

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/21623>

Please be advised that this information was generated on 2017-09-25 and may be subject to change.

Cardiovascular Morbidity and Mortality in Type 2 Diabetic Patients: a 22-year Historical Cohort Study in Dutch General Practice

W.J.C. de Grauw, E.H. van de Lisdonk, H.J.M. van den Hoogen, C. van Weel

Department of General Practice and Social Medicine, University of Nijmegen, The Netherlands

A historical cohort study was performed to assess cardiovascular morbidity and mortality in Type 2 (non-insulin-dependent) diabetic patients. The data were collected from 1967 to 1989 in four Dutch general practices performing the Continuous Morbidity Registration Nijmegen. Each newly diagnosed Type 2 diabetic patient fulfilling the WHO criteria ($n = 265$) was matched to a control patient for practice, sex, age, and social class. Inclusion started in 1967, the first year of the still ongoing, Continuous Morbidity Registration Nijmegen. On average, a follow-up of 6.8 years (range 1 month–22 years) was realized. Compared to the non-diabetic control patients, the Type 2 diabetic patients showed higher cardiovascular morbidity (risk ratio 1.76, 95 % CI 1.34–2.30) and a higher mortality rate (risk ratio 1.54, 95 % CI 1.07–2.23). Mortality after 10 years was 36 % vs 20 % ($p < 0.01$), the median survival time 16 years vs 19 years. The cumulative survival rates were significantly different ($p < 0.01$) between patients and controls in the age group 65–74 years. The higher mortality in Type 2 diabetic patients was completely due to an excess of cardiovascular death (risk ratio 2.05, 95 % CI 1.24–3.37).

KEY WORDS Type 2 diabetes Cardiovascular morbidity Mortality General practice

Introduction

In the Netherlands, as in the United Kingdom, the majority of Type 2 (non-insulin-dependent) diabetic patients are treated in general practice.^{1–3} However, knowledge about Type 2 diabetes is mainly based on patient groups selected from hospital care.⁴ It is apparent that Type 2 diabetes can be characterized as a risk factor for cardiovascular disease,⁵ particularly for stroke,⁶ ischaemic heart disease,^{7,8} and peripheral vascular disease.⁹ The prevalence of hypertension is also higher.¹⁰

Panzram has reported an increased mortality in Type 2 diabetes, particularly in females.¹¹ He has stated that mortality statistics on diabetes are frequently biased by factors including referral bias in hospital populations. The most reliable results can be expected from prospective studies of defined cohorts recruited from general practice population surveys.¹² This paper reports an analysis of cardiovascular morbidity and causes of death in a cohort of Type 2 diabetic patients from general practice covering an observation period of up to 22 years. The aim of the study was to assess the impact of cardiovascular morbidity and mortality on Type 2 diabetic patients in general practice.

Patients and Methods

Continuous Morbidity Registration Nijmegen

The ongoing Continuous Morbidity Registration Nijmegen started in 1967 in four general practices in and around Nijmegen.¹³ This registration aims to study the epidemiological aspects of diseases in general practice, including the incidence, prevalence, and the course of the disease in time.

Every episode of illness seen by or reported to the general practitioner (GP) is registered as soon as it is established. In the Netherlands specialist care is only available after referral by the GP, and for the specialist it is a routine procedure to report back to the GP about diagnosis and treatment in referred patients. All referrals and specialist-reported diagnoses are also recorded in the registration system. To register diagnoses the adapted E-list¹⁴ is used, with a fourth digit extension to make it compatible with the International Classification of Health Problems in Primary Care (ICHPPC-2).¹⁵ The GPs also register causes of death, including those of patients dying in hospital.

The four practices have a practice population of approximately 12000. This number has remained stable over the years with a turnover of less than 5 % per year. For each patient the following data are available: sex, date of birth, date of entry or departure in the Continuous

Correspondence to: Dr W.J.C. de Grauw, Department of General Practice and Social Medicine, Postbus 9101, 6500 HB Nijmegen, The Netherlands.

Morbidity Registration, family composition, and social class. Social class is defined according to profession as well as education. A validated Dutch list of 11 categories is usually reduced to 3 as is the case here.

Selection of Patients and Controls

All newly diagnosed Type 2 diabetic patients between 1967 and 1989 ($n = 265$), including those who were under specialist medical care, were included in the study cohort if the diagnostic evidence was in agreement with the WHO criteria.¹⁶ The diagnosis of all cases was reviewed using all available data from the patients' files. Patients treated with insulin within 1 year of diagnosis and who remained on it were regarded as Type 1 (insulin-dependent) diabetes mellitus. All other patients with diabetes mellitus were considered Type 2, irrespective of their current treatment.

For each patient a control was selected, matched for practice, sex, age (± 3 months), and social class. Controls were selected from all patients on the practice lists at the time of diagnosis of the patients with Type 2 diabetes, with the exception of patients with known diabetes mellitus. There were no further exclusion criteria for controls. Patients and controls were followed up for mortality, cardiovascular morbidity, as well as cardiovascular risk factors from the time of diagnosis of the Type 2 diabetic patient.

Cardiovascular morbidity included cerebrovascular accident, myocardial infarction, angina pectoris, heart failure, and peripheral vascular disease. The following risk factors were taken into account: hypertension, obesity, and hypercholesterolaemia. Mortality was specified according to the direct cause of death recorded.

A control patient developing clinical diabetes during follow-up was included in the study cohort. As a consequence two new controls were selected.

Statistical Procedure

The cumulative incidence rates (first occurrence of the disease) of cardiovascular morbidity in the year of diagnosis and after 5, 10, and 15 years as well as mortality rates were calculated using the cohort life-table method.¹⁷ Statistical analysis was performed using the Mantel Haenszel procedure and the Cox Proportional Hazard regression model. Variables were entered into the multivariate regression model using the maximum partial likelihood ratio method. The data were analysed at the University of Nijmegen by means of the Statistical Analysis System (SAS 6.06).¹⁸

Results

A total number of 427 patients were registered between 1967 and 1989 as newly diagnosed diabetic patients by their GP. In 111 it was not possible to confirm the diagnosis for various reasons: in 43 no blood glucose

values could be traced in their records (diagnosis and follow-up had only been based on urine glucose values), in 61 only normal blood glucose levels were found or only the criteria for impaired glucose tolerance were met and in 7 the medical records were incomplete.

The remaining 316 patients met the 1985 WHO-criteria for diabetes mellitus. Type 1 diabetes mellitus was diagnosed in 35 patients, in 9 it remained inconclusive whether they had Type 1 or 2 diabetes, and in 7 other patients a secondary cause of diabetes mellitus was present: pregnancy in 6 cases and pancreatectomy in 1.

Thus 265 Type 2 diabetic patients (112 men (40.3 %) and 153 women) were included in the study cohort. At diagnosis 60 % of these were aged 65 or under. The mean follow-up was 6.8 years (range from 0.8 to 22 years). The matching succeeded completely for practice (100 %), sex (100 %), age (100 %, range 3 months), and social class (98 %).

Cardiovascular Morbidity

Prevalence at diagnosis and cumulative incidence rates after diagnosis of cardiovascular morbidity are presented in Table 1. The relative risk amounted to 1.76 (95 % CI 1.34–2.30) in Type 2 diabetic patients compared to controls. It was higher in men (1.94, 95 % CI 1.28–2.93) than in women (1.63, 95 % CI 1.15–2.32). Moreover, 5 years after diagnosis the cumulative incidence rates for cardiovascular diseases in this study cohort were already significantly higher ($p < 0.05$) in patients than in controls, except for myocardial infarction and peripheral vascular disease.

Data related to cardiovascular risk factors are presented in Table 2. A higher prevalence of hypertension, obesity, and hypercholesterolaemia were present in patients compared to controls already at the time of diagnosis ($p < 0.05$).

Mortality

Within the follow-up period 71 patients and 50 controls died resulting in a relative risk of mortality in Type 2 diabetic patients of 1.54 (95 % CI 1.07–2.23) compared to controls. It was more predominant in women (1.61, 95 % CI 0.97–2.68) than in men (1.47, 95 % CI 0.86–2.50).

The 10-year mortality rates of the patients and controls were 20 % vs 36 % ($p < 0.01$), the median survival time 16 years vs 19 years (Figure 1). The cumulative survival rates of Type 2 diabetic patients turned out to be significantly different ($p < 0.01$) from those of controls in the age group 65–74 (Figure 2).

The majority of deaths in the patient group were due to cardiovascular disease, accounting for 46 of the 71 deaths (64 %), with coronary heart disease (32 %) as the most prominent cause of death (Table 3). The relative risk in Type 2 diabetic patients of death due to cardiovascular morbidity was 2.05 (95 % CI 1.24–3.37)

Table 1. Prevalence rates at diagnosis and cumulative incidence rates after diagnosis of cardiovascular morbidity in Type 2 diabetic patients ($n = 265$) compared to controls ($n = 265$), matched for practice, sex, age, and social class

	At diagnosis		After 5 years		After 10 years		After 15 years		End of study (22 years)	
	Control	Type 2	Control	Type 2	Control	Type 2	Control	Type 2	Risk ratio	95 % CI
Cerebrovascular accident	1 (3)	2 (6)	3 (6)	7 ^a (17)	6 (9)	12 ^a (22)	8 (10)	14 ^a (23)	1.34	0.84–2.14
Myocardial infarction	5 (13)	6 (17)	9 (22)	14 (33)	13 (25)	24 ^b (45)	20 (29)	32 ^b (49)	1.82	1.57–2.86
Angina pectoris	6 (17)	13 (34)	13 (31)	19 ^a (50)	13 (32)	22 ^a (52)	15 (33)	26 ^a (54)	1.78	1.14–2.77
Heart failure	9 (24)	15 (40)	14 (34)	22 ^a (55)	24 (45)	30 ^a (65)	30 (49)	40 ^a (70)	1.52	1.04–2.21
Peripheral vascular disease	3 (8)	5 (14)	8 (20)	12 (27)	10 (22)	23 ^a (38)	11 (23)	33 ^b (43)	2.12	1.28–3.51
Total cardiovascular morbidity ^c	19 (52)	24 (63)	30 (75)	46 ^b (115)	44 (91)	62 ^b (138)	56 (100)	74 ^b (148)	1.76	1.34–2.30

Results as percentage (the absolute number of cases are presented between parentheses).

Statistical differences were calculated using the log-rank test.

Cox proportional hazard regression was used to calculate risk ratio for Type 2 diabetic patients compared to controls.

^a $p < 0.05$, ^b $p < 0.01$.

^cTotal cardiovascular morbidity represents all patients with at least one of the cardiovascular diagnoses.

Table 2. Prevalence rates at diagnosis and cumulative incidence rates after diagnosis of cardiovascular risk factors in Type 2 diabetic patients ($n = 265$) compared to controls ($n = 265$), matched for practice, sex, age, and social class

	At diagnosis		After 5 years		After 10 years		After 15 years		End of study (22 years)	
	Control	Type 2	Control	Type 2	Control	Type 2	Control	Type 2	Risk ratio	85 % CI
Hypertension	23 (61)	40 ^a (108)	27 (69)	47 ^b (122)	32 (75)	53 ^b (128)	32 (75)	45 ^b (130)	1.83	1.31–2.57
Obesity	34 (91)	62 ^b (163)	41 (108)	68 ^b (179)	48 (115)	70 ^b (182)	50 (116)	72 ^b (183)	1.91	1.41–2.60
Body mass index $\geq 27^c$										
Hypercholesterolaemia ^d	3 (7)	10 ^a (26)	6 (13)	15 ^b (37)	6 (13)	17 ^b (39)	8 (14)	20 ^b (40)	2.70	1.12–6.56

Results as percentage (the absolute number of cases are presented between parentheses).

Statistical differences were calculated using the log-rank test.

Cox proportional hazard regression was used to calculate risk ratio for Type 2 diabetes patients and controls.

^a $p < 0.05$; ^b $p < 0.01$.

^cWeight (kg)/height (m²).

^dMean result of three measurements > 7.0 mmol l⁻¹.

compared to controls. There was only a slight difference between men (2.01, 95 % CI 0.95–4.27) and women (2.07, 95 % CI 1.06–4.04).

Cox proportional hazard regression analysis of all patients and controls was used to determine the independent factors significantly related with mortality. Diabetes itself ($p = 0.02$) and pre-existing hypertension ($p = 0.02$) turned out to be statistically significant factors related to mortality. Obesity ($p = 0.55$) and hypercholesterolaemia ($p = 0.63$) did not show statistical significance.

Discussion

This study clearly demonstrates that Type 2 diabetic patients in general practice are at higher risk of cardiovascular morbidity and mortality. The latter was more predominant in women than in men. In both sexes the excess mortality was completely due to an excess in cardiovascular mortality. Population-based studies have reported an approximately two-fold excess risk of all causes of death and a two- to four-fold excess risk from cardiovascular diseases among diabetic patients.¹¹ The

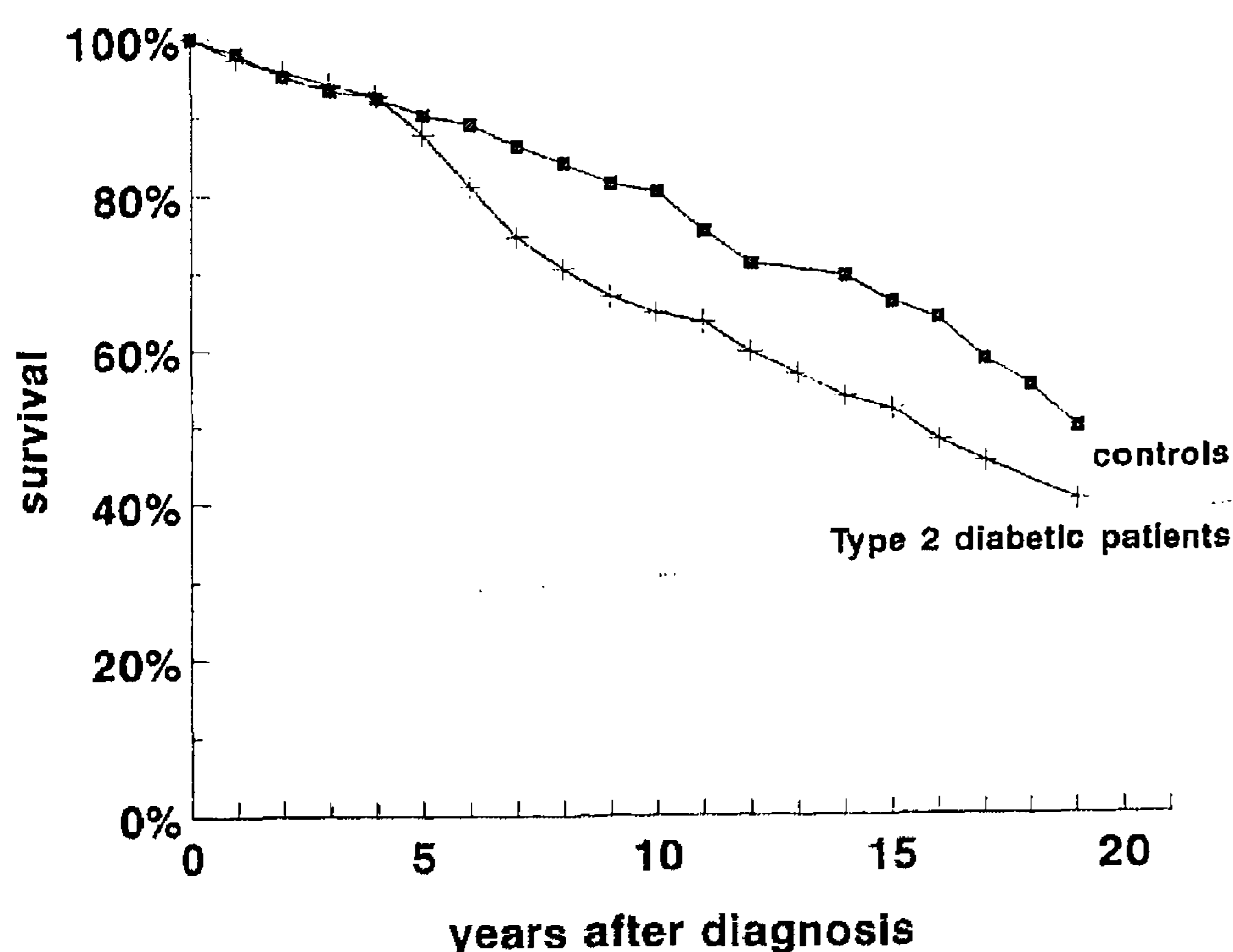


Figure 1. Survival curves of Type 2 diabetic patients in general practice [+]
($n = 265$) and controls [■] ($n = 265$), matched for practice, sex, age, and social class in the period 1967–1989. Within the follow-up period 71 patients and 50 controls died resulting in a relative risk of mortality in Type 2 diabetic patients of 1.54 (95 % CI 1.07–2.23) compared to controls. The 10-year mortality rates of the patients and controls were 20 % vs 36 % ($p < 0.01$), the median survival time 16 years vs 19 years

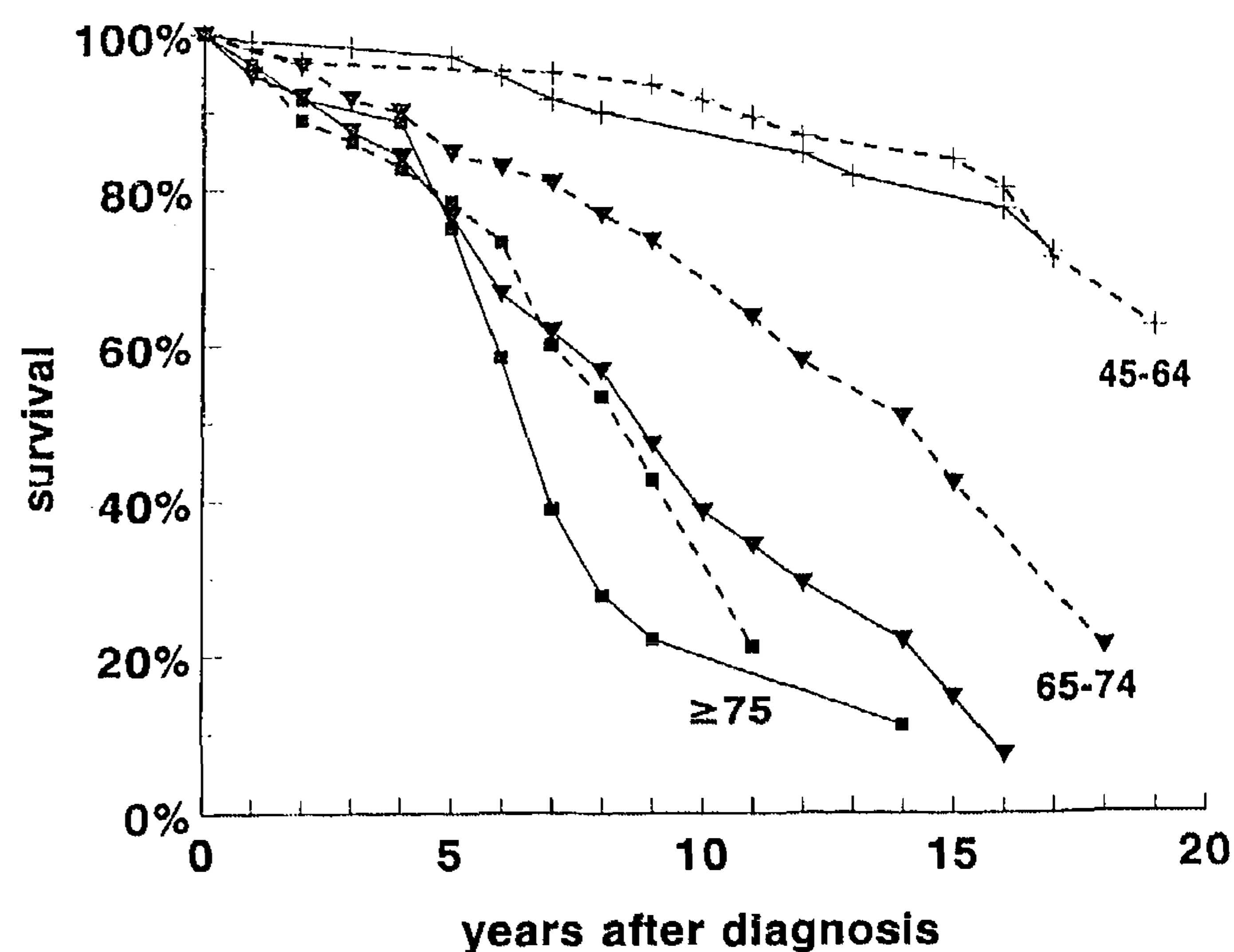


Figure 2. Survival curves for three age categories of Type 2 diabetic patients [—] in general practice and controls [---], matched for practice, sex, age, and social class in the period 1967–1989. The survival rates of Type 2 diabetic patients turned out to be significantly different ($p < 0.01$) from those of controls in the age group 65–74 [▼] ($n = 77$). In the age group 45–64 years [+]
($n = 114$) statistical significance was not reached due to shortage of follow-up. In the age group over 75 years [■] ($n = 52$) it is age itself that has become the most powerful predictive factor

Table 3. Causes of death in Type 2 diabetic patients ($n = 265$) and controls ($n = 265$), matched for practice, sex, age, and social class in the period 1967–1989

	Men		Women	
	Control ($n = 112$)	Type 2 ($n = 112$)	Control ($n = 153$)	Type 2 ($n = 153$)
Myocardial infarction	7	12	3	11 ^a
Cerebrovascular accident	1	0	3	10 ^a
Heart failure	2	5	5	3
Peripheral vascular disease	1	2	2	3
Total cardiovascular deaths	11	19	13	27 ^a
Renal failure	1	0	1	0
Neoplasm	11	7	5	4
Others	2	6	6	8
Total number of deaths	25	32	25	39

Results as absolute numbers.
^a $p < 0.01$.

majority of these studies gave excess mortality rates that were higher in women than in men.^{19–23} Other studies showed a higher excess mortality in Type 2 diabetic men compared to women.^{24–26} However, there were no such data available from general practice. Moreover, the different methodological approaches in the design of these studies lead particularly to selection bias.^{11,12} At least this problem was avoided in this study, which was based on all cases of diabetes mellitus diagnosed in routine general practice care over a period of 22 years. Patients who had moved to another area or died since the first diagnosis were included. Patients referred for hospital-based care were included as well, thus avoiding

referral bias.¹² Although the diagnostic criteria for diabetes mellitus have changed considerably during the observation period, all cases included in this study had diabetes mellitus according to the currently applied criteria.¹⁶ The definition of type of diabetes (1 or 2) was applied consistently throughout this study group. All morbidity data have been collected prospectively with scrupulous care for quality and consistency of registration.¹³

Type 2 diabetic patients in this study were also characterized by the well-known risk factors such as hypertension, obesity, and lipid abnormalities, associated with insulin resistance, known by Reaven's syndrome

X.²⁷ The high prevalence of hypertension at the time of diagnosis possibly reflects the increased risk of hypertension and hypertension treatment for the development of diabetes.^{28,29} In the years following the diagnosis, hypertension was diagnosed in a steadily increasing number of Type 2 diabetic patients, possibly reflecting the cardiovascular consequence of having diabetes mellitus.

Some limitations of this study should be taken into consideration as well. Firstly, it has been demonstrated that probably 50 % of all Type 2 diabetic patients are not known to their GP.³⁰ It is unlikely that this might be the case in this study with its special attention for cardiovascular morbidity and risk factors, including diabetes mellitus itself.^{31,32} Secondly, statistical significance was not reached for the differences in mortality, if distinguished for men and women separately, which was probably due to small absolute numbers. In the specific age group 45–64 years statistical significance was not reached due to shortage of follow-up. In the age group over 75 years it is age itself that has become the most powerful predictive factor. Thirdly, in theory bias might have been introduced by the exclusion of the 43 newly diagnosed Type 2 diabetic patients with no blood glucose values on their records. The diagnostic criteria and the definition of the different types of diabetes in these patients could not be verified. Uncertainty in these respects would have damaged the study more than the exclusion of 14 % of the potential diabetic patients. Moreover, it seems unlikely that this exclusion will have influenced the results essentially because this selection was based on diagnostic criteria and not on the course, severity or outcome of the disease.

Acknowledgements

This study was supported by a grant from the Diabetes Fonds Nederland. We are grateful for the continuing help and data collection of all GPs and practice nurses in the Continuous Morbidity Registration practices during so many years. We also wish to thank W. van Gerwen, H. Bor, and J. van Doremalen for their help in processing the data.

References

1. Balme M. *Diabetes in General Practice*. London: The Royal College of General Practitioners, Members Reference Book, 1990: 201–207.
2. Reenders K, Nobel E de, Hoogen HJM van den, Rutten GEHM, Weel C van. Diabetes and its long-term complications in general practice: a survey in a well-defined population. *Fam Pract* 1993; **10**: 169–172.
3. Verhoeven S, Ballegooye E van, Casparie AF. Impact of late complications in Type 2 diabetes in a Dutch population. *Diabetic Med* 1991; **8**: 435–438.
4. Królewski AS, Warram JH, Christlieb AR. Onset, course, complications and prognosis of diabetes mellitus. In:

- Marble A, Krall LP, Bradley RF, Christlieb AR, Soeldner J, eds. *Joslin's Diabetes Mellitus*, 12th edn. Philadelphia: Lea and Febiger, 1985: 251–275.
5. Jarrett RJ. Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease—chicken, egg or neither? *Diabetologia* 1984; **26**: 99–102.
6. Apslund K, Hägg E, Helmers C, Lithner F, Strand T, Wesler P-O. The natural history of stroke in diabetic patients. *Acta Med Scand* 1980; **207**: 417–424.
7. Fein FS, Scheuer J. Heart disease in diabetes. In: Rifkin H, Porte D Jr, eds. *Ellenberg and Rifkin's Diabetes Mellitus: Theory and Practice*, 4th edn. New York: Elsevier Science, 1990.
8. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979; **59**: 8–13.
9. Kreines K, Johnson E, Albrink M, Knatterud GL, Levin ME, Lewitan A, et al. The course of peripheral vascular disease in non-insulin-dependent diabetes. *Diabetes Care* 1985; **8**: 235–243.
10. Fuller JH. Epidemiology of hypertension associated with diabetes mellitus. *Hypertension*. 1985; **7** (suppl II): II-3–II-7.
11. Panzram G. Mortality and survival in Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1987; **30**: 123–131.
12. Melton LJ, Ochi JW, Palumbo PJ, Chu CP. Referral bias in diabetes research. *Diabetes Care* 1984; **7**: 13–18.
13. Weel C van, Bosch WJHM van den, Hoogen HJM van den, Smits AJA. Development of respiratory illness in childhood—a longitudinal study in general practice. *J R Coll Gen Pract* 1987; **37**: 404–408.
14. Eimerl TS. A practical approach to the problem of keeping records for research purposes in general practice. *J R Coll Gen Pract* 1960; **3**: 246–252.
15. *ICHPPC-2 Defined WONCA*, 3rd edn. Oxford: Oxford University Press, 1983.
16. World Health Organization. *Expert Committee on Diabetes Mellitus*. Technical Report No. 727. Geneva: WHO, 1985.
17. Matthews DE, Farewell VT. *Using and Understanding Medical Statistics*, 2nd edn. Basel: Karger, 1988.
18. *SAS Procedures Guide, Version 6*, 3rd edn. Cary, NC: SAS Institute Inc., 1990.
19. Knuiman WM, Welborn TA, Whittall DE. An analysis of excess mortality rates for persons with non-insulin-dependent diabetes mellitus in Western Australia using the Cox Proportional Hazards Regression Model. *Am J Epidemiol* 1992; **135**: 638–648.
20. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. *Diabetes* 1974; **23**: 105–111.
21. Panzram G, Zabel-Langhennig R. Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia* 1981; **20**: 587–591.
22. Wong JSK, Pearson DWM, Murchison LE, Williams MJ, Narayan V. Mortality in diabetes mellitus: experience of a geographically defined population. *Diabetic Med* 1991; **8**: 135–139.
23. Sprafka JM, Pankow J, McGovern PG, French LR. Mortality among Type 2 diabetic individuals and associated risk factors: the three city study. *Diabetic Med* 1993; **10**: 627–632.
24. Królewski AS, Czyzyk A, Janeczko D, Kopczyński J. Mortality from cardiovascular diseases among diabetics. *Diabetologia* 1977; **13**: 345–350.
25. Morrish NH, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London cohort of the WHO

- multinational study of vascular disease in diabetics) I: causes and death rates. *Diabetologia* 1990; **33**: 538–541.
26. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DW. Mortality among diabetics in a national sample. *Am J Epidemiol* 1998; **128**: 389–401.
27. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
28. Skarfors ET, Selinus KI, Lithel HO. Risk factors for developing non-insulin dependent diabetes mellitus: a 10 year follow-up of men in Uppsala. *Br Med J* 1991; **303**: 755–760.
29. Bengtsson G, Blohmé G, Lapidus L, et al. Do antihypertensive drugs precipitate diabetes. *Br Med J* 1984; **289**: 1495–1497.
30. Harris MI, Hadden WC, Knowler WC, Bennet PH. Prevalence of diabetes mellitus and impaired glucose tolerance and plasma glucose levels in US population aged 20–74 years. *Diabetes* 1987; **36**: 523–534.
31. Seidell JC, Bakx JC, Boer E de, et al. Fat distribution of overweight persons in relation to morbidity and subjective health. *Int J Obs* 1985; **9**: 363–374.
32. Hoogen JPH van den, Ree JW van. Preventive cardiology in general practice: computer-assisted hypertension care. *J Hum Hypertens* 1990; **4**: 365–367.