Prevalence and Prognostic Significance of Asymptomatic Peripheral Arterial Disease in 68-year-old Men with Diabetes. Results from the Population Study 'Men Born in 1914' from Malmo, Sweden.

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Prevalence and prognostic significance of asymptomatic peripheral arterial disease in 68-year-old men with diabetes.

Results from the population study "Men born in 1914" from Malmö, Sweden.

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Running title: Asymptomatic PAD in diabetes

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Abstract

Objective

To assess the prevalence of asymptomatic peripheral arterial disease (PAD) in older men with diabetes and to compare the incidence of cardiac events and deaths in diabetic and non-diabetic men with abnormal and normal systolic ankle-brachial pressure index, respectively.

Research Design and Methods

Population-based cohort of 68-year-old men (n=474). Diabetes was defined as history of diabetes or an fasting blood glucose ≥6.1 mmol/L. PAD was defined as an ankle-brachial pressure index (ABI) <0.9 in either leg. Fourteen-year mortality and cardiac event rates were based on record linkage with regional and national registers.

Results

The prevalence of PAD in men with and without diabetes was 29% and 12%, respectively (p=0.003). The incidence of cardiac events was 22.9/1000 person years in men free from both diabetes and PAD. In the absence of an abnormal pressure index, diabetes was associated with an event rate of 28.4 (p=0.469). In the presence of an abnormal index the incidence was 102 (p<0.001). This pattern remained in the multivariate analysis when other atherosclerotic risk factors were taken into account. Cardiovascular mortality rates similarly differed substantially between diabetic men with and without PAD.

Conclusions

A fB-Glucose value above 6.1 mmol/L even in the absence of symptoms indicating diabetes was associated by an increased prevalence of asymptomatic PAD. The cardiovascular risk in diabetes varied widely between men with and without abnormal ankle-brachial pressure index.

Introduction

Diabetes is associated by an increased incidence of myocardial infarction, stroke and peripheral arterial disease (PAD) [1-5]. This risk remains when other major cardiovascular risk factors are taken into account.

Measurement of the systolic ankle-brachial pressure index (ABI) is a simple method with demonstrated validity in population settings for the detection of even pre-symptomatic stages of atherosclerotic PAD [6-8]. The increased cardiovascular risk associated with a low ABI has been demonstrated in several cohort studies and reflects the generalised nature of atherosclerotic disease [9-12]. In apparently healthy subjects exposed to risk factors associated with the occurrence of cardiovascular disease, measurement of the ABI can be used as a prognostic marker to identify those who are most vulnerable.

Whether non-invasively detected PAD is a similar prognostic marker in diabetes has not been evaluated in population-based studies. Since diabetes is associated with vascular manifestations apart from atherosclerotic disease, so called “small vessel disease” [13], this cannot be readily assumed. The present follow-up study from the population based cohort “Men born in 1914” has as its aim to evaluate the prognostic significance of a low ankle-brachial index in relation to diabetes in 68-year-old men.

Materials and methods

Study population

The cohort study “Men born in 1914“, Malmö, Sweden, was designed to identify determinants for cardiovascular and pulmonary diseases in elderly men [14]. All men born in even months in 1914 and residing in the city were in 1982-1983, close to their 68th birthday, invited to a health examination. Of 621 invited 474 (76.4%) took part in the assessment of diabetes and peripheral arterial disease.

Diabetes mellitus

Blood samples for determination of blood glucose were drawn after a minimum fasting period of 8 hours. Diabetes mellitus, defined as either of history of diabetes mellitus at the health examination, or an fasting blood (fB) glucose ≥6.1 mmol/L [15] was found in 48 (10.1%) of the 474 men. Twenty men had a history of diabetes; of these, two received insulin treatment, 12 had medication with oral antidiabetics whereas the remaining six were on dietary control only.

Cardiovascular risk factors

Smoking habits were assessed by means of a structured questionnaire, and the men were grouped into current smokers, ex-smokers (those who had stopped smoking and maintained cessation for more than one month prior to the examination) and never smokers. The validity of smoking data was analysed by comparison with blood concentrations of carbon monoxide [16]. Systolic and diastolic (phase V) blood pressure was measured sphygmomanometrically with the subject in the sitting position after 15 minutes of rest. Blood pressure was recorded to the nearest 5 mm Hg. Hypertension was defined as systolic or diastolic brachial blood pressure ≥160/95 mm Hg or treatment for hypertension [17]. Blood cholesterol and triglyceride levels were analysed by standard methods and expressed in mmol/L. Body mass index (BMI) was expressed as body weight (kg)/height^2 (m^2).

Ankle-brachial blood pressure index (ABI) measurement

The recording system consisted of pulse sensors (mercury-in-Silastic strain gauges) placed on the big toes and thumbs; two Wheatstone bridges with amplifier to record changes in the resistance of the strain gauges; blood pressure cuffs (18x60 cm to measure ankle systolic pressure and 12x35 cm to measure the upper arm systolic pressure); a pressure transducer (Siemens-Elema EMT 746 with amplifier EMT 311) to record cuff pressures; and a six-channel ink-jet recorder (Siemens-Elema; Mingograph) [18-19]. Duplicate recordings were made with the subject in the supine position, and the arithmetic average used. For each leg, an arm-ankle pressure index (ABI) was calculated by dividing the ankle systolic pressure with the highest upper arm systolic pressure value.

Definition of PAD

Peripheral arterial disease (PAD) at 68 years of age was defined as an ABI <0.9 in one or both legs [6-8]. Subjects with an ABI $\geq$0.9 in both legs were considered free from PAD. An ABI >1.3 was considered abnormally high [20].

Mortality and morbidity surveillance

Mortality rate

All 474 participants in the 1982-1983 health examination were followed from this first examination until their death or until December 31, 1996. Median (range) follow-up time was 13.2 (0.3 – 14.3) years. The follow-up analysis was based on a total of 5044 person years. Mortality data were obtained by record linkage with the Mortality Registry of the Swedish National Bureau of Statistics. In 50% of the deaths, necropsy was performed.

Mortality rates were expressed as deaths per 1000 person years of observation. Cases coded 390– 448 according to the International Classification of Diseases (ICD) code (8^{th} revised version through 31 December 1986; 9^{th} revised version since 1 January 1987) were counted as deaths from cardiovascular disease.

Cardiac event rate

The follow-up period was from the 1982-1983 health examination until the first cardiac event, death or December 31, 1996. Median (range) follow-up time was 12.0 (0.3 – 14.3) years, with a total follow up of 4717 person years. Cases with myocardial infarction were retrieved by record linkage with the Malmö Heart Infarction Register [21]. A cardiac event was defined as fatal or nonfatal myocardial infarction (ICD-8 and ICD-9: code 410.0-410.9) or death from ischaemic heart disease (ICD-8 and ICD-9: code 410-414).

Statistical methods

Distributions of ankle-brachial indices and cardiovascular risk factors were expressed in terms of mean and SD. ANOVA was used to compare distributions of means and the chi square test to evaluate differences in proportions. Differences in blood triglyceride levels were evaluated using the Kruskal-Wallis non-parametric test. Survival analysis, using the Kaplan-Meier method with the generalised Wilcoxon rank sum test, and Cox's proportional hazards model for multivariate analysis were used to study mortality and cardiac event rate in relation to presence of diabetes and PAD.

Results

Assessment of PAD in relation to diabetes in 68-year-old men

The prevalence of PAD was 29% (14 out of 48) in men with diabetes (table 1). Eight (17%) had bilateral disease. Corresponding prevalences in men free from diabetes were 12% (52 out of 426) (p=0.003) and 4% (16 out of 425) (p=0.001), respectively. Nine men (2%) had an ABI exceeding 1.3. Only one of them had diabetes.

Cardiovascular risk factors in relation to diabetes and PAD

Of the 48 men with diabetes, 42 (87.5%) were or had been smokers. Of those having an abnormal pressure index 36% were smokers (table 2). Among those who had diabetes and who had a normal pressure index 68% (23 out of 34) had quit smoking. Men with both diabetes and PAD had the highest mean systolic blood pressure and the highest prevalence of hypertension. No major differences were found when comparing plasma cholesterol, but diabetes was, as expected, associated with higher levels of triglycerides (table 2).

Cardiac event and mortality rates in relation to diabetes and PAD

Men who had diabetes and whose ABI was below 0.9 had a markedly higher cardiac event rate (102 events per 1000 person years of follow up) when compared to those with a normal pressure index (28 events /1000 person years; p=0.005). The cardiac event rate in men having neither diabetes nor PAD was 223 events /1000 person years (table 3)(fig 1).

Diabetes was in the absence of PAD associated by an increased rate of mortality (77 vs. 38 deaths per 1000 person years; p<0.001) (table 3) (fig 2). This could not entirely be accounted for by an increased cardiovascular mortality rate (31 and 20 deaths /1000 person years, p=0.065) (table 3)(fig 3). Among those with diabetes, presence of an abnormal ankle-brachial index was not associated by any statistically significant increase of the incidence of deaths.

Multivariate analysis of cardiac event and mortality rates

In the multivariate analysis of the 14-year follow up, PAD but not diabetes was associated by an increased cardiac event rate (R.R. 1.8; 95% C.I. 1.1-3.0) when entering smoking, hypertension, blood cholesterol and BMI as covariates (table 4). Diabetes and PAD were both associated with an increased risk of death (R.R.1.9; 95% C.I.1.2-2.8 and R.R. 2.0; 95% C.I.1.4-2.9).

Discussion

The association between diabetes and peripheral arterial disease has been addressed and established in a number of cross-sectional and prospective studies. Most of them have been based on the occurrence of symptomatic disease, i.e. intermittent claudication or severe limb ischaemia, in patients with insulin and non-insulin dependent diabetes [22-25].

In this study less than half of the men with diabetes were aware of their condition, i.e. the diagnosis was based on a fasting blood sugar level above 6.1 mmol/L. Almost one third of those with diabetes had an ankle-brachial index below 0.9 in the absence of symptoms of PAD. Despite the apparently silent state of their disease, two thirds of the men with diabetes as compared with 47% of the healthy controls were no longer alive at the end of follow up. Forty per cent of the diabetic men and 25 per cent of the controls had experienced a cardiac event.

Measurement of the ankle-brachial pressure index is a simple and valid method for the detection of early, non-symptomatic stages of atherosclerosis between heart and ankle level [6-8]. In studies on apparently healthy subjects exposed to risk factors associated with the occurrence of atherosclerotic disease the ankle-brachial index can be used as a test to identify those who are most vulnerable [26]. It is our conclusion that the cardiovascular risk varies widely between diabetic men with without PAD

While blood flow impairment in PAD not associated with diabetes is usually caused by lesions in the major leg arteries, it is in many patients with diabetes caused by obstructions in arteriolae and capillaries i.e. small vessel disease [27]. Patients with isolated small vessel disease have a normal ankle-brachial pressure index. It remains to be evaluated whether these patients similarly are exposed to an increased cardiovascular risk. The absence of a significantly increased cardiovascular risk among men with diabetes whose pressure index was above 0.9 should be viewed with caution with regard to the likelihood of beta error, but does not support this assumption.

Contrary to what might have been expected from clinical studies of diabetes and PAD [20] there were no findings of clearly abnormally high ankle-brachial indices indicative of medial sclerosis or calcification. With respect to the association with diabetic neuropathy one might consider the possibility of such changes being more characteristic of later stage of disease. Follow up studies indicate that these patients are exposed to an increased risk of amputation [28]. Whether it similarly is a marker of an increased risk of myocardial infarction and stroke remains to be evaluated.

The cardiovascular risk and the magnitude of PAD prevalence should be viewed against the high degree of exposure to smoking and hypertension in this cohort. This is unlikely to be a result of selection – 85% of the invited random sample of men born in 1914 participated in the study – but reflects the pattern of exposure in this age cohort of men. In terms of risk factor exposure, men with diabetes and low ankle-brachial index deviated from those who had a normal index in number of ways that could contribute to the occurrence of PAD. The nature of the present study does not allow any evaluation of relationship between degree of glycaemic control and severity of leg artery disease.

Some methodological issues need to be addressed. Change in exposure is an inborn problem in long-term cohort studies [29]. We have no information on how many of those with hyperglycemia that developed symptoms of diabetes during the follow-up period. Neither do we know to what extent patients with diabetes were appropriately treated with regard to glycaemic control. Participants without symptoms of leg artery disease were not informed about the results from the ankle-brachial pressure recording. The cut-off point for plasma glucose indicating diabetes was at the time for the baseline examination, i.e. 1982-83, far above 6.1 mmol/L and very few of those with values above 6.1 mmol/L were therefore recommended to see their physician for further evaluation of their blood glucose level. The incidence of cardiovascular events is based on record linkage with regional and national registers with documented completeness and validity. None of the participants was lost for follow up.

Almost one third of the men with diabetes in this population bases cohort had asymptomatic leg artery disease. It is our conclusion from this study that a blood glucose value above 6.1 mmol/L even in the absence of symptoms indicating diabetes is associated by an increased prevalence of asymptomatic leg artery disease and furthermore that cardiovascular vulnerability in diabetes patients can be assessed with measurements of the systolic ankle-brachial pressure index.

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Table 1.

Distribution of ankle-brachial indices and prevalence of intermittent claudication and PAD in relation to diabetes at 68 years of age.

Diabetes at 68 years of age	N	Intermittent claudication at 68 years of age	Ankle-brachial index (ABI) measurements at 68 years of age				
			Distribution of ABI		Prevalence of ABI<0.9		Prevalence of ABI>1.3 In either leg
			Best leg	Worst leg	In either leg	In both legs	
		N (%)	Mean (95% CI)	Mean (95% CI)	N (%)	N (%)	N (%)
No	426	16 (4%)*)	1.08 (1.07-1.09)*)	1.01 (1.00-1.02)*)	52 (12%)*)	16 (4%)*)	9 (2%)*)
Yes	48	1 (2%)*)	1.03 (0.99-1.08)*)	0.95 (0.89-1.01)*)	14 (29%)*)	8 (17%)*)	1 (2%)*)
Hyperglycemia only	*28*	*0 (0%)*	*1.05 (1.00-1.11)*	*0.97 (0.91-1.04)*	*7 (25%)*	*3 (11%)*	*0 (0%)*
History of diabetes	*20*	*1 (5%)*	*1.01 (0.91-1.11)*	*0.92 (0.81-1.02)*	*7 (35%)*	*5 (25%)*	*1 (5%)*
		*) p=0.471	*) p=0.025	*) p=0.003	*) p=0.003	*) p=0.001	*) p=0.731

Table 2.

Cardiovascular risk factors in relation to diabetes and PAD at 68 years of age.

Diabetes and PAD at 68 years of age		N	Cardiovascular risk factors at 68 years of age							
			Smoking habits			Blood pressure (mm Hg)		Hypertension	Cholesterol (mmol/L)	Triglycerides (mmol/L)
Diabetes	PAD		Current N (%)	Ex N (%)	Never N (%)	Systolic Mean (95% CI)	Diastolic Mean (95% CI)	(%)	Mean (95% CI)	Mean (95% CI)
Yes	Yes	14	5 (36%)	8 (57%)	1 (7%)	164 (153-176)	90 (85- 96)	11/11 (100%)	6.5 (5.6-7.4)	3.14 (1.54-4.74)
Yes	No	34	6 (18%)	23 (68%)	5 (15%)	158 (151-165)	96 (91-100)	27/32 (84%)	5.9 (5.4-6.3)	2.01 (1.47-2.54)
No	Yes	52	20 (39%)	26 (50%)	6 (11%)	158 (152-164)	95 (92- 98)	39/48 (81%)	6.1 (5.8-6.3)	1.61 (1.40-1.82)
No	No	374	135 (36%)	163 (44%)	75 (20%)	152 (150-155)	92 (91- 93)	206/347 (59%)	6.0 (5.9-6.1)	1.42 (1.36-1.48)
				p=0.096		p=0.023	p=0.068	p<0.001	p=0.297	p<0.001

Table 3.

Cardiac event rate, total and cardiovascular (CV) mortality rates in relation to diabetes and PAD at 68 years of age.

Diabetes and PAD at 68 years of age		N	Cardiac event rate							Mortality rates												
			Follow up (years)	Events		Events per 1000 person years	p-value			Follow up (years)	All cause mortality						CV mortality					
Diabetes	PAD			N	%						Deaths N	%	Deaths /1000 person years	p-value			Deaths N	%	Deaths /1000 person years	p-value		
Yes	Yes	14	98.1	10	71%	102.0	<0.001	0.026	0.005	122.1	10	71%	81.9	0.011	0.602	0.591	7	50%	57.3	<0.001	0.778	0.183
Yes	No	34	282.2	8	24%	28.4	0.469	0.379	*)	286.6	22	65%	76.8	<0.001	0.591	*)	9	27%	31.4	0.065	0.141	*)
No	Yes	52	403.2	16	31%	39.7	0.018	*)		423.6	41	79%	96.8	<0.001	*)		25	48%	59.0	<0.001	*)	
No	No	374	3933.4	90	24%	22.9	*)			4211.5	160	43%	38.0	*)			83	22%	19.7	*)		

* reference category

Table 4.

Cox' regression analysis of cardiac event rates and all cause mortality rates in relation to diabetes, PAD and risk factors for atherosclerosis in 68-year-old men.

Risk factor		Cardiac event rate R.R. (95%C.I.)	All cause mortality rate R.R. (95%C.I.)	Cardiovascular mortality rate R.R. (95% C.I.)
Diabetes	*(yes vs. no)*	1.6 (0.9 – 2.9)	1.9 (1.2 – 2.8)	1.5 (0.8 – 2.8)
PAD	*(yes vs. no)*	1.8 (1.1 – 3.0)	2.0 (1.4 – 2.9)	2.3 (1.5 – 3.7)
Smoking	*(ex vs. never)*	1.7 (1.0 – 3.1)	1.4 (1.0 – 2.2)	1.7 (0.9 – 3.1)
	(current vs. never)	1.9 (1.0 – 3.5)	2.0 (1.3 – 3.0)	2.3 (1.2 – 4.2)
Hypertension	*(yes vs. no)*	1.5 (1.0 – 2.3)	1.7 (1.2 – 2.3)	2.1 (1.3 – 3.3)
Blood cholesterol	*(per mmol/L)*	1.1 (0.9 – 1.4)	1.0 (0.8 – 1.1)	1.1 (0.9 – 1.3)
Body mass index	*(per kg/m^2)*	1.0 (1.0 – 1.1)	1.0 (0.9 – 1.0)	1.0 (1.0 – 1.1)

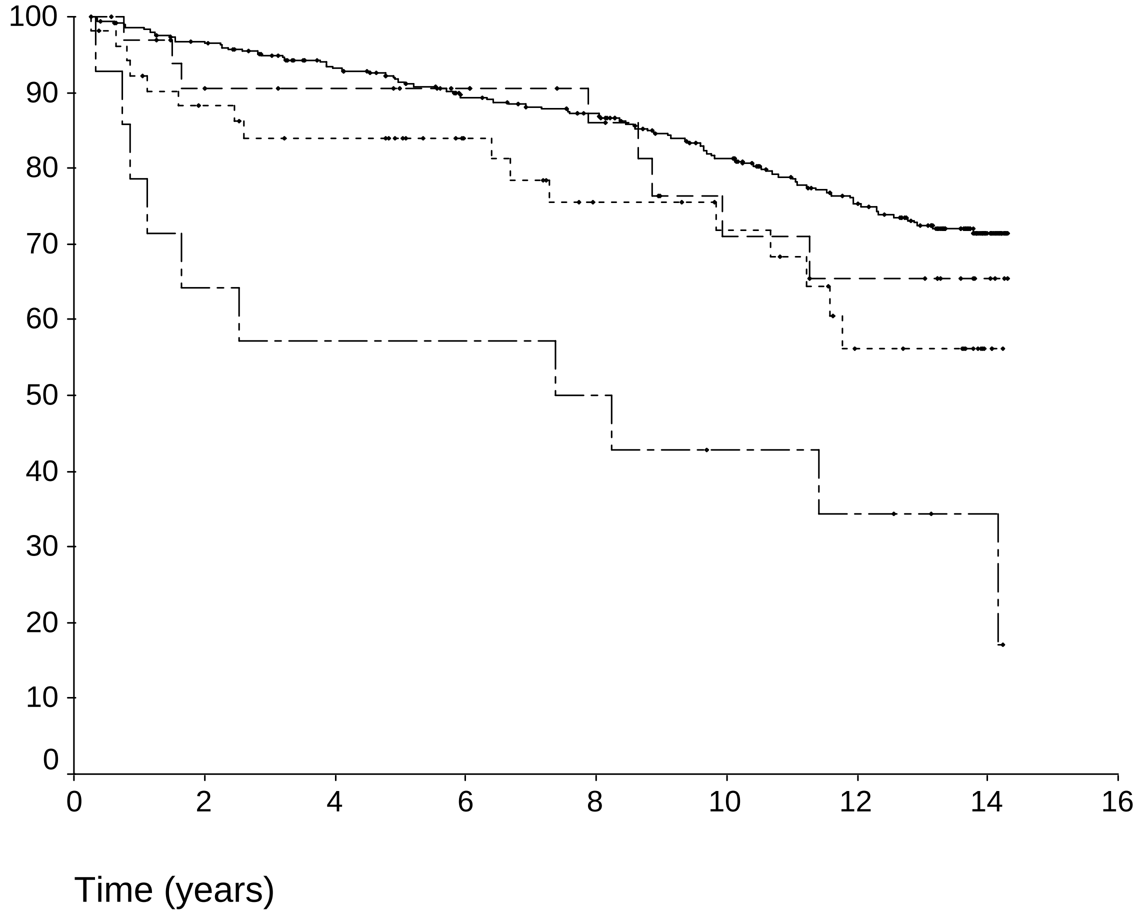


Fig 1.

Cardiac event-free survival rate during 16-year follow up in the (a) absence of both diabetes and PAD (solid line); (b) presence of PAD and absence of diabetes (dotted line); (c) absence of PAD and presence of diabetes (dashed line); and (d) presence of both PAD and diabetes (dashed-dotted line) at 68 years of age.

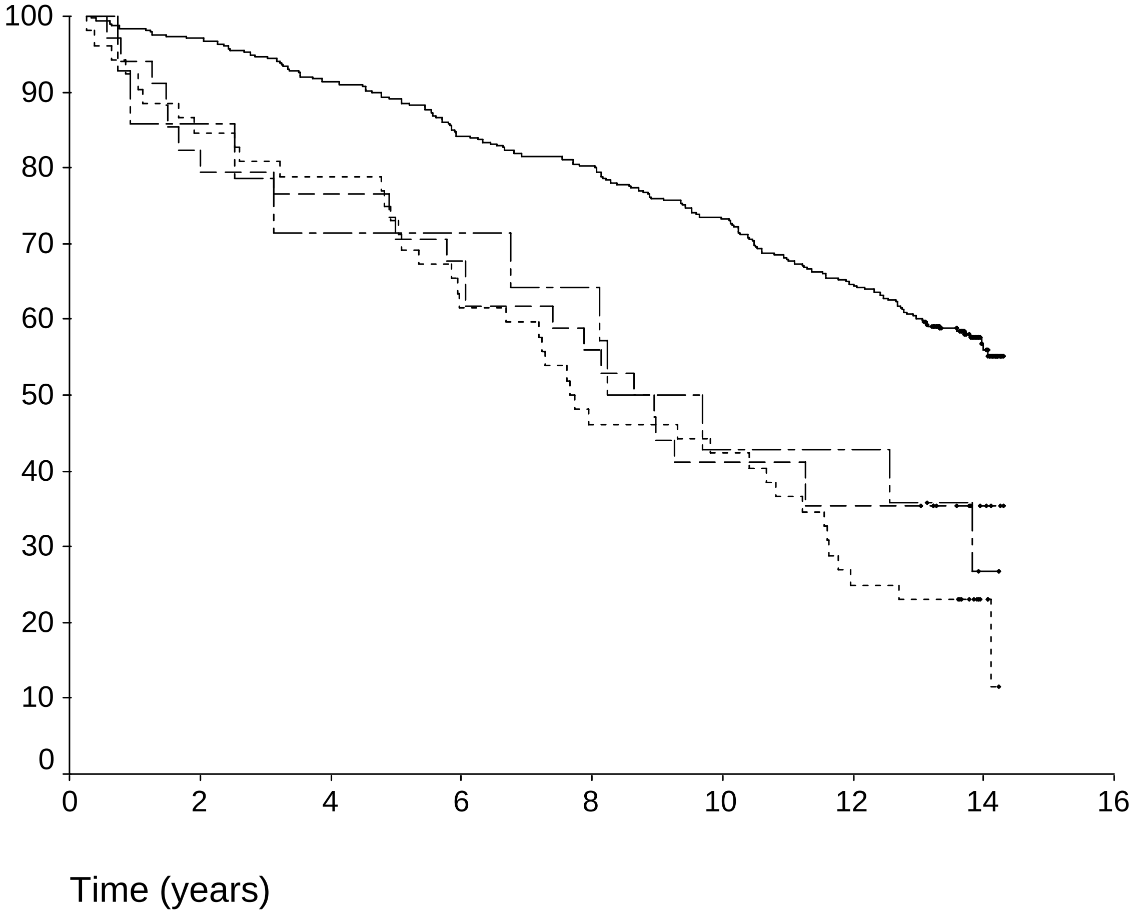
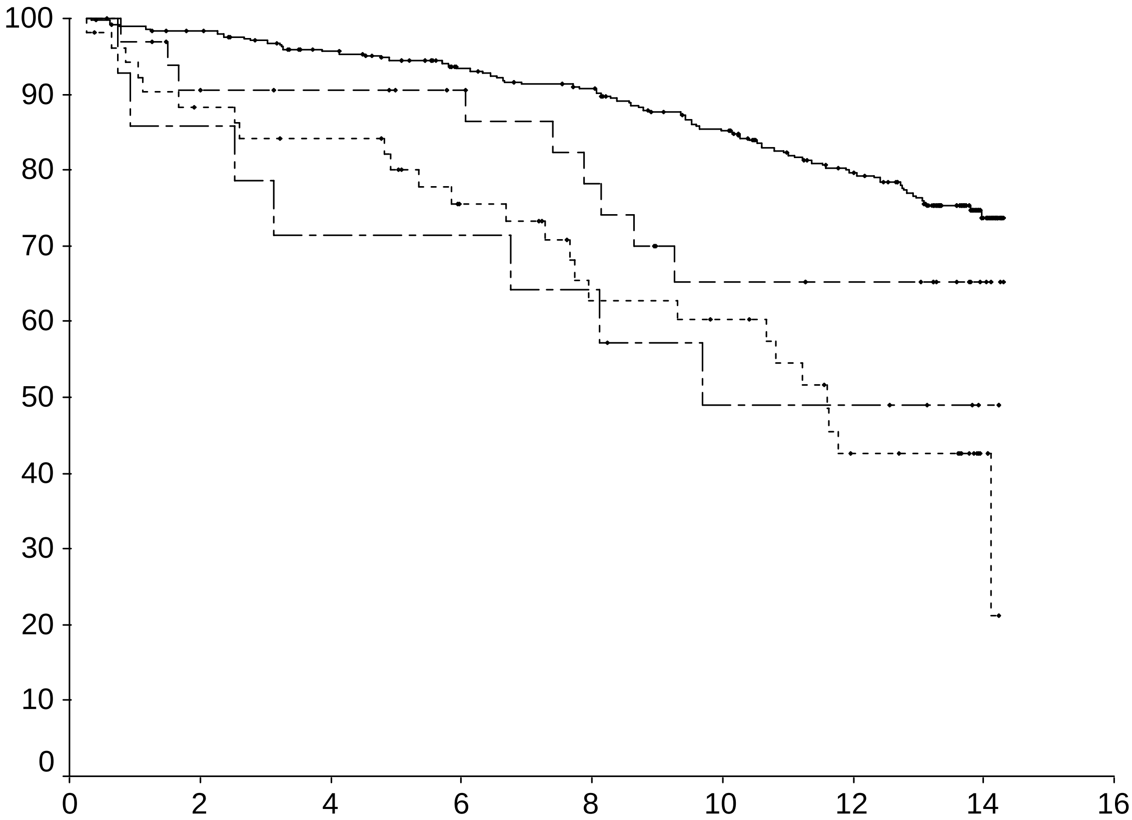


Fig 2.

Survival rate during 16-year follow up in the (a) absence of both diabetes and PAD (solid line); (b) presence of PAD and absence of diabetes (dotted line); (c) absence of PAD and presence of diabetes (dashed line); and (d) presence of both PAD and diabetes (dashed-dotted line) at 68 years of age.



(Time (years))

Fig 3.

Cardiovascular death-free survival rate during 16-year follow up in the (a) absence of both diabetes and PAD (solid line); (b) presence of PAD and absence of diabetes (dotted line); (c) absence of PAD and presence of diabetes (dashed line); and (d) presence of both PAD and diabetes (dashed-dotted line) at 68 years of age.