

Survival in Patients With Type 2 Diabetes in a Swedish Community

Skarborg Hypertension and Diabetes Project

CARL JOHAN ÖSTGREN, MD^{1,2}
ULF LINDBLAD, MD, PHD^{1,3}

ARNE MELANDER, MD, PHD^{1,4}
LENNART RÅSTAM, MD, PHD^{1,5}

OBJECTIVE — To explore risk factors for all-cause mortality in patients with type 2 diabetes treated in primary care.

RESEARCH DESIGN AND METHODS — A prospective population-based study of 400 patients with type 2 diabetes who consecutively completed an annual checkup in primary care in Skara, Sweden, during 1992–1993. Vital status was ascertained to year 2000. Baseline characteristics as predictors for mortality were analyzed by Cox regression and expressed as relative risks (RRs), with 95% CIs.

RESULTS — During a mean follow-up time of 5.9 years, 131 patients died (56 deaths per 1,000 patients per year). In both sexes, all-cause mortality was predicted by HbA_{1c} (by 1%; RR 1.14, 95% CI 1.01–1.27), and by LDL-to-HDL cholesterol ratios (1.15, 1.00–1.32). Increased mortality was also seen with prevalent hypertension (1.72, 1.21–2.44), microalbuminuria (1.87, 1.27–2.76), and previous cardiovascular disease (1.70, 1.15–2.50). Subanalyses revealed that increased mortality related to HbA_{1c} was restricted to hypertensive patients with type 2 diabetes (1.23, 1.04–1.47). Serum triglycerides (by 1 mmol/l) predicted all-cause mortality in women (1.25, 1.06–1.47).

CONCLUSIONS — Poor glucose and lipid control and hypertension predicted all-cause mortality. Survival was also predicted by prevalent microalbuminuria and by previous cardiovascular disease. Confirming results from clinical trials, this population-based study has implications for primary and secondary prevention.

Diabetes Care 25:1297–1302, 2002

Mortality in patients with diabetes is about four times higher than in nondiabetic subjects (1,2). In a large clinical trial (the U.K. Prospective Diabetes Study [UKPDS]), mortality did not differ significantly between those with intensive treatment of blood glucose and those with conventional treatment (3). However, in a subanalysis in overweight patients, a significant difference was found favoring intensive treatment of hy-

perglycemia (4). It was also demonstrated that intensive lowering of blood pressure was beneficial compared with less intensive lowering of blood pressure (5). Similar results have been reported from subanalyses in other randomized clinical trials on hypertension (6–8). From observational analyses, it has been shown that intensive blood glucose control is associated with a lower risk of any diabetes-related end point, diabetes-related death,

and all-cause mortality in patients with type 2 diabetes (9,10). Furthermore, strong predictors for all-cause mortality, excluding increased blood glucose levels and hypertension, include lipoprotein abnormalities, high levels of serum triglycerides, and microalbuminuria (10–14).

In Sweden, the annual incidence of type 2 diabetes is ~16.1 per 100,000 inhabitants, and mortality in patients with diabetes is almost four times higher than in the general population (2). The objective of this population-based prospective study was to explore predictors for all-cause mortality identified in the UKPDS in patients with type 2 diabetes subjected to a structured diabetes education program in primary care in a Swedish community.

RESEARCH DESIGN AND METHODS

Skarborg Hypertension and Diabetes Project

Since the 1970s, structured treatment and education programs for patients with hypertension and type 2 diabetes, respectively, have been used at the Primary Health Care Center in the municipality of Skara, Sweden. Annual check-ups of these patients have been performed (15–19), and the information has been computerized according to structured forms. In 1986, the hypertension and diabetes outpatient clinics in Skara merged, making a joint clinic with nurses educated on both diseases, supervised by the family physicians.

Subjects

Skara Health Care Center is the only available primary health care facility in the community and serves a total population of ~19,000 residents. Patients with type 2 diabetes who completed an annual check-up at the hypertension and diabetes outpatient clinic in Skara from June 1992 through September 1993 were eligible for the present study, and every patient seen gave informed consent to

From the ¹Department of Community Medicine, Malmö University Hospital, Malmö, Sweden; the ²Ödeshög Health Care Centre, Sweden; the ³Skarborg Institute, Skövde, Sweden; the ⁴NEPI Foundation (the Swedish Network for Pharmacoepidemiology), Malmö, Sweden; and the ⁵National Public Health Institute, Stockholm, Sweden.

Address correspondence and reprint requests to Ulf Lindblad, Department of Community Medicine, Malmö University Hospital, S-205 02 Malmö, Sweden. E-mail: ulf.lindblad@smi.mas.lu.se.

Received for publication 22 November 2001 and accepted in revised form 17 April 2002.

Abbreviations: RR, relative risk; RRadj, age- and sex-adjusted RR; UKPDS, U.K. Prospective Diabetes Study; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

participate in this study. The study enrolled 433 patients with diabetes. After exclusion of 33 patients with type 1 diabetes according to clinical criteria, 400 patients with type 2 diabetes (202 men and 198 women) remained for further analysis (20).

At the time of the study surveillance, 83% of the patients with diabetes residing in Skara who were found in the Skaraborg Diabetes Register (21) were reported from the Skara Health Care Center (B. Berger, personal communication). Of the 17% ($n = 128$) reported from other clinics in Skaraborg County, 40% were categorized as having type 1 diabetes and were thus not the target of our study. The remaining patients would mainly comprise patients with severe complications requiring specialist care at hospital clinics or with preferences for other clinics for other reasons. Accordingly, we assumed that the current study population, with few exceptions, would include nearly all of the patients with type 2 diabetes in Skara.

Methods

Nurses at the hypertension and diabetes outpatient clinic, who were specially trained for this task, carried out the examinations. The procedure has been described in detail previously (15). Information on medical history at baseline included information about when the patient with type 2 diabetes was first diagnosed. Blood specimens were drawn in the morning after a 10-h overnight fast. Routine tests, including fasting blood glucose and HbA_{1c} (normal range 3.7–5.5%), were analyzed at the local hospital laboratory (Kärnsjukhuset, Skövde, Sweden). HbA_{1c} was measured by ion exchange high-performance liquid chromatography Mono S column (22). Serum samples for other tests were immediately frozen at -80°C and later analyzed for lipids (Lipids Laboratory, Lund University Hospital, Lund, Sweden) and serum insulin using a radioimmunoassay with $<0.3\%$ cross-reactivity for proinsulin (23) (kit from Pharmacia, Uppsala, Sweden; tests performed at the Wallenberg Laboratory, Malmö University Hospital, Malmö, Sweden). Height (to the nearest centimeter) and weight (to the nearest 0.1 kg) were measured (light indoor clothes and no shoes). BMI was calculated by dividing weight by height squared (kg/m^2), and the waist-to-hip ratio (WHR) was cal-

culated by dividing waist circumference (cm) by hip circumference (cm).

Diagnostic criteria for hypertension followed contemporary national guidelines. According to guidelines from 1987 up to the time of the present study, the definition was based on either ongoing treatment for hypertension or at least three consecutive readings of diastolic blood pressure ≥ 90 mmHg, irrespective of systolic blood pressure, in individuals older than 20 years of age (24). The treatment goal was set at diastolic blood pressure ≤ 90 mmHg.

Presence of microalbuminuria in urine was ascertained using a dipstick (Micral-Test) (25). Microalbuminuria was defined as ≥ 20 $\mu\text{g}/\text{l}$ in the first morning sample of urine. A structured interview performed by the nurses included questions about medical history and current medications. The participants completed a detailed questionnaire about smoking habits, current alcohol consumption, and physical exercise in leisure time. The vital status of the cohort was ascertained through 31 December 1999 by record linkage with the Cause of Death Register at the National Board of Health and Welfare, Stockholm, Sweden.

Survival rate was modeled using Cox's proportional hazard model. With a level of significance at 0.05, there was an 80% power to detect a relative risk (RR) of 2.0 for all-cause mortality associated with a risk factor with a prevalence of 25%, given the rate of all-cause mortality during follow-up in this study population. To account for baseline imbalances in age and sex, these factors were included as covariates in all models; the results are thus presented in terms of age- and sex-adjusted RRs (RRadj) with 95% CIs. The RRadj for fasting blood glucose, total cholesterol, LDL cholesterol, and serum triglycerides relates to the marginal effect on survival of 1 mmol/l. The corresponding unit is 1% for HbA_{1c}, 10 mmHg for systolic blood pressure, 5 mmHg for diastolic blood pressure, 5 years for duration of type 2 diabetes, 1 kg/m^2 for BMI, and 1 SD for fasting serum insulin, HDL cholesterol, and WHR. Because of skewed distributions, serum insulin and serum triglycerides were log-transformed in analyses and retransformed for tabulations. Cross-product interaction terms were used when further exploring the interactive aspects of significant findings in

different subsamples in the study population.

The study protocol was approved by the Research Ethics Committee of the Medical Faculty, Göteborg University.

RESULTS— A total of 400 consecutively examined patients with type 2 diabetes (202 men and 198 women) were included in the present study. The mean follow-up time was 5.9 years, and 131 patients (67 men and 64 women) died during the observation time. The annual mortality rate was 56 deaths per 1,000 patients. Baseline characteristics and risk estimates for all-cause mortality are presented in Table 1. All-cause mortality was predicted by HbA_{1c}, serum triglycerides, LDL-to-HDL cholesterol ratios, and comorbidity presented as hypertension, previous cardiovascular disease, and microalbuminuria. An increased risk associated with current smoking was borderline significant (RRadj 1.66, 95% CI 0.99–2.76, $P = 0.052$). When stratified for sex, a similar pattern was found in both men and women.

In an analysis using all of the risk factors (except serum triglycerides) that were significant in Table 1, only previous cardiovascular disease (RRadj 1.67, 95% CI 1.04–2.68, $P = 0.034$) and microalbuminuria (1.88, 1.23–2.87, $P = 0.003$) were significant predictors for all-cause mortality, and hypertension (1.53, 0.997–2.34, $P = 0.052$) was a borderline significant predictor. When LDL-to-HDL cholesterol ratios were substituted by serum triglycerides in a corresponding analysis, only microalbuminuria (1.90, 1.26–2.87, $P = 0.002$) remained significant.

Survival curves of patients with type 2 diabetes stratified by the presence of hypertension and microalbuminuria without adjustment, respectively, are shown in Figs. 1 and 2. Hypertension (RRadj 1.81, 95% CI 1.23–2.67) and microalbuminuria (1.85, 1.21–2.83) were statistically significant predictors for mortality when also adjusting for differences in HbA_{1c}, triglycerides, and LDL-to-HDL cholesterol ratios in addition to age and sex.

When comparing women with men and adjusting for differences in age, overall mortality risk was similar (RR 0.80, 95% CI 0.56–1.13). Age (1.57, 1.41–1.75, RR by 5 years) was a strong predictor for mortality but not diabetes duration (1.08, 0.95–1.23, RR by 5 years), with

Table 1—Baseline characteristics and corresponding RRs for all-cause mortality through 31 December 1999 in 400 subjects with type 2 diabetes in the Skaraborg Hypertension and Diabetes Project, 1992–1993

Variables	Baseline characteristics	RR	95% CI	P
Presence of hypertension	204 (51)	1.72	1.21–2.44	0.003
Previous cardiovascular disease	81 (20)	1.70	1.15–2.50	0.007
Presence of microalbuminuria	111 (28)	1.87	1.27–2.76	0.002
Current smoking	66 (17)	1.66	0.99–2.76	0.052
HbA _{1c} (by 1%)	6.6 ± 1.5	1.14	1.01–1.27	0.031
Fasting blood glucose (by 1 mmol/l)	8.5 ± 2.5	1.05	0.96–1.14	0.284
Duration of type 2 diabetes (by 5 years)	8.3 ± 6.7	1.08	0.95–1.23	0.221
Systolic blood pressure (by 10 mmHg)	160 ± 22	1.06	0.98–1.15	0.150
Diastolic blood pressure (by 5 mmHg)	84 ± 10	1.03	0.94–1.12	0.548
BMI (by 1 kg/m ²)	28 ± 4.6	0.99	0.95–1.03	0.654
WHR (by 1 SD)	0.92 ± 0.08	1.07	0.88–1.30	0.479
Fasting serum insulin (by 1 SD) (mU/l)*	22 ± 88	1.02	0.53–1.96	0.961
Total cholesterol (by 1 mmol/l)	5.9 ± 1.1	1.11	0.94–1.30	0.208
LDL cholesterol (by 1 mmol/l)	4.1 ± 1.0	1.12	0.93–1.34	0.226
HDL cholesterol (by –1 SD)	1.0 ± 0.2	1.15	0.98–1.35	0.084
LDL-to-HDL ratio (by 1 step)	4.2 ± 1.3	1.15	1.00–1.32	0.048
Triglycerides (by 1 mmol/l)*	1.8 ± 1.1	1.18	1.03–1.36	0.045

Data are n (%) or means ± SD. RR and P values for all-cause mortality were analyzed by Cox regression adjusted for age and sex. *Fasting serum insulin and triglycerides were log-transformed before analysis.

RRs adjusted for differences in sex. When stratified for sex and adjusted for age, hypertension (1.99, 1.20–3.31), microalbuminuria (2.85, 1.67–4.87), and previous cardiovascular disease (1.79, 1.03–3.10) predicted mortality in men. In women,

mortality was predicted only by fasting serum triglycerides (1.25, 1.06–1.47).

In hypertensive patients (both sexes combined) with type 2 diabetes, HbA_{1c} (RRadj 1.23, 95% CI 1.04–1.47) and microalbuminuria (2.00, 1.20–3.31) were

associated with increased mortality. All significant findings between sexes and the occurrence of hypertension were explored with analyses that used cross-product interaction terms. We were then able to confirm a sex-specific interaction in association with microalbuminuria ($P = 0.02$), but no other interaction terms were significant.

CONCLUSIONS— The main finding in this population-based prospective study was that survival in patients with type 2 diabetes is inversely related to poor glucose and lipid metabolism as well as to prevalent hypertension, microalbuminuria, and previous cardiovascular disease. Thus, the findings in the UKPDS (14) were confirmed in this community-based sample of patients with type 2 diabetes.

Markers for insulin resistance, such as overall (BMI) and central (WHR) obesity and fasting serum insulin, were not associated with increased mortality in this population. This is in accordance with previous results from the UKPDS showing that these factors did not predict coronary heart disease (14). In the general population, both overall and central obesity confer an increased risk of cardiovascular disease (26). However, results on the association between serum insulin and mortality are conflicting (27,28). Insulin resistance (29–31) and obesity (32–

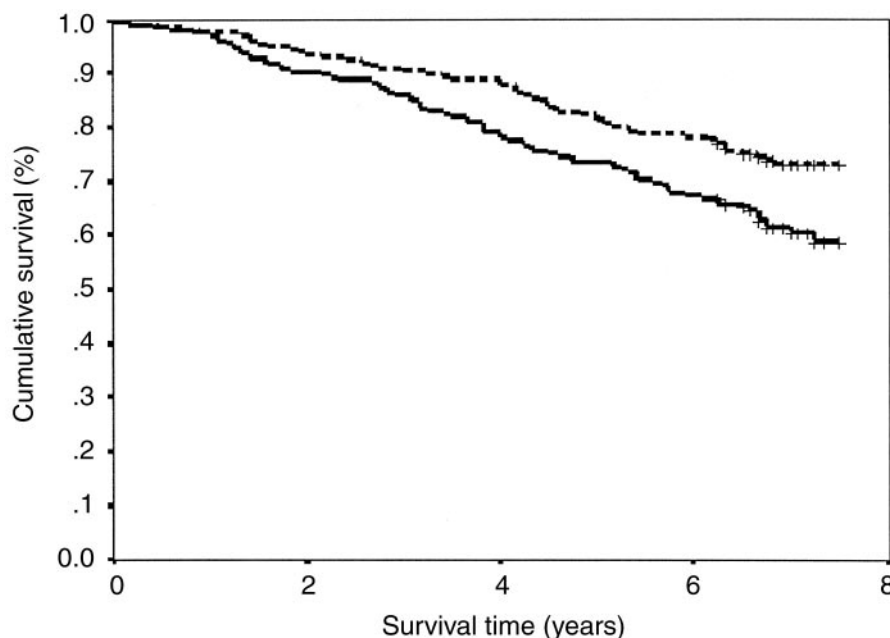


Figure 1—Survival curves of patients with type 2 diabetes with and without hypertension. The broken line represents patients without hypertension, and the filled line represents patients with hypertension. RR = 1.58 and 95% CI = 1.11–2.25, without adjustment, for patients with hypertension.

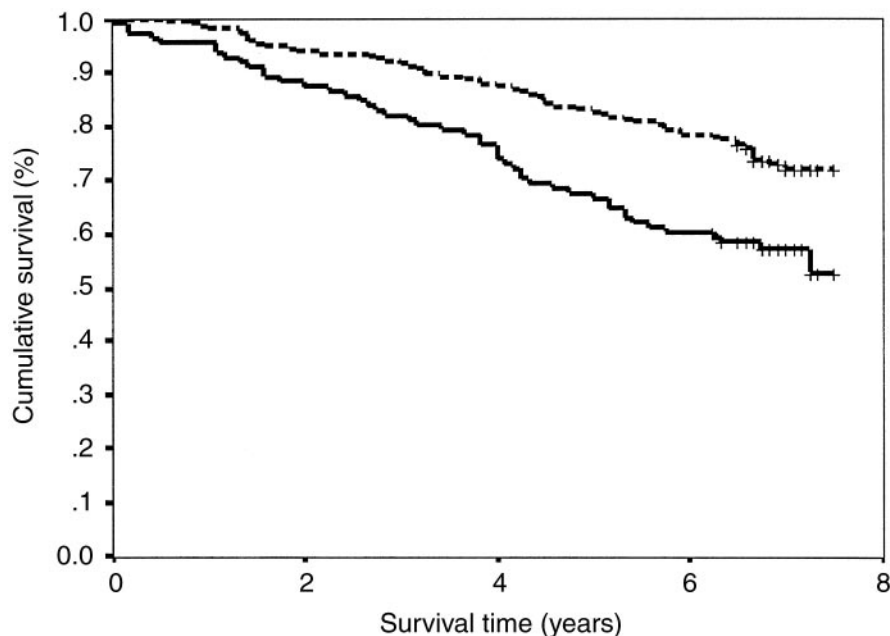


Figure 2—Survival curves of patients with type 2 diabetes with and without microalbuminuria. The broken line represents patients without microalbuminuria, and the filled line represents patients with microalbuminuria. RR = 1.86 and 95% CI = 1.26–2.74, without adjustment, for patients with microalbuminuria.

34) are important in the development of type 2 diabetes and impaired glucose tolerance (35,36). However, once diabetes is established, these factors do not seem to be associated with higher mortality; instead, other risk factors become predominant determinants for all-cause mortality.

The results from our community-based cohort of patients with type 2 diabetes are consistent with previous clinical trials and observational studies reporting mortality in patients with type 2 diabetes. Predictors generally included high LDL cholesterol, low HDL cholesterol, high levels of serum triglycerides, high blood pressure, and high levels of HbA_{1c} (5–14). A recent prospective observational analysis from the UKPDS did show that each percent reduction in mean HbA_{1c} was associated with a 14% reduction in all-cause mortality (9). In our study, a corresponding 13% difference in survival was seen per 1% difference in HbA_{1c}. A high prevalence of hypertension in patients with type 2 diabetes (15,37) and data showing hypertension as a risk factor for mortality in these patients have previously been reported in Skaraborg and other populations (5,38).

In a multivariate analysis including all risk factors associated with mortality, the strongest impact came from previous car-

diovascular disease, prevalent microalbuminuria, and hypertension, confirming the importance of these risk factors in patients with type 2 diabetes.

The current antidiabetic treatment at baseline in the study population has been described in detail before (20), with the most frequent treatments being recommendations on diet (42%) and treatment with sulfonylureas (31%), metformin (0.5%), and insulin (11%). All patients categorized as hypertensive did receive pharmacological treatment, and the most frequently used antihypertensive drugs were β -blockers and diuretics. A possible protective effect from the use of β -blockers would, however, tend to underestimate the difference found in survival. We were not able to account for treatment modifications that took place after the baseline survey.

The finding of smoking being a statistically weak predictor for mortality may be due to an inadequate number of patients or to misclassification of smoking habits because of patients changing their behaviors after the diagnosis of diabetes. However, previous smokers might still have suffered from a remaining negative effect related to smoking.

No sex difference in survival was found in patients with type 2 diabetes, in

accordance with previous reports (2,11). Indeed, type 2 diabetes appears to eliminate the relative protection against coronary heart disease and death seen in women without diabetes (39). We found increased levels of serum triglycerides to be a risk factor for mortality in women with type 2 diabetes, but not in men. This is in contrast to other prospective studies, where high serum triglycerides predicted mortality only in men (11) or overall (12).

It is plausible that increased serum triglycerides convey a higher mortality in diabetic women than in men, since increased triglycerides predict cardiovascular disease more consistently in women (40,41). One possible explanation is that women with type 2 diabetes respond differently to increased levels of serum triglycerides than do diabetic men. Alternatively, increased serum triglycerides in women with type 2 diabetes might express a more profound metabolic disturbance; the most commonly recognized risk factors of insulin resistance are highly correlated to each other (42). Furthermore, women have a more significant increase in triglyceride levels with the onset of diabetes (43). Microalbuminuria predicted mortality only in men, also in accordance with a previous report (11). In our study, we were also able to confirm this finding within the full sample by using cross-product interaction terms. However, the conclusions regarding microalbuminuria are limited by the fact that optimal ascertainment of microalbuminuria as a diagnosis requires timed overnight urine samples on two or three different days (25). However, even if our dichotomization of microalbuminuria as present or absent confers some misclassification in terms of standardized diagnosis, we still found significant differences associated with survival.

Thus, the pattern of predictors for mortality in men was different from that seen in women. A true sex-specific interaction was found in association with microalbuminuria using a cross-product interaction term. However, cross-product interaction terms including sex and other risk factors were not significant, and consequently no other difference between the sexes could be confirmed. From these data, it is hard to conclude whether this could be explained by an inadequate number of patients (because the evaluation of cross-product interaction terms re-

quires a higher power) or by a lack of a true difference.

A previous analysis of the same population indicated that patients with both type 2 diabetes and hypertension had higher BMIs, higher triglycerides, higher LDL-to-HDL cholesterol ratios, and higher fasting serum insulin. Conversely, glucose levels were lower than those in normotensive patients with type 2 diabetes (20). The clustering of cardiovascular risk factors has been found to elevate the mortality risk profoundly (38). These observations contribute to the understanding of the increased mortality associated with the combined occurrence of type 2 diabetes and hypertension.

In the present study, the only predictor for mortality in patients with both type 2 diabetes and hypertension was HbA_{1c} level, despite their lower mean HbA_{1c} levels compared with those with type 2 diabetes alone. Moreover, in this population it has previously been shown that patients with both type 2 diabetes and hypertension constitute a high-risk category, with a more atherogenic risk factor profile related to the insulin resistance syndrome. On the other hand, patients with type 2 diabetes without hypertension seem to constitute a subgroup of type 2 diabetes with predominately impaired β -cell function (20).

These differences suggest that type 2 diabetes with and without hypertension may represent two pathogenetically different mechanisms for the development of type 2 diabetes. Indeed, in the same population, genetic variation in the β_2 -adrenergic receptor and in the ACE gene have been associated with the combined occurrence of type 2 diabetes and hypertension (44,45). It may well be that the high mortality seen in patients with both type 2 diabetes and hypertension could be explained by factors associated with these mechanisms in addition to the risk carried by the increase in blood glucose itself.

In conclusion, risk factors for mortality in this community-based cohort of patients with type 2 diabetes were poor glycemic control, dyslipidemia, and hypertension. Survival also differed in subgroups of comorbidity. Previous findings in clinical trials and observational studies were thus consistently confirmed in this ethnically homogeneous primary care population that included the vast majority of people with type 2 diabetes in a

geographically defined area. Implications for primary and secondary prevention are evident.

Acknowledgments— This study was supported by grants from the Swedish Heart Lung Foundation, the Swedish Medical Research Council, the National Public Health Institute, the Skaraborg Institute and Skaraborg County Council, the NEPI Foundation (the Swedish Network for Pharmacoepidemiology), and the Faculty of Medicine, Lund University.

We are indebted to Dr. Bo Berger, MD (senior consultant in internal medicine at the Central Hospital in Skövde, Skaraborg, Sweden), for generously providing information from the Skaraborg Diabetes Register. We are also indebted to Bo Gullberg (Senior Lecturer in medical statistics, Department of Community Medicine, Malmö University Hospital, Lund University in Malmö, Malmö, Sweden) for excellent statistical guidance in the revision of this manuscript.

References

1. Morgan C, Currie C, Peters J: Relationship between diabetes and mortality: a population study using record linkage. *Diabetes Care* 23:1103–1107, 2000
2. Berger B, Stenström G, Sundkvist G: Incidence, prevalence, and mortality of diabetes in a large population: a report from the Skaraborg Diabetes Registry. *Diabetes Care* 22:773–778, 1999
3. 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* 352:837–853, 1998
4. 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* 352:854–865, 1998
5. Adler A, Stratton IM, Neil AW, Yudkin J, Matthews DR, Manley SE, Cull CA, Wright A, Turner RC, Holman R, on behalf of the UK Prospective Diabetes Study Group: Associations of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 321:412–419, 2000
6. Staessen JA, Thijs L, Gasowski J, Cells H, Fagard RH: Treatment of isolated systolic hypertension in the elderly: further evidence from the systolic hypertension in Europe (Syst-Eur) trial. *Am J Cardiol* 12: 20R–22R, 1998
7. Hansson L, Zanchetti A, Carruthers G, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Heinz K, Wedel H, Westerling S, for the HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755–1762, 1998
8. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklasson A, Luomanmaki K, Dahlöf B, de Faire U, Morlin C, Karlberg BE, West PO, Björk JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Catopril Prevention Project (CAPP) randomised trial. *Lancet* 353:611–616, 1999
9. Stratton IM, Adler A, Neil AW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman R, on behalf of the UK Prospective Diabetes Study Group: Associations of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
10. Andersson D, Svärdsudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18:1534–1543, 1995
11. Biderman A, Rosenblatt I, Rosen S, Zangwill L, Shalev R, Friger M, Weitzman S: Sex differentials in predictors of mortality for patients with adult onset diabetes: a population-based follow-up study in Beer-Sheva, Israel. *Diabetes Care* 23:602–605, 2000
12. Uusitupa MJ, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K: Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
13. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes: a 10-year follow-up study of 503 patients. *Diabet Med* 5:126–134, 1988
14. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependant diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23). *BMJ* 316:823–828, 1998
15. Bøg-Hansen E, Lindblad U, Bengtsson K, Ranstam J, Melander A, Råstam L: Risk factor clustering in patients with hypertension and NIDDM. *J Int Med* 243:223–232, 1998
16. Berglund G, Isacson S-O, Rydén L: The Skaraborg project: a controlled trial regarding the effect of structured hypertension care. *Acta Med Scand* 205 (Suppl.)

- 626:64–68, 1979
17. Råstam L, Berglund G, Isacson S-O, Rydén L: The Skaraborg hypertension project. III. Influence on blood pressure of a medical care program for hypertension. *Acta Med Scand* 219:261–269, 1986
 18. Lindblad U, Råstam L, Rydén L, Ranstam J, Berglund G, Isacson S-O: Reduced stroke incidence with structured hypertension care: the Skaraborg Hypertension Project. *J Hypertens* 8:1147–1153, 1990
 19. Lindblad U, Råstam L, Rydén L, Ranstam J, Isacson S-O, Berglund G: Control of blood pressure and risk of myocardial infarction: Skaraborg hypertension project. *BMJ* 308:681–686, 1994
 20. Östgren CJ, Lindblad U, Bøg-Hansen E, Ranstam J, Melander A, Råstam L: Differences in treatment and metabolic abnormalities between normo- and hypertensive patients with type 2 diabetes: the Skaraborg Hypertension and Diabetes Project. *Diabetes Obes Metab* 1:105–112, 1999
 21. Berger B, Stenstrom G, Chang YF, Sundkvist G: The prevalence of diabetes in a Swedish population of 280,411 inhabitants: a report from the Skaraborg Diabetes Registry. *Diabetes Care* 21:546–548, 1998
 22. Eckerbom S, Bergqvist Y, Jeppson JO: Improved method for analysis of glycated haemoglobin by ion exchange chromatography. *Ann Clin Biochem* 31:355–360, 1994
 23. Andersen L, Dinesen B, Jørgensen PN, Poulsen F, Røder ME: Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* 38:578–558, 1993
 24. National Board of Health and Welfare, Drug Information Committee: *Treatment of Mild Hypertension*. Stockholm, Sweden, Socialstyrelsen, 1987
 25. Spooren PF, Lekkerkerker JF, Vermes I: Micral-Test: a qualitative dipstick test for microalbuminuria. *Diabetes Res Clin Pract* 18:83–87, 1992
 26. Byers T: Body weight and mortality. *N Engl J Med* 333:723–724, 1995
 27. Desprès JP, Lamarche B, Mauriège P, Cantin B, Daganais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952–957, 1996
 28. Ferrara A, Barrett-Connor EL, Edelstein SL: Hyperinsulinemia does not increase the risk of fatal cardiovascular disease in elderly men or women without diabetes: the Rancho Bernardo Study, 1984–1991. *Am J Epidemiol* 140:857–869, 1994
 29. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley J, Ravussin E, Knowler W, Bennett P, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992, 1993
 30. Martin B, Warram J, Krolewski A, Bergman R, Soeldner S, Kahn R: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340:925–929, 1992
 31. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
 32. Pi-Sunyer X: Weight and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 63 (Suppl. 3):426S–429S, 1996
 33. Wannamethee SG, Shaper AG: Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care* 22:1266–1272, 1999
 34. Colditz G, Willett W, Rotnitzky A, Manson J: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481–487, 1995
 35. Fujimoto WY: The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Am J Med* 17 (Suppl. 1):9–14, 2000
 36. Haffner S, Miettinen H, Gaskill SP, Stern MP: Decreased insulin action and insulin secretion predict the development of impaired glucose tolerance. *Diabetologia* 39:1201–1207, 1996
 37. Hypertension in Diabetes Study (HDS). I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 11:309–317, 1993
 38. Hypertension in Diabetes Study (HDS). II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. *J Hypertens* 11:319–325, 1993
 39. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 265:627–631, 1991
 40. Avins AL, Neuhaus JM: Do triglycerides provide meaningful information about heart disease risk? *Arch Intern Med* 130:1937–1944, 2000
 41. Sprecher D, Pearce G, Park E, Pashkow F, Hoogwerf B: Preoperative triglycerides predict post-coronary artery bypass graft survival in diabetic patients: a sex analysis. *Diabetes Care* 23:1648–1653, 2000
 42. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991
 43. Ezenwaka CE, Davis G: Increased risk of cardiovascular disease in newly diagnosed type 2 diabetic patients in a primary health care center in Trinidad. *Diabetes Res Clin Pract* 2:137–145, 2000
 44. Bengtsson AK, Melander O, Orho M, Lindblad U, Ranstam J, Råstam L, Groop L: Beta(2)-adrenergic receptor gene variation and hypertension in subjects with type 2 diabetes. *Hypertension* 37:1303–1308, 2000
 45. Bengtsson AK, Orho M, Lindblad U, Melander O, Bøg-Hansen E, Ranstam J, Råstam L, Groop L: Polymorphisms in the angiotensin converting enzyme but not in the angiotensinogen gene is associated with hypertension and type 2 diabetes: the Skaraborg Hypertension and Diabetes Project. *J Hypertens* 17:1569–1575, 1999