglobin level outside the target range was the strongest predictor of stroke and acute myocardial infarction; smoking was the strongest predictor of death.

CONCLUSIONS

Patients with type 2 diabetes who had five risk-factor variables within the target ranges appeared to have little or no excess risk of death, myocardial infarction, or stroke, as compared with the general population. (Funded by the Swedish Association of Local Authorities and Regions and others.)

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N Engl J Med 2018;379:633-44.
DOI: 10.1056/NEJMoa1800256
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Type 2 diabetes is a complex disease that leads to continuous medical care with comprehensive, multifactorial strategies for reducing cardiovascular risk. Patients with type 2 diabetes have risks of death and cardiovascular events that are 2 to 4 times as great as the risks in the general population.[1] Results from randomized trials support a range of interventions that target isolated risk factors such as elevated levels of glycated hemoglobin, blood pressure, and cholesterol to prevent or postpone complications of type 2 diabetes. The Steno-2 Study investigated the effects of multifactorial risk-factor control by means of behavior modification and pharmacologic therapy and showed long-lasting reductions in the risks of death and cardiovascular events among patients in whom these risks were reduced, as compared with patients who had been randomly assigned to usual care.[2,3]

The extent to which the excess risk associated with type 2 diabetes may be mitigated, or potentially eliminated, by contemporary evidence-based treatment and multifactorial risk-factor modification is unclear. In a nationwide cohort, we evaluated the association between the excess risks of death and cardiovascular outcomes among patients with type 2 diabetes, according to the number of risk-factor variables within therapeutic guideline levels, as compared with controls who were matched for age, sex, and county in Sweden. Risk-factor data were not available for controls.

In ancillary analyses, we estimated the strength of the associations between various risk factors and the incremental risks of death and cardiovascular outcomes associated with diabetes. Moreover, we examined the association between selected risk-factor variables such as levels of glycated hemoglobin, systolic blood pressure, and low-density lipoprotein (LDL) cholesterol within evidence-based target ranges and these outcomes.

METHODS

STUDY DESIGN AND SUPPORT

The Regional Ethics Review Board of Gothenburg, Sweden, approved the study. All the patients provided written informed consent before inclusion in the Swedish National Diabetes Register. The Swedish Association of Local Authorities and Regions and other nonprofit agencies supported the study; no industry support was provided.

DATA SOURCES AND STUDY COHORT

The Swedish National Diabetes Register has been described previously.[1,4] Type 2 diabetes was defined according to epidemiologic criteria — treatment with diet, with or without the use of oral antihyperglycemic agents, or treatment with insulin, with or without the use of oral antihyperglycemic agents. The latter category (insulin use) applied only to patients who were 40 years of age or older at the time of diagnosis. Patients with at least one entry in the register between January 1, 1998, and December 31, 2012, were included in the study. At baseline (defined as the first entry in the register), each patient with type 2 diabetes was matched for age, sex, and county with five controls without diabetes who were randomly selected from the Swedish population register by Statistics Sweden.

We constructed two cohorts of patients with type 2 diabetes. One cohort excluded patients with previous stroke, acute myocardial infarction, or amputation; those who had undergone dialysis or renal transplantation; and those with a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5. The second cohort of patients with type 2 diabetes had exclusion criteria that were similar to those of the first cohort but also excluded patients with previous coronary heart disease, atrial fibrillation, or heart failure. Controls who met any of these criteria were excluded without the exclusion of their matched patient.

OUTCOMES

We assessed death from any cause, fatal or nonfatal acute myocardial infarction (henceforth referred to as acute myocardial infarction), fatal or nonfatal stroke (henceforth referred to as stroke), and hospitalization for heart failure. Outcomes were identified in hospital discharge records with use of codes in the *International Classification of Diseases, 9th Revision* and *10th Revision*. The specific codes are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Patients were followed until an event occurred or until December 31, 2013, for all the outcomes except for death from any cause, for which follow-up ended on December 31, 2014.

STATISTICAL ANALYSIS

Crude incidence rates were calculated according to the number of risk-factor variables within tar-

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get ranges and are presented as events per 10,000 patient-years of observation with exact Poisson confidence intervals of 95%. We constructed Cox regression models and included baseline values in the models. All the models were adjusted for socioeconomic variables (income, marital status, immigrant status, and educational level), with stratification according to sex to allow for different underlying baseline hazards among men and women, and age was used as the time scale. Some models were adjusted for preexisting conditions. For death from any cause, we adjusted for coronary heart disease and heart failure; for myocardial infarction, we adjusted for atrial fibrillation and heart failure; for stroke, we adjusted for atrial fibrillation, heart failure, and coronary heart disease; and for hospitalization for heart failure, we adjusted for atrial fibrillation and coronary heart disease.

For the main analyses, we estimated the risk of each outcome among patients with type 2 diabetes, according to the number of risk-factor variables within target ranges, as compared with the controls matched for age, sex, and county. We defined whether the risk-factor variables were within target ranges on the basis of guideline-recommended target levels.[5,6] The regression models included the covariable "category," which denoted the number of risk-factor variables that were not within the target range (scale, none to five variables). The following five risk factors were considered: the glycated hemoglobin level (cutoff value, ≥7.0% or ≥53 mmol per mole), systolic and diastolic blood pressure (cutoff value, ≥140 mm Hg for systolic blood pressure or ≥80 for diastolic blood pressure), albuminuria (the presence of microalbuminuria or macroalbuminuria), smoking (being a current smoker at study entry), and the LDL cholesterol level (cutoff value, ≥2.5 mmol per liter [97 mg per deciliter]).

We constructed a separate Cox model for each age category, according to age at baseline: younger than 55 years of age, 55 years to younger than 65 years of age, 65 years to younger than 80 years of age, and 80 years of age or older. We adjusted for the duration of diabetes by assigning matched controls a duration of 0 years, and patients with type 2 diabetes had their duration of diabetes centralized around the grand mean (the mean duration among all the study participants).

Among patients with type 2 diabetes, we analyzed the relative importance of the risk factors. Relative importance provides an estimate of how important each risk factor is in terms of predicting the outcome. Several methods are available for this task; we chose to calculate the relative importance as measured by the R^2 values of the models,[7] and we tested the consistency of the results by calculating the explainable log-likelihood that was attributable to each risk factor.

We assessed the level associated with the lowest risk, given the glycated hemoglobin level, systolic blood pressure, and LDL cholesterol level, by modeling the association between each risk factor and the outcomes using restricted cubic splines. The evidence-based target level was set as the reference for each risk factor; not smoking was set as the reference for smoking status.

Missing data were imputed with the multivariate imputation by chained equations (MICE) algorithm. We imputed five complete data sets; a list of the variables that were used in the imputation model is provided in Table S3 in the Supplementary Appendix. The estimates from each imputed data set were combined into one overall estimate with the use of Rubin's rule. Figures S4 and S5 in the Supplementary Appendix show the frequency of missing-data elements and the distribution of each variable before and after the imputation. For the main analysis, we pooled the results across all five imputed data sets; the results of the analyses with the imputed data sets were virtually identical to those in the cohort with complete cases and were thus consistent with a complete-case analysis. For the ancillary analyses, we used the first imputed data set. All the analyses were performed with the use of RStudio software, version 3.2.3.

RESULTS

STUDY POPULATION

A total of 433,619 patients with type 2 diabetes and 2,168,095 controls were identified, and 271,174 patients with type 2 diabetes and 1,355,870 matched controls were included in the study (Fig. S1 in the Supplementary Appendix). The median follow-up among all the study participants was 5.7 years, during which 175,345 deaths occurred. The baseline characteristics of the patients with complete data on all five risk factors (96,673 patients with diabetes [35.6%]) and their matched controls are presented in Table 1. The number of patients in each risk-factor group in

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the imputed data sets is also shown in Table 1. The complete data regarding the characteristics of the participants at baseline are presented in Table S4 in the Supplementary Appendix.

The mean age of the patients was 60.60 years, and 47,777 of 96,673 patients (49.4%) were women. Table S5 in the Supplementary Appendix shows the baseline characteristics of the patients for whom data were missing for at least one risk factor. Figure S6 in the Supplementary Appendix shows the trends in risk factors over the period from 1998 through 2012, and Figure S7 in the Supplementary Appendix shows how causes of death varied among the groups according to the number of risk-factor variables in the target ranges.

RISK OF CARDIOVASCULAR EVENTS

A total of 37,825 patients with diabetes (13.9%) and 137,520 controls (10.1%) died during the study period. The numbers of events, incidence rates, and hazard ratios for all the outcomes among patients with diabetes, as compared with controls, at increasing numbers of risk-factor variables, as well as the risks of death among men and women, are presented in Table S2 in the Supplementary Appendix.

Figure 1 shows the adjusted hazard ratios for the outcomes, according to age category and the number of risk-factor variables within target ranges, among patients with diabetes as compared with matched controls. The results show a stepwise increase in the hazard ratios for each additional variable that was not within the target range among patients with diabetes, and the incremental risks of cardiovascular events and death that were associated with diabetes decreased in a stepwise fashion from younger to older age groups. Patients with diabetes who were 80 years of age or older at baseline had the lowest incremental risk of cardiovascular events and death, as compared with controls. In the overall cohort, patients with type 2 diabetes who had no risk-factor variables outside the target ranges had a marginally higher risk of death than the controls (hazard ratio, 1.06; 95% confidence interval [CI], 1.00 to 1.12).

Patients with diabetes who were 80 years of age or older at baseline and had no risk factors outside target ranges had the lowest hazard ratio, as compared with controls, for acute myocardial infarction across all the groups (hazard ratio, 0.72; 95% CI, 0.49 to 1.07) (Fig. 1B). Overall, patients with type 2 diabetes who had no risk-factor variables outside the target ranges had a lower risk of acute myocardial infarction than the matched controls (hazard ratio, 0.84; 95% CI, 0.75 to 0.93). Corresponding estimates for the excess risk of stroke are shown in Figure 1C. The overall hazard ratio for stroke among patients with no risk-factor variables outside the target ranges, as compared with controls, was 0.95 (95% CI, 0.84 to 1.07) (Table S2 in the Supplementary Appendix). Similar to the findings with acute myocardial infarction, there was a higher incremental risk of stroke in the younger age categories and for each variable that was not within the target range. Estimates regarding hospitalization for heart failure are shown in Figure 1D. Patients with type 2 diabetes who were younger than 55 years of age and had all five risk-factor variables outside the target ranges had the highest excess risk of hospitalization for heart failure of all the outcomes assessed (hazard ratio vs. control, 11.35; 95% CI, 7.16 to 18.01). The overall hazard ratio for hospitalization for heart failure among patients with no risk-factor variables outside the target ranges, as compared with controls, was 1.45 (95% CI, 1.34 to 1.57) (Table S2 in the Supplementary Appendix).

RISK-FACTOR STRENGTH AND LEVELS IN PATIENTS WITH TYPE 2 DIABETES

Figure 2A shows the predictors with the apparent greatest importance with regard to death from any cause. The five strongest predictors regarding the risk of death among patients with type 2 diabetes were smoking, physical activity, marital status, glycated hemoglobin level, and use of statins (lipid-lowering medication). The data shown in Figure 3A suggest that lower glycated hemoglobin levels than are currently recommended in guidelines were associated with a lower risk of death.

The strongest predictors regarding the risk of acute myocardial infarction were the glycated hemoglobin level, systolic blood pressure, LDL cholesterol level, physical activity, and smoking (Fig. 2B). These risk factors showed a linear association with the risk of acute myocardial infarction (Fig. 3B).

The strongest predictors regarding the risk of stroke were the glycated hemoglobin level, systolic blood pressure, duration of diabetes, physical ac-

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Table 1. Baseline Characteristics of the Patients with Type 2 Diabetes and Matched Controls.*

Variable	Matched Controls	Patients with Diabetes with Complete Data on All Risk Factors						
		Overall	No. of Risk-Factor Variables outside Target Range					
			0	1	2	3	4	5
No. of participants								
Complete-case data set	483,365	96,673	4,852	22,584	39,673	24,341	4927	296
Imputed data set 1	1,355,870	271,174	11,612	57,000	107,840	76,325	17,227	1,170
Imputed data set 2	1,355,870	271,174	11,569	57,033	107,709	76,455	17,213	1,195
Imputed data set 3	1,355,870	271,174	11,685	57,164	107,521	76,517	17,102	1,185
Imputed data set 4	1,355,870	271,174	11,669	57,217	107,551	76,431	17,137	1,169
Imputed data set 5	1,355,870	271,174	11,562	57,246	107,551	76,392	17,219	1,204
Female sex — no. (%)	238,885 (49.4)	47,777 (49.4)	2,525 (52.0)	11,528 (51.0)	19,799 (49.9)	11,713 (48.1)	2,085 (42.3)	127 (42.9)
Age — yr	60.58±10.89	60.58±10.89	60.96±12.06	61.04±11.23	60.93±10.79	60.00±10.54	58.32±10.06	57.27±10.21
Duration of diabetes — yr	—	4.53±5.75	4.09±5.28	4.08±5.35	4.29±5.61	5.19±6.18	5.51±6.41	6.09±6.60
Age at diagnosis of diabetes — yr	—	56.09±11.11	56.84±12.20	56.97±11.44	56.69±11.02	54.87±10.64	52.76±10.20	51.34±11.11
Glycated hemoglobin†								
Millimoles per mole	—	53.22±13.96	44.31±5.14	46.75±8.67	51.10±12.32	61.58±15.25	66.28±15.01	70.51±15.45
Percent	—	7.02±1.28	6.21±0.47	6.43±0.79	6.83±1.13	7.79±1.39	8.22±1.37	8.60±1.41
LDL cholesterol								
Millimoles per liter‡	—	3.00±0.95	1.98±0.39	2.55±0.87	3.09±0.92	3.38±0.85	3.50±0.84	3.65±0.81
Milligrams per deciliter	—	116.0±36.7	76.5±15.1	98.6±33.6	119.5±35.5	130.7±32.8	135.3±32.4	141.1±31.3
Total cholesterol — mmol/liter‡	—	5.11±1.05	4.04±0.58	4.64±0.95	5.20±1.01	5.51±0.97	5.67±0.98	5.88±0.99
Current smoker — no. (%)	—	16,486 (17.1)	0	886 (3.9)	4,268 (10.8)	7,125 (29.3)	3,911 (79.4)	296 (100)
Body-mass index§	—	30.36±5.53	29.53±5.48	29.85±5.37	30.40±5.48	30.85±5.68	30.74±5.67	30.85±5.86
Blood pressure — mm Hg								
Systolic	—	137.94±17.01	123.02±9.38	131.58±15.38	139.37±16.63	142.96±16.63	144.84±17.17	147.79±18.71
Diastolic	—	79.16±9.57	69.54±5.88	75.08±8.89	80.08±9.17	82.35±8.88	83.89±8.92	84.53±9.88
Macroalbuminuria — no. (%)	—	4,695 (4.9)	0	177 (0.8)	908 (2.3)	1,802 (7.4)	1,512 (30.7)	296 (100)
Estimated GFR — ml/min/1.73 m^2¶	—	84.19±21.52	82.29±20.71	83.01±20.59	83.43±20.94	85.90±22.39	88.76±24.72	91.93±29.16
Treatment — no. (%)‖								
Statin	—	57,945 (61.5)	2,907 (61.5)	13,312 (60.4)	24,206 (62.6)	14,449 (61.0)	2,862 (59.8)	209 (73.1)
Antihypertensive agent	—	40,553 (42.4)	2,934 (61.0)	11,035 (49.3)	15,839 (40.4)	8,809 (36.7)	1,823 (37.6)	113 (38.4)

* Plus–minus values are means ±SD. Controls were matched for age, sex, and county, on the basis of data from Statistics Sweden. All information regarding patients with type 2 diabetes was obtained from the National Diabetes Register. Missing data were imputed with the multivariate imputation by chained equations (MICE) algorithm. We imputed five complete data sets (for details, see Table S3 and Figs. S4 and S5 in the Supplementary Appendix). Percentages in this table are based on the complete-case data set. LDL denotes low-density lipoprotein.

† Concentrations of glycated hemoglobin were based on values from the International Federation of Clinical Chemistry and Laboratory Medicine. Percentages for the glycated hemoglobin level were based on values from the National Glycohemoglobin Standardization Program.

‡ To convert values for cholesterol to milligrams per deciliter, divide by 0.02586.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The glomerular filtration rate (GFR) was estimated with the use of the Modification of Diet in Renal Disease equation.

‖ Treatment was assessed only in patients with diabetes. Overall, data on statin use were missing for 1106 patients, and data on the use of an antihypertensive agent were missing for 2445. Percentages were calculated on the basis of patients with available data.

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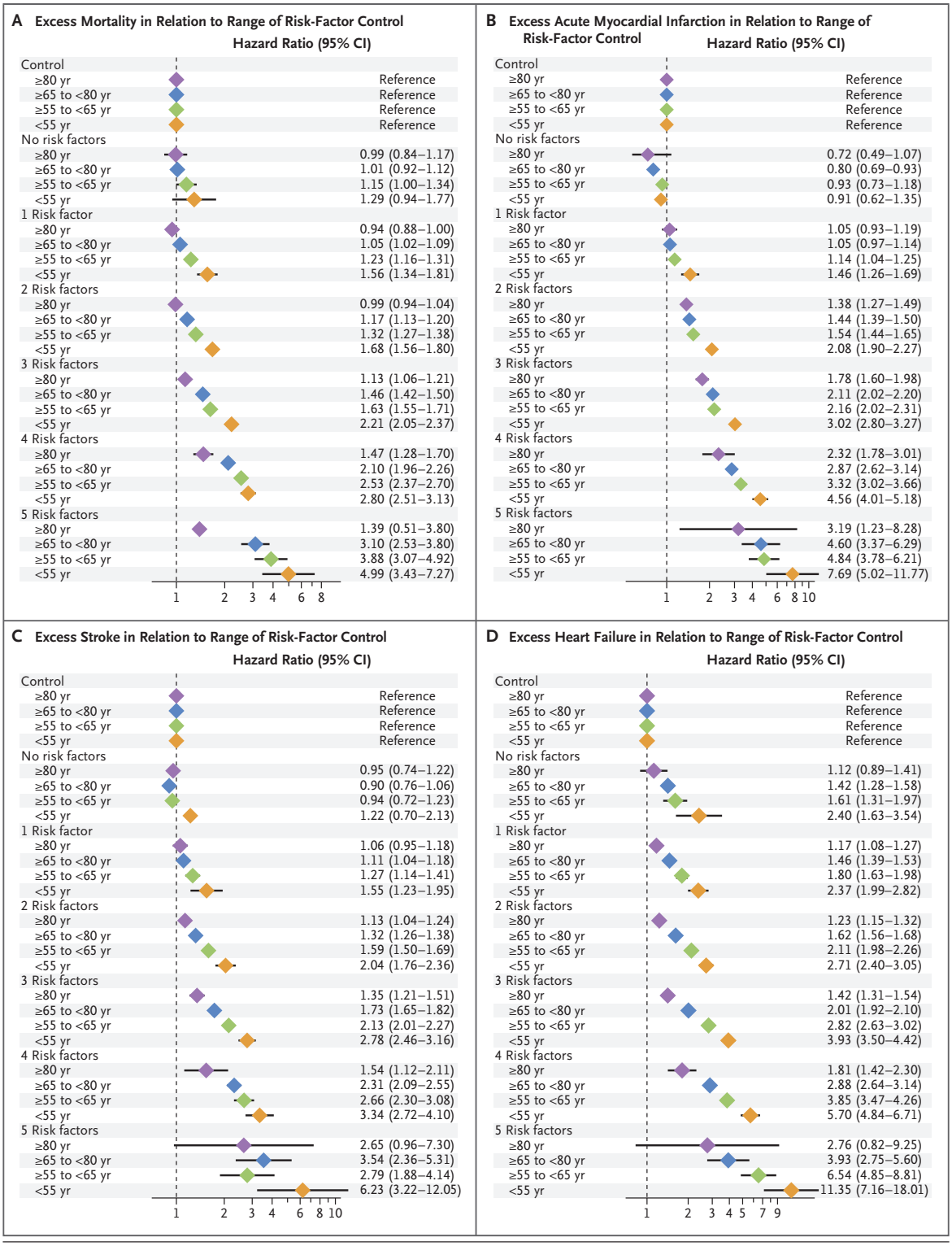

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Figure 1 (facing page). Adjusted Hazard Ratios for Outcomes, According to Age Category and Number of Risk-Factor Variables outside Target Ranges, among Patients with Type 2 Diabetes, as Compared with Matched Controls.

Hazard ratios show the excess risk of each outcome among patients with type 2 diabetes, as compared with matched controls from the general population, according to age categories and to the number of risk-factor variables (scale, none to five) that were outside target ranges currently recommended in guidelines. The analysis included patients with type 2 diabetes and controls matched for age, sex, and county in Sweden. We constructed a Cox hazards model for each age category, and these models were adjusted for the covariable "category"; this covariable denotes the number of risk-factor variables that were within target ranges. These Cox model analyses were performed on five imputed data sets for each age category, and hazard ratios were pooled from all the data sets with the use of Rubin's rule.

tivity, and atrial fibrillation (Fig. 2C). Levels below the guideline target levels for glycated hemoglobin and systolic blood pressure were associated with lower risks of stroke (Fig. 3C).

Hospitalization for heart failure was predicted primarily by atrial fibrillation and a body-mass index outside the target range; a low estimated glomerular filtration rate and high glycated hemoglobin level were also strong predictors of this outcome (Fig. 2D). The risk of hospitalization for heart failure was marginally lower at glycated hemoglobin levels of less than 53 mmol per mole (Fig. 3D).

The glycated hemoglobin level was the strongest or the second strongest predictor regarding the risk of the outcomes in five of the eight models (Fig. 2). Smoking was the strongest predictor of death.

RELATIVE RISK-FACTOR STRENGTH AND EXPLAINED LOG LIKELIHOOD

Figures S2 and S3 in the Supplementary Appendix show the relative strength of the associations for predictors of cardiovascular outcomes in patients with type 2 diabetes, with or without preexisting conditions, with the use of explained log-likelihood. The results were broadly consistent with the results obtained with the use of explained relative risk (R^2) models.

DISCUSSION

Our analysis of Swedish nationwide registry data from 1998 through 2012 showed that patients with type 2 diabetes and five selected risk-factor variables within target range had, at most, marginally higher risks of death, stroke, and myocardial infarction than the general population. The study indicates that having all five risk-factor variables within the target ranges could theoretically eliminate the excess risk of acute myocardial infarction. However, there was a substantial excess risk of hospitalization for heart failure among patients who had all the variables within target ranges. We identified a monotonic relationship among younger age, increasing number of variables not within target ranges, and a higher relative risk of adverse cardiovascular outcomes. The results suggest that there may be greater potential gains from more aggressive treatment in younger patients with diabetes.

The following risk factors were considered to be the strongest predictors for cardiovascular outcomes and death: low physical activity, smoking, and glycated hemoglobin, systolic blood-pressure, and LDL cholesterol levels outside the target ranges. Using real-world data, we found that levels of glycated hemoglobin, systolic blood pressure, and LDL cholesterol that were lower than target levels were associated with lower risks of acute myocardial infarction and stroke.

Randomized trials investigating the effect of multifactorial cardiovascular risk-factor intervention in patients with type 2 diabetes are scarce, and contemporary studies were designed to measure the cumulative incidence of cardiovascular events among patients with various risk factors (e.g., hyperglycemia, hypertension, dyslipidemia, and microalbuminuria) who received intensive therapy, as compared with those who received conventional therapy.[2,3,8,9] Observational studies and randomized trials have shown inconsistent evidence of effects of glycated hemoglobin levels below contemporary guideline levels (<7.0%) with regard to cardiovascular events and death.[10-15]

In the present analyses, a glycated hemoglobin level outside the target range was a strong predictor for all outcomes, especially for atherothrombotic events, which shows the importance of dysglycemia with regard to these complications.

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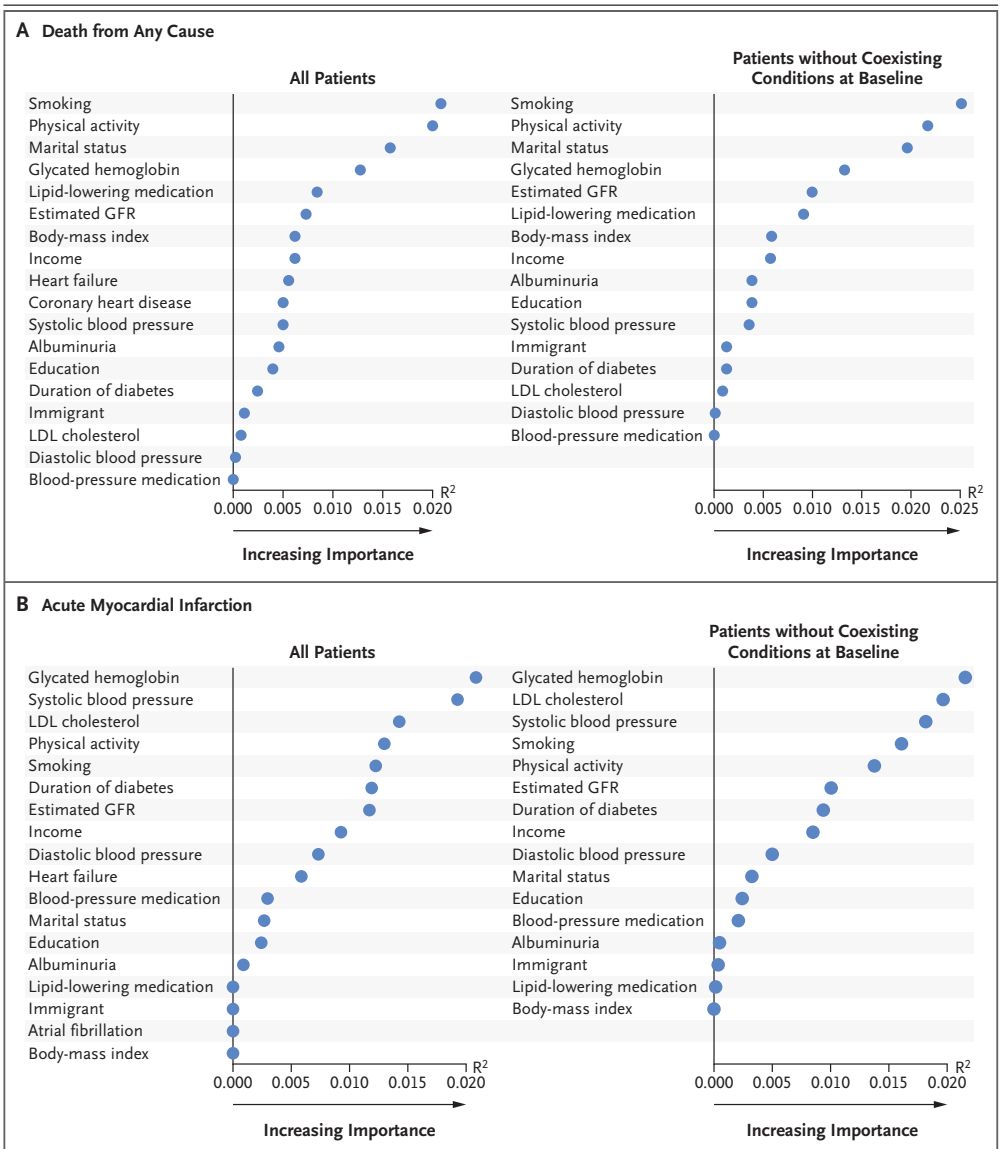

Figure 2. Relative Importance of Risk Factors for Predicting Death from Any Cause, Acute Myocardial Infarction, Stroke, and Hospitalization for Heart Failure among Patients with Type 2 Diabetes, with or without Preexisting Conditions.

The estimated explained relative risk (i.e., relative importance) shows the strength of the association for various risk-factor variables (with values outside the target ranges) for predicting death (Panel A), acute myocardial infarction (Panel B), stroke (Panel C, facing page), and hospitalization for heart failure (Panel D, facing page) among patients with type 2 diabetes. Results were obtained from the first imputed data set; there were no significant differences between the sets. The analysis was restricted to patients with type 2 diabetes. We constructed a Cox hazard model for each outcome, which included every predictor. We then constructed a separate Cox model for each predictor and permutated covariables from each of these Cox models to estimate the explained relative risk (R^2). R^2 was generated by developed applications for the Cox model and is bounded between 0 and 1. Risk factors showing a clear and substantial R^2 measure, as compared with other adjacent predictors, are considered to be relevant. Full definitions of the risk factors and the values that were considered to be outside the target ranges are provided in the Supplementary Appendix. The body-mass index is the weight in kilograms divided by the square of the height in meters. LDL denotes low-density lipoprotein, and GFR glomerular filtration rate.

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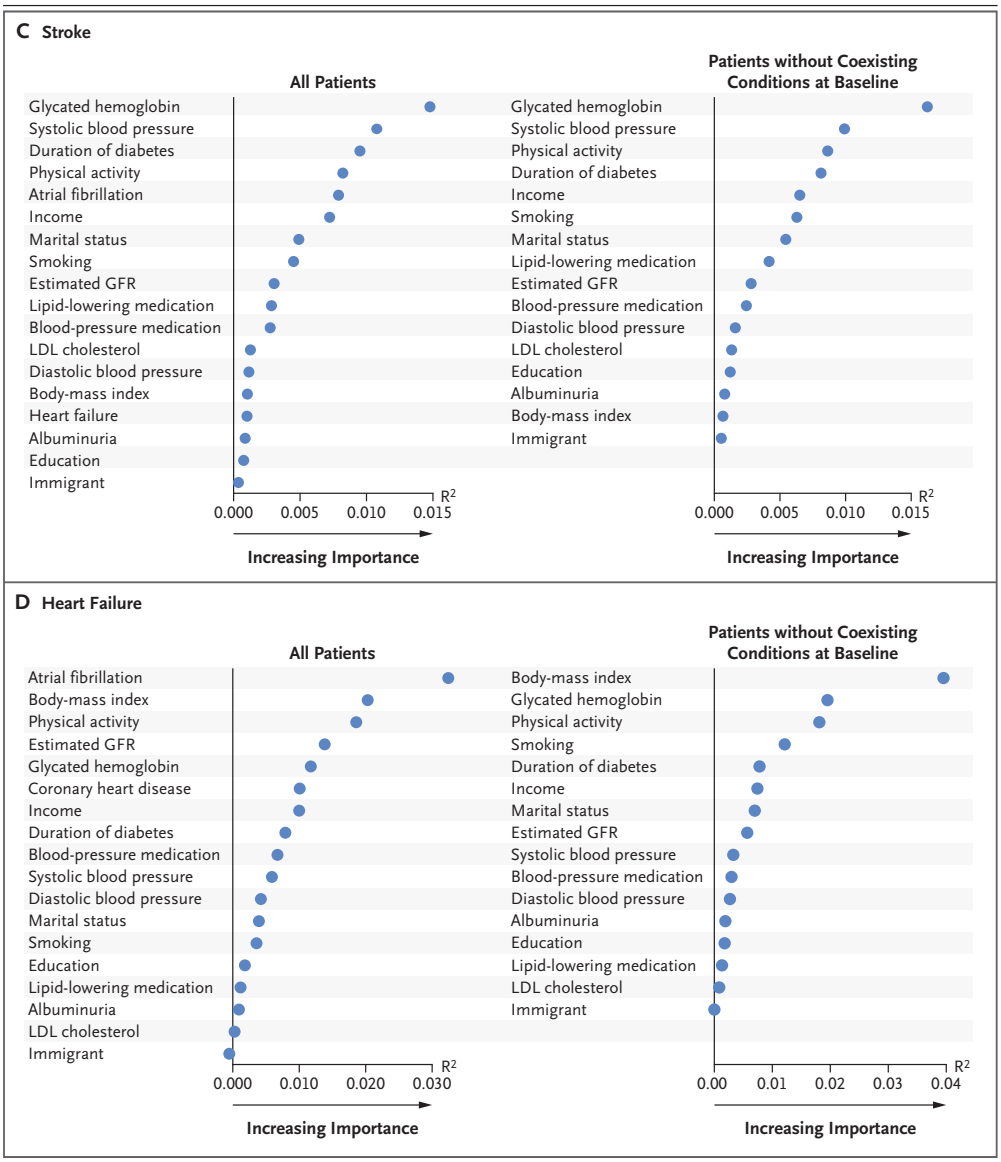

Low physical activity was also a strong predictor of cardiovascular outcomes and death, but randomized trials have not shown long-lasting beneficial effects from increased physical activity in patients with diabetes.[16-18]

With regard to hospitalization for heart failure, the present analyses showed that the presence of atrial fibrillation, a high body-mass index, and a glycated hemoglobin level and renal function outside the target ranges were the strongest predictors. These findings indicate that cardiorenal mechanisms may contribute to the development of heart failure in patients with type 2 diabetes. A high body-mass index was a stronger risk factor for heart failure than for other outcomes, which may explain why the risks associated with this outcome may continue to be higher among patients with type 2 diabetes than among controls, since patients with diabetes are, on average, heavier than compared controls.

Our study shows, in accordance with previous studies, that lower systolic blood pressure is asso-

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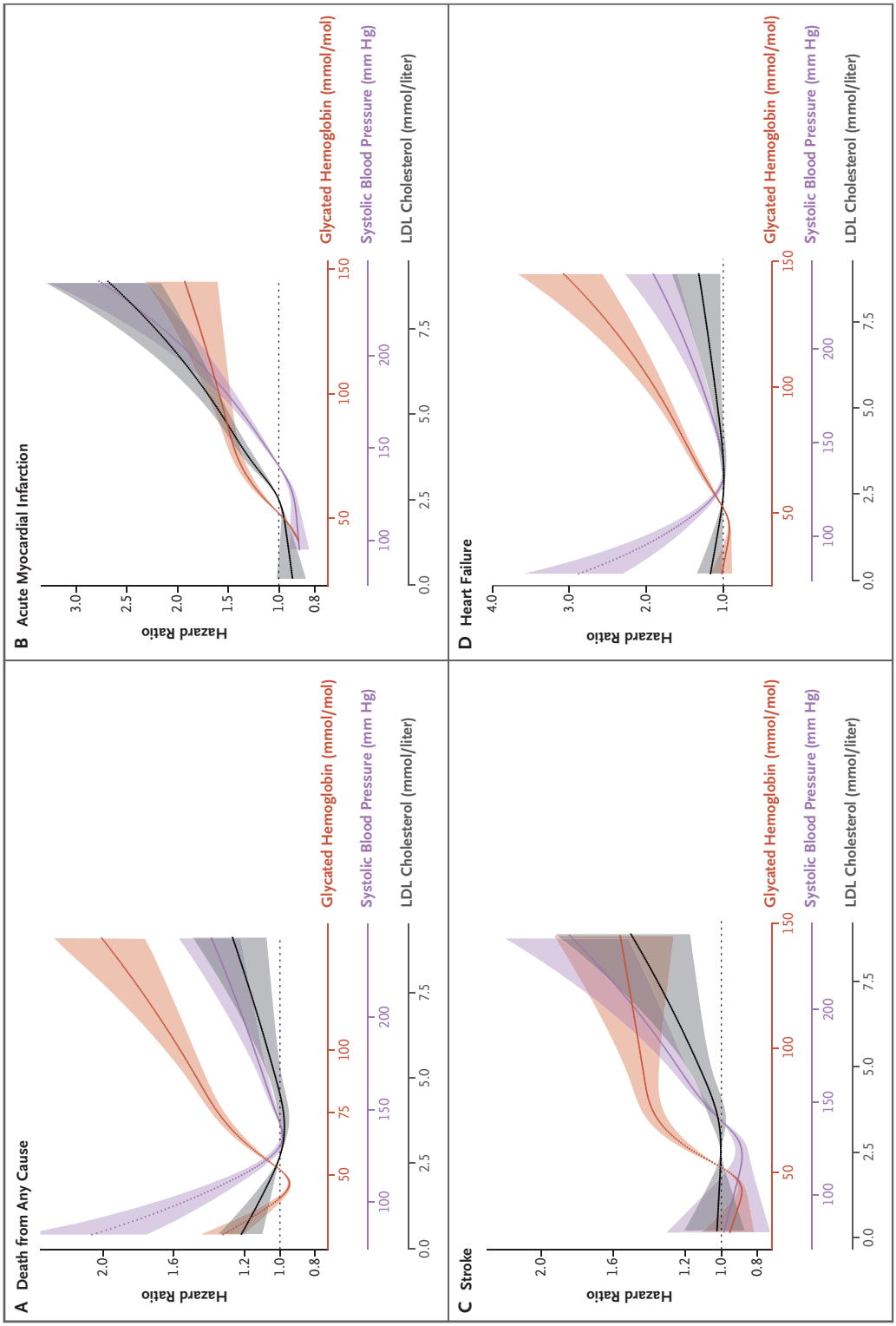

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Figure 3 (facing page). Association between Levels of Glycated Hemoglobin, Systolic Blood Pressure, and LDL Cholesterol and Death from Any Cause, Acute Myocardial Infarction, Stroke, and Heart Failure in Patients with Type 2 Diabetes.

We constructed a Cox model for each outcome and applied a prediction function to assess the relationship between glycated hemoglobin, systolic blood-pressure, and LDL cholesterol levels and the risks of death from any cause (Panel A), acute myocardial infarction (Panel B), stroke (Panel C), and hospitalization for heart failure (Panel D). Reference values were the contemporary guideline levels: 53 mmol per mole for the glycated hemoglobin level, 140 mm Hg for the systolic blood pressure, and 2.5 mmol per liter (97 mg per deciliter) for the LDL cholesterol level. The dark lines indicate the hazard function, and the shaded areas 95% confidence intervals. Continuous variables were modeled with restricted cubic splines, whereas all the categorical variables were stratified. This analysis was restricted to patients with type 2 diabetes. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586.

ciated with lower risks of cardiovascular outcomes and death.[19] The Systolic Blood Pressure Intervention Trial (SPRINT) showed that systolic blood-pressure targets below guideline levels in patients without diabetes were associated with a lower risk of cardiovascular outcomes and death.[20] However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial examined the same systolic blood-pressure targets in patients with type 2 diabetes (<120 mm Hg vs. <140 mm Hg) and did not show a significant effect on cardiovascular mortality.[15,21] Our analysis implies that systolic blood pressure is a central factor for virtually all outcomes in patients with diabetes, and lower levels of systolic blood pressure are associated with significantly lower risks of acute myocardial infarction and stroke among patients with diabetes. The assessment of systolic blood pressure and its relation to death and heart failure is more difficult, owing to potential reverse causality. More-specific trials of blood-pressure reduction to differential targets in patients with type 2 diabetes may be warranted.[20,22]

Our observational study has several strengths but also some notable limitations. Almost all the patients with type 2 diabetes in Sweden were included. The epidemiologic definitions of type 2 diabetes and the outcomes are well validated. We did not consider changes in the risk-factor variables during follow-up, and although this would have some advantages, the approach we used minimizes the risk of reverse causation in the interpretation of the results. In addition, we did not distinguish between patients with all or some variables within target range without any specific intervention and patients who had been medically treated to attain the observed risk-factor levels. We also acknowledge that residual confounding and reverse causation are impossible to overcome fully. Finally, given the observational nature of this work, this cannot be a complete comparison of the effects of treating risk factors; rather, because some patients may have had risk-factor variables in the target ranges without treatment, the findings represent the prognostic importance of such risk factors for persons with diabetes.

In conclusion, patients with type 2 diabetes who had five risk-factor variables within target ranges appeared to have little or no excess risks of death, myocardial infarction, and stroke as compared with the general population.

The views expressed in this article are those of the authors and are not necessarily the views of the Swedish Medical Products Agency.

Supported by grants from the Swedish Association of Local Authorities and Regions, the Swedish State under the agreement concerning research and education of doctors, Region Västra Götaland, the Swedish Diabetes Foundation, the Swedish Heart and Lung Foundation, the Swedish Research Council (2013-5187 SIMSAM), the Wilhelm and Martina Lundgren Science Foundation, and the Swedish Council for Health, Working Life, and Welfare.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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