Nephropathy, but not retinopathy, is associated with the development of heart disease in Type 1 diabetes: a 12-year observation study of 462 patients.

Torffvit, Ole; Lövestam Adrian, Monica; Agardh, Elisabet; Agardh, Carl-David

Published in:
Diabetic Medicine

DOI:
10.1111/j.1464-5491.2005.01476.x

2005

Ole Torffvit, Monica Löwenstam-Adrian,
Elisabeth Agardh and Carl-David Agardh

"The prognostic value of microangiopathy, i.e. nephro- and retinopathy on heart disease. A 12-year observation study of 462 type 1 diabetic patients."

Diabet Med. 2005 Jun;22(6):723-9.

Publisher: Blackwell.

Alternative location: http://dx.doi.org/10.1111/j.1464-5491.2005.01476.x

The prognostic value of microangiopathy, i.e. nephro- and retinopathy on heart disease. A 12-year observation study of 462 type 1 diabetic patients.

Running headline: Microangiopathy and Heart in type 1 diabetes.

Ole Torffvit[1], MD, PhD, Monica Löwenstam-Adrian[2], Elisabeth Agardh[3] and Carl-David Agardh[4], MD, PhD
[1]Dep. of Medicine, [2]Dep. of Ophthalmology, University Hospital,
S-221 85 Lund, [3]Dep. of Ophthalmology and [4]Dep. of Endocrinology, University Hospital MAS, S-205 02 Malmö, Sweden.

Corresponding author:
Ole Torffvit, MD, PhD,
Associate professor
Department of Medicine,
University Hospital, S-221 85 Lund,
Sweden.
Tel.: +46-46-2220702, Fax.: +46-46-2110908.
E-mail: Ole.Torffvit@med.lu.se

ABSTRACT

The objective was to study the development and progression of heart disease in type 1 diabetic patients and to evaluate the presence of microangiopathy i.e. retino- and nephropathy on its outcome. A 12-year observation study in 462 patients without a history of heart disease attending a hospital based outpatient clinic was performed. Results. A total of 85/462 patients developed myocardial infarction (n=41), angina (n=23), heart failure (n=17) or died (n=56). A high mortality was seen in patients with myocardial infarction (51%) and heart failure (65%), in contrast, to patients with angina (26%). The relative risk for death was 7 times higher and the risk for coronary heart disease event 4.4 times higher in patients with severe retinopathy than in patients without. The risk was similarly increased 9 times and 4.3 times in patients with macroalbuminuria and microalbuminuria.

Conclusion. This study shows a high incidence of heart disease in patients with type 1 diabetes. The prognosis was worse in patients with severe retinopathy and micro-macroalbuminuria at baseline.

Keywords: Albuminuria, angina pectoris, myocardial infarction, heart failure, retinopathy, type 2 diabetes mellitus.

INTRODUCTION

Type 1 diabetic patients have an increased risk for atherosclerotic heart disease [1, 2]. Micro-macroalbuminuria has been taken as a sign of widespread vascular disease associated with an increased mortality [3]. Presence of proteinuria is a key determinator of risk following percutaneous transluminal coronary angioplasty (PTCA) [4]. Although there has been a decline in heart disease mortality in the general population this has been found to a lesser extent in the diabetic population [5]. The reason for this discrepancy is presently unknown but, it has been proposed that there is a specific heart disease of diabetes [6]. This might be suspected to be caused by microangiopathy. There is a clear association between two common signs of microangiopathy, i.e. degree of retino- and nephropathy [7] although in some patients there may be a marked discordance [8]. If retino- or nephropathy is associated with increased risk of heart disease this would be of value in designing specific medical treatment. Very few studies have followed type 1 diabetic patients for sufficient time, i.e. more than ten years, and analysed albuminuria [1, 3] or retinopathy [9-11] as a predictive factors for mortality [12]. The results on retinopathy have been contradictory. None of the studies have coupled both retinopathy and micro-macroalbuminuria to development of heart disease. Thus, the aim of the present study was to investigate the development of heart disease in relation to degree of microvascular disease, i.e. degree of albuminuria and retinopathy, and to adjust for confounders like age, gender and metabolic and blood pressure control and type of medical treatment during a 12-year observation period in type 1 diabetic patients.

SUBJECTS AND METHODS

Patients.

All type 1 diabetic patients (diabetes diagnosis < 30 years of age and with insulin from the onset) attending our out-patient clinic 1985-1986 participated in this 10-year study. They were examined three times per year (median, range 2-4 times a year). Out of the

476 patients initially studied [13], five patients were lost for follow-up. Nine patients with history of heart disease at entry were excluded: myocardial infarction (n=8) or angina pectoris (n=1). The remaining 462 patients (216 females) are included in the present study. The patients were grouped in accordance to the level of albumin creatinine clearance ratio (ACCR) at entry: (1) normoalbuminuria < 0.01 x 10^{-3}, (2) microalbuminuria 0.01-0.1 x 10^{-3} and (3) macroalbuminuria > 0.1 x 10^{-3}. The ACCR was calculated as the ratio between albumin and creatinine clearance: ACCR=(u-albumin x s-creatinine) / (s-albumin x u-creatinine). Microalbuminuria as defined above corresponds in our hands to the definition of microalbuminuria of 20-200 µg/min. Progression of albuminuria was defined as increase from one group to at least one level above according to the highest degree of albuminuria achieved during the study in order to account effect of drugs used for antihypertensive treatment.

End-points at follow-up were myocardial infarction, angina, heart failure and death. One diagnosis did not exclude the other. Medical treatment and whether or not the patients were examined with coronary angiography and treated with PTCA or CABG were registered. The diagnostic criterions for myocardial infarction have been given previously [14]. Angina pectoris was confirmed by a physical bicycle exercise test. Heart failure was based on x-ray evidence of congestion. Data from patients were registered from the medical records and mean values were calculated for each calendar year. The cause of death was taken from death certificates, medical records and in twenty cases by post mortem examination. We were not able to get information on smoking or lipid status as this was not registrated regularly.

Retinopathy

A description of the examination and classification of retinopathy has previously been described [15]. In the present study we used three levels of retinopathy based on the worst eye affected: no, background or sight-threatening retinopathy. The latter included macula edema and/or proliferative retinopathy. Thirty-six had missing data at entry.

Progression of retinopathy was defined as increase from one group to at least one level above according to the worst degree of retinopathy achieved during the study.

Analytical techniques.

Glycosylated haemoglobin (HbA_{1c}) was analysed by ion-exchange chromatography (Bio-Rad, Richmond, CA) (1985-1987), by FPLC (Pharmacia, Uppsala, Sweden) (1988-1994) and by HPLC (1995-). The last methods were adjusted to give similar results as the first one. Normal value was 4.0-5.3%. Serum and urinary creatinine concentrations were analysed by a kinetic Jaffe reaction (1985-1990) or by an enzymatic method (creatinine-amidino-hydrolase; KODAK EKTACHEM -analyser, Instrument Kodak)(1991-). The last method was adjusted to give the same values as the first one. Urinary albumin concentration was measured with an electroimmunoassay (Kabi Vitrum, Stockholm, Sweden)(1985-1993)(detection limit, 12.5 mg/l) or by turbidimetry (Cobas Mira S, Roche)(1994-)(detection limit, 5 mg/l). The two methods gave comparable results ($R = 0.99$; $n = 68$). A urinary albumin level below 12.5 mg/l was allocated the value 10 mg/l. Serum albumin was measured by a spectrophotometric method.

Statistics

Mann-Whitney U-test for two independent samples or Wilcoxon paired test for two related samples were used. To evaluate differences in proportions between groups, the chi-square test or Fisher's exact test were used. A difference in mean values between several groups was conducted by one-way analysis of variance with Bonferronis test for post hoc analysis of multiple comparisons or with Kruskall Wallis test. The association between heart disease or death and medical variables were investigated by the Cox regression analysis with forward stepwise selection. ACCR or retinopathy at entry was included in the analysis as a variable consisting of three levels as defined above. Kaplan-Meier estimates of survival curves for the three levels of albuminuria or retinopathy were compared with log rank test. In order to find an association between

progression of microangiopathy and development of heart disease we used the maximal degree of albuminuria during the study and the degree of retinopathy at the last examination. The criteria for determining variables to be added to the model were based on the maximum partial likelihood estimate. In the case of vascular morbidity or death, the "survival time" was the time from baseline to the date of event or until end of follow-up. In the latter case it was censored. Odds ratios for death were calculated from crosstabulations with risk estimate calculated by likelihood ratio.

RESULTS

Patient characteristics

The presented data are values measured during 11 years (median, range 0-12 years). During the follow-up period, 85 patients developed one of the events considered as end-points, i.e. myocardial infarction (n=41), angina (n=23), heart failure (n=17) and death (n=56). In addition 16 had a stroke. The causes of death were myocardial infarction (n=18), uraemia (n=5), stroke (n=6), sudden death (n=1), heart failure (n=0), cancer (n=4), ketoacidosis (n=4) and other causes (n=18).

At baseline (Table 1)

The patients who developed angina were older, had higher blood pressure and serum creatinine levels but similar age at diagnosis, insulin dose, BMI, HbA_{1c}, degree of urinary albumin and retinopathy at baseline as those who did not develop angina. Patients who had had a myocardial infarction were older but younger at diabetes diagnosis, had higher HbA_{1c}, blood pressure, serum creatinine levels and degree of albuminuria and retinopathy but similar insulin dose, and BMI at baseline compared to patients who did not had had a myocardial infarction. Patients with heart failure were older at baseline but younger at diabetes diagnosis, had higher blood pressure and serum creatinine and degree of albuminuria and retinopathy but similar insulin dose, BMI, HbA_{1c} levels as patients who did not develop heart failure (Table 1).

During the study period (Table 2)

During the study the systolic blood pressure, maximal creatinine and urinary albumin levels were higher while the HbA_{1c} and diastolic blood pressure levels and degree of retinopathy were not in patients who developed angina compared with patients who got no angina. In patients who had myocardial infarction all these parameters were clearly higher than in patients who did not have an infarction. Patients who got heart failure had similar findings except for no difference with respect to HbA_{1c} and retinopathy (Table 2).

Cox regression analysis

The relative risk for death, cardiovascular disease mortality, coronary heart disease event and death from coronary heart disease, angina, myocardial infarction, heart failure and heart disease adjusted for age and gender and confounders as mean systolic and diastolic blood pressure and HbA_{1c} levels, treatment with drugs for hypertension during the study is shown in Table 3 for severe sight-threatening and backgrounds retinopathy in comparison with no retinopathy. The relative risk for death was 7 times higher and the risk for coronary heart disease event 4.4 times higher in patients with severe retinopathy than in patients without. The risk was 3.9 times increased for getting a myocardial infarction. This is also illustrated in the Kaplan-Meier survival curves (Figure 1). The risk was similarly increased 9 times and 4.3 times in patients with macroalbuminuria but even in patients with microalbuminuria (Table 4). The Kaplan-Meier survival curve is even more pronounced in these patients than in patients with retinopathy (Figure 2).

Progression of retinopathy and albuminuria was not associated with development of heart disease.

Treatment for heart disease

Eighty-two percent of the patients with heart failure, 78% of the patients with angina and 61% of those with myocardial infarction received ACE inhibitors. Similarly a high proportion of the patients were treated with Ca-blockers (53%, 74% and 54%,

respectively), lesser were treated with ß– blockers (35%, 61% and 44%, respectively). Out of the patients who developed heart disease, 43% were treated for hypertension.

Mortality

Sixteen patients had a coronary angiography because of angina, out of which 12 were revascularised. One (8%) of patients with bypass surgery or angioplasty died compared with 24 (57%) of the 42 patients with heart disease with no intervention ($p<0.01$). The mortality increased from 8% in patients with no heart disease to 26% angina, 51% in myocardial infarction and highest 65% in patients with heart failure (Table 2).

DISCUSSION

In this study, particularly the degree of albuminuria but even of retinopathy was associated with development of heart disease and death. The prognosis was better in patients who had had a revascularisation. We found a high mortality rate in patients with myocardial infarction (53%) and heart failure (68%). Albuminuria has previously been reported to be an important risk marker for cardiovascular events and death [1, 3]. Even microalbuminuria [16, 17] or even slightly elevated urinary albumin excretion independently predicted atherosclerotic vascular disease [18]. Presence of more severe retinopathy or visual impairment has been shown to be a risk factor for ischemic heart disease in some studies [9, 11] but not in others [10]. In other studies retinopathy was not of predictive value for mortality whereas nephropathy was [12]. Most studies have not tested the association between retinopathy and ischemic heart disease [1, 12, 18]. The mortality rate in patients with angina was lower than in patients with myocardial infarction but a higher proportion (48% vs. 20%) of the patients with angina was treated with coronary revascularisation. In the study by Manske et al [19], most patients medically treated while a few patients treated with revascularisation had a cardiovascular endpoint such as unstable angina, myocardial infarction and cardiac death. CABG and PTCA are particularly effective in diabetic patients [19].

The development of ischemic heart disease (angina and myocardial infarction) and heart failure was clearly associated with age, high systolic blood pressure levels and diastolic blood pressure and HbA_{1c} levels seemed to be of importance too. In spite of this, i.e. adjusting for these confounding factors we were still able to see sight –threatening retinopathy was a risk factor for death and, while background retinopathy was too weak a risk factor to be of significance. In contrast the development of heart disease was more associated with the confounding factors. Albuminuria was independently of the confounding factors associated with development of heart disease and particularly heart failure. Whereas, microalbuminuria was found to be a weaker risk factor.

Conclusion. This study shows a high incidence of heart disease in patients with type 1 diabetes. The prognosis was worse in patients with severe retinopathy and micro-macroalbuminuria at baseline.

Acknowledgements

The study was supported by grants from the Almér foundation, Malmoe Diabetes Association, the Skane County Council Foundation for Research and Development, the Swedish Diabetes Federation, the University of Lund.

REFERENCES

[1]. Rossing P, Hougaard P, Borch-Jonhsen K, Parving H-H. Predictors of mortality in insulin dependent diabetes: 10 year observational study. BMJ 1996;313:779-784

[2]. Laing S, Swerdlow A, Slater S et al. The brittish diabetic association cohort study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabet Med 1999;16:466-471

[3]. Borch-Jonhsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. BMJ 1987;294:1651-1654

[4]. Marso S, Ellis S, Tuzcu E et al. The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics. J Am Coll Cardiol 1999;33(5):1269-1277

[5]. Gu K, Cowie C, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999;281(14):1291-1297

[6]. Fisher B, Frier BM. Evidence for a specific heart disease of diabetes in humans. Diabet Med 1990;7:478-489

[7]. El-Asrar A, Al-Rubeaan K, Al-Amro S, Moharram O, Kangave D. Retinopathy as a predictor of other diabetic complications. Int Ophthalmol 2002;24:1-11

[8]. Chavers B, Mauer S, Ramsay R, Steffes MW. Relationship between retinal and glomerular lesions in IDDM patients. Diabetes 1994;43:441-446

[9]. Klein R, Klein B, Moss S, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. Archives of Ophthalmology 1999;117:1487-1495

[10]. Krolewski A, Kosinski E, Warram J et al. Magnitude and determinants of coronary artery disease in juvenile-onset. insulin-dependent diabetes mellitus. Am J Cardiol 1987;59:750-755

[11]. Fuller J, Stevens L, Wang S-L, the WHO Multinational Study Group. Risk factors for cardiovascular mortality and morbidity: The WHO multinational study of vascular disease in diabetes. Diabetologia 2001;44(SUPPL 2):S54-S64

[12]. Mühlhauser I, Overmann H, Bender R, Jörgens V, Berger M. Predictors of mortality and end-stage diabetic complications in patients with type 1 diabetes mellitus on intensified insulin therapy. Diabet Med 2000;17:727-734

[13]. Torffvit O, Agardh E, Agardh C-D. Albuminuria and associated medical risk factors: A cross-sectional study in 476 type I (insulin-dependent) diabetic patients. Part 1. J Diabet Complications 1991;5(1):23-28

[14]. Torffvit O, Agardh C-D. The predictive value of albuminuria for cardiovascular and renal disease. A 5-year follow-up study of 476 patients with type I diabetes mellitus. J Diabet Complications 1993;7:49-56

[15]. Lövestam-Adrian M, Agardh C-D, Torffvit O, Agardh E. Diabetic retinopathy, visual acuity, and medical risk indicators. A continuous 10-year follow-up study in type 1 diabetic patients under routine care. J Diabet Complications 2001;15:287-294

[16]. Earle K, Mishra M, Morocutti A et al. Microalbuminuria as a marker of silent myocardial ischaemia in IDDM patients. Diabetologia 1996;39:854-856

[17]. Kimball T, Daniels S, Khoury P, Magnotti R, Turner A, Dolan LM. Cardiovascular status in young patients with insulin-dependent diabetes mellitus. Circulation 1994;90:357-361

[18]. Deckert T, Yokoyama H, Mathiesen E et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. BMJ 1996;312:871-874

[19]. Manske C, Wang Y, Rector T, Wilson R, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. Lancet 1992;340:998-1002

Table 1. Medical risk indicators at baseline in patients without or with heart disease.

	No heart disease (n=408)	Angina (n=23)	Myocardial infarction (n=41)	Heart failure (n=17)
Women/men (n)	193/215	12/11	15/26	7/10
Age (years)	33±10***	43±10***	45±10***	47±12***
Age at diagnosis (years)	16±7*	13±7	12±7*	11±7*
Insulin dose (U/day)	45±16	41±16	43±16	42±14
BMI (kg/m^2)	23±3	23±2	24±3	24±2
HbA_{1c} (%)	8.4±1.4*	8.8±1.1	9.0±1.0*	8.8±1.3
Systolic BP (mmHg)	130±16***	147±19***	150±19***	151±20***
Diastolic BP (mmHg)	78±8***	84±9**	85±7***	85±8**
Serum creatinine (µmol/L)	77 (35-444)***	84 (63-155)*	90 (55-224)***	96 (63-155)***
Albuminuria	***		***	***
Normoalbuminuria (n)	258	9	11	3
Microalbuminuria (n)	107	8	13	6
Macroalbuminuria (n)	43	6	17	8
Retinopathy	***		**	*
None (n)	137	2	3	1
Background (n)	127	8	12	6
Sight-threatening (n)	116	10	19	9

Data are shown as mean and SD. Serum creatinine is shown as median and range. Albuminuria and retinopathy as number of patients within the group. * = $p<0.05$, ** = $p<0.01$ and *** = $p<0.001$ compared with patients without the specified diagnosis, i.e. angina pectoris, myocardial infarction and heart failure.

Table 2. Mean values of HbA_{1c} and blood pressure and the highest levels of serum creatinine and albuminuria and degree of retinopathy at end in patients without or with heart disease.

	No heart disease (n=408)	Angina (n=23)	Myocardial infarction (n=41)	Heart failure (n=17)
Mean HbA_{1c} (%)	8.3±1.2**	8.6±0.9	8.9±0.8***	8.4±0.9
Mean systolic BP (mmHg)	133±14***	147±15***	150±15***	150±16***
Mean diastolic BP (mmHg)	78±6***	81±6	82±6***	79±6**
Max serum creatinine (µmol/L)	93 (40-1197)***	118 (70-960)**	118 (70-1234)***	148 (101-710)***
Max albuminuria level	***	**	***	***
Normoalbuminuria (n)	154	1	2	2
Microalbuminuria (n)	169	12	16	4
Macroalbuminuria (n)	85	10	23	11
Retinopathy at end	**		*	
None (n)	63	0	0	1
Background (n)	116	5	8	4
Sight-threatening (n)	201	15	26	11
Mortality Number of deaths (%)	31 (7.6)***	6 (26)*	21 (51)***	11 (65)***

Data are shown as mean and SD. Max serum creatinine is shown as median and range. Albuminuria and retinopathy as number of patients within the group. * = $p<0.05$, ** = $p<0.01$ and *** = $p<0.001$ compared with patients without the specified diagnosis, i.e. angina pectoris, myocardial infarction and heart failure.

Table 3. Relative risk for death, cardiovascular death, coronary heart event or death in patients with or without sight-threatening or background retinopathy at baseline.

	Total for study		Sight-threatening retinopathy vs. No retinopathy		Background retinopathy vs. No retinopathy	
Type of outcome	Number with outcome	Number with no outcome	RR adjusted for age and gender & 95% CI	RR adjusted for age, gender and other confounders[1] & 95% CI	RR adjusted for age and gender & 95% CI	RR adjusted for age, gender and other confounders[1] & 95% CI
Any death	56	406	7.0 (2.1-23.6)**	4.3 (1.2-15.5)*	NS	NS
CVD death[2]	25	437	NS	NS	NS	NS
CHD event[3]	47	415	4.4 (1.3-15.1)*	NS	NS	NS
CHD death[4]	19	443	NS	NS	NS	NS
Angina	23	439	NS	NS	NS	NS
Myocardial infarction	41	421	3.9 (1.1-13.8)*	NS	NS	NS
Heart failure	17	445	NS	NS	NS	NS
Heart disease	54	408	3.8 (1.3-11.2)*	NS	NS	NS

[1]adjusted for age, gender and confounders = mean systolic and diastolic blood pressure and HbA_{1c} levels, treatment for hypertension.

[2]CVD = cardiovascular disease mortality (coronary, stroke or other vascular death)

[3]CHD event = coronary heart disease event (i.e. non-fatal myocardial infarction or CHD death)

[4]CHD death = coronary heart disease (i.e. fatal myocardial infarction or other CHD death)

RR = relative risk, CI = confidence interval

* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$ vs. no retinopathy

Table 4. Relative risk for death, cardiovascular death, coronary heart event or death in patients with or without macro- and microalbuminuria at baseline.

	Total for study		MACRO albuminuria vs. normoalbuminuria		MICRO albuminuria vs. normoalbuminuria	
Type of outcome	Number with outcome	Number with no outcome	RR adjusted for age and gender & 95% CI	RR adjusted for age, gender and other confounders[1] & 95% CI	RR adjusted for age and gender & 95% CI	RR adjusted for age, gender and other confounders[1] & 95% CI
Any death	56	406	9.0 (4.5-18.1)***	4.9 (2.3-10.6)***	1.1 (1.04-1.1)***	NS
CVD death[2]	25	437	18.3 (5.2-64.1)***	8.2 (2.1-31.7)**	4.9 (1.2-19.8)*	NS
CHD event[3]	47	415	4.3 (2.1-8.9)***	NS	NS	NS
CHD death[4]	19	443	12.9 (3.5-47.3)***	8.5 (2.1-34.0)**	NS	NS
Angina	23	439	3.1 (1.1-8.6)*	NS	NS	NS
Myocardial infarction	41	421	6.3 (2.9-13.6)***	6.3 (2.9-13.6)***	NS	NS
Heart failure	17	445	11.1 (2.9-42.3)***	11.1 (2.9-42.3)***	4.6(1.0-20.7)*	4.9(1.1-22.4)*
Heart disease	54	408	5.1 (2.6-9.9)***	5.1 (2.6-9.9)***	NS	NS

[1]adjusted for age, gender and confounders = mean systolic and diastolic blood pressure and HbA_{1c} levels, treatment for hypertension.

[2]CVD = cardiovascular disease mortality (coronary, stroke or other vascular death)

[3]CHD event = coronary heart disease event (i.e. non-fatal myocardial infarction or CHD death)

[4]CHD death = coronary heart disease (i.e. fatal myocardial infarction or other CHD death)

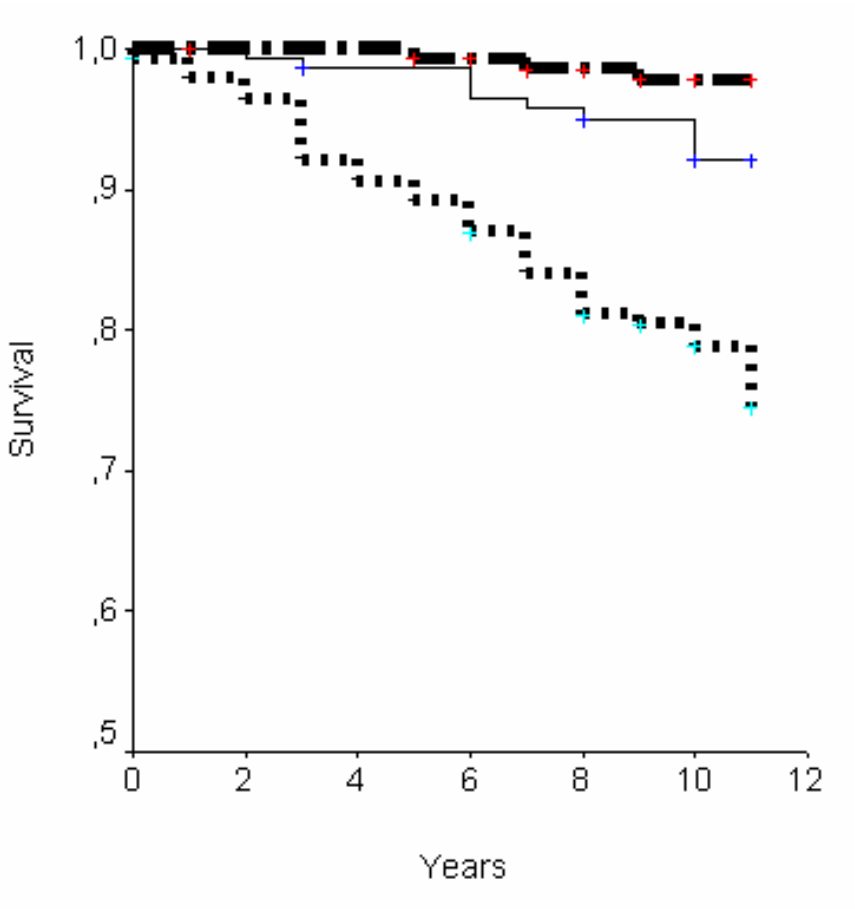
RR = relative risk, CI = confidence interval

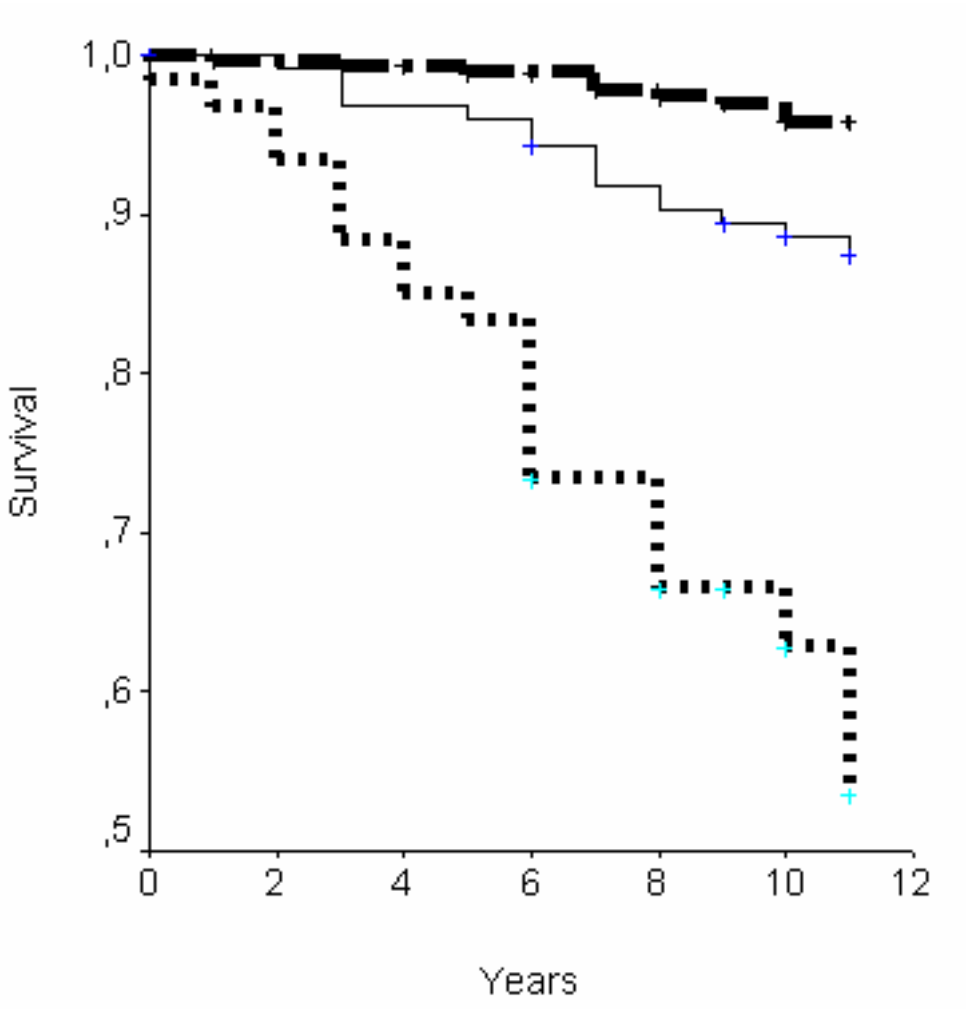
* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$ vs. normoalbuminuria

Legends to Figures

Figure 1. Kaplan-Meier estimates of survival curves with respect to all cause mortality for the three levels of retinopathy at baseline: No, background and severe sight-threatening. Log rank test: no vs. background $p<0.05$, no vs. severe or background vs. severe $p<0.001$.

Figure 2. Kaplan-Meier estimates of survival curves with respect to all cause mortality for the three levels of albuminuria at baseline: Normal, micro- and macroalbuminuria. Log rank test: normal vs. micro- $p<0.01$, normal vs. macro- and micro- vs. macroalbuminuria $p<0.001$.


1,0
,9
,8
,7
,6
,5
Survival
0
2
4
6
8
10
12
Years


1,0
,9
,8
,7
,6
,5
Survival
0
2
4
6
8
10
12
Years