Epidemiology

Diabetes Patients Requiring Glucose-Lowering Therapy and Nondiabetics With a Prior Myocardial Infarction Carry the Same Cardiovascular Risk
A Population Study of 3.3 Million People

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Background—Previous studies reveal major differences in the estimated cardiovascular risk in diabetes mellitus, including uncertainty about the risk in young patients. Therefore, large studies of well-defined populations are needed.

Methods and Results—All residents in Denmark $\geq$30 years of age were followed up for 5 years (1997 to 2002) by individual-level linkage of nationwide registers. Diabetes patients receiving glucose-lowering medications and nondiabetics with and without a prior myocardial infarction were compared. At baseline, 71 801 (2.2%) had diabetes mellitus and 79 575 (2.4%) had a prior myocardial infarction. Regardless of age, age-adjusted Cox proportional-hazard ratios for cardiovascular death were 2.42 (95% confidence interval [CI], 2.35 to 2.49) in men with diabetes mellitus without a prior myocardial infarction and 2.44 (95% CI, 2.39 to 2.49) in nondiabetic men with a prior myocardial infarction ($P=0.60$), with nondiabetics without a prior myocardial infarction as the reference. Results for women were 2.45 (95% CI, 2.38 to 2.51) and 2.62 (95% CI, 2.55 to 2.69) ($P=0.001$), respectively. For the composite of myocardial infarction, stroke, and cardiovascular death, the hazard ratios in men with diabetes only were 2.32 (95% CI, 2.27 to 2.38) and 2.48 (95% CI, 2.43 to 2.54) in those with a prior myocardial infarction only ($P=0.001$). Results for women were 2.48 (95% CI, 2.43 to 2.54) and 2.71 (95% CI, 2.65 to 2.78) ($P=0.001$), respectively. Risks were similar for both diabetes types. Analyses with adjustments for comorbidity, socioeconomic status, and prophylactic medical treatment showed similar results, and propensity score–based matched-pair analyses supported these findings.

Conclusions—Patients requiring glucose-lowering therapy who were $\geq$30 years of age exhibited a cardiovascular risk comparable to nondiabetics with a prior myocardial infarction, regardless of sex and diabetes type. Therefore, requirement for glucose-lowering therapy should prompt intensive prophylactic treatment for cardiovascular diseases. (***Circulation***. 2008;117:1945-1954.)

Key Words: cardiovascular diseases ■ coronary disease ■ diabetes mellitus ■ epidemiology ■ mortality ■ prognosis ■ stroke

It is unclear when primary prevention for cardiovascular disease (CVD) should be introduced in the treatment of diabetes mellitus, particular in the case of young individuals with diabetes. Major clinical practice guidelines feature significant disparities in recommendations for primary prevention in diabetes mellitus. Several guidelines recommend target cholesterol levels in type 2 diabetes mellitus without preexisting CVD similar to the secondary prevention of patients with established CVD.[1–6] These recommendations apply to all individuals with type 2 diabetes mellitus regardless of age in some guidelines,[4,5] whereas others adopt an age threshold of 40 years[1–3] or are restricted to individual risk assessment.[3,6] Similar disparities are acknowledged in guidelines recommending primary prevention in patients with type 1 diabetes mellitus.[2,3,5] Furthermore, current guidelines for antiplatelet therapy in patients with diabetes feature various age limits and requirements for additional risk factors to merit therapy.[2,3,5,6] Despite the increasing incidence and decreasing age of onset in diabetes mellitus,[7] only a few larger

studies have considered cardiovascular risk in younger patients with diabetes mellitus.[8–11]

Editorial p 1914
Clinical Perspective p 1954

To obtain accurate estimates for all combinations of sex and age, we performed a nationwide study of cardiovascular risk in patients with diabetes requiring glucose-lowering therapy and compared the risk with that of nondiabetics with a previous myocardial infarction (MI). The study included the entire Danish population ≥30 years of age (3.3 million individuals).

Methods

Population and Data Sources

Through the Danish Civil Registration system, we identified all inhabitants in Denmark at least 30 years of age and older and alive on January 1, 1997. All deaths (including deaths occurring in other countries) were identified from the Central Population Register, in which deaths are recorded within 2 weeks. Causes of death were obtained from the National Causes of Death Register, in which immediate, contributory, and underlying causes are recorded using the *International Classification of Diseases* (ICD). Morbidity was obtained from the Danish National Patient Register,[12] in which hospital admissions and diagnoses have been recorded since 1978 with ICD codes. All medications dispensed from pharmacies were obtained from the National Prescription Registry (the Danish Registry of Medicinal Product Statistics), which has recorded all dispensed prescriptions since 1995. The following ICD-10 codes were used for end points in this study; MI, I21 to I22 (and ICD-8 code 410 for prior MI before 1994); stroke, I61 to I64; CVDs, I00 to I99; and coronary heart diseases, I20 to I25 and I46.

Diabetes Mellitus

Patients with diabetes mellitus were identified as individuals claiming at least 1 prescription of glucose-lowering medication (oral or insulin) in the 6-month period before January 1, 1997. Patients initiating glucose-lowering agents during the follow-up period were included in the reference population.

Prior MI

Previous cases of MI were identified as hospitalization with an MI as the primary or secondary diagnosis in the 19-year period before inclusion.

Comorbidity

Comorbidity was assessed as the Charlson comorbidity index score using ICD-10 codes[13] or by registration of hospital admittance up to 1 year before the inclusion date of diagnoses listed in Table 1 using ICD 10 codes.

Medical Treatment

Medical treatment with statins, β-blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was registered as prescription claims up to 6 months before the inclusion date and during follow-up.

Statistical Analyses

Cox multivariable proportional-hazard regression models were performed to estimate differences among risk groups. All Cox models were censored for deaths resulting from causes unrelated to the end point of interest. For combined end points, the time to event was estimated for the first event. Cox analyses were performed with adjustment for age and with multivariable adjustment for age, gross income, comorbidity, and time-dependent adjustment for medical treatment during follow-up.

Specifically, we used propensity score analysis to identify a set of cases (subjects with diabetes only) and controls (nondiabetics with a prior MI) who were matched for age, sex, gross income, comorbidity (Table 1), and medical treatment up to 6 months before inclusion date. A propensity score for the likelihood of receiving glucose-lowering medication was quantified by multivariable logistic regression. The C statistic was 0.74, indicating a good discriminative power of the model. A Greedy matching macro (by Lori S. Parsons, accessed January 1, 2007, at http://www2.sas.com/proceedings/sugi26/p214–26.pdf) was used to match each case (n=64 111) to 1 control. A multivariable-adjusted Cox model was fitted including the propensity score.

A sensitivity analysis was performed in an age-adjusted Cox analysis for cardiovascular death comparing patients with new requirement for glucose-lowering agents in 1997 who survived >30 days with incident first-time MI in 1997 with various survival times of 30-day intervals. Secular trends for different end points were obtained by age-adjusted Cox proportional-hazard analyses performed for each year during follow-up.

Model assumptions—linearity of continuous variables, the proportional-hazard assumption, and lack of interactions—were tested and found to be valid except when otherwise indicated. Tests for interactions were performed for age and sex, diabetes mellitus and a prior MI, diabetes mellitus and sex, diabetes mellitus and age, a prior MI and sex, and a prior MI and age. All statistical calculations were performed with the SAS statistical software package for UNIX servers, version 9.1 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

On January 1, 1997, 3 274 472 individuals ≥30 years of age lived in Denmark; of these, 71 801 (2.2%) received glucose-lowering treatment and were categorized as patients with diabetes mellitus. Glucose-lowering treatment was oral or combined oral and insulin in 45 827 (64%) subjects and insulin only in 25 974 subjects (36%).

Baseline characteristics before inclusion according to risk groups are summarized in Table 1. Numbers of events during follow-up according to the groups at risk are summarized in Table 2; the risk of selected end points is shown in Table 3. Multivariable analyses revealed no interaction between age and the different risk groups, whereas significant interactions (P<0.001) were found between sex and diabetes and a prior MI for most end points; thus, subsequent analyses were stratified by sex. The magnitudes of sex differences conferred by a prior MI were more pronounced than those conferred by diabetes mellitus, particularly for coronary end points.

Cardiovascular Morbidity and Mortality

As shown in Table 3 and Figure 1, cardiovascular death risks were similar between men without diabetes mellitus but a prior MI and men with diabetes mellitus but no prior MI (hazard ratio, 2.44 and 2.42 in the 2 groups, respectively; P=0.60), and in women, cardiovascular death was slightly, albeit significantly, higher in those without diabetes mellitus but with a prior MI (hazard ratio, 2.62 and 2.45 in the 2 groups; P<0.001; Table 3). Similar results were obtained for the composite of MI, stroke, or cardiovascular death, although a significant difference was found between the 2 groups (P<0.001 for both sexes; Table 3 and Figure 2). Multivariable adjustment did not change these results, and the propensity score–based matched-pair analyses supported

Table 1. Baseline Personal Characteristics Stratified by Sex in Relation to Diabetes Mellitus and a Prior MI

		No Diabetes Mellitus (n=3 202 671)		Diabetes Mellitus (n=71 801)		
	Total	No Prior MI (n=3 129 516)	Prior MI (n=73 155)	No Prior MI (n=65 382)	Prior MI (n=6419)	P
Sex, n (%)*						
Men	1 582 217 (48.3)	1 494 969 (47.77)	49 357 (67.47)	33 741 (51.61)	4150 (64.65)	<0.001
Women	1 692 255 (51.9)	1 634 547 (52.23)	23 798 (32.53)	31 641 (48.39)	2269 (35.35)	<0.001
Age, y†						
Men	51.3±14.7	50.0±14.5	66.5±11.5	60.4±14.2	66.5±11.5	<0.001
Women	53.9±16.2	53.4±16.1	72.1±11.7	65.0±15.1	72.2±11.7	<0.001
Person-years						
Men	7 551 639	7 181 806	208 202	146 029	15 602	<0.001
Women	8 083 750	7 842 902	96 410	136 285	8153	<0.001
Exposure time, y†						
Men	4.8±0.8	4.8±0.8	4.2±1.4	4.3±1.4	3.8±1.7	<0.001
Women	4.8±0.8	4.8±0.8	4.1±1.5	4.3±1.4	3.6±1.7	<0.001
Comorbidity, n (%)‡						
Congestive heart failure						
Men	7346 (0.46)	6212 (0.42)	745 (1.51)	309 (0.92)	80 (1.93)	<0.001
Women	6729 (0.40)	6052 (0.37)	359 (1.51)	277 (0.88)	41 (1.81)	<0.001
Cardiac dysrhythmia						
Men	10 255 (0.65)	8994 (0.57)	825 (1.67)	357 (1.06)	79 (1.90)	<0.001
Women	9766 (0.58)	8999 (0.53)	377 (1.58)	344 (1.09)	46 (2.03)	<0.001
Peripheral vascular disease						
Men	6858 (0.43)	5955 (0.40)	525 (1.06)	308 (0.91)	70 (1.69)	<0.001
Women	5502 (0.33)	5057 (0.31)	217 (0.91)	211 (0.67)	17 (0.75)	<0.001
Cerebrovascular disease						
Men	9127 (0.58)	8027 (0.54)	658 (1.33)	368 (1.09)	74 (1.78)	<0.001
Women	8681 (0.51)	7997 (0.49)	323 (1.36)	312 (0.99)	49 (2.16)	<0.001
Dementia						
Men	584 (0.03)	505 (0.03)	44 (0.09)	26 (0.08)	3 (0.07)	<0.001
Women	578 (0.04)	529 (0.03	34 (0.14)	18 (0.06)	3 (0.05)	<0.001
Chronic pulmonary disease						
Men	11 529 (0.73)	10 313 (0.69)	758 (1.54)	406 (1.20)	52 (1.25)	<0.001
Women	13 512 (0.80)	12 780 (0.78)	361 (1.52)	342 (1.08)	29 (1.28)	<0.001
Peptic ulcer disease						
Men	6478 (0.41)	5833 (0.39)	383 (0.78)	232 (0.69)	30 (0.72)	<0.001
Women	8595 (0.51)	8055 (0.49)	279 (1.17)	242 (0.76)	19 (0.84)	<0.001
Liver disease						
Men	1270 (0.08)	1173 (0.08)	50 (0.10)	42 (0.12)	5 (0.12)	0.01
Women	832 (0.05)	808 (0.05)	8 (0.03)	13 (0.04)	3 (0.13)	0.19
Hemiplegia						
Men	451 (0.03)	425 (0.03)	14 (0.03)	10 (0.03)	2 (0.05)	0.90
Women	366 (0.02)	351 (0.02)	6 (0.03)	8 (0.03)	1 (0.04)	0.83
Acute renal failure						
Men	1128 (0.07)	955 (0.06)	109 (0.22)	60 (0.18)	4 (0.10)	<0.001
Women	779 (0.05)	725 (0.04)	27 (0.11)	25 (0.08)	2 (0.09	<0.001
Chronic renal failure						
Men	190 (0.01)	169 (0.01)	9 (0.02)	9 (0.03)	3 (0.07)	<0.001
Women	230 (0.01)	218 (0.01)	9 (0.04)	3 (0.01)	0	0.01

(*Continued*)

Table 1.   Continued

| | | No Diabetes Mellitus (n=3 202 671) | | Diabetes Mellitus (n=71 801) | | |
	Total	No Prior MI (n=3 129 516)	Prior MI (n=73 155)	No Prior MI (n=65 382)	Prior MI (n=6419)	P
Pulmonary edema						
Men	7026 (0.44)	6201 (0.41)	521 (1.06)	255 (0.76)	49 (1.18)	<0.001
Women	7384 (0.44)	6846 (0.42)	287 (1.21)	227 (0.72)	24 (1.06)	<0.001
Shock						
Men	699 (0.04)	607 (0.04)	55 (0.11)	30 (0.09)	7 (0.17)	<0.001
Women	748 (0.04)	688 (0.04)	23 (0.10)	31 (0.10)	6 (0.26)	<0.001
Malignancy						
Men	16 991 (1.07)	15 186 (1.02)	1117 (2.26)	585 (1.73)	103 (2.48)	<0.001
Women	23 048 (1.36)	21 794 (1.33)	556 (2.34)	635 (2.01)	63 (2.78)	<0.001
Charlson index†						
Men	0.06 (0.37)	0.05 (0.34)	0.20 (0.61)	0.16 (0.57)	0.31 (0.69)	<0.001
Women	0.06 (0.36)	0.05 (0.35)	0.21 (0.62)	0.14 (0.52)	0.31 (0.70)	<0.001
Medication before admission,‡ n (%)§						
Statins						
Men	15 310 (1.0)	7945 (0.5)	6351 (12.9)	554 (1.6)	460 (11.1)	<0.001
Women	10 396 (0.6)	7318 (0.5)	2361 (9.9)	511 (1.6)	206 (9.1)	<0.001
β-Blockers						
Men	59 014 (3.7)	43 722 (2.9)	12 191 (24.7)	2134 (6.3)	967 (23.3)	<0.001
Women	81 258 (4.8)	72 477 (4.4)	5561 (23.4)	2702 (8.5)	518 (22.8)	<0.001
ACE inhibitors/ARBs						
Men	63 296 (4.0)	44 488 (3.0)	9822 (19.9)	7374 (21.9)	1612 (38.8)	<0.001
Women	60 948 (3.6)	49 477 (3.0)	4355 (18.3)	6272 (19.8)	844 (37.2)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

*In percentages of the respective risk group (eg, number of men with diabetes mellitus and prior MI in percentage of all patients with diabetes mellitus and prior MI).

†Mean±SD.

‡In percentages of the respective risk group (eg, numbers of men with diabetes and prior MI with congestive heart failure in percentage of all men with diabetes and prior MI).

§Medical treatment registered up to 6 months before inclusion date.

these findings for men, whereas a slightly lower risk was obtained in women with diabetes only compared with a prior MI for both end points (Table 3).

Coronary Morbidity and Mortality

Results for coronary and composite coronary end points revealed notably higher risks in patients with diabetes only compared with the reference population, although they were lower than for a prior MI only (Table 3). At all coronary end points, women exhibited substantially higher relative risks than men did (P=0.001; Table 3). Results were similar after multivariable adjustments, whereas in the matched-pair analyses, the differences between the 2 groups were slightly increased (Table 3).

All-Cause Mortality

All-cause mortality was increased in subjects with diabetes only compared with those with a prior MI only (Table 3). The multivariable-adjusted and matched-pair analyses indicated smaller differences between the 2 risk groups (Table 3). Women with a prior MI only had a relatively higher risk than

men (P=0.001), whereas no sex differences were evident for patients with diabetes mellitus (P=0.09 and P=0.45 for sex differences for diabetic patients without and with a prior MI, respectively; the corresponding multivariable-adjusted values were P=0.99 and P=0.07).

Other End Points

Patients with diabetes mellitus exhibited an increased risk of stroke (fatal and nonfatal) relative to nondiabetics with prior MI (Table 3), although this difference was eliminated for women in the matched-pair analyses (Table 3). No sex differences were demonstrated in patients with diabetes mellitus.

Diabetes Mellitus and Prior MI

Patients with both diabetes and a prior MI generally had more comorbidity (Table 1) and demonstrated additive and very high risks at all end points except stroke (Table 3).

Type 1 and Type 2 Diabetes Mellitus

Patients <40 years of age were subdivided into those receiving insulin only (defined as type 1 diabetes mellitus) and

Table 2. Numbers of Events During the Study Period (1997–2002) for Different End Points Stratified by Sex in Relation to Diabetes Mellitus and a Prior MI

	Events, n (%)*				
	No Diabetes Mellitus		Diabetes Mellitus		
	No Prior MI	Prior MI	No Prior MI	Prior MI	Total
MI (fatal or nonfatal)					
Men	32 231 (2.2)	7846 (15.9)	2466 (7.3)	984 (23.7)	71 374 (2.2)
Women	21 787 (1.3)	3325 (14.0)	2168 (6.9)	567 (25.0)	
Stroke (fatal or nonfatal)					
Men	36 878 (2.5)	3937 (7.8)	3245 (9.6)	544 (27.4)	90 731 (2.8)
Women	40 535 (2.5)	2152 (9.0)	3118 (10.0)	322 (14.2)	
Coronary death					
Men	24 135 (1.6)	8226 (16.7)	2511 (7.4)	1137 (27.4)	67 816 (2.1)
Women	24 394 (1.5)	4321 (18.2)	2392 (7.6)	700 (30.9)	
Cardiovascular death					
Men	51 698 (3.5)	9928 (20.1)	4937 (14.6)	1417 (34.1)	139 985 (4.3)
Women	60 311 (3.7)	5842 (24.5)	4950 (15.64)	902 (39.8)	
MI or coronary death					
Men	44 579 (3.0)	12 461 (25.2)	3735 (11.1)	1583 (38.14)	108 882 (3.3)
Women	36 369 (2.2)	5887 (24.7)	3348 (10.6)	920 (40.5)	
MI, stroke, or cardiovascular death					
Men	95 603 (6.4)	16 026 (32.5)	7854 (23.3)	2046 (49.3)	233 170 (7.1)
Women	94 922 (5.8)	8190 (34.4)	7332 (23.2)	1197 (52.8)	
All-cause mortality					
Men	114 931 (7.7)	14 375 (29.1)	8566 (25.4)	1851 (44.6)	287 471 (8.8)
Women	129 844 (7.9)	8393 (35.3)	8365 (26.4)	1146 (50.5)	

*In percentages of the respective risk group (eg, number of MI in men with diabetes mellitus and prior MI in percentage of all men with diabetes mellitus and prior MI).

those receiving oral glucose-lowering agents only or in combination with insulin (type 2 diabetes mellitus). No important interactions were evident between type 1 and type 2 diabetes at all end points explored; therefore, type 1 and type 2 patients expressed the same risk.

Furthermore, all analyses were repeated in patients with type 2 diabetes only at all ages by the exclusion of patients receiving insulin-only treatment. Results similar to those for the total diabetes population were demonstrated.

Supplementary Analyses

All analyses were repeated with a prior MI defined as the occurrence of an MI within 5 years before inclusion, which was taken to be a recent MI. At all end points, results were similar to those presented. Furthermore, patients with a new requirement for glucose-lowering agents exhibited a risk of cardiovascular death similar to that of patients with incident MI who had survived 180 days (men) or 330 days (women).

Secular changes were demonstrated in medical treatment during follow-up (Figure 3). For most end points, patients with a prior MI experienced a decrease in risk from 1997 to 2001, whereas the risks for patients with diabetes only were unchanged during follow-up (Figure 4).

Discussion

The major finding of this study is that all patients requiring glucose-lowering treatment who are ≥30 years of age are at a particularly high risk of cardiovascular mortality and morbidity, comparable to that of nondiabetics with a prior MI, regardless of sex and diabetes type.

Previous reports have documented that patients requiring glucose-lowering agents with or without prior CVD exhibit a particularly high risk.[14,15] Compared with our study, most previous reports on larger populations included both patients on glucose-lowering medication and those on dietary-only treatment[8,9,14,16–18] and revealed a generally lower diabetes-related cardiovascular risk relative to patients with prior CVD.[8,14,16–18]

Consistent with our results, a Finnish study of middle-aged patients[19,20] and the Multiple Risk Factor Intervention Trial (MRFIT) of men 35 to 57 years of age[14] demonstrated that patients with diabetes receiving glucose-lowering agents had a risk of cardiovascular and all-cause mortality similar to that of patients with prior MI or CVD, respectively. We found a substantially increased risk of MI and coronary death in patients with diabetes only, although the risk was slightly lower than for patients with a prior MI only. Our results were corroborated by the MRFIT study,[21] whereas the magnitude of coronary death was similar for diabetes only and a prior MI only in the Finnish population.[19,20]

As demonstrated in our study, it was previously shown that the diabetes-related risk attributable to coronary events is

Table 3. Age- and Multivariable-Adjusted Cox Multivariable Proportional-Hazard Analysis Stratified by Sex Demonstrating Relative Hazards for Different End Points in Relation to Diabetes Mellitus and a Prior MI

End Points	Age-Adjusted Analyses HR‡ (95% CI)				Multivariable-Adjusted Analyses* HR‡ (95% CI)				Matched-Pair Sample*† Diabetes Mellitus vs Prior MI, HR (95% CI)	
	Prior MI	Diabetes Mellitus	P§	Diabetes Mellitus and Prior MI	Prior MI	Diabetes Mellitus	P§	Diabetes Mellitus and Prior MI		P§
MI (fatal or nonfatal)										
Men	3.97 (3.87–4.07)	2.30 (2.21–2.40)	<0.001	6.81 (6.40–7.25)	3.01 (2.93–3.09)	1.85 (1.77–1.92)	<0.001	4.24 (3.97–4.53)	0.55 (0.53–0.58)	0.001
Women	5.34 (5.15–5.54)	3.32 (3.18–3.47)	<0.001	11.48 (10.56–2.47)	4.20 (4.05–4.36)	2.69 (2.57–2.81)	<0.001	7.32 (6.72–7.97)	0.52 (0.49–0.54)	0.001
Stroke (fatal or nonfatal)										
Men	1.53 (1.48–1.58)	2.51 (2.43–2.61)	<0.001	2.91 (2.67–3.16)	1.16 (1.12–1.20)	1.92 (1.85–1.99)	<0.001	1.72 (1.58–1.88)	1.30 (1.23–1.37)	0.001
Women	1.64 (1.57–1.71)	2.45 (2.36-2.54)	<0.001	3.08 (2.76–3.43)	1.27 (1.21–1.32)	1.90 (1.83–1.97)	<0.001	1.82 (1.63–2.04)	1.01 (0.96–1.06)	0.78
Coronary death										
Men	4.15 (4.04–4.25)	2.61 (2.51–2.72)	<0.001	7.90 (7.44–8.38)	3.07 (2.99–3.15)	1.91 (1.84–2.00)	<0.001	4.28 (4.02–4.55)	0.75 (0.71–0.79)	0.001
Women	4.61 (4.46-4.76)	2.81 (2.69–2.93)	<0.001	9.62 (8.93–10.32)	3.53 (3.41–3.65)	2.09 (2.00–2.18)	<0.001	5.18 (4.80–5.60)	0.65 (0.62–0.68)	0.001
Cardiovascular death										
Men	2.44 (2.39–2.49)	2.42 (2.35-2.49)	0.60	4.73 (4.49–0.4.97)	1.77 (1.73–1.81)	1.78 (1.73–1.84)	0.67	2.65 (2.51–2.80)	1.02 (0.98–1.06)	0.44
Women	2.62 (2.55–2.69)	2.45 (2.38–2.51)	<0.001	5.23 (4.90–5.57)	1.96 (1.90–2.01)	1.77 (1.71–1.82)	<0.001	2.87 (2.68–3.07)	0.72 (0.69–0.74)	0.001
MI or coronary death										
Men	4.05 (3.96–4.13)	2.32 (2.25–2.40)	<0.001	7.06 (6.72–7.43)	3.06 (3.00–3.13)	1.78 (1.72–1.84)	<0.001	4.15 (3.94–4.37)	0.63 (0.60–0.65)	0.001
Women	5.01 (4.87–5.15)	2.85 (2.75–2.96)	<0.001	9.97 (9.34–10.65)	3.92 (3.81–4.03)	2.22 (2.14–2.30)	<0.001	5.94 (5.55–6.35)	0.54 (0.52–0.57)	0.001
MI, stroke, or CVD Death										
Men	2.48 (2.44–2.52)	2.32 (2.27–2.38)	0.005	4.34 (4.25–4.63)	1.84 (1.80–1.87)	1.76 (1.72–1.81)	0.005	2.58 (2.47–2.70)	0.94 (0.91–0.97)	0.001
Women	2.71 (2.65–2.78)	2.48 (2.43–2.54)	<0.001	5.13 (4.85–5.43)	2.01 (2.02–2.12)	1.87 (1.83–1.92)	<0.001	2.98 (2.82–3.16)	0.69 (0.67–0.71)	0.001
All-cause mortality										
Men	1.63 (1.60–1.66)	1.96 (1.92–2.01)	<0.001	2.86 (2.73–2.99)	1.22 (1.20–1.25)	1.33 (1.30–1.36)	<0.001	1.39 (1.33–1.46)	1.16 (1.12–1.20)	0.001
Women	1.79 (1.75–1.83)	1.91 (1.87–1.95)	<0.001	3.12 (2.94–3.02)	1.31 (1.28–1.34)	1.33 (1.30–1.36)	0.29	1.50 (1.41–1.59)	0.86 (0.84–0.89)	0.001

*Analyses were adjusted for age, comorbidity (in the matched-pair analyses as comorbidity covariates in Table 1; otherwise as the Charlson index), socioeconomic factors, and time-dependent adjustment for medical treatment with lipid-lowering drugs, β-blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers during follow-up. HR indicates hazard ratio.

†Propensity score was based on matched-pair analyses.

‡Reference is nondiabetics without a prior MI.

§Probability value for the comparison of diabetes versus a prior MI.

higher in women than in men.[8] Previous smaller studies demonstrated that the diabetes-related risk for cardiovascular death and total death was relatively higher in women than in men,[20,22] whereas almost similar relative risks for the 2 sexes were demonstrated in our study. Furthermore, because of a higher impact of a prior MI on sex differences in the matched-pair analyses, diabetes mellitus conferred a lower risk in women compared with men relative to their counterparts with a prior MI at all end points, whereas women expressed higher relative risks in other studies.[20,22] In agreement with our results was a large Canadian study demonstrating that the impact of diabetes mellitus was similar in the 2 sexes for total death and further that the impact of a prior MI was more pronounced than diabetes on sex differences for a MI.[8] Importantly, the studies addressing these issues have notable differences in age ranges, designs, and definitions of the study populations that could explain the discrepancies with our study.

Presumably induced by more baseline comorbidity (Table 1), additive risks were demonstrated for patients with both diabetes mellitus and a prior MI. These findings are corroborated by several other studies[8,9,14,17,18,20] and support the notion of diabetes mellitus as a cardiovascular risk equivalent for both men and women.

Another population study demonstrated relatively lower cardiovascular risk in younger diabetes patients.[8] The inclusion of diabetes patients on dietary-only treatment in this study could explain the discrepancies with our study. Indeed, the MRFIT study, which included only patients requiring glucose-lowering agents, confirmed our finding of a high diabetes-related cardiovascular risk at younger ages.[21]

A British study reported a markedly elevated risk of cardiovascular death in patients with type 1 diabetes mellitus without prior CVD for all ages.[11] A smaller study demonstrated that the increased mortality in patients with type 1 diabetes who were >30 years of age was attributable to
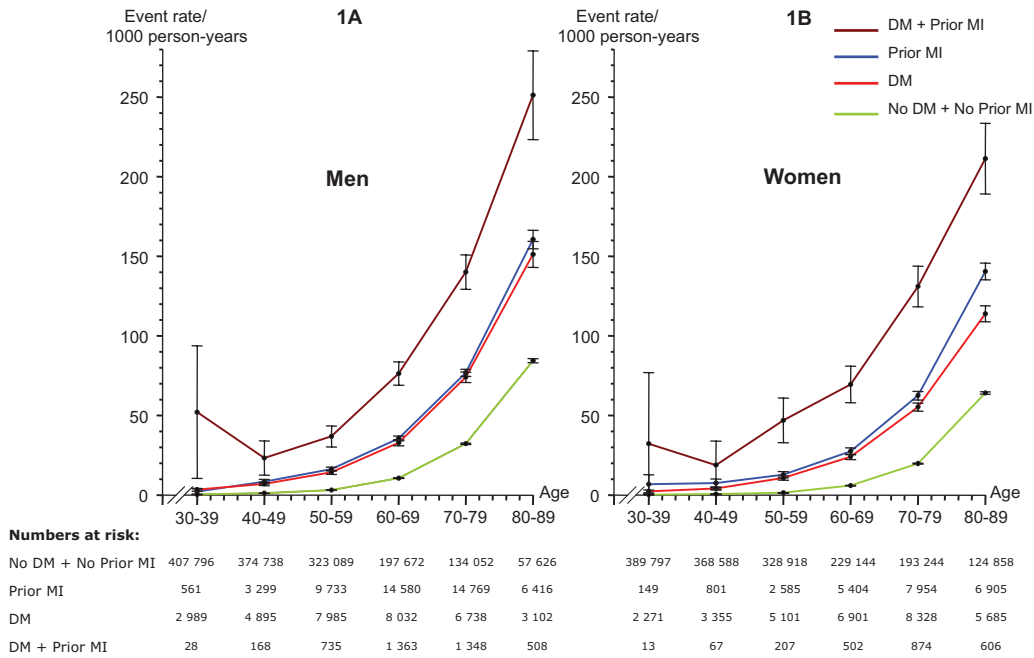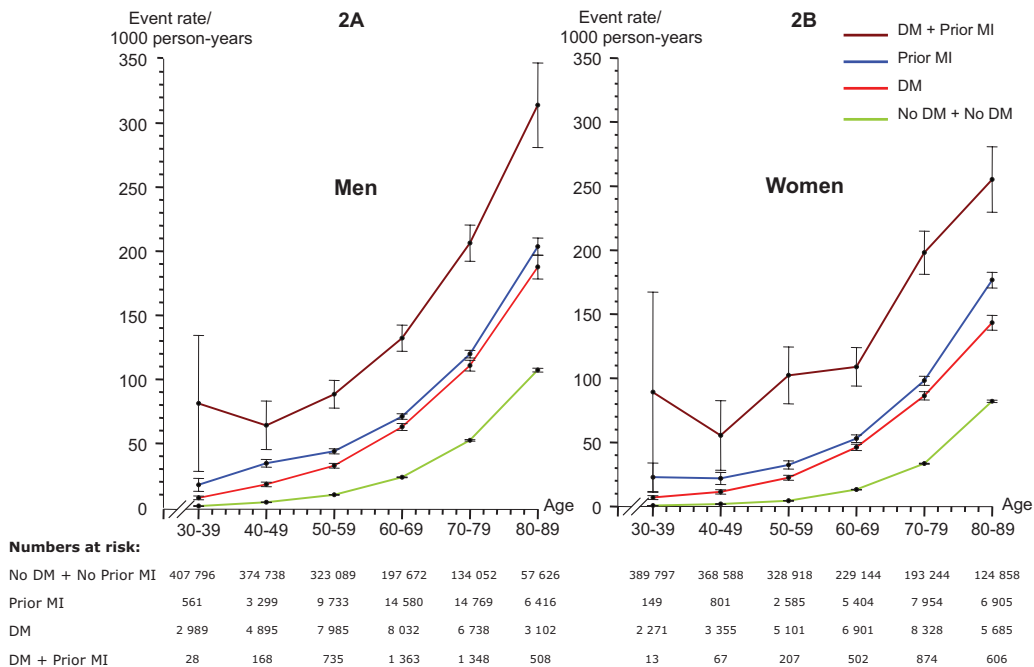
Figure 1. Event rates for cardiovascular mortality in men (A) and women (B) stratified by age and sex in relation to diabetes mellitus (DM) and a prior MI.

cardiovascular events.[10] In the Diabetes Control and Complication Trial, excess cardiovascular mortality in patients with type 1 diabetes mellitus also was evident after adjustment for diabetic nephropathy.[23] These studies are consistent with our indication of a particularly high cardiovascular risk in patients with type 1 diabetes mellitus even at younger ages.

By including the entire population of Denmark who were ≥30 years of age, we avoided any selection bias related to age, sex, income, willingness to participate, relation to a physician, or

health insurance organizations. The diagnosis of MI in the National Patient Registry has proved to be valid, with a sensitivity of 91% and a positive predictive value of 93%.[24] The stroke diagnoses chosen for this study in the National Patient Registry had positive predictive values of 74% to 97%.[25] Validation of coronary and cardiovascular events in similar populations demonstrated acceptable levels of sensitivity, with a tendency to overestimate cardiovascular deaths, although this overestimation would occur in all risk groups in our study.[26,27]

Figure 2. Event rates for the composite end point of MI (nonfatal), stroke (nonfatal), and cardiovascular death in men (A) and women (B) stratified by age in relation to diabetes mellitus (DM) and a prior MI.
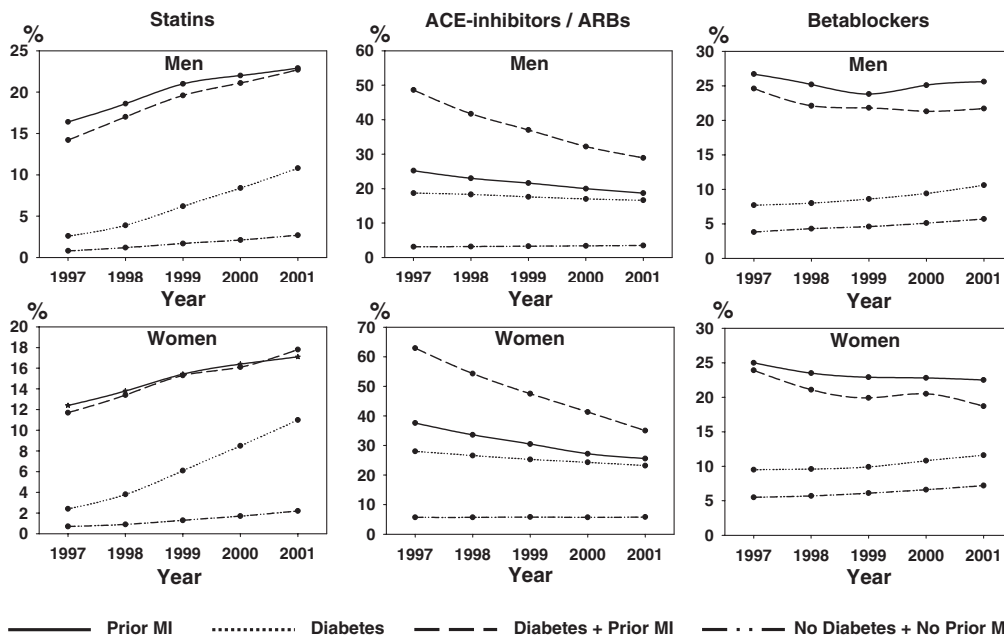
Figure 3. Secular trends for medical treatment in percentage during follow-up in relation to diabetes mellitus and a prior MI. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Glucose-lowering medications are dispensed only on prescription in Denmark, and the National Prescription Register is linked to the partial reimbursement policy for drug expenses by the national health security systems and has been shown to be accurate.[28]

This study also has important limitations that should be acknowledged. We were unable to study patients on diet-only treatment, which makes our population similar to that of the Haffner et al study[19] but different from those of several
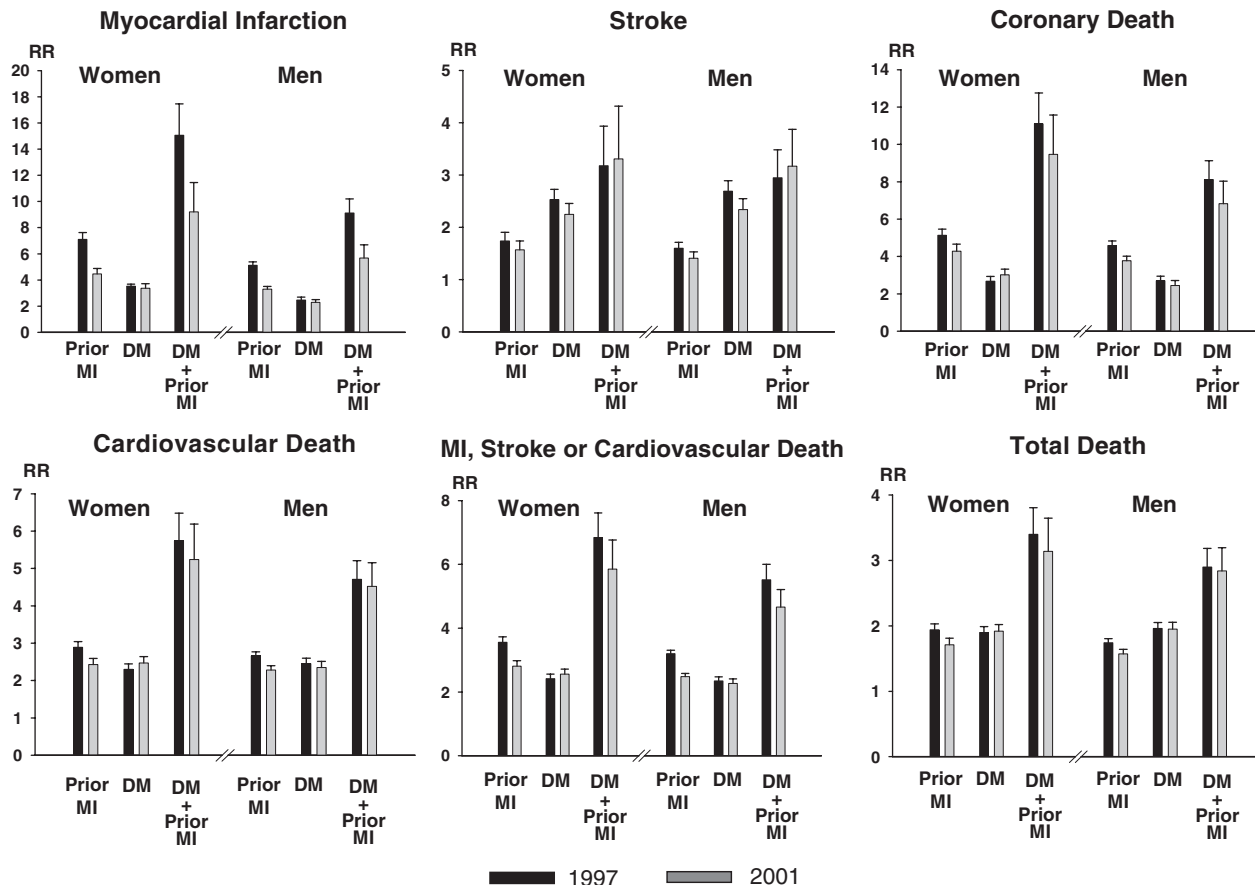
Figure 4. Age-adjusted Cox multivariable proportional-hazard analysis stratified by sex demonstrating secular trends in relative risks (RR) for different end points in relation to diabetes mellitus and a prior MI, with nondiabetics without a prior MI as the reference.

others.[8,9,14,16–18] Nevertheless, the cardiovascular risk in diabetes patients on dietary-only treatment needs attention.

Type 1 and type 2 diabetes mellitus could not be differentiated precisely in our study, although by investigating patients <40 years of age, we distinguished subgroups with a high probability of type 1 (insulin-only treatment) and type 2 (tablets) diabetes mellitus. Therefore, type 2 patients receiving insulin only could be misclassified as type 1, but presumably this would be a minority in this age group. Furthermore, in our substudy of patients receiving oral glucose-lowering medications only, we demonstrated that our results are applicable to patients with type 2 diabetes mellitus of all ages and for both sexes. Unfortunately, we were unable to adjust for well-known risk factors such as hypertension, lipid disorders, body mass index, smoking, physical activity, dietary factors, and blood glucose levels in our study. Although some reports have indicated that the diabetes-related cardiovascular risk depends on the numbers of preexisting risk factors,[29] the degree of arteriosclerosis was shown to be unrelated to the number of risk factors in diabetes mellitus.[30] Analysis of the Framingham population demonstrated that, independently of other coexisting risk factors, coronary mortality was influenced by diabetes duration.[31] We were unable to account for diabetes duration, but from estimates of expected time with diabetes before diagnosis[32] and before initiation of glucose-lowering therapy,[33] it is reasonable to assume that diabetes duration in our study was >7 to 10 years, implying a diabetes population at high risk. Because the study population consisted mainly of whites, the generalizability of this study to other ethnicities is uncertain.

Conclusions and Clinical Implications

Results of our present study indicate that all patients ≥30 years of age with diabetes who require glucose-lowering therapy should also receive intensive primary prevention for CVD, regardless of other risk factors, sex, or type of diabetes mellitus. Therefore, when glucose-lowering medications are required in the treatment of diabetes mellitus, antiplatelet therapy, statins, and possibly an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker should be added to the treatment because these pharmaceuticals are proven to be safe and effective in the primary prevention of cardiovascular events in diabetes mellitus.[34–36] Further research is needed to clarify if these diabetic patients profit from the very low low-density lipoprotein cholesterol goals for MI patients. Only 38% of patients undergoing treatment with glucose-lowering agents who have had no prior MI in our country received treatment with statins in 2004 (T.K.S., unpublished data, 2007), suggesting that the potential for improving treatment is substantial.

Source of Funding

Disclosures

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CLINICAL PERSPECTIVE

It is widely acknowledged that the presence of diabetes mellitus implies the presence of atherosclerotic cardiovascular disease. Studies of cardiovascular risk in patients with diabetes mellitus, combined with clinical trials and subgroup analyses of clinical trials, have resulted in recommendations for treatment with statins, aspirin, and inhibitors of the renin-angiotensin system for many patients with diabetes mellitus. Guidelines vary considerably, particularly for young patients with diabetes. The discrepancies between guidelines are driven mainly by the uncertainties of the cardiovascular risk in diabetes. In the present nationwide study of 3.3 million Danish residents ≥30 years of age, it was demonstrated that the risk of cardiovascular death over 5 years was nearly identical in patients with diabetes mellitus requiring glucose-lowering therapy and in patients with a prior myocardial infarction regardless of age, sex, and type of diabetes. Similar results were obtained for the combined occurrence of myocardial infarction, stroke, or cardiovascular death, whereas coronary morbidity/mortality was lower in patients with diabetes mellitus without a prior myocardial infarction compared with nondiabetics with a prior myocardial infarction. With limited access to controlled trials in patients with diabetes mellitus, guidelines for prophylactic treatment are currently driven mainly by analyses of cardiovascular risk in these patients. Specific recommendations on aspirin, statins, and possibly an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker depend on randomized controlled trial data. However, our study provides further evidence supporting the recommendation that all patients ≥30 years of age with diabetes mellitus who require glucose-lowering therapy should be considered for aggressive primary prevention interventions.

Circulation

Diabetes Patients Requiring Glucose-Lowering Therapy and Nondiabetics With a Prior Myocardial Infarction Carry the Same Cardiovascular Risk: A Population Study of 3.3 Million People

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