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Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

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ABSTRACT

BACKGROUND

Long-term trends in excess risk of death and cardiovascular outcomes have not been extensively studied in persons with type 1 diabetes or type 2 diabetes.

METHODS

We included patients registered in the Swedish National Diabetes Register from 1998 through 2012 and followed them through 2014. Trends in deaths and cardiovascular events were estimated with Cox regression and standardized incidence rates. For each patient, controls who were matched for age, sex, and county were randomly selected from the general population.

RESULTS

Among patients with type 1 diabetes, absolute changes during the study period in the incidence rates of sentinel outcomes per 10,000 person-years were as follows: death from any cause, −31.4 (95% confidence interval [CI], −56.1 to −6.7); death from cardiovascular disease, −26.0 (95% CI, −42.6 to −9.4); death from coronary heart disease, −21.7 (95% CI, −37.1 to −6.4); and hospitalization for cardiovascular disease, −45.7 (95% CI, −71.4 to −20.1). Absolute changes per 10,000 person-years among patients with type 2 diabetes were as follows: death from any cause, −69.6 (95% CI, −95.9 to −43.2); death from cardiovascular disease, −110.0 (95% CI, −128.9 to −91.1); death from coronary heart disease, −91.9 (95% CI, −108.9 to −75.0); and hospitalization for cardiovascular disease, −203.6 (95% CI, −230.9 to −176.3). Patients with type 1 diabetes had roughly 40% greater reduction in cardiovascular outcomes than controls, and patients with type 2 diabetes had roughly 20% greater reduction than controls. Reductions in fatal outcomes were similar in patients with type 1 diabetes and controls, whereas patients with type 2 diabetes had smaller reductions in fatal outcomes than controls.

CONCLUSIONS

In Sweden from 1998 through 2014, mortality and the incidence of cardiovascular outcomes declined substantially among persons with diabetes, although fatal outcomes declined less among those with type 2 diabetes than among controls. (Funded by the Swedish Association of Local Authorities and Regions and others.)

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Diabetes mellitus is a complex and heterogeneous group of chronic metabolic diseases that are characterized by hyperglycemia. Type 1 diabetes occurs predominantly in young people (diagnosis at 30 years of age or younger) and is generally thought to be precipitated by an immune-associated destruction of insulin-producing pancreatic beta cells, leading to insulin deficiency and an absolute need for exogenous insulin replacement.[1] Type 2 diabetes is a progressive metabolic disease that is characterized by insulin resistance and eventual functional failure of pancreatic beta cells.[2] The prevalence of type 2 diabetes has been increasing dramatically over the past few decades,[3] with projections of an even greater growth over coming decades.[4]

Landmark studies such as the Diabetes Control and Complications Trial, United Kingdom Prospective Diabetes Study, Collaborative Atorvastatin Diabetes Study, and several others have shown the importance of glucose-lowering therapy, statin use, blood-pressure control, and multifactorial intervention in reducing the risk of cardiovascular outcomes among patients with diabetes.[5-18] These trial results and the clinical application of their findings, along with lifestyle interventions (including smoking cessation), are likely to have improved outcomes in patients with diabetes during the past two decades. We set out to investigate the long-term trends (1998 through 2014) in all-cause mortality and the incidence of major diabetes-related cardiovascular complications, as compared with contemporary trends in the general population.

Methods

Study Design and Support

The study was supported by the Swedish Association of Local Authorities and Regions and other nonprofit agencies; no industry support was provided. The ethics review board at the University of Gothenburg approved the study.

Data Sources

The Swedish National Diabetes Register (NDR), initiated in 1996, has been described previously.[19,20] This registry includes information on risk factors, complications of diabetes, and medications for patients 18 years of age or older. Each patient provides informed consent (oral or written) for inclusion in the register, and virtually all patients in Sweden with diabetes are included.[21] Persons with at least one observation in the NDR between January 1, 1998, and December 31, 2012, were included in the study.

Type 1 diabetes was defined according to epidemiologic criteria: treatment with insulin and diagnosis at 30 years of age or younger. Type 2 diabetes was also 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 applied only to patients who were 40 years of age or older at the time of diabetes diagnosis.

At the time of the first registration of each person with diabetes in the NDR, controls, randomly selected from the general population, were identified who were matched for age, sex, and county.[20,22] Separate controls were selected for the cohort with type 1 diabetes and the cohort with type 2 diabetes; no person served as a control in both analyses. Information with respect to cardiovascular outcomes and deaths was retrieved from the Swedish Inpatient Registry and the Swedish Cause of Death Registry. Data linkage is virtually complete owing to the use of unique personal identification numbers, which are assigned to all Swedes at birth or at the time of immigration.

Outcomes

The outcomes that we assessed included death from any cause, acute myocardial infarction, coronary heart disease, all cardiovascular disease, stroke, and heart failure. The composite outcome of cardiovascular disease was defined as the first occurrence of acute myocardial infarction or stroke. Outcomes were identified in hospital discharge records with the 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.

The last date for inclusion in the current analysis cohort was December 31, 2012. Patients were followed until December 31, 2013, for all outcomes, except for death from any cause, for which follow-up ended on December 31, 2014.

Statistical Analysis

Follow-up was stratified according to seven 2-year periods for all outcomes, except for death from any cause, for which we used eight periods

(with the final period including only 1 year). Incidence rates for each time period were calculated for each outcome of interest; the rates were standardized to the age and sex distribution from the initial time period. For the incidence analyses, each person with diabetes was matched with five controls who were randomly selected from the general population. Numerators were the number of first events in a particular time period, and denominators were the number of persons at risk during the same time period. Incidence rates are expressed as the number of events per 10,000 person-years of observation.

Data on persons who had a nonfatal outcome, even before inclusion in the NDR, were censored at the time of the outcome, and persons with that outcome were not included in the numerator or denominator for that specific outcome but could be included in the numerator and denominator for fatal and other nonfatal outcomes. Data on persons who died were censored at the time of death. If a study participant had a nonfatal cardiovascular event but died within the first 30 days after that event, the participant was considered to have had a fatal outcome.

We also constructed Cox regression models for all outcomes to compare the change in event rates over time between patients with diabetes and matched controls. For the regression models, each person with type 1 diabetes along with the five matched controls were followed from the index date (first observation in the NDR) until an event or appropriate censoring. Persons with type 2 diabetes were matched with one control only. The regression models included sex, time-updated age categories, time period, and a "group" variable denoting patient or control. Changes in the rates of individual and composite outcomes over a 10-year period were assessed separately for patients with diabetes and for controls. In order to compare differences in the change in event rates over time between patients and controls, we introduced terms in the models for the interaction of group with each of the main effects, including time period. The test for the interaction between time period and group yielded a coefficient that showed the relative trend difference between patients and controls. The coefficient was raised to the fifth power, which yielded a hazard ratio for a period of 10 years (each time period includes 2 years). Thus, the Cox regression estimated the difference between patients and controls over a period of 10 years. Estimates significantly above 1.0 were interpreted as a greater event-rate reduction among patients with diabetes than among controls.

Because of the exploratory nature of this study, two-sided P values of less than 0.05 were considered to indicate statistical significance. No adjustments were made for multiple comparisons. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION

A total of 36,869 patients with type 1 diabetes and 457,473 patients with type 2 diabetes were included, along with matched controls for each diabetes cohort. Baseline characteristics of the patients with type 1 diabetes are presented in Table 1, and those of the patients with type 2 diabetes are shown in Table 2. The mean age at entry was 35.3 years among people with type 1 diabetes and 65.2 years among people with type 2 diabetes. The mean glycated hemoglobin level was 8.2% (66.0 mmol per mole) in patients with type 1 diabetes and 7.1% (54.5 mmol per mole) in patients with type 2 diabetes. The mean duration of diabetes before entry into the registry was 20.0 years among patients with type 1 diabetes and 5.7 years among patients with type 2 diabetes. As expected, histories of acute myocardial infarction, coronary heart disease, stroke, heart failure, amputation, and end-stage kidney disease were more frequent among patients with diabetes than among controls. The mean duration of follow-up was 11.2 years for patients with type 1 diabetes and 6.5 years for patients with type 2 diabetes.

CARDIOVASCULAR RISK FACTORS

Over a median of 15 years of observation, the mean baseline glycated hemoglobin level at the time of initial registry enrollment changed from 66.2 to 68.4 mmol per mole in patients with type 1 diabetes and from 60.2 to 56.7 mmol per mole in patients with type 2 diabetes. In both groups, significant decreases were observed in levels of low-density lipoprotein (LDL) cholesterol and systolic blood pressure, the prevalence of macroalbuminuria, and the frequency of prescription of statins and antihypertensive medications. Baseline characteristics according to period of regis-

Table 1. Baseline Characteristics of Patients with Type 1 Diabetes and Matched Controls from the General Population.*

Characteristic	Controls for All Analyses (N=184,110)	Patients with Type 1 Diabetes (N=36,869)
Female sex — no. (%)	83,194 (45.2)	16,655 (45.2)
Mean age at entry into registry — yr	35.3±14.7	35.3±14.7
Information from Inpatient Registry before baseline — no. (%)†		
Atrial fibrillation	857 (0.5)	235 (0.6)
Acute myocardial infarction	868 (0.5)	878 (2.4)
Coronary heart disease	1,749 (0.9)	1,716 (4.7)
Stroke	765 (0.4)	588 (1.6)
Heart failure	467 (0.3)	552 (1.5)
Amputation	23 (<0.1)	242 (0.7)
End-stage kidney disease	73 (<0.1)	424 (1.2)
Information from National Diabetes Register		
Mean duration of diabetes at entry into registry — yr	—	20.0±14.8
Age at diagnosis of diabetes — yr	—	15.3±7.7
Glycated hemoglobin		
Millimoles per mole‡	—	66.0±15.9
Percent§	—	8.2±1.5
Cholesterol — mmol/liter		
LDL	—	2.7±0.8
Total	—	4.7±1.0
Smoking — no. (%)		
No	—	29,182 (79.2)
Yes	—	4,688 (12.7)
Missing data	—	2,999 (8.1)
Body-mass index¶	—	25.1±4.1
Blood pressure — mm Hg		
Systolic	—	126.6±16.9
Diastolic	—	73.5±9.2
Estimated GFR — ml/min/1.73 m^2‖		
Median	—	96.4
Interquartile range	—	78.0–120.0
Antihypertensive medication — no. (%)		
No	—	27,089 (73.5)
Yes	—	7,653 (20.8)
Missing data	—	2,127 (5.8)
Statin medication — no. (%)		
No	—	29,813 (80.9)
Yes	—	3,933 (10.7)
Missing data	—	3,123 (8.5)
Aspirin — no. (%)		
No	—	17,006 (46.1)
Yes	—	3,043 (8.3)
Missing data	—	16,820 (45.6)

Table 1. (Continued.)

Characteristic	Controls for All Analyses (N=184,110)	Patients with Type 1 Diabetes (N=36,869)
Method of insulin delivery — no. (%)		
Multiple daily injections	—	13,883 (37.7)
Insulin pump	—	2,612 (7.1)
Missing data	—	20,374 (55.3)
Albuminuria — no. (%)		
No albuminuria	—	24,214 (65.7)
Microalbuminuria	—	2,831 (7.7)
Macroalbuminuria	—	2,296 (6.2)
Missing data	—	7,528 (20.4)

* Plus–minus values are means ±SD. Controls were matched for age, sex, and county. Each patient with type 1 diabetes was matched with five controls (incidence analysis and Cox regression analysis). Data on patients and their controls are for the time of the patient's entry into the National Diabetes Register. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. LDL denotes low-density lipoprotein.
† Diagnostic codes for the conditions listed are from the *International Classification of Diseases, 9th Revision* and *10th Revision*.
‡ 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.
¶ 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.

try enrollment are shown in Tables S2 and S3 in the Supplementary Appendix. Overall group characteristics according to period of clinic evaluation on the basis of all visits for each time period are shown in Tables S4 and S5 in the Supplementary Appendix.

MORTALITY

The absolute change in all-cause mortality among patients with type 1 diabetes from 1998 to 2014 was −31.4 deaths (95% confidence interval [CI], −56.1 to −6.7) per 10,000 person-years. The corresponding change among matched controls was −13.9 deaths (95% CI, −20.1 to −7.7) per 10,000 person-years (Fig. 1A, and Table S6 in the Supplementary Appendix). The mortality rate declined by 29% in the group with type 1 diabetes (hazard ratio, 0.71; 95% CI, 0.66 to 0.78) and by 23% in controls (hazard ratio, 0.77; 95% CI, 0.72 to 0.83) (Table 3). The ratio of hazard ratios for patients with type 1 diabetes as compared with controls indicated that the change in all-cause mortality among patients with type 1 diabetes did not differ significantly from the change among controls (hazard ratio, 1.08; 95% CI, 0.99 to 1.18; P=0.09) (Table 3).

From 1998 to 2014, all-cause mortality among patients with type 2 diabetes changed by −69.6 deaths (95% CI, −95.9 to −43.2) per 10,000 person-years (Fig. 2A, and Table S7 in the Supplementary Appendix), with a relative event-rate reduction over the study period of 21% (hazard ratio, 0.79; 95% CI, 0.78 to 0.80) (Table 3). The corresponding absolute change in all-cause mortality among matched controls was −134.7 deaths (95% CI, −145.2 to −124.1) per 10,000 person-years, with a relative event-rate reduction of 31% (hazard ratio, 0.69; 95% CI, 0.68 to 0.70). The decline in the all-cause mortality rate was 13% greater among controls than among patients with type 2 diabetes (hazard ratio, 0.87; 95% CI, 0.85 to 0.89; P<0.001).

With respect to death from cardiovascular disease, the absolute change among patients with type 1 diabetes was −26.0 cases (95% CI, −42.6 to −9.4) per 10,000 person-years (Fig. 1B, and Table S6 in the Supplementary Appendix). The relative event-rate reduction was 42% (hazard ratio, 0.58; 95% CI, 0.50 to 0.68) among patients with type 1 diabetes and 38% (hazard ratio, 0.62; 95% CI, 0.53 to 0.72) among controls. There was a nonsignificant difference between patients with type 1 diabetes and controls for this outcome (hazard ratio, 1.06; 95% CI, 0.89 to 1.26; P=0.53) (Table 3).

The change in the incidence of death from cardiovascular disease among patients with type 2 diabetes was −110.0 cases (95% CI, −128.9 to

Table 2. Baseline Characteristics of Patients with Type 2 Diabetes and Matched Controls from the General Population.*

Characteristic	Controls for Incidence Analysis (N = 2,287,365)	Controls for Cox Regression Analysis (N = 457,473)	Patients with Type 2 Diabetes (N = 457,473)
Female sex — no. (%)	1,040,095 (45.5)	208,019 (45.5)	208,019 (45.5)
Mean age at entry into registry — yr	65.2±12.6	65.2±12.6	65.2±12.6
Information from Inpatient Registry before baseline — no. (%)†			
Atrial fibrillation	111,976 (4.9)	22,368 (4.9)	34,571 (7.6)
Acute myocardial infarction	100,027 (4.4)	19,856 (4.3)	41,681 (9.1)
Coronary heart disease	200,912 (8.8)	40,181 (8.8)	79,096 (17.3)
Stroke	95,664 (4.2)	19,099 (4.2)	30,086 (6.6)
Heart failure	74,807 (3.3)	15,032 (3.3)	30,686 (6.7)
Amputation	2,368 (0.1)	488 (0.1)	1,729 (0.4)
End-stage kidney disease	3,004 (0.1)	645 (0.1)	1,021 (0.2)
Information from National Diabetes Register			
Mean duration of diabetes at entry into registry — yr	—	—	5.7±7.1
Age at diagnosis of diabetes — yr	—	—	59.4±13.0
Glycated hemoglobin			
Millimoles per mole‡	—	—	54.5±14.9
Percent§	—	—	7.1±1.4
Cholesterol — mmol/liter			
LDL	—	—	2.9±1.0
Total	—	—	5.1±1.1
Smoking — no. (%)			
No	—	—	310,178 (67.8)
Yes	—	—	57,437 (12.6)
Missing data	—	—	89,858 (19.6)
Body-mass index	—	—	29.7±5.4
Blood pressure — mm Hg			
Systolic	—	—	140.2±18.3
Diastolic	—	—	78.7±9.9
Estimated GFR — ml/min/1.73 m^2¶			
Median	—	—	80.5
Interquartile range	—	—	64.8–94.3
Antihyperglycemic treatment — no. (%)			
Diet only	—	—	172,543 (37.7)
Oral antihyperglycemic agents only	—	—	195,133 (42.7)
Insulin only	—	—	47,575 (10.4)
Insulin and oral agents	—	—	42,222 (9.2)
Antihypertensive medication — no. (%)			
No	—	—	153,223 (33.5)
Yes	—	—	275,881 (60.3)
Missing data	—	—	28,369 (6.2)

Table 2. (Continued.)

Characteristic	Controls for Incidence Analysis (N=2,287,365)	Controls for Cox Regression Analysis (N=457,473)	Patients with Type 2 Diabetes (N=457,473)
Statin medication — no. (%)			
No	—	—	257,286 (56.2)
Yes	—	—	170,302 (37.2)
Missing data	—	—	29,885 (6.5)
Albuminuria — no. (%)			
No albuminuria	—	—	212,017 (46.3)
Microalbuminuria	—	—	39,073 (8.5)
Macroalbuminuria	—	—	21,967 (4.8)
Missing data	—	—	184,416 (40.3)

* Plus–minus values are means ±SD. Controls were matched for age, sex, and county. In the incidence analysis, each patient with type 2 diabetes was matched with five controls. In the Cox regression analysis, each patient was matched with one control. Data on patients and their controls are for the time of the patient's entry into the National Diabetes Register. Percentages may not sum to 100 because of rounding.
† Diagnostic codes for the conditions listed are from the *International Classification of Diseases, 9th Revision* and *10th Revision*.
‡ 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.
¶ The GFR was estimated with the use of the Modification of Diet in Renal Disease equation.

–91.1) per 10,000 person-years (Fig. 2B, and Table S7 in the Supplementary Appendix). The corresponding event-rate reduction was 46% (hazard ratio, 0.54; 95% CI, 0.52 to 0.55). There was a 6% greater reduction in death from cardiovascular disease among controls than among patients with type 2 diabetes (hazard ratio, 0.94; 95% CI, 0.90 to 0.98; P=0.004) (Table 3).

The results for death from coronary heart disease were broadly similar to those for death from cardiovascular disease. The absolute change was –21.7 deaths (95% CI, –37.1 to –6.4) per 10,000 person-years among patients with type 1 diabetes and –91.9 deaths (95% CI, –108.9 to –75.0) per 10,000 person-years among patients with type 2 diabetes (Figs. 1C and 2C). There was a nonsignificant difference between patients with type 1 diabetes and controls for this outcome (hazard ratio, 0.97; P=0.74) and a 6% greater reduction in death from coronary heart disease among controls than among patients with type 2 diabetes (hazard ratio for patients with type 2 diabetes vs. controls, 0.94; P=0.009) (Table 3).

HOSPITALIZATIONS

With respect to hospitalization for cardiovascular disease, the event-rate reduction was 36% among patients with type 1 diabetes (hazard ratio, 0.64; 95% CI, 0.56 to 0.72) and 44% among patients with type 2 diabetes (hazard ratio, 0.56; 95% CI, 0.54 to 0.57) (Figs. 1D and 2D, and Tables S8 and S9 in the Supplementary Appendix). There was a greater decline in hospitalization for cardiovascular disease among patients with either type of diabetes than among controls (Table 3). Findings with respect to hospitalization for acute myocardial infarction, coronary heart disease, and stroke were broadly similar (Table 3, and Figs. S1 and S2 in the Supplementary Appendix).

There was no significant reduction in the rate of hospitalization for heart failure among either patients with type 1 diabetes or controls (Table 3). By contrast, we observed a 29% reduction in hospitalization for heart failure among patients with type 2 diabetes (hazard ratio, 0.71; 95% CI, 0.69 to 0.73). There was an 18% greater reduction in the rate of hospitalization for heart failure among patients with type 2 diabetes than among controls (hazard ratio, 1.18; 95% CI, 1.12 to 1.23; P<0.001) (Figs. S1 and S2 and Tables S8 and S9 in the Supplementary Appendix).

DISCUSSION

Our analysis of Swedish nationwide registry data from 1998 to 2014 showed marked reductions in mortality and in the incidence of cardiovascular complications among adults with either type 1 diabetes or type 2 diabetes. The reduction in the rate of fatal outcomes did not differ significantly

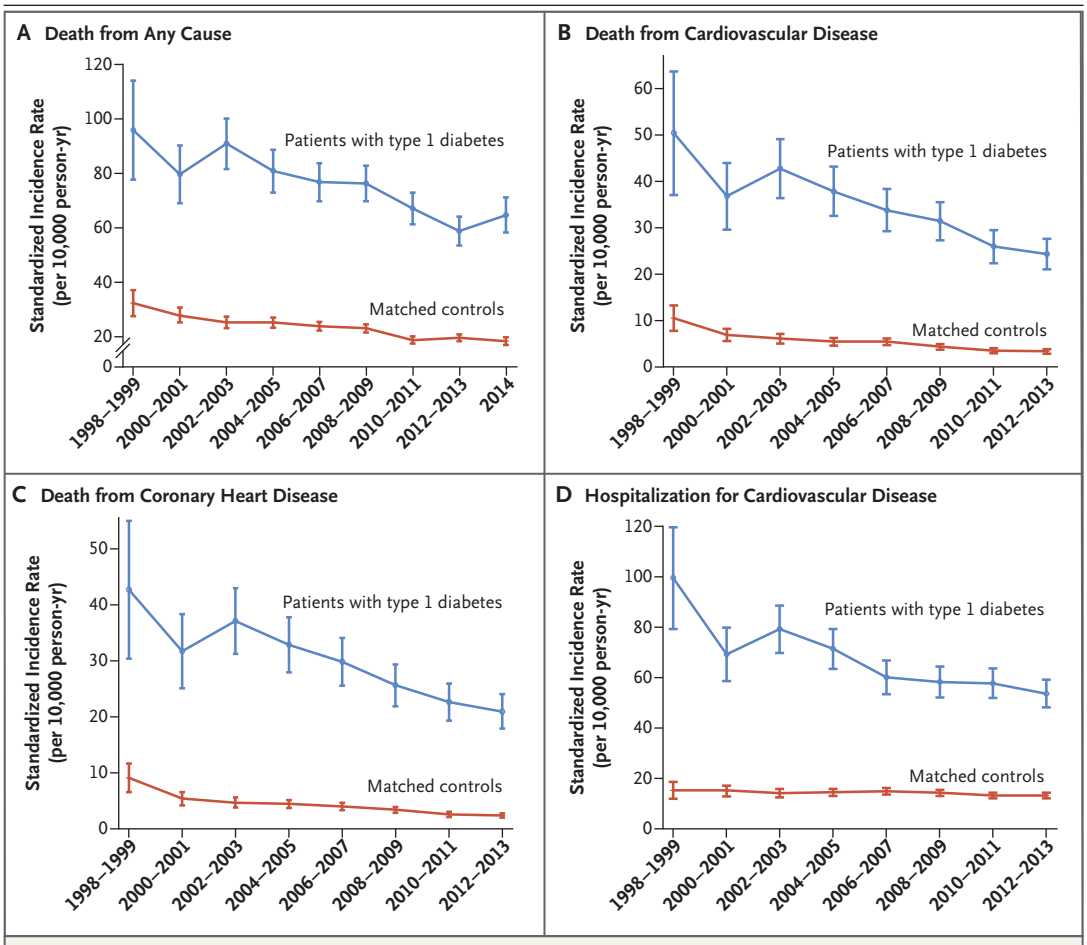

Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

between patients with type 1 diabetes and controls, whereas patients with type 2 diabetes had less reduction in the rate of fatal outcomes than controls. The rate of nonfatal outcomes, however, was reduced to a greater degree among patients with either type of diabetes than in the respective matched control group. There remains a substantial excess overall rate of all outcomes analyzed among persons with either type 1 diabetes or type 2 diabetes as compared with the general population. Although it is difficult to compare event-rate reductions across countries owing to differences in access to care, standards of clinical care, and diagnostic criteria for diabetes, our findings are generally consistent with trends in overall mortality and cardiovascular disease associated with diabetes that have been observed in North America and Europe.[23-30]

The changes observed in our study most likely reflect a combination of advances. The increasing emphasis on integrated care of patients with chronic disease, improved patient education in disease management, and advancements in clinical decision-making support have probably reduced the rates of cardiovascular complications among patients with diabetes.[31] Advances in revascularization and increased use of glucose-monitoring systems may have also played a role.[32] Perhaps most important, improved management of risk factors such as hypertension, elevated levels of LDL cholesterol and glycated hemoglobin, and macroalbuminuria and the associated higher frequency of treatment with statins and antihypertensive medications have transformed cardiovascular risk reduction.[5,9,14,17,33,34] As is apparent from our data, rates of major cardiovascular risk

Table 3. Adjusted Hazard Ratios for All Outcomes.*

Outcome	Patients with Type 1 Diabetes	Matched Controls	Patients with Type 1 Diabetes vs. Matched Controls		Patients with Type 2 Diabetes	Matched Controls	Patients with Type 2 Diabetes vs. Matched Controls	
	Hazard Ratio during a 10-Year Period		Hazard Ratio†	P Value for Interaction‡	Hazard Ratio during a 10-Year Period		Hazard Ratio†	P Value for Interaction‡
Death								
From any cause	0.71 (0.66–0.78)	0.77 (0.72–0.83)	1.08 (0.99–1.18)	0.09	0.79 (0.78–0.80)	0.69 (0.68–0.70)	0.87 (0.85–0.89)	<0.001
From cardiovascular disease	0.58 (0.50–0.68)	0.62 (0.53–0.72)	1.06 (0.89–1.26)	0.53	0.54 (0.52–0.55)	0.50 (0.49–0.52)	0.94 (0.90–0.98)	0.004
From coronary heart disease	0.56 (0.48–0.67)	0.55 (0.46–0.65)	0.97 (0.80–1.18)	0.74	0.52 (0.50–0.53)	0.48 (0.46–0.50)	0.94 (0.89–0.98)	0.009
Hospitalization								
For cardiovascular disease	0.64 (0.56–0.72)	0.91 (0.82–1.01)	1.43 (1.25–1.62)	<0.001	0.56 (0.54–0.57)	0.71 (0.68–0.73)	1.27 (1.22–1.32)	<0.001
For acute myocardial infarction	0.63 (0.55–0.73)	0.87 (0.75–1.00)	1.37 (1.16–1.62)	<0.001	0.50 (0.48–0.52)	0.62 (0.59–0.65)	1.24 (1.18–1.31)	<0.001
For coronary heart disease	0.56 (0.50–0.64)	0.78 (0.70–0.87)	1.39 (1.22–1.58)	<0.001	0.55 (0.53–0.57)	0.67 (0.65–0.69)	1.22 (1.17–1.27)	<0.001
For stroke	0.65 (0.55–0.77)	0.95 (0.82–1.10)	1.47 (1.22–1.76)	<0.001	0.61 (0.59–0.63)	0.76 (0.73–0.79)	1.24 (1.18–1.31)	<0.001
For heart failure	0.87 (0.74–1.01)	1.01 (0.86–1.18)	1.16 (0.97–1.40)	0.10	0.71 (0.69–0.73)	0.84 (0.81–0.87)	1.18 (1.12–1.23)	<0.001

* The analysis based on Cox regression was adjusted for time-updated age, time-updated time period, sex, and interaction terms.
† Values are ratios of hazard ratios for patients with type 1 diabetes or type 2 diabetes as compared with controls, during a 10-year time period. A value above 1 means a greater event-rate reduction, and a value below 1 a lesser event-rate reduction, in the patients with diabetes than in the matched controls (see the Supplementary Appendix).
‡ The P value is for the interaction between time period and group — that is, patients with either type 1 diabetes or type 2 diabetes and matched controls.

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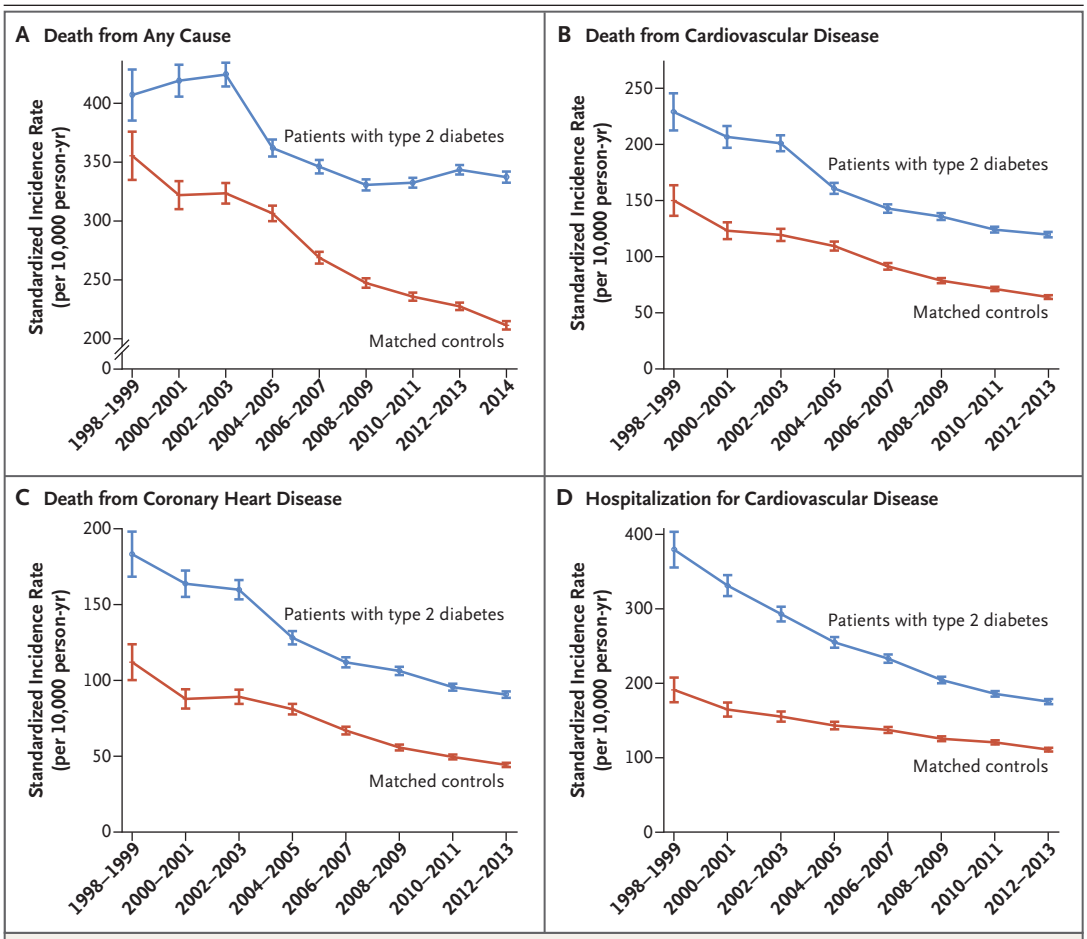

Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

factors are gradually decreasing, with improved control in patients with type 1 diabetes and those with type 2 diabetes.

Heart failure has been a somewhat neglected complication of diabetes.[23,35] Hospitalizations for heart failure did not decline significantly among either patients with type 1 diabetes or their matched controls. However, patients with type 2 diabetes had a greater event-rate reduction than controls. These findings are somewhat surprising, because rates of hospitalization for coronary heart disease and acute myocardial infarction, as well as the number of persons with hypertension and the rate of macroalbuminuria (risk predictors for heart failure), have decreased to a greater degree among patients with type 1 diabetes than among those with type 2 diabetes. These observations suggest that other processes, less well appreciated and therefore less well treated, that contribute to heart-failure risk are not affected by contemporary clinical care for patients with type 1 diabetes.

Some limitations of our study should be noted. First, classification of diabetes type was not based on detection of islet autoantibodies or measurement of C-peptide levels. However, we believe that misclassification is unlikely to have biased our findings. The epidemiologic definitions that we used have been validated as accurate in 97% of cases, as reported previously.[36] (See the Supplementary Appendix for a more detailed discussion of this issue.[37]) Second, we cannot exclude the possibility that secular trends, such as evolving diagnostic thresholds or admissions criteria, could have influenced the changes in event rates that we have reported. Third, our results are model-dependent and could change slightly with different approaches to the data. Finally, correction for

multiple testing was not performed, and thus caution is needed with respect to the interpretation of significance tests.

In conclusion, we report a decline in all-cause mortality and the incidence of cardiovascular complications among patients with type 1 diabetes or type 2 diabetes in the Swedish NDR. The reduction in fatal outcomes did not differ significantly between patients with type 1 diabetes and controls, and the reduction in such outcomes was smaller among patients with type 2 diabetes than among controls. Nonfatal outcomes decreased more rapidly among patients with either type of diabetes than among controls, but the event rates of all outcomes studied remained significantly higher among patients with diabetes.

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REFERENCES

1. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature 2010; 464:1293-300.
2. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014;383:1068-83.
3. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94: 311-21.
4. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010;8:29.
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65.
8. Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long term mortality. JAMA 2015;313:45-53.
9. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-53.
10. Cleary PA, Orchard TJ, Genuth S, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes 2006; 55:3556-65.
11. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-96.
12. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-25.
13. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
14. Holman RR, Paul SK, Bethel MA, Neil HAW, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359: 1565-76.
15. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
16. Orchard TJ, Forrest KY, Kuller LH, Becker DJ. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care 2001;24:1053-9.
17. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. Lancet 2015;385:1397-405.
18. Hero C, Rawshani A, Svensson A-M, et al. Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes. Diabetes Care 2016;39:996-1003.
19. Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, Svensson A-M, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet 2011; 378:140-6.
20. Lind M, Svensson A-M, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014; 371:1972-82.
21. Rawshani A, Landin-Olsson M, Svensson A-M, et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014;57: 1375-81.
22. Rosengren A, Vestberg D, Svensson A-M, et al. Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study. Lancet Diabetes Endocrinol 2015;3:876-85.
23. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med 2014;370:1514-23.
24. Gregg EW, Gu Q, Cheng YJ, Narayan KMV, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. Ann Intern Med 2007;147:149-55.
25. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care 2012;35:1252-7.
26. Booth GL, Kapral MK, Fung K, Tu JV. Recent trends in cardiovascular complications among men and women with and without diabetes. Diabetes Care 2006;29: 32-7.
27. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016; 39:1378-83.

28. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008;371:1777-82.
29. Secrest AM, Becker DJ, Kelsey SF, LaPorte RE, Orchard TJ. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry. Diabetes Care 2010;33:2573-9.
30. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK General Practice Research Database, 1992-1999. Diabetologia 2006;49:660-6.
31. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet 2012;379:2252-61.
32. Steineck I, Cederholm J, Eliasson B, et al. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study. BMJ 2015;350:h3234.
33. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580-91.
34. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. BMJ 1994;309:23-7.
35. McMurray JJV, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol 2014;2:843-51.
36. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care 2010;33:1640-6.
37. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.