Improved Survival Among Patients With Complicated Type 2 Diabetes in Denmark: A Prospective Study (2002–2010)

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Context: It is unclear to what extent recent advances in diabetes care have reduced the excess mortality in patients with complicated type 2 diabetes.

Objective: The aim of this study was to estimate time trends in mortality among patients with complicated type 2 diabetes at the Steno Diabetes Center relative to the general Danish background population.

Design, Setting, and Study Participants: We performed a longitudinal follow-up study from 2002 to 2010 of 5844 patients with type 2 diabetes at the Steno Diabetes Center, Denmark. All-cause and cause-specific mortality was identified from the national death register.

Main Outcome Measures: Poisson regression was used to model mortality rates by sex, age, age of diabetes onset, and calendar time.

Results: A total of 1341 deaths occurred (802 men and 539 women) during 32 913 person-years of follow-up. Total mortality rates in the diabetes population decreased by 5.5% (95% confidence interval 2.9%–8.0%) per year in men and by 3.3% (0.0%–6.4%) per year in women. Among men but not women, this decline was significantly steeper than the decline in mortality in the Danish background population (men, −3.0% [−5.6% to −0.4%]; women, −1.4 [−4.6% to 2.0%]). The decline in overall mortality was explained by a decline in cardiovascular mortality for both men and women.

Conclusion: Overall and cardiovascular mortality have decreased during the last decade among Danish patients with complicated type 2 diabetes, and for men, the decline in mortality was more pronounced than in the general population. **(*J Clin Endocrinol Metab* 99: E642–E646, 2014)**

For many years, it has been a well-known phenomenon that patients with type 2 diabetes have a doubled risk of all-cause mortality as compared with the general population (1–3). However, data from recent years indicate that this gap is narrowing (4–6). The Steno-2 Study, performed from 1993 to 2001, showed that aggressive multifactorial treatment significantly reduced the risk of cardiovascular disease (CVD) and death (7, 8). As a result of this and other studies, more aggressive treatment strategies based on targeting multiple risk factors have been implemented in the clinical care of patients with type 2 diabetes (9). The ultimate goal of such strategies is to reduce the mortality among patients with type 2 diabetes to a level comparable to nondiabetic individuals. However, it is unclear to what extent recent advances in diabetes care have reduced the excess mortality in patients with complicated type 2 diabetes. Therefore, we estimated mortality rates for patients with type 2 diabetes at the Steno Diabetes Center in Denmark in the period from 2002 to 2010 and compared these rates

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Abbreviations: CVD, cardiovascular disease; SMR, standardized mortality rate.

with the concomitant mortality rates in the general Danish background population.

Patients and Methods

Patient population

A total of 5844 patients with type 2 diabetes from the Steno Diabetes Center in Gentofte, Denmark, were followed in the period January 1, 2002, to December 31, 2010, for deaths and causes of death. All type 2 diabetes patients recorded in the Steno electronic medical record system including patients entering during the follow-up period were extracted. Via a unique personal identification number used in Denmark, patients were linked to the Danish Civil Registration System and to the Danish Register of Causes of Death for vital status and cause of death. For all patients in the analysis, we have recordings of date of birth, date of diabetes diagnosis, presence of complications within the first year of inclusion in the study, and date and cause of death.

Information on diabetes type, date of diagnosis, and complications was drawn from the electronic patient record at the Steno Diabetes Center. Any nephropathy, retinopathy, and neuropathy are measured annually in 96% to 99% of all patients, and quality of care exceeds the national standards for 8 of 10 indicators (10). Diabetic nephropathy was defined as a urinary albumin to creatinine ratio $\geq$3.5 mg/mmol (30 mg/g) in 2 of 3 consecutive sterile urine samples. Retinopathy was defined as any retinopathy and diagnosed based on mydriatic nonstereoscopic fundus photography and graded and classified using the 5-step Steno retinopathy scale (11). Information on CVD was obtained from the Danish National Patient Register using ICD-10 codes for ischemic heart disease, cerebrovascular disease, heart failure, peripheral arterial disease, or revascularization.

General population

From Statistics Denmark, we obtained data on the total Danish population size from January 1, 2002, to December 31, 2010, by gender and age as well as the number of deaths in the Danish population subdivided by gender, age, and date of death.

Ethics

Informed consent and ethical approval are not required for register studies in Denmark. Access to and use of the described data are approved by the Danish Data Protection Agency (journal number: 2007–58-0015).

Statistical analysis

Mortality rates were analyzed by a Poisson model, using log-person-time as offset variable. Similarly, using log-expected deaths as offset, the standardized mortality rate (SMR) was modeled. For all-cause mortality, the patients' follow-up (risk time and deaths) data were split into 3-month intervals, each interval recording the current age, date, and diabetes duration. For each interval, we attached the corresponding overall population mortality rate (in 1-year age and calendar time intervals) and computed the expected number of deaths. Based on the underlying cause of death for the patients at the Steno Diabetes Center, we calculated cause-specific mortality for deaths due to CVD, cancer, or other causes.

Both absolute mortality and SMR were analyzed with smooth terms of current age, date of follow-up, and duration of diabetes, with a simple 1-parameter (product) interaction between age and diabetes duration. The midpoints of age, period, and duration categories were used as continuous covariates, and the effect of these were taken as smooth parametric functions, implemented as natural splines. All analyses were done separately for men and women, and data are reported with 95% confidence intervals. All analyses and graphs were generated with R version 3.0.1 (www.R-project.org). A complete account of all statistical analyses is available at http://bendixcarstensen.com/SDC/EPJmort/MortT2.pdf.

Results

Patient population

The characteristics of men and women with type 2 diabetes at inclusion in the study are shown in Table 1. The median follow-up time was 6 years. A large proportion of the type 2 diabetes population had complications at inclusion in the study, with approximately 70% of the patients having CVD and 40% to 47% having neuropathy or retinopathy (Table 1).

In the period 2002 to 2010, 1341 deaths occurred in the population during 32 913 person-years of follow-up, corresponding to 23% of men and 22% of women. The most common cause of death was CVD followed by cancer (Table 1).

Absolute mortality rates

Absolute mortality rates by age and sex for patients with diabetes onset at ages 40, 50, 60, and 70 years are shown in Figure 1, A and B. The absolute mortality in-

Table 1. Characteristics of Type 2 Diabetes Patients at Study Entry and Causes of Deaths During Follow-up

	Men	Women
Baseline characteristics		
n (%)	3423 (59)	2421 (41)
Age, y	61 (53–69)	62 (53–72)
Follow-up time, y	6.0 (2.8–9.0)	6.1 (3.1–9.0)
Diabetes duration, y	7 (3–13)	8 (3–14)
Nephropathy	1173 (34)	566 (23)
Neuropathy	1613 (47)	963 (40)
Retinopathy	1426 (42)	983 (41)
CVD	2423 (71)	1630 (67)
Causes of death during follow-up		
Total number of deaths	802 (23.4)	539 (22.3)
CVD	276 (34.4)	197 (36.5)
Cancer	174 (21.7)	111 (20.6)
Kidney disease	21 (2.6)	13 (2.4)
Lung disease (including pneumonia)	50 (6.2)	32 (5.9)
Gastrointestinal disease	45 (5.6)	21 (3.9)
Infection	52 (6.5)	37 (6.9)
Accident	7 (0.9)	8 (1.5)
Other	177 (22.1)	120 (22.3)

Data are median (interquartile range) or number (%).

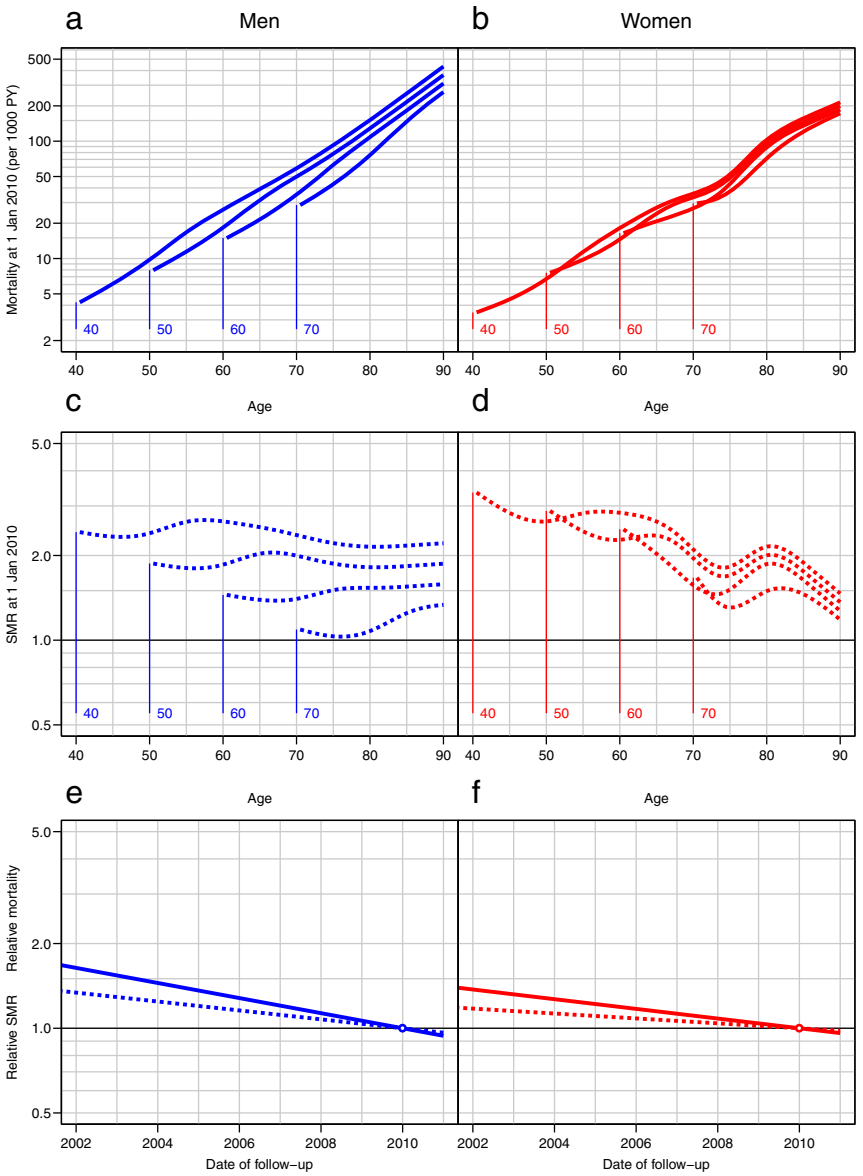

Figure 1. Mortality rates (A and B), SMRs (C and D), and changes in these parameters (E and F) for type 2 diabetes patients diagnosed at ages 40, 50, 60, and 70 years. Solid lines are absolute mortality, and dotted lines are SMRs. Blue curves represent men, and red curves represent women.

creased exponentially with increasing age (linearly on a log-scale) for both sexes. For men, we found that the mortality was higher the younger the age at diagnosis, a tendency that was only very weak among women. In general, absolute mortality rates were higher for men than for women at any age (Figure 1, A and B).

Standardized mortality rates

Relative mortality rates in the diabetes population as compared with the background population (SMR) are shown in Figure 1, C and D. In men, SMR was some 2-fold higher for those diagnosed with diabetes at age 40 compared with those diagnosed at age 70, and SMR decreased by 3.2% (2.1%–4.3%) per year of age at diagnosis. Among women, age at diagnosis had a smaller effect on SMR with a decline of 1.5% (0.1%–2.9%) per year of age at diagnosis (P for difference between men and women = .061).

Time trends in mortality rates

The absolute mortality rate in the diabetes population decreased linearly over the study period in both men (5.5% [2.9%–8.0%] per year; Figure 1E) and women (3.3% [0.0%–6.4%] per year; Figure 1F). This decline was significantly steeper than the corresponding decline in the Danish background population among men (SMR, −3.0% [−5.6% to −0.4%] per year; Figure 1E) but not among women (SMR, −1.4% (−4.6% to 2.0%) per year; Figure 1F). However, neither decline was significantly different between men and women (mortality, P = .293; SMR, P = .433).

The decline in absolute mortality among type 2 diabetes patients over time was predominantly explained by a decline in CVD mortality of −9.8% (5.6%–13.9%) per year in men and −9.0% (3.9%–13.9%) per year in women. Death from cancer did not change significantly over time (men, −1.9% [−7.4% to 4.0%] per year; women, 0.6% [−6.5% to 8.3%] per year), and death from other causes changed in men (−4.1% [−8.0% to −0.1%] per year) but not in women (−1.0% [−5.9% to 4.1%] per year).

Discussion

Our study showed that total and CVD mortality rates among Danish patients with complicated type 2 diabetes have decreased during the last decade, and among men, mortality decreased faster than the mortality in the general Danish population. However, type 2 diabetes patients still have a substantial excess mortality, and especially men with an early age at diagnosis and women at younger ages are at increased risk compared with the general population.

The annual decline in absolute mortality of 5.5% for men and 3.3% for women is comparable with results from

the entire Danish diabetes population, where an average decline in absolute mortality of ~4% per year was seen from 1995 to 2006 (5). Interestingly, the decline in excess mortality (SMR) of 3% per year for men was more pronounced in our population with type 2 diabetes than in the entire Danish diabetes population, where SMR decreased by only 1% per year from 1995 to 2006 (5). This finding is surprising, because 70% of the patients followed in our study had CVD, making our study population at higher risk than the general Danish diabetes population. However, our finding corresponds well with a recent study that reported a decline in excess mortality of 43% to 44% (~3% per year) among diabetic vs nondiabetic individuals from Canada and the United Kingdom in the period 1996 to 2009 (6). Also, other studies have found significant declines in total mortality, cardiovascular mortality, and SMR during the last 2 decades in patients with type 2 diabetes (12, 13). These improvements are likely to be a result of intensified multifactorial treatment, which was implemented in many clinics following the results from the Steno-2 (7, 8) and other studies.

Interestingly, we found that the younger the age at diagnosis, the higher was the mortality and the SMR, although this was less pronounced among women. In contrast, the inverse relationship between age and SMR seemed to exist only for women. The latter finding is supported by a Scottish study, showing that younger women with type 2 diabetes have a higher all-cause mortality than their older counterparts and that the difference between diabetic men of different ages is smaller (14). Whether these findings are caused by gender differences in treatment and care of the patients (15) or in the pathogenesis of type 2 diabetes (16) should be examined in future studies.

Linkage of local patient data with national registers substantially strengthens the quality of data used in this study. Thus, our study was based on precise estimates of mortality, and a direct comparison with the total population in Denmark was possible. It should be noted, however, that the patient population studied is not representative of the general type 2 diabetes population. In Denmark, most patients with type 2 diabetes are treated by general practitioners, and only complicated cases (including severe hyperglycemia or progressive diabetes complications) are referred to treatment in hospital outpatient clinics like the Steno Diabetes Center. Thus, the absolute mortality in the studied patients is likely to be higher than in other populations of patients with type 2 diabetes. Therefore, the results reported mostly apply to people with complicated diabetes treated in specialist centers. Another limitation was that we could not exclude patients with diabetes from the background comparison population. Assuming that mortality is higher among Danish diabetes patients than among people without diabetes, the reported SMR in our study may be slightly underestimated.

In conclusion, the absolute mortality of complicated type 2 diabetes is decreasing, and for men, the decline in mortality is greater than that of the general population. However, people with type 2 diabetes, and especially men with long diabetes duration and younger women, still have a markedly increased mortality compared with the age-matched background population, suggesting that further improvements in treatment and care of type 2 diabetes are needed.

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Author Contributions: K.F. and M.E.J. wrote the manuscript, B.C. performed the statistical analysis, M.E.J. was responsible for study design and data management, and T.P.A. contributed to writing and interpretation of results. All authors interpreted the results and critically reviewed and revised the manuscript.

Disclosure Summary: K.F., B.C., and M.E.J. are employed by Steno Diabetes Center A/S, a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. All authors own shares in Novo Nordisk A/S.

References

1. **Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC.** Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med*. 2007;147(3):149–155.
2. **Dale AC, Vatten LJ, Nilsen TI, Midthjell K, Wiseth R.** Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. *BMJ*. 2008;337:a236.
3. **Eliasson M, Talback M, Rosen M.** Improved survival in both men and women with diabetes between 1980 and 2004–a cohort study in Sweden. *Cardiovasc Diabetol*. 2008;7:32.
4. **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(6):1252–1257.
5. **Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K.** The Danish National Diabetes Register: trends in incidence, prevalence and mortality. *Diabetologia*. 2008;51(12):2187–2196.
6. **Lind M, Garcia-Rodriguez LA, Booth GL, et al.** Mortality trends in patients with and without diabetes in Ontario, *Canada and the UK from 1996 to 2009: a population-based study*. *Diabetologia*. 2013;56(12):2601–2608.
7. **Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O.**

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2003;348(5):383–393.
8. **Gæde P, Lund-Andersen H, Parving HH, Pedersen O.** Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. *N Engl J Med*. 2008;358(6):580–591.
9. **American Diabetes Association.** Standards of medical care in diabetes - 2011. *Diabetes Care*. 2011;34(Suppl 1):S11–S61.
10. Regionernes Kliniske Kvalitetsudviklingsprogram. Dansk Voksen Diabetes Database. National Årsrapport 2011. Version 1.4, 2012 (in Danish): http://www.regionsjaelland.dk/dagsordener/Dagsordener2013/Documents/1629/2075104.PDF.
11. **Sander B, Larsen M, Andersen EW, Lund-Andersen H.** Impact of changes in metabolic control on progression to photocoagulation for clinically significant macular oedema: a 20 year study of type 1 diabetes. *Diabetologia*. 2013;56(11):2359–2366.
12. **Alleman S, Saner C, Zwahlen M, Christ E, Diem P, Stettler C.** Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: a 30-year follow-up in Switzerland. *Swiss Med Wkly*. 2009;139(39–40):576–583.
13. **Olafsdottir E, Aspelund T, Sigurdsson G, et al.** Similar decline in mortality rate of older persons with and without type 2 diabetes between 1993 and 2004 the Icelandic population-based Reykjavik and AGES-Reykjavik cohort studies. *BMC Public Health*. 2013;13(1):36.
14. **Walker JJ, Livingstone SJ, Colhoun HM, et al.** Effect of Socioeconomic Status on Mortality Among People With Type 2 Diabetes: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetes Care*. 2011;34(5):1127–1132.
15. **Kramer HU, Raum E, Ruter G, et al.** Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes: results from the DIANA study. *Cardiovasc Diabetol*. 2012;11:88.
16. **Vistisen D, Witte DR, Tabak AG, Brunner EJ, Kivimaki M, Faerch K.** Sex differences in glucose and insulin trajectories prior to diabetes diagnosis: the Whitehall II study [published online September 16, 2012]. *Acta Diabetol*. doi:10.1007/s00592-012-0429-7.