# Nationwide Trends in Cardiac Risk and Mortality in Patients With Incident Type 2 Diabetes: A Danish Cohort Study

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## OBJECTIVE

**Trends in cardiac risk and death have not been examined in patients with incident type 2 diabetes and no prior cardiovascular disease. Therefore, we aimed to examine trends in cardiac risk and death in relation to the use of prophylactic cardiovascular medications in patients with incident type 2 diabetes without prior cardiovascular disease.**

## RESEARCH DESIGN AND METHODS

**In this population-based cohort study, we included patients with incident type 2 diabetes between 1996 and 2011 through national health registries. Each patient was matched by age and sex with up to five individuals without diabetes from the general population. All individuals were followed for 7 years.**

## RESULTS

**We identified 209,311 patients with incident diabetes. From 1996–1999 to 2008–2011, the 7-year risk of myocardial infarction decreased from 6.9 to 2.8% (adjusted hazard ratio [aHR] 0.39 [95% CI 0.37–0.42]), cardiac death from 7.1 to 1.6% (aHR 0.23 [95% CI 0.21–0.24]), and all-cause death from 28.9 to 16.8% (aHR 0.68 [95% CI 0.66–0.69]). Compared with the general population, 7-year risk differences decreased from 3.3 to 0.8% for myocardial infarction, from 2.7 to 0.5% for cardiac death, and from 10.6 to 6.0% for all-cause death. Use of cardiovascular medications within ±1 year of diabetes diagnosis, especially statins (5% of users in 1996–1999 vs. 60% in 2008–2011), increased during the study period.**

## CONCLUSIONS

**From 1996 to 2011, Danish patients with incident type 2 diabetes and no prior cardiovascular disease experienced major reductions in cardiac risk and mortality. The risk reductions coincided with increased use of prophylactic cardiovascular medications.**


Type 2 diabetes is considered a major risk factor for cardiovascular disease and mortality (1). Current guidelines recommend extensive management of cardiovascular risk factors for high-risk patients with diabetes, including lifestyle interventions such as smoking cessation and physical activity, treatment with lipid-lowering agents and antihypertensive drugs, and consideration of aspirin (1,2). Randomized clinical trials have documented that multifactorial intervention reduces cardiovascular outcomes

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among patients with type 2 diabetes, and this approach has been introduced into clinical guidelines over the past decades (3,4). Accordingly, a few cohort studies have demonstrated declining cardiovascular morbidity and mortality rates in patients with diabetes (5–7). These studies included patients with prevalent diabetes and cardiovascular disease where prophylactic cardiovascular treatment is always indicated (5–7). However, less examined is how guideline recommendations have been implemented on a nationwide level and whether such implementations were temporally correlated with prognostic improvements among patients with incident type 2 diabetes without prior cardiovascular disease.

We therefore examined temporal trends in the use of prophylactic cardiovascular medications and risk of adverse cardiovascular events by linking Danish national health registries. We hypothesized that *1*) cardiac risk and all-cause death in patients with incident type 2 diabetes and no prior cardiovascular disease have decreased over time, *2*) the gap in cardiovascular risk between patients with incident type 2 diabetes and the general population has narrowed over time, and *3*) these trends are temporally correlated with intensified use of prophylactic cardiovascular medications.

## RESEARCH DESIGN AND METHODS

### Data Collection

Each Danish resident is assigned a unique permanent 10-digit personal identifier at birth or upon immigration. This identifier is used in every Danish health registry, allowing virtually complete long-term follow-up. We used the following databases in the current study: the Danish Civil Registration System, which maintains data on all Danish residents' vital status (dead, alive, or emigrated); the Danish National Patient Registry, which records all admission and outpatient hospital diagnoses; the Danish Causes of Death Registry, which contains data on cause of death of all Danish residents; and the Danish Prescription Registry, which records data on all reimbursed prescriptions redeemed at Danish pharmacies (8–11).

### Study Population

A flowchart of the study population is presented in Supplementary Fig. 1. Eligible participants in our study were selected from an a priori matched research data set at the Danish Health Data Authority. The data set includes all people in Denmark with incident diabetes, defined as a first-ever redemption of a prescription for a glucose-lowering drug at any pharmacy in Denmark as recorded in the Danish Prescription Registry (relevant anatomical therapeutic chemical codes are provided in Supplementary Table 1). The data set also includes five age- and sex-matched individuals from the general population who have not previously redeemed any prescriptions for glucose-lowering drugs on the matching date (i.e., on the inclusion date of their corresponding patient who initiated a glucose-lowering drug). The eligible diabetes cohort included all patients with a first glucose-lowering drug prescription from 1 January 1996 to 31 December 2011. We ended the inclusion period in 2011 to obtain 7 years of follow-up for all patients and to avoid the substantial change in diagnostic criteria for type 2 diabetes that occurred in 2011 and was implemented in Denmark in 2012 (12).

Patients who had resided in Denmark for $<$1 year prior to the inclusion date were excluded. Patients $<$30 years of age when redeeming first-ever glucose-lowering drugs were excluded as likely having type 1 diabetes. Women giving birth within 9 months after inclusion were excluded as likely having gestational diabetes mellitus. Women with preexisting hospital-diagnosed polycystic ovary syndrome or who redeemed any metformin prescription in combination with clomifen within 12 months following inclusion were excluded as likely having polycystic ovary syndrome. Finally, all patients with previous atherosclerotic cardiovascular disease, defined as previous diagnoses of ischemic stroke, myocardial infarction, coronary revascularization, peripheral artery disease, peripheral revascularization, and lower-limb amputation registered in the Danish National Patient Registry (the specific codes are listed in Supplementary Tables 2 and 3) were excluded. This left a study cohort of patients with incident type 2 diabetes and no prior atherosclerotic cardiovascular disease.

We applied these same exclusion criteria to the a priori 5:1 matched general population comparison cohort. Afterward, we excluded comparisons from matched sets without a remaining incident type 2 diabetes patient (after exclusion criteria had been applied to patients initiating glucose-lowering drugs). This left a comparison cohort of up to five age- and sex-matched individuals (exact ratio 4.6:1) for each patient with incident type 2 diabetes.

### Outcomes

Outcomes included myocardial infarction, cardiac death, and all-cause death. Outcomes were identified through the Danish National Patient Registry and the Danish Causes of Death Registry (Supplementary Table 2). Cardiac death was defined as death caused by ischemic heart disease, cardiac arrest with unspecified cause, ventricular tachycardia or other specified cardiac arrythmias, heart failure, sudden death with unspecified cause, or unattended death with unspecified cause.

### Prophylactic Cardiovascular Medications

Records of treatment with statins, β-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazides, aspirin, ADP receptor inhibitors, and vitamin K antagonists were obtained from the Danish Prescription Registry (Supplementary Table 1). Treatment before study inclusion (baseline) was defined as redemption of one or more prescriptions within 12 months before or on the inclusion date. Treatment after study inclusion was defined as redemption of one or more prescriptions within 12 months after the inclusion date.

### Statistical Analyses

Follow-up began on the date of first redemption of a glucose-lowering drug prescription and continued until an end point event, emigration, or a maximum of 7 years of follow-up, with the last patient concluding follow-up on 31 December 2018. Inclusion of patients with diabetes and individuals from the general population comparison cohort was stratified by calendar period in 4-year intervals: 1996–1999, 2000–2003, 2004–2007, and 2008–2011. Number of

events, 7-year cumulative incidence proportion using the Kaplan-Meier estimator from the survival package in R, 7-year risk difference, and 7-year crude and adjusted hazard ratios (aHRs) estimated by Cox regression were computed for each outcome. HRs were estimated among *1*) patients with type 2 diabetes by calendar period, using patients with diabetes diagnosed in 1996–1999 as reference, and *2*) patients with type 2 diabetes versus individuals from the general population comparison cohort, using the comparison cohort from the same calendar period as reference. HRs were adjusted for age and sex in a first regression model and additionally for heart failure, renal disease, hypertension (antihypertensive treatment), markers of smoking, obesity, hypercholesterolemia (statin treatment), and alcohol-related disorders in a second adjusted regression model (codes are provided in Supplementary Tables 1 and 2). Cumulative incidence proportions of myocardial infarction and cardiac death were estimated to account for the competing risk of all-cause death and noncardiac death, respectively. The proportion of patients with type 2 diabetes redeeming prescriptions for prophylactic cardiovascular medications was calculated by calendar period. Further, we performed a sensitivity analysis with stratification by sex and age-group at study inclusion ($<$60, 60 to $<$70, 70 to $<$80, and $>$80 years) for both study groups. In an additional analysis, we examined the impact of early initiation of statin treatment (i.e., before the inclusion date or within 12 months after the inclusion date) in patients with incident type 2 diabetes from the last inclusion interval. We chose to examine patients only from the last inclusion period to include a high proportion of statin users and to reduce the risk of confounding by indication. All analyses were performed using R 3.4 software. According to Danish law, approval from an ethics committee was not required.

## RESULTS

We included 209,311 patients with incident type 2 diabetes. The patients were matched with 962,438 people from the general population. In the diabetes cohort, 1,910 patients emigrated during follow-up and were censored on the day of emigration, and 64 patients were lost during follow-up. In the general population cohort, 6,932 individuals emigrated during follow-up and were censored on the day of emigration, while 203 individuals were lost during follow-up.

### Baseline Characteristics of the Study Population

Baseline characteristics of the patient and comparison cohorts are presented in Table 1. The number of patients with incident type 2 diabetes increased from 39,546 in 1996–1999 to 71,279 in 2008–2011. In the diabetes cohort, the median age at study entry was 62.7 years in 1996–1999, 61.1 years in 2000–2003, 60.5 years in 2004–2007, and 61.4 years in 2008–2011. The frequency of redeemed insulin and sulfonylurea prescriptions decreased over time, whereas the frequency of biguanides increased. Baseline characteristics of people from the general population stratified by calendar period are provided in Supplementary Table 4.

### Cardiac Outcomes and Death

Number of events, 7-year risk, 7-year risk difference, and 7-year HR for patients with type 2 diabetes are presented in Table 2. From 1996–1999 to 2008–2011, the 7-year risk of myocardial infarction decreased from 6.9 to 2.8% (aHR 0.39 [95% CI 0.37–0.42]). For cardiac death, the 7-year risk declined from 7.1% in 1996–1999 to 1.6% in 2008–2011 (aHR 0.23 [95% CI 0.21–0.24]). For all-cause death, the 7-year risk decreased as well from 28.9% in 1996–1999 to 16.8% in 2008–2011 (aHR 0.68 [95% CI 0.66–0.69]).

The risk of myocardial infarction, cardiac death, and all-cause death also decreased over time in the general population cohort. From 1996–1999 to 2008–2011, we observed a substantial decline in the risk difference between patients with type 2 diabetes and the comparison cohort. The risk difference decreased from 3.3% (aHR 1.92 [95% CI 1.86–1.99]) to 0.8% (aHR 1.29 [95% CI 1.22–1.35]) for myocardial infarction and from 2.7% (aHR 1.62 [95% CI 1.56–1.67]) to 0.5% (aHR 1.35 [95% CI 1.26–1.44]) for cardiac death (Fig. 1 and Supplementary Table 5). For all-cause death, the 7-year risk difference between the diabetes and the general population cohort decreased from 10.6% (aHR 1.63 [95% CI 1.61–1.65]) to 6.0% (aHR 1.51 [95% CI 1.48–1.54]).

### Prophylactic Cardiovascular Medications

The proportion of patients with incident type 2 diabetes who redeemed prescriptions for prophylactic cardiovascular medications are presented in Fig. 2 and Supplementary Table 6. Use of statins (5 vs. 60%), β-blockers (12 vs. 21%), ACE inhibitors (19 vs. 36%), angiotensin II receptor blockers (5 vs. 21%), calcium channel blockers (16 vs. 25%), and aspirin (18 vs. 27%) all increased from the first to the last inclusion interval. This increase in redemption of prescriptions for cardiovascular medications was mainly observed before initiation of glucose-lowering drugs, while treatment with prophylactic cardiovascular medications within the first 12 months following initiation of glucose-lowering drugs was stable over time, except for statins, which seemed to increase over time.

### Sensitivity and Additional Analyses

Results for myocardial infarction, cardiac death, and all-cause death were robust when stratifying for sex and age-group at study inclusion in patients with type 2 diabetes, using patients with diabetes diagnosed in 1996–1999 as reference (Supplementary Fig. 2). When we investigated the impact of initiation of statin therapy before the inclusion date or within 12 months after the inclusion date compared with late or no onset of statin therapy, we observed that early initiation of statin therapy reduced risks of myocardial infarction (aHR 0.80 [95% CI 0.71–0.90]), cardiac death (aHR 0.82 [95% CI 0.70–0.97]), and all-cause death (aHR 0.68 [95% CI 0.65–0.71]) in patients with incident type 2 diabetes (Supplementary Table 7).

## CONCLUSIONS

This Danish nationwide cohort study compared trends in cardiac outcomes and mortality among 209,311 patients with incident type 2 diabetes and no prior cardiovascular disease and a matched general population cohort of nearly 1 million people. The 7-year relative risks based on aHRs declined by 61% for myocardial infarction, 77% for cardiac death, and 32% for all-cause death among patients with diabetes. The risk of these outcomes decreased over time in the general population cohort as

**Table 1—Baseline characteristics of patients with incident type 2 diabetes and matched individuals from the general population**

| | All matched individuals ($n$ = 962,438) | Patients with diabetes | | | | |
|---|---|---|---|---|---|---|
| | | All ($n$ = 209,311) | 1996–1999 ($n$ = 39,546) | 2000–2003 ($n$ = 44,364) | 2004–2007 ($n$ = 54,122) | 2008–2011 ($n$ = 71,279) |
| Male sex | 517,916 (54) | 113,669 (54) | 21,976 (56) | 24,627 (56) | 28,775 (53) | 38,291 (54) |
| Median age, years (QL, QU) | 60.5 (50.9, 69.9) | 61.3 (51.5, 70.8) | 62.7 (52.6, 73.2) | 61.1 (52.1, 71.6) | 60.5 (50.4, 69.8) | 61.4 (51.3, 69.7) |
| Hypertension | 261,949 (27) | 120,674 (58) | 20,156 (51) | 23,852 (54) | 31,561 (58) | 45,105 (63) |
| Heart failure | 11,468 (1) | 8,049 (4) | 1,674 (4) | 2,061 (5) | 2,075 (4) | 2,239 (3) |
| Moderate to severe renal disease | 6,056 (1) | 2,461 (1) | 419 (1) | 463 (1) | 618 (1) | 961 (1) |
| Atrial fibrillation | 5,752 (1) | 3,298 (2) | 506 (1) | 740 (2) | 899 (2) | 1,153 (2) |
| Connective tissue disease | 21,881 (2) | 6,598 (3) | 1,136 (3) | 1,329 (3) | 1,665 (3) | 2,468 (3) |
| Any malignancy (excluding skin cancer) | 60,851 (6) | 17,091 (8) | 3,004 (8) | 3,531 (8) | 4,216 (8) | 6,340 (9) |
| Moderate to severe liver disease | 5,752 (1) | 3,298 (2) | 506 (1) | 740 (2) | 899 (2) | 1,153 (2) |
| Obesity (ICD registered) | 11,108 (1) | 14,675 (7) | 1,246 (3) | 2,512 (6) | 4,250 (8) | 6,667 (9) |
| Markers of smoking | 89,742 (9) | 30,618 (15) | 5,402 (14) | 6,313 (14) | 7,797 (14) | 11,106 (16) |
| Insulin | 0 (0) | 15,224 (7) | 3,811 (10) | 3,665 (8) | 3,932 (7) | 3,816 (5) |
| Biguanides | 0 (0) | 118,441 (57) | 5,190 (13) | 16,908 (38) | 33,896 (63) | 62,447 (88) |
| Sulfonylureas | 0 (0) | 76,608 (37) | 30,150 (76) | 23,566 (53) | 17,144 (32) | 5,748 (8) |
| DPP-4is | 0 (0) | 646 (0) | 0 (0) | 0 (0) | 48 (0) | 598 (1) |
| Glitazone | 0 (0) | 284 (0) | 0 (0) | 18 (0) | 176 (0) | 90 (0) |
| Statins | 64,476 (7) | 55,391 (26) | 1,012 (3) | 4,517 (10) | 17,036 (31) | 32,826 (46) |
| β-Blocker | 77,740 (8) | 36,263 (17) | 4,916 (12) | 7,057 (16) | 10,038 (19) | 14,252 (20) |
| ACE inhibitor | 72,070 (7) | 47,595 (23) | 5,547 (14) | 7,769 (18) | 12,656 (23) | 21,623 (30) |
| ARB | 47,474 (5) | 25,911 (12) | 1,347 (3) | 4,056 (9) | 7,820 (14) | 12,688 (18) |
| Calcium channel blocker | 80,016 (8) | 37,334 (18) | 6,089 (15) | 6,657 (15) | 8,856 (16) | 15,732 (22) |
| Thiazide | 93,086 (10) | 40,386 (19) | 6,509 (16) | 8,161 (18) | 11,305 (21) | 14,411 (20) |
| Aspirin | 81,206 (8) | 41,606 (20) | 5,894 (15) | 7,569 (17) | 11,896 (22) | 16,247 (23) |
| ADP receptor inhibitor | 1,115 (0) | 435 (0) | <5 (0) | 41 (0) | 115 (0) | 275 (0) |
| Vitamin K antagonist | 17,267 (2) | 9,215 (4) | 1,245 (3) | 1,748 (4) | 2,530 (5) | 3,692 (5) |

Data are $n$ (%) unless otherwise indicated. ARB, angiotensin II receptor blocker; DPP-4i, dipeptidyl peptidase 4 inhibitor; QL, lower quartile; QU, upper quartile.

well but to a smaller extent than among patients with diabetes. Thus, the initial large risk differences between the diabetes and comparison cohorts narrowed over time for all outcomes, with only 0.5–0.8% risk differences for myocardial infarction and cardiac death over a 7-year follow-up for the last inclusion interval. During the study period, redemption of prescriptions especially for statins but also for aspirin, β-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers increased.

The major prognostic improvements documented in this cohort study show that it was possible to reduce the risks of myocardial infarction and cardiac death in patients with incident type 2 diabetes without prior cardiovascular disease to levels almost similar to those in the

**Table 2—Risk of cardiac outcomes and all-cause death in patients with incident type 2 diabetes**

| | Patients with diabetes, *n* | Events, *n* | Event rate per 100 person-years (95% CI) | 7-year CIP* (95% CI) | 7-year risk difference | Crude 7-year HR | Adjusted 7-year HR† (95% CI) | Adjusted 7-year HR‡ (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Myocardial infarction | | | | | | | | |
| 1996–1999 | 39,546 | 4,605 | 1.0 (0.9–1.0) | 6.9 (6.7–7.2) | Reference | Reference | Reference | Reference |
| 2000–2003 | 44,364 | 3,724 | 0.7 (0.7–0.7) | 5.2 (5.0–5.4) | −1.7 | 0.76 | 0.76 (0.73–0.79) | 0.75 (0.71–0.78) |
| 2004–2007 | 54,122 | 2,758 | 0.5 (0.5–0.5) | 3.5 (3.3–3.6) | −3.5 | 0.52 | 0.54 (0.51–0.56) | 0.52 (0.49–0.54) |
| 2008–2011 | 71,279 | 2,203 | 0.4 (0.4–0.4) | 2.8 (2.7–2.9) | −4.1 | 0.42 | 0.41 (0.39–0.44) | 0.39 (0.37–0.42) |
| Cardiac death | | | | | | | | |
| 1996–1999 | 39,546 | 4,544 | 0.9 (0.9–0.9) | 7.1 (6.8–7.4) | Reference | Reference | Reference | Reference |
| 2000–2003 | 44,364 | 2,959 | 0.6 (0.5–0.6) | 4.2 (4.0–4.4) | −2.9 | 0.62 | 0.62 (0.59–0.65) | 0.59 (0.56–0.61) |
| 2004–2007 | 54,122 | 1,885 | 0.3 (0.3–0.4) | 2.5 (2.4–2.7) | −4.6 | 0.37 | 0.38 (0.36–0.40) | 0.36 (0.34–0.38) |
| 2008–2011 | 71,279 | 1,204 | 0.2 (0.2–0.2) | 1.6 (1.5–1.7) | −5.5 | 0.24 | 0.24 (0.22–0.25) | 0.23 (0.21–0.24) |
| All-cause death | | | | | | | | |
| 1996–1999 | 39,546 | 26,436 | 5.2 (5.1–5.3) | 28.9 (28.5–29.4) | Reference | Reference | Reference | Reference |
| 2000–2003 | 44,364 | 22,855 | 4.3 (4.2–4.3) | 24.3 (24.0–24.8) | −4.6 | 0.82 | 0.87 (0.86–0.89) | 0.87 (0.85–0.88) |
| 2004–2007 | 54,122 | 18,748 | 3.3 (3.3–3.4) | 20.0 (19.6–20.3) | −9.0 | 0.64 | 0.75 (0.73–0.76) | 0.78 (0.76–0.79) |
| 2008–2011 | 71,279 | 15,097 | 2.7 (2.7–2.8) | 16.8 (16.5–17.1) | −12.1 | 0.52 | 0.62 (0.61–0.63) | 0.68 (0.66–0.69) |

CIP, cumulated incidence proportion. *Seven-year CIP for myocardial infarction and cardiac death was adjusted for the competing risk of death. †Adjusted for age and sex. ‡Adjusted for age, sex, heart failure, renal disease, hypertension, markers of smoking, obesity, hypercholesterolemia, and alcohol-related disorders.

general population. Moreover, the 7-year risk of all-cause death among patients with incident type 2 diabetes was reduced from 29 to 17% in the same 15-year study period. These results were independent of sex and age-group at time of diagnosis. There are several potential reasons for these findings. First, our nationwide cohort results are consistent with landmark randomized trials that provided a causal relationship by showing that it is possible to reduce the risk of cardiovascular events in patients with diabetes through multifactorial interventions, including intensive control of blood glucose, blood pressure, and lipid levels (3,4). Our results also correspond with other cohort studies demonstrating that use of prophylactic cardiovascular medications and reaching target ranges correlate with reduced risk of death and cardiovascular outcomes in patients with diabetes with or without prior cardiovascular disease (13,14). We extend these results by using a nationwide cohort, representing daily clinical practice in Denmark, to show that implementation of such multifactorial cardiovascular prophylaxis coincides with major prognostic benefits among patients with newly diagnosed type 2 diabetes without prior cardiovascular disease.

In the current study, we observed that the number of patients with incident type 2 diabetes increased from 1996–1999 to 2008–2011, and similar temporal trends have been reported in the U.S. and Sweden (5,7). Such changes may reflect a true increased incidence as well as an improved awareness of the disease. The latter is probably reflected in the 1.3-year decline in the median age at diagnosis observed in our study, but such earlier diagnosis can also lead to earlier, and potentially more effective, prophylactic intervention. The small decline in median age at diagnosis may also be explained by increasing prevalence of obesity as well as a more sedentary lifestyle in Denmark, both associated with earlier development of diabetes. Accordingly, we observed that the prevalence of obesity increased from 3 to 9% in patients with diabetes during the study period, although this increase also might reflect surveillance bias or improved registration of the diagnosis. It is noteworthy that most prophylactic cardiovascular medications were initiated prior to the first filling of glucose-lowering drugs, a finding that may reflect initiation in the grace period from first measurement of a high blood glucose or $HbA_{1c}$ to the initiation of a glucose-lowering drug. Another possible explanation for this finding could be that undetected dysglycemia is highly prevalent (39%) in patients treated for hypertension and/or hypercholesterolemia, which would appear in routine laboratory tests in these patients (15). We observed that especially early initiation of statin treatment increased, and our additional analysis revealed that receiving statin treatment within 12 months after first filling of a glucose-lowering drug was associated with decreased cardiac risk and mortality. Accordingly, results from the Intensified Multifactorial

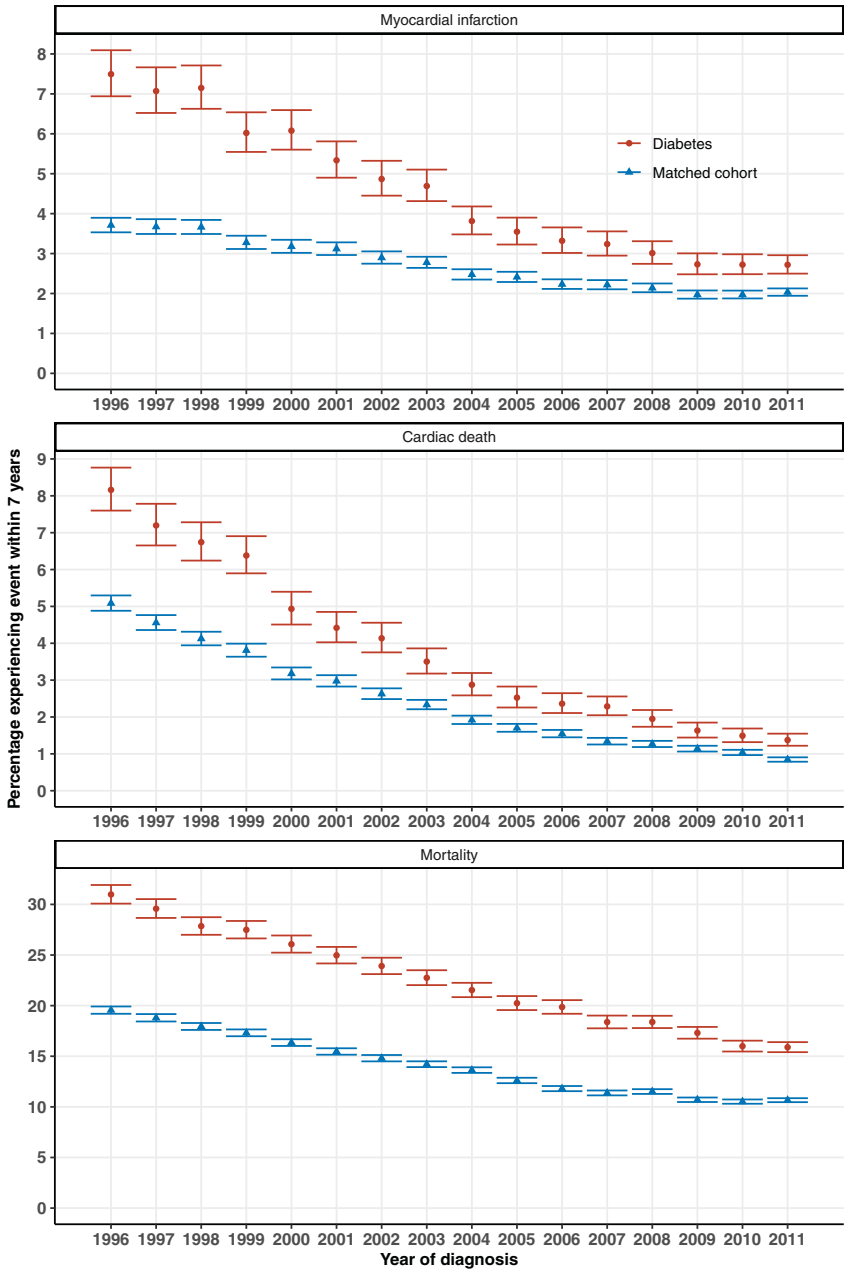


**Figure 1**—Seven-year cumulative incidence proportions of myocardial infarction, cardiac death, and all-cause death in patients with incident diabetes and matched individuals from the general population.

Intervention in Patients with Type 2 Diabetes and Microalbuminuria (Steno-2) study showed that statins and blood pressure–lowering medications probably were the most important part of the cardiovascular risk–reducing therapy (16). Thus, the observed major prognostic risk improvements were likely caused by a combination of multifactorial prophylactic interventions (both those accounted for in the current study, i.e., statin, aspirin, antihypertensive medications, and those not examined, e.g., physical activity, smoking) as well as earlier diagnosis and earlier prophylactic interventions.

Our study is the first nationwide study to document such major risk reductions among patients with recent-onset type 2 diabetes without prior cardiovascular disease. However, our findings are consistent with trends in cardiovascular disease and mortality in patients with prevalent diabetes, with or without prior cardiovascular disease, observed in North America, Sweden, and South Korea (5–7,17,18). A Canadian cohort study examined trends in patients with prevalent diabetes between 1992 and 2000 and observed a decline in cardiovascular event rates (15% reduction in the 8-year rate of myocardial infarction) (17). In contrast to our study, they did not report information on cardiovascular disease status at study entry and were unable to discriminate between type 1 and type 2 diabetes. More recently, cross-sectional data from the National Health Interview Survey of U.S. adults showed declining rates of myocardial infarction (68% reduction from 1990 to 2010) and mortality (20% reduction per 10 years from 1988–1994 to 2010–2015) in patients with prevalent type 1 or type 2 diabetes (5,6). Furthermore, a Swedish cohort study reported declining rates of cardiovascular outcomes and mortality in patients with prevalent type 2 diabetes between 1998 and 2014 (7). The Swedish study followed patients from inclusion in the Swedish National Diabetes Register initiated in 1996. This meant that age at entry declined from 67.1 years in 1998 to 61.4 in 2012 and that duration of type 2 diabetes at entry declined from 9.5 years to 2.0 years in the same period. The Swedish study findings were thus biased by age and duration of diabetes at entry into the study. In contrast, we followed all patients from the onset of treated type 2 diabetes. A nationwide cohort study from South Korea also demonstrated declining rates between 2006 and 2013 of cardiovascular disease (37% relative reduction in the 8-year rate of myocardial infarction) in patients with prevalent diabetes (18). In the South Korean study, information on prior cardiovascular disease at study entry and duration of diabetes was unknown. Thus, none of the studies from North America, Sweden, and South Korea examined patients with recent-onset type 2 diabetes without prior cardiovascular disease. For this group of patients, it is crucial to initiate sufficient prevention in early disease stages to prevent or delay diabetes-related complications.

Strengths of the current study include accurate individual-level record linkage among all data sources in a tax-supported, public health care system with equal access for all citizens, which reduces the risk of selection bias. Moreover, previous validation studies have found a high positive predictive value

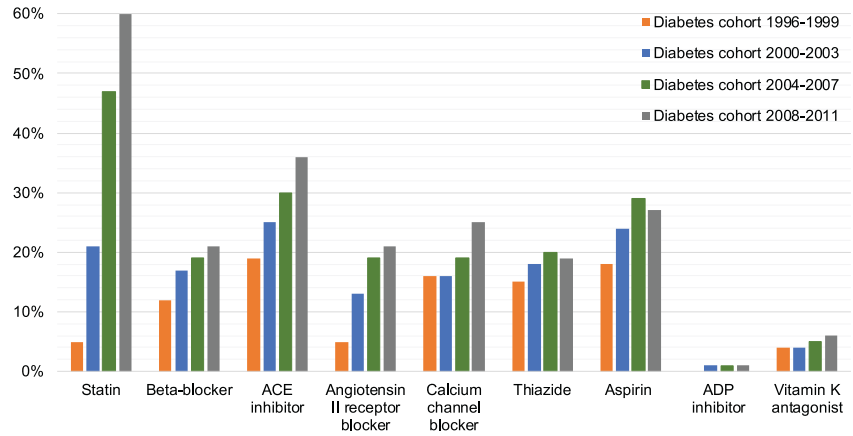


**Figure 2**—Proportion of patients with incident type 2 diabetes with a redemption of one or more prescriptions within 12 months before and/or 12 months after the study inclusion date stratified by calendar period.

(≥97%) of the myocardial infarction diagnosis used in the current study (19,20).

Some study limitations must be noted. First, we could not assess lifestyle changes such as smoking cessation, physical activity level, and dietary changes. Danish national surveys have shown that the percentage of adult smokers has gradually decreased from 44% in 1994 to 28% in 2010, and these changes likely contributed to the overall reduction in adverse cardiovascular outcomes (21). Second, $HbA_{1c}$ levels are only available for a subgroup of patients and were only measured in selected patients in the earlier years of the interval assessed in this study, while later becoming available for all patients. We have previously published $HbA_{1c}$ and LDL cholesterol data from 2000 to 2017 for patients with recent-onset type 2 diabetes in northern Denmark (22). These data revealed that mean pre- and posttreatment levels of $HbA_{1c}$ and LDL cholesterol decreased during the study period, suggesting great improvements in monitoring of diabetes and hypercholesterolemia (22). Third, our diagnosis of type 2 diabetes relied on Danish registries and use of glucose-lowering medications. Thus, type 2 diabetes treated with diet alone was not included but may have been included in the general population comparison cohort. Fourth, classification of myocardial infarction changed in 2007 and 2012 according to universal definitions (23,24). Moreover, registration of cardiac death varied during the study period. Until 2007, registration of cause of death was coded centrally in the National Board of Health based on the medical information on death certificates filled out by physicians (25). Since 2007, cause-of-death registration has relied entirely on coding done by physicians when issuing the death certificate. Still, this should not affect the comparison between the diabetes and general population cohorts. Finally, while this observational study shows that increased use of prophylactic medications coincides with decreased cardiac risk and mortality in patients with diabetes, the causal relationship relies on previous randomized clinical trials (3,4).

In conclusion, patients with incident type 2 diabetes and no prior cardiovascular disease experienced major reductions in risk of myocardial infarction, cardiac death, and all-cause death in Denmark from 1996 to 2011. These risk reductions were much larger than those observed in the general population. During the study period, use of prophylactic cardiovascular medications increased markedly in patients with diabetes, which probably contributed to the observed risk reductions.

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