

EXPLAINING THE DECLINE IN EARLY MORTALITY IN MEN AND WOMEN WITH TYPE 2 DIABETES. Population-based cohort study

Judith Charlton MSc, Radoslav Latinovic BSc and Martin C Gulliford FFPH

King's College London, Division of Health and Social Care Research, Department of Public Health Sciences

Correspondence:

Martin Gulliford

E mail: martin.gulliford@kcl.ac.uk

Running title: Declining early mortality in type 2 diabetes

Received 21 January 2008 and accepted 16 May 2008.

Objective: To test the hypothesis that changing utilisation of lipid-lowering, antihypertensive and oral hypoglycemic drugs may be associated with trends in all-cause mortality in men and women with type 2 diabetes.

Research design and methods: Cohort study in 197 general practices in the UK General Practice Research Database including 48,579 subjects with type 2 diabetes first diagnosed between 1996 and 2006. Measures included all-cause mortality; prescription of hypoglycemic, lipid lowering and antihypertensive drugs.

Results: From 1996 to 2006 incidence of type 2 diabetes increased and the mean age at diagnosis declined in women. Prescription of statins within 12 months of diagnosis increased (1996, women 4.9% men 5.1%; 2005, women 63.5%, men 71.0%), as did drugs acting on the renin-angiotensin system (1996, women 19.4%, men, 21.5%; 2005, women 45.5%, men 54.6%) and metformin (1996, women 19.1%, men 15.8%; 2005, women 45.5%, men 42.8%) while prescription of sulphonylureas declined. All-case mortality in the first 24 months following diabetes diagnosis declined in men from 47.9 per 1000 person years for subjects diagnosed in 1996 to 25.2 in 2006, and women from 37.4 in 1996 to 27.6 in 2006. In a multiple regression model adjusting for age and comorbidity, prescription of statins before or after diagnosis, renin-angiotensin system drugs before or after diagnosis and metformin after diagnosis were associated with lower mortality.

Conclusion: Widespread implementation of more effective prescribing to control lipids, blood glucose and blood pressure may have contributed to recent declines in early mortality in men and women with type 2 diabetes.

ABBREVIATIONS: BNF, British National Formulary; GPRD, general practice research database; RAS, renin-angiotensin system;

The epidemiology of type 2 diabetes mellitus is changing. The prevalence of diagnosed diabetes has increased rapidly in national health survey data from a number of countries including the US and the UK(1,2). Epidemiological studies also show that the incidence of type 2 diabetes is increasing(3). This increasing frequency of type 2 diabetes has been associated with increased occurrence of diabetes at younger ages, with some studies suggesting a decline in the mean age at diagnosis of diabetes in the US.(4)

At the same time, evidence has accumulated for the potential effectiveness of cholesterol-lowering therapy with statin drugs (5,6) and antihypertensive therapy(7), especially with drugs acting on the renin-angiotensin system (RAS) (8), for reducing cardiovascular events and mortality in type 2 diabetes. When good blood glucose control is achieved, oral hypoglycemic therapy reduces diabetes-related end-points (9). Therapy with metformin has been specifically associated with reduced all-cause mortality in diabetes(10). In the UK Prospective Diabetes Study, therapy with sulphonylurea drugs was not associated with increased mortality compared with insulin therapy(9) but several non-randomised studies have associated sulphonylurea drugs with increased mortality compared with metformin. (11,12)

The present study aimed to analyse the significance of these developments for the prognosis of newly diagnosed patients with type 2 diabetes. We aimed to evaluate the extent and time course of changes in utilisation of statins, antihypertensive drugs and oral hypoglycaemic drugs among patients with

type 2 diabetes and determine whether changes in drug utilisation are associated with changing early mortality in men and women with type 2 diabetes.

METHODS

Design and subjects: We analysed data from the UK General Practice Research Database (GPRD), a large database including electronic patient records for approximately 5% of UK family practices (13). In the UK, there is population-based provision of primary care with 98% of the population being registered with a family practice. The quality of GPRD data has been evaluated in several studies.(13)

The present longitudinal study included all 197 family practices, with a registered population of approximately 1.63 million, that contributed data to GPRD continuously between 1995 and 2006. We selected the population aged 30 years and over, because type 1 and type 2 diabetes are less readily distinguished at younger ages. Prevalent cases of diabetes were identified from the electronic clinical record if they were ever diagnosed with diabetes or prescribed oral hypoglycaemic drugs or insulin. The date of diagnosis was identified as the earlier of the first medical diagnosis for diabetes or the first medical prescription for hypoglycemic drugs and only subjects newly diagnosed between 1st January 1996 and 31st December 2006 were included. There were 93.6% identified with diagnostic codes and only 6.4% initially identified with therapy codes only. There were 399/22,997 (1.7%) women first diagnosed with codes associated with 'diabetes in pregnancy' but there was no increase in this proportion over the time of study. All subjects had a minimum period of 12 months record prior to the

diabetes diagnosis date. Incident cases that were ever diagnosed with type 1 diabetes or prescribed insulin within six months of diagnosis were excluded as cases of type 1 diabetes. Prevalent cases were excluded because both therapy and hazards vary with duration of diabetes.

Analysis: Age-specific incidence rates for type 2 diabetes were estimated using the number of incident cases as numerator and the registered person years at risk as the denominator. Age-standardised rates were estimated using the European Standard Population for reference. The mean age at diagnosis and the proportion of diagnoses that were at ages 30-44 were also estimated. Trends by study year were estimated using linear regression using means or proportions as observations.

The characteristics of subjects at diagnosis were evaluated including whether coronary heart disease (13), stroke (13) or renal disease (including any mention of a diagnosis associated with the kidney) were ever diagnosed before diabetes diagnosis using appropriate medical codes (13). Drug prescriptions were analysed by mapping drug codes to chapter sub-headings in the British National Formulary (BNF).⁽¹⁴⁾ We analysed whether statins or antihypertensive drugs were ever prescribed before diagnosis, with drugs acting on the renin-angiotensin system as a separate class. Antihypertensive drugs included angiotensin converting enzyme inhibitors, adrenergic neuron inhibiting drugs, angiotensin II receptor blockers, beta-blockers, calcium channel antagonists, centrally acting drugs, thiazide diuretics and potassium sparing diuretics, and vasodilators. Oral hypoglycemic drugs were grouped into metformin and sulphonylurea drugs. In order to analyse drug utilisation following

the diagnosis of diabetes while taking into account both calendar time and the duration of the diabetic illness, subjects were grouped by year of diagnosis. Then for each cohort defined by year of diagnosis, prescriptions were analysed by year following the diagnosis of diabetes.

Mortality from all causes was estimated using the death records within the GPRD. In order to compare mortality of patients diagnosed in different years, only the first two years following diagnosis were considered. This was because duration of follow-up was longer for earlier years of study but mortality varies with diabetes duration. In order to avoid confounding of year of diagnosis with diabetes duration analyses were restricted to the first two years after diagnosis. Mortality rates were estimated per 1000 person years of follow-up for men and women with diabetes and were standardised to the sample distribution for 2001 as reference. In order to adjust for explanatory variables, Cox's proportional hazards models were fitted with date of diabetes diagnosis as the start date and the earliest of the date of death or 24 months following diagnosis or the end of the patient's record as the end date. Explanatory variables were year of diagnosis, age, prevalent CHD, stroke and renal disease, use of statins, antihypertensive therapy and RAS drugs before diagnosis, and whether metformin, sulphonylurea drugs, statins, antihypertensive drugs or RAS drugs were prescribed following diagnosis. Robust standard errors were estimated to allow for clustering by practice. Since use of drugs after diagnosis varied over time, utilisation of each drug was also fitted separately as a time-dependent covariate adjusting for prediagnosis events. Estimates from the two models were compared.

RESULTS

In the registered population aged 30 years and over there were 953,223 person years in 1996 rising to 1,048,067 in 2006. The proportion of registered subjects aged 30-44 years was 35% in 1996 and 34% in 2006. The female: male sex ratio was 1.08 in 1996 and 1.05 in 2006. There were 29,068 prevalent cases of diagnosed diabetes in 1996 and 62,455 in 2006. There were 2,636 incident cases of type 2 diabetes in 1996 and 5,416 in 2006 with 48,579 subjects with newly diagnosed diabetes in total between 1996 and 2006.

Table 1 shows age-standardised type 2 diabetes incidence rates for men and women by study year. The incidence of new diagnoses of type 2 diabetes increased in women from 2.23 per 1,000 in 1996 to 4.37 per 1,000 in 2006. In men, the increase was from 3.00 per 1,000 in 1996 to 5.24 per 1,000 in 2006. The mean age at first diagnosis of diabetes decreased in women from 66.1 years in 1996 to 62.5 years in 2006, but there was no trend in men (Table 1). The proportion of incident diabetes diagnoses in the 30-44 year age group increased in women from 7.5% in 1996 to 15.8% in 2006.

Table 1 also shows comorbidity and co-prescribing in newly diagnosed subjects with type 2 diabetes by year of diagnosis. Approximately 16% of women and 22% of men had prevalent coronary heart disease at diagnosis, while approximately 4% of women and 5% of men had prevalent stroke. There was weak evidence of a decreasing trend in prevalent CHD and stroke in women. The proportion of subjects that was prescribed statins before the date of diagnosis increased from 2% in both men and women in 1996 to 32% in women and 37% in men in 2006. The prescription of

antihypertensive drugs before diagnosis increased over time, more in men and the increase was especially marked for the prescription of RAS drugs.

Figure 1 shows trends in drug utilisation by patients with type 2 diabetes by year of diagnosis and duration of diabetes. Utilisation of metformin, sulphonylurea drugs and drugs acting on the renin-angiotensin system show a cohort effect, increasing as the duration of diabetes increases. However, utilisation of metformin and RAS drugs increased for successive years of diagnosis while utilisation of sulphonylurea drugs declined. Utilisation of statins only showed a period effect with increasing utilisation over time independent of duration of diabetes. There were very large increases in prescribing of statins, metformin and RAS drugs during the period. Prescription of statins within 12 months of diagnosis increased (1996, women 4.9% men 5.1%; 2005, women 63.5%, men 71.0%), as did drugs acting on the renin-angiotensin system (1996, women 19.4%, men, 21.5%; 2005, women 45.5%, men 54.6%) and metformin (1996, women 19.1%, men 15.8%; 2005, women 45.5%, men 42.8%) increased while prescription of sulphonylureas declined (1996, women 32.8% men 34.3%; 2005, women 12.5% men 14.1%). Utilisation of insulin and other oral hypoglycemic drugs, including glitazones, increased during the period but were used by fewer than 10% of subjects within two years of diagnosis. Note that mortality analyses only included the first two years following diagnosis.

Table 2 shows changes in all-cause mortality in men and women in the first two years following diagnosis of diabetes in subjects with diabetes aged 30 years and over. In men, the relative decrease in mortality was 47% over the

period while in women, in whom absolute mortality was lower, the relative decline over the period was 26%.

In the proportional hazards model (Table 3), higher mortality was associated with older age and prevalent CHD, stroke or renal disease. Prescription of statin drugs before or after diabetes diagnosis, prescription of drugs acting on the renin-angiotensin system before or after diagnosis, and prescription of metformin after diagnosis were associated with lower mortality and accounted for the association of year of diagnosis with mortality. After adjustment, increasing year of diagnosis was positively associated with mortality but the significance of this is unclear. Hazard ratios were generally similar for men and women but hazard ratios associated with prevalent coronary heart disease and stroke appeared to be higher for men while the hazard ratio associated with prevalent renal disease was slightly higher in women. Fitting drug classes prescribed after diagnosis separately as time dependent covariates generally led to a similar interpretation.

CONCLUSIONS

Main findings: Over the last 10 years there has been a substantial reduction in early mortality of type 2 diabetic patients within the first two years of diagnosis. Variables that may explain this decline in mortality include a decrease in the age at diagnosis in women, a slight fall in the proportion of women who have cardiovascular disease including coronary heart disease and stroke at diagnosis. Even allowing for case-mix, there is evidence that a rapid increase in the proportion of newly diagnosed men and women already prescribed statin drugs may be associated with lower mortality. Changing

patterns of drug utilisation after diagnosis of diabetes, including increased use of statins and metformin and decreased use of sulphonylurea drugs, may also be associated with lower mortality. These observations must be interpreted with caution as confounding by indication is generally important in non-randomised studies and the effects may be difficult to anticipate. The role of unmeasured risk factors such as cigarette smoking must also be considered. Earlier diagnosis may be contributing to increasing prevalence and could also contribute to declining mortality in clinical diabetes consistent with lead-time bias. This effect might be important for early mortality while changes in drug utilisation after diagnosis may be more relevant for later mortality after the first two years. Nevertheless, these analyses provide suggestive evidence that widespread implementation of preventive medical care both before and after the time of diagnosis may be contributing to the improving prognosis of type 2 diabetes. Trends in drug utilisation were generally similar in men and women but the decline in mortality was greater in men in whom absolute mortality rates were higher.

Comparison with other studies: The present observations must be set in the context of long-term declining trends in risk factors, such as smoking (15), as well as declining cardiovascular mortality in the general population (16). A number of studies have evaluated trends in all-cause mortality, cardiovascular mortality and incident cardiovascular events in type 2 diabetes (17-22). Reports from Dundee, Scotland from 1993 to 2004 (17) and Ontario, Canada from 1992 to 2000 (18) show declining all-cause mortality in diabetic populations. These findings are consistent with a report from Rochester, Minnesota which found that between

1970 and 1994 mortality declined in diabetic subjects although this decline was smaller than the mortality decrease observed in the non-diabetic population (19). Data from Ontario (17) and from the Framingham study (20) also demonstrate declining incidence of new cardiovascular events. However, there is evidence that trends may differ for men and women. Data from the US National Health and Nutrition Examination Survey show that mortality of diabetic men declined between 1971 and 2000 (21,22). In women with diabetes, mortality initially increased (21) and then later showed no decline up to 2000.(22) Our results up to 2006 suggest that female as well as male mortality in diabetes is now declining. All-cause mortality in the general population has declined during this period and further research is required to evaluate trends in relative mortality in type 2 diabetes. It would also be desirable to evaluate cause-specific mortality. Analysis of GPRD data allows us to link individual patient survival data to information concerning comorbidity and prescribing. Results from these analyses show that across the diabetic population there have been major changes in drug utilisation during this period and these changes are associated with differences in mortality risk. In particular, utilisation of statins either before or after diabetes diagnosis and use of metformin rather than sulphonylurea drugs after diagnosis may be associated with lower mortality risk.

Strengths and limitations: The validity of GPRD data have been demonstrated in several studies. In particular Shah and Martinez (23) reported that mortality rates estimated from GPRD data were comparable to those observed in the UK general population. Mulnier et al (24) reported a

mortality rate for prevalent cases of diabetes in GPRD of 60.2 per 1000 patient years which is higher than we report for incident cases with short durations of diabetes. The validity of clinical event data in GPRD has been shown to be good (13). However, causes of death were not readily available for analysis and cause-specific mortality was not estimated. Clinical information for measures including smoking, blood pressure, cholesterol and HbA1c is included in GPRD but there were secular trends in recording in the present period that would complicate interpretation. Classification of drug prescribing was based on one or more prescriptions but interpretation did not differ if two or more prescriptions were used. Drug combinations were not explicitly modelled.

While overall data for mortality can be viewed with confidence, in this non-randomised study, associations identified may be explained by unmeasured or misclassified confounders. When unmeasured and imprecisely measured confounding is present, associations may be incorrectly ascribed to more precisely measured exposures such as drug utilisation. We caution that the results should not be used to estimate the benefits or harms of particular therapies. Rather, the present results suggest that findings from randomised clinical trials may hold in the general population and contribute to improving survival trends. Combinations of these interventions may be particularly beneficial (25).

Summary: Mortality of newly diagnosed men and women with type 2 diabetes has declined between 1996 and 2006. Widespread use of statins before and after diagnosis, and metformin rather than sulphonylurea drugs after diagnosis,

may be associated with improving mortality trends.

ACKNOWLEDGEMENT:

This study is based in part on data from the Full Feature General Practice Research Database obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone. Access to the GPRD database was funded through the Medical Research Council's licence agreement with MHRA.

REFERENCES

1. Centers for Disease Control. Division of Diabetes Translation. *Diabetes data and trends*. 2007. Available from <http://apps.nccd.cdc.gov/DDTSTRS/default.aspx> accessed January 10th 2008.
2. Sproston K, Primatesta: *Health Survey for England 2003. Volume 2. Risk factors for cardiovascular disease*. London, The Stationery Office, 2004
3. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid Rise in the Incidence of Type 2 Diabetes From 1987 to 1996: Results From the San Antonio Heart Study. *Arch Int Med* 159:1450-1456, 1999
4. Koopman RJ, Mainous AG, III, Diaz VA, Geesey ME: Changes in Age at Diagnosis of Type 2 Diabetes Mellitus in the United States, 1988 to 2000. *Ann Fam Med* 3:60-63, 2005
5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360:7-22, 2002
6. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study. *Lancet* 364:685-96, 2004.
7. UK Prospective Diabetes Study Group: Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. *BMJ* 317:720-726, 1998
8. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253-259, 2000
9. UK Prospective Diabetes Study 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
10. 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). *The Lancet* 352:854-865, 1998
11. Evans J, Ogston S, Emslie-Smith A, Morris A: Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulphonylureas and metformin. *Diabetologia* 49:930-936, 2006
12. Johnson JA, Simpson SH, Toth EL, Majumdar SR: Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabetic Medicine* 22:497-502, 2005
13. National statistics: *Key health statistics from general practice 1998. Series MB6 No 2*. London, National Statistics, 2000.
14. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary. Number 44*. London, British Medical Association and Royal Pharmaceutical Society of Great Britain, 2002
15. Goddard E. *Smoking and drinking among adults, 2006. General household survey 2006*. Newport: Office for National Statistics, 2008.
16. Rautio A, Lundberg V, Messner T, Nasic S, Stegmayr B, Eliasson M. Favourable trends in the incidence and outcome of myocardial infarction in nondiabetic, but not in

diabetic, subjects: findings from the MONICA myocardial infarction registry in northern Sweden in 1989-2000. *J Intern Med* 258:369-77, 2005.

17. Evans J, Barnett K, Ogston S, Morris A: Increasing prevalence of type 2 diabetes in a Scottish population: effect of increasing incidence or decreasing mortality? *Diabetologia* 50:729-732, 2007

18. Booth GL, Kapral MK, Fung K, Tu JV: Recent Trends in Cardiovascular Complications Among Men and Women With and Without Diabetes. *Diabetes Care* 29:32-37, 2006

19. Thomas RJ, Palumbo PJ, Melton III LJ, Roger VL, Ransom J, O'Brien PC, Leibson CL: Trends in the Mortality Burden Associated With Diabetes Mellitus: A Population-Based Study in Rochester, Minn, 1970-1994. *Arch Int Med* 163:445-451, 2003

20. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB, Sr. et al.: Trends in Cardiovascular Complications of Diabetes. *JAMA* 292:2495-2499, 2004

21. Gu K, Cowie CC, Harris MI: Diabetes and Decline in Heart Disease Mortality in US Adults. *JAMA* 281:1291-1297, 1999

22. Gregg EW, Gu Q, Cheng YJ, Venkat Narayan KM, Cowie CC: Mortality Trends in Men and Women with Diabetes, 1971 to 2000. *Ann Intern Med* 147:149-155, 2007

23. Shah AD, Martinez C: A comparison of the cause of death recorded in GPRD with national mortality statistics in England and Wales. *Pharmacoepidemiology and Drug Safety* 13:S2-S3, 2004

24. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA: Mortality in people with Type 2 diabetes in the UK. *Diabetic Medicine* 23:516-521, 2006

25. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 358:580-91, 2008.

Table 1: Trends in type 2 diabetes incidence, mean age at diagnosis of diabetes, and co-morbidity and drug utilisation at diagnosis by year of diagnosis. Figures are percent of subjects diagnosed with diabetes in year except where indicated.

Year of diagnosis	Diabetes incidence ≥30 years Rate per 1,000 person years (SE) ^a		Mean (SD) age (years) at first diabetes diagnosis		Proportion (%) of all new diabetes diagnoses that were aged 30-44 years	
	Women	Men	Women	Men	Women	Men
1996	2.23 (0.07)	3.00 (0.08)	66.1 (13.4)	62.5 (12.2)	7.5	7.9
1997	2.29 (0.07)	3.07 (0.08)	65.5 (13.8)	62.3 (12.1)	8.6	7.9
1998	2.36 (0.07)	3.39 (0.08)	65.3 (14.3)	62.1 (12.5)	9.4	9.5
1999	2.66 (0.07)	3.66 (0.09)	65.3 (14.2)	62.5 (12.1)	9.3	7.6
2000	3.50 (0.08)	4.58 (0.10)	64.6 (14.5)	62.3 (12.1)	10.9	7.9
2001	3.83 (0.09)	5.24 (0.10)	64.1 (14.3)	62.1 (12.2)	11.0	8.5
2002	4.31 (0.09)	5.63 (0.11)	63.6 (14.7)	62.0 (12.2)	12.8	8.8
2003	4.62 (0.09)	5.65 (0.11)	63.0 (14.6)	62.0 (12.5)	13.4	9.2
2004	4.99 (0.10)	5.81 (0.11)	63.3 (15.1)	62.8 (12.5)	13.6	8.1
2005	4.71 (0.09)	5.54 (0.10)	62.9 (15.6)	62.0 (12.3)	15.7	9.3
2006	4.37 (0.09)	5.24 (0.10)	62.5 (15.3)	62.0 (12.4)	15.8	9.2
P value ^b	<0.001	<0.001	<0.001	0.330	<0.001	0.097

^a age-standardised to European Standard Population

^b test for linear trend by year

/ cont . . .

/ cont. Table 1.

Prevalent CHD at diagnosis		Prevalent stroke at diagnosis		Prevalent renal disease before diagnosis		Prescribed statins before diagnosis		Prescribed other antihypertensives before diagnosis		Prescribed RAS drugs before diagnosis	
Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
17.2	19.6	6.1	5.4	3.7	5.1	1.9	2.2	58.9	44.0	13.2	13.9
15.9	19.9	4.9	5.1	3.0	5.8	3.5	4.3	61.5	41.9	16.5	15.4
16.4	21.0	4.2	4.6	3.1	6.0	5.0	6.4	60.8	44.8	17.8	17.3
16.5	22.9	4.6	5.9	2.3	5.2	8.1	9.9	63.4	50.9	19.6	19.6
17.8	22.1	5.2	4.7	3.2	6.0	10.5	13.6	64.0	50.8	21.7	20.9
17.0	22.8	4.1	4.0	3.3	5.6	14.0	15.8	65.4	53.9	24.4	24.2
16.2	23.8	4.0	4.6	3.2	5.5	14.8	20.8	66.8	56.5	27.4	26.9
17.2	21.7	3.7	5.0	2.9	6.5	19.5	25.0	68.1	58.1	29.6	29.5
16.9	23.3	4.6	5.4	3.0	6.2	24.5	30.1	69.2	61.2	30.7	33.0
14.2	21.3	3.8	4.8	3.3	6.5	27.6	33.5	67.0	59.3	33.1	34.4
14.0	19.9	3.8	4.2	3.9	6.9	31.5	36.8	65.6	59.7	34.4	36.3
0.089	0.414	0.011	0.271	0.508	0.005	<0.001	<0.001	0.001	<0.001	<0.001	<0.001

Table 2: Age-standardised rates for mortality within two years of diabetes diagnosis by year of diagnosis. Rates were standardised to the sample distribution for 2001 for reference.

Year of diagnosis	Deaths (person years)		Age-standardised mortality (per 1000 person years) within 24 months of diagnosis ^a	
	Women	Men	Women	Men
1996	101 (2387)	127 (2637)	37.4	47.9
1997	107 (2437)	105 (2749)	40.7	37.7
1998	118 (2558)	148 (3055)	41.0	49.7
1999	134 (2923)	129 (3413)	40.7	37.6
2000	153 (3838)	151 (4326)	37.1	34.5
2001	166 (4134)	158 (5009)	39.9	31.5
2002	123 (4792)	176 (5458)	25.3	32.2
2003	147 (5099)	158 (5595)	30.7	28.1
2004	171 (5675)	167 (5918)	30.1	26.2
2005	118 (4526)	131 (4780)	25.9	27.2
2006^a	48 (1751)	50 (1906)	27.6	25.2
P value^b			0.002	<0.001

^a two-year follow-up incomplete

^b test for linear trend

Table 3: Variables associated with mortality in first two years after diabetes diagnosis for men and women. Hazard ratios were adjusted for each of the variables shown.

	WOMEN		MEN	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Year of diagnosis (per year)	1.04 (1.02 to 1.06)	<0.001	1.02 (1.00 to 1.04)	0.113
Age (per year)	1.073 (1.067 to 1.078)	<0.001	1.071 (1.066 to 1.076)	<0.001
Prevalent CHD at diagnosis	1.15 (1.00 to 1.32)	0.044	1.25 (1.10 to 1.43)	0.001
Prevalent stroke at diagnosis	1.38 (1.13 to 1.69)	0.002	1.71 (1.48 to 2.00)	<0.001
Prevalent renal diseases at diagnosis	1.58 (1.25 to 1.99)	<0.001	1.19 (0.98 to 1.44)	0.071
Statin use before diagnosis	0.52 (0.43 to 0.63)	<0.001	0.56 (0.48 to 0.65)	<0.001
Statins prescribed after diagnosis ^a	0.29 (0.24 to 0.35)	<0.001	0.34 (0.29 to 0.40)	<0.001
RAS drugs before diagnosis	0.85 (0.75 to 0.96)	0.007	0.90 (0.78 to 1.05)	0.171
RAS drugs prescribed after diagnosis ^a	0.45 (0.37 to 0.55)	<0.001	0.56 (0.47 to 0.66)	<0.001
Other antihypertensive treatment before diagnosis	0.91 (0.80 to 1.04)	0.158	1.18 (1.03 to 1.34)	0.016
Other antihypertensive prescribed after diagnosis ^a	0.83 (0.62 to 1.10)	0.206	0.86 (0.68 to 1.09)	0.218
Metformin prescribed after diagnosis ^a	0.70 (0.60 to 0.80)	<0.001	0.61 (0.54 to 0.68)	<0.001
Sulphonylurea drugs prescribed after diagnosis ^a	1.44 (1.27 to 1.64)	<0.001	1.60 (1.43 to 1.78)	<0.001
Insulin prescribed after diagnosis ^a	1.20 (0.68 to 2.10)	0.527	1.48 (0.92 to 2.36)	0.103

^a within two years of diagnosis

Figure 1: Trends in drug utilisation by patients with type 2 diabetes by year of diagnosis and duration of diabetes. Solid lines connect values for patients diagnosed in the same year and with data points representing increasing durations of diabetes.

a) Men

b) Women

