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# Arteriosclerosis, Thrombosis, and Vascular Biology

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Agnes Jager, Piet J. Kostense, Henricus G. Ruhé, Robert J. Heine, Giel Nijpels,  
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# Microalbuminuria and Peripheral Arterial Disease Are Independent Predictors of Cardiovascular and All-Cause Mortality, Especially Among Hypertensive Subjects

## Five-year Follow-up of the Hoorn Study

Agnes Jager, Piet J. Kostense, Henricus G. Ruhé, Robert J. Heine, Giel Nijpels, Jacqueline M. Dekker, Lex M. Bouter, Coen D.A. Stehouwer

**Abstract**—Microalbuminuria (MA) is associated with increased cardiovascular and all-cause mortality. It has been proposed that MA reflects generalized atherosclerosis and may thus predict mortality. To investigate this hypothesis, we studied the associations between, on the one hand, MA and peripheral arterial disease (PAD), a generally accepted marker of generalized atherosclerosis, and, on the other hand, cardiovascular and all-cause mortality in an age-, sex-, and glucose tolerance-stratified sample (n=631) of a population-based cohort aged 50 to 75 years followed prospectively for 5 years. At baseline, the albumin-to-creatinine ratio (ACR) was measured in an overnight spot urine sample; MA was defined as ACR >2.0 mg/mmol. PAD was defined as an ankle-brachial pressure index below 0.90 and/or a history of a peripheral arterial bypass or amputation. After 5 years of follow-up, 58 subjects had died (24 of cardiovascular causes). Both MA and PAD were associated with a 4-fold increase in cardiovascular mortality. After adjusting for age, sex, diabetes mellitus, hypertension, levels of total and HDL-cholesterol and triglyceride, body mass index, smoking habits, and preexistent ischemic heart disease, the relative risks (RR) (95% confidence intervals) were 3.2 (1.3 to 8.1) for MA and 2.4 (0.9 to 6.1) for PAD. When both MA and PAD were included in the multivariate analysis, the RRs were 2.9 (1.1 to 7.3) for MA and 2.0 (0.7 to 5.7) for PAD. MA and PAD were both associated with an about 2-fold increase in all-cause mortality. The RRs of all-cause mortality associated with MA and PAD were about 4 times higher among hypertensive than among normotensive subjects. We conclude that both MA and PAD are associated with an increased risk of cardiovascular mortality. MA and PAD are mutually independent risk indicators. The associations of MA and PAD with all-cause mortality are somewhat weaker. They are more pronounced in the presence of hypertension than in its absence. These data suggest that MA affects mortality risk through a mechanism different from generalized atherosclerosis. (*Arterioscler Thromb Vasc Biol.* 1999;19:617-624.)

**Key Words:** microalbuminuria ■ peripheral arterial disease ■ mortality ■ noninsulin dependent diabetes mellitus ■ hypertension

The estimation of individual cardiovascular risk over and above the assessment of classic risk factors, such as age, hypercholesterolemia, and hypertension, is an important prerequisite for focusing preventive measures. It has been suggested that the presence of microalbuminuria (MA) and peripheral arterial disease (PAD) can identify subjects at especially high risk.<sup>1-8</sup>

It is thought that the excess risk associated with MA and PAD cannot be attributed solely to an increased prevalence of conventional risk factors, such as hypertension, smoking, and noninsulin-dependent diabetes mellitus.<sup>4,8-13</sup> Current hypotheses aiming to explain the association of MA and PAD with incident cardiovascular disease have focused on the possibil-

ity that both MA and PAD may be markers of generalized atherosclerosis.<sup>14-17</sup> The evidence for this is stronger for PAD than for MA. An alternative hypothesis is that MA is a marker of a generalized vascular, possibly endothelial, dysfunction that is distinct from atherosclerosis.<sup>18</sup>

To investigate these issues, we examined, in a prospective cohort study, the relations between MA and PAD on the one hand and cardiovascular and all-cause mortality on the other. We reasoned that, if MA affects risk of mortality through generalized atherosclerosis, the association of MA with mortality would be weakened by adjusting for the presence of PAD, which, as a marker of generalized atherosclerosis, would be an intermediate in the causal pathway linking MA

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with mortality. If, on the other hand, MA and PAD confer mutually independent excess risks of mortality, this would argue against the idea that MA affects risk through generalized atherosclerosis. In addition, such a finding would have important consequences for individual risk assessment because both measurements would be useful for estimation of cardiovascular risk.

## Subjects and Methods

The study population consisted of an age-, sex-, and glucose tolerance-stratified sample of the Hoorn study, a population-based cohort study of disturbances of glucose tolerance in a white population aged 50 to 75 years conducted from October 1989 until February 1992, as described previously.<sup>19</sup> In brief, 2484 white subjects (71% of those invited) participated. All subjects, except previously diagnosed diabetic subjects treated with oral glucose-lowering agents or insulin, underwent an oral glucose tolerance test (OGTT) according to the WHO guidelines.<sup>20</sup> Subjects with a 2-hour post-load glucose  $\geq 7.5$  mmol/L, all subjects with noninsulin-dependent diabetes mellitus (NIDDM), and a random sample of subjects with a 2-hour post-load glucose  $< 7.5$  mmol/L stratified by age and sex were invited within 4 weeks for a second visit to investigate glucose intolerance-related complications (709 invited, of whom 631 (89%) participated). These subjects underwent a second OGTT (except those who already used blood glucose-lowering agents;  $n=67$ ). On the basis of the 2 OGTTs, glucose tolerance was divided into 3 categories<sup>20</sup>: normal glucose tolerance (NGT;  $n=288$ ), impaired glucose tolerance (IGT;  $n=170$ ), and NIDDM ( $n=173$ ).

We chose this procedure for reasons of efficiency, because we wished to study a smaller, but still random, sample in more detail. Subjects with NGT, IGT, or NIDDM in the present study population were thus a random sample of all subjects with NGT, IGT, or NIDDM in the initial cohort. The prevalences of NGT, IGT, and NIDDM, and of associated variables, such as microalbuminuria, in the present study population are not the same as in the initial cohort, but because the exact sampling procedure is known, we can back-calculate the prevalences in the initial cohort ( $n=2484$ ) from those in the second sample ( $n=631$ ), as previously described in detail.<sup>19,21</sup>

From these subjects, we obtained an ankle-brachial blood pressure index (ABPI) ( $n=631$ ), a resting ECG (ECG) ( $n=625$ ), and an early-morning, first-voided spot urine sample to measure the urinary albumin-to-creatinine ratio (ACR) ( $n=607$ ). Urinary albumin was measured by rate nephelometry (Array Protein System, Beckman) with a threshold of 6.2 mg/L and intra- and interassay coefficients of variation of  $\leq 5\%$  and  $\leq 8\%$ , respectively.<sup>22</sup> Urinary creatinine was measured by a modified Jaffé method. Subjects were classified as having PAD when they had an ABPI  $< 0.9$  and/or when they had undergone a peripheral arterial bypass or amputation. (A reproducibility test of the Doppler-assisted systolic blood pressure measurements to obtain the ABPI was performed in a random sample ( $n=41$ ), within 6 to 9 months after the first measurement.) The agreement between the 2 examinations for the criteria of ABPI  $< 0.90$ , expressed as kappa, was 0.73 [95% confidence interval (CI) 0.49 to 0.98] indicating good agreement. An ABPI  $> 1.50$  (a level possibly indicating medial arterial calcification<sup>23</sup>) could not be detected in any of the subjects. Subjects were classified as having preexistent ischemic heart disease (IHD) when they had an ECG with a Minnesota code 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 and/or had undergone coronary bypass surgery or angioplasty; as having cerebrovascular disease when they had evidence of a past transient ischemic attack or stroke according to the WHO cardiovascular questionnaire<sup>24</sup>; and as having microalbuminuria (MA) when they had a urinary albumin concentration greater than the assay threshold (6.2 mg/L;  $n=336$ ) and an ACR  $> 2.0$  mg/mmol. (An overnight ACR  $> 2.0$  mg/mmol has a high sensitivity to detect an albumin excretion rate  $> 30$   $\mu\text{g}/\text{min}$ <sup>25</sup>). Of all urine samples, 32 were excluded because of the use of an angiotensin-converting enzyme inhibitor. In a representative sample of 174 subjects, 2 urine collections were available and the presence of MA for these subjects was therefore based on the mean ACR of the urine collections.

Blood pressure was calculated as the mean of 4 measurements, performed on 2 different occasions, using a random-zero sphygmomanometer under standardized conditions. Hypertension was defined as diastolic pressure  $\geq 95$  mm Hg, systolic pressure  $\geq 160$  mm Hg and/or the use of antihypertensive drugs.<sup>26</sup> Data on weight, height, body mass index (BMI), smoking habits, glycated hemoglobin (HbA1c), fasting specific plasma insulin, fasting serum creatinine, total cholesterol, HDL-cholesterol, and triglyceride levels were obtained.<sup>19,21</sup> Low density lipoprotein-cholesterol was calculated by the Friedewald formula,<sup>27</sup> except when triglyceride level was  $> 4.55$  mmol/L ( $n=23$ ). The creatinine clearance was calculated from serum creatinine using the Cockcroft and Gault formula.<sup>28</sup> Normal renal function and mild and moderate renal failure were defined as creatinine clearance  $> 80$ , 51 to 80, and  $< 51$  mL/min, respectively. (There were no subjects with creatinine clearance  $< 24$  mL/min.) Smoking habits were obtained from a standardized questionnaire. Current smoking was defined as currently smoking cigarettes and/or cigars.

## Follow-up Measurements

Data on the subjects' vital status on April 1, 1997 were collected from the mortality register of the municipality of Hoorn. Of 49 subjects who moved out of town, information on vital status was obtained from the new local municipalities. For each subject, we determined whether or not death had occurred in the first 5 years of follow-up. For all subjects who died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn, verified by 2 physicians and classified according to the ninth edition of the *International Classification of Diseases*. Cardiovascular mortality was defined as codes 390 to 459, cancer mortality as codes 140 to 240, and sudden death as code 798. Information on cause of death could not be obtained for 6 (10%) of the deceased subjects.

All participants gave informed consent for this study, which was approved by the local ethics committee.

## Statistical Analyses

All analyses were performed with the *Statistical Package for the Social Sciences* (SPSS). Survival during 5 years of follow-up was calculated by Kaplan-Meier curves for different groups and differences were tested by the logrank test. Predictors of 5-year cardiovascular and all-cause mortality were determined by Cox proportional hazards multiple regression analysis, in all cases—because of the stratification procedure—with adjustment for age, sex, IGT, and NIDDM. Results are described as relative risks (RRs) (hazard ratios) with 95% CIs.

Potential risk factors measured on a continuous scale were used as such in the regression models, except for HDL-cholesterol and BMI, because the association of these variables with all-cause mortality was nonlinear. Therefore, a low HDL-cholesterol was defined as a level  $< 0.9$  mmol/L<sup>29</sup> and obesity as BMI  $> 27$  kg/m<sup>2</sup> for men and  $> 26$  kg/m<sup>2</sup> for women.<sup>30</sup> Levels of fasting insulin and triglyceride were log-transformed because of a better fit of the regression model. To evaluate a possible effect-modifying role of potential risk factors, Cox regression analyses were performed with the risk factor of interest, MA (or PAD), and their product term in the model. A significant relative risk for the product term was considered as effect modification by that risk factor. To assess whether MA and PAD were independently associated with mortality, regression analyses were primarily adjusted for all risk factors that were statistically significant in initial analyses and secondarily for other potential risk factors of interest which showed no significant association in the initial analyses.

To investigate whether MA and PAD affected risk of mortality through similar pathways, regression analyses were performed that included both MA and PAD as independent variables. Two-sided probability values  $< 0.05$  were considered statistically significant.

## Results

Table 1 shows characteristics of the study population. Of all subjects with MA ( $n=66$ ), 23% had PAD, whereas among all subjects without MA ( $n=568$ ), 21% had MA. After 5 years of

**TABLE 1. Baseline Characteristics of Survivors and Nonsurvivors after 5 Years of Follow-up**

Characteristic	Survivors (n=573)	Nonsurvivors	
		Deaths from All-Causes (n=58)	Cardiovascular Deaths (n=24)
Age, y	64 (7)	69 (6)	69 (7)
Gender, % male	48	55	54
Body mass index, kg/m <sup>2</sup>	27.1 (3.9)	28.5 (4.3)	28.3 (3.9)
Current smokers, %	27	39	39
Diastolic blood pressure, mm Hg	83 (10)	81 (12)	80 (12)
Systolic blood pressure, mm Hg	139 (19)	142 (23)	141 (24)
Hypertension, %	37	59	75
Antihypertensive drug treatment, %	26	52	71
Total cholesterol, mmol/L	6.6 (1.2)	6.6 (1.1)	6.8 (1.1)
LDL cholesterol, mmol/L	4.6 (1.1)	4.4 (0.8)	4.6 (0.9)
HDL cholesterol, mmol/L	1.29 (0.36)	1.18 (0.39)	1.1 (0.4)
Triglycerides, mmol/L	1.5 (0.8–3.0)*	2.1 (1.0–4.2)*	2.2 (1.1–4.4)*
NIDDM, %	24	57	67
Impaired glucose tolerance, %	28	19	8
HbA1c, % of hemoglobin	5.8 (1.2)	6.8 (2.0)	6.8 (1.3)
Fasting insulin, pmol/L	83 (48–162)*	98 (53–189)*	95 (45–183)*
Serum creatinine, μmol/L	91 (16)	104 (36)	117 (47)
Creatinine clearance, mL/min†	79 (18)	72 (21)	66 (24)
Mild renal failure, %‡	52	52	58
Moderate renal failure, %§	2	14	21
Preexistent IHD, %	13	32	42
Stroke, %¶	5	2	0
Peripheral arterial disease, %#	9	28	42
Microalbuminuria, %**	10	26	48

Data are mean (standard deviation) unless otherwise indicated. LDL indicates low density lipoprotein; HDL, high density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; HbA1c, glycated hemoglobin; IHD, ischemic heart disease.

\*Median (10 to 90th percentiles).

†Calculated from serum creatinine using the Cockcroft and Gault formula.

‡Creatinine clearance, 51 to 80 mL/min.

§Creatinine clearance, 24 to 50 mL/min.

||Minnesota code, 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on the ECG, coronary bypass operation, or angioplasty.

¶Stroke or transient ischemic attack according to the WHO questionnaire.

#Ankle-brachial blood pressure index <0.90 or peripheral arterial bypass operation or amputation.

\*\*Albumin-to-creatinine ratio >2.0 mg/mmol.

follow-up, 58 of the 631 subjects had died, of whom 24 (41%) died of cardiovascular disease. Among NGT subjects, 22% (2/9) of those with MA died and 18% (4/22) of those with PAD; for IGT subjects, the rates were 7% (1/14) and 6% (1/17), respectively; and for NIDDM subjects, 30% (10/33) and 37% (11/30), respectively.

**Cardiovascular Mortality**

Age, hypertension, a low HDL-cholesterol level, triglyceride level, NIDDM, and preexistent IHD were significantly associated with cardiovascular mortality after adjusting for age, gender, IGT, and NIDDM (Table 2). In the entire group, MA and PAD were both associated with about 4-fold increased risk of cardiovascular death after adjusting for age, gender, IGT, and NIDDM (Table 3).

Figure 1a and 1b). After further adjustment for hypertension, low level of HDL-cholesterol, triglyceride level, and preexistent IHD, the RRs associated with MA and PAD were 3.3 and 3.6, respectively (Table 3). After additional adjustment for current smoking, obesity, and total cholesterol level, the RR of MA was similar and the RR of PAD decreased to 2.4 (Table 3; models 1 to 3).

Further analyses were aimed at investigating whether cardiovascular mortality risks associated with MA and PAD were independent of each other. Mutual adjustment of MA and PAD did not materially change the RR for cardiovascular mortality, even after adjusting for other risk factors (Table 3, models 4 to 6). The risk of cardiovascular mortality showed around 13-fold (2.98×4.31; Table 3) increase if both MA and PAD were present compared with absent (Figure 2).



**TABLE 2. Relative Risk of 5-year Cardiovascular and All-Cause Mortality Associated with Potential Risk Factors**

Risk Factor	RR (95% CI)*	
	Cardiovascular Mortality	All-Cause Mortality
Age, y	1.66 (1.15–2.39)†	1.63 (1.29–2.06)†
Gender, % male	1.62 (0.72–3.65)	1.73 (1.03–2.92)
Body mass index, kg/m <sup>2</sup>	1.61 (0.61–4.21)‡	1.39 (0.76–2.51)‡
Current smokers, %	2.35 (0.99–5.54)	2.21 (1.28–3.82)
Hypertension, %	3.36 (1.29–8.76)	1.56 (0.91–2.69)
Total cholesterol, mmol/L	1.30 (0.95–1.79)	1.14 (0.92–1.40)
LDL cholesterol, mmol/L	1.31 (0.90–1.90)	1.09 (0.85–1.40)
HDL cholesterol, mmol/L	4.00 (1.66–9.65)§	2.38 (1.28–4.43)§
Triglycerides, mmol/L	2.73 (1.28–5.80)	1.94 (1.17–3.21)
NIDDM, %	4.19 (1.63–10.76)	3.72 (1.99–6.99)
Impaired glucose tolerance, %	0.50 (0.10–2.47)	1.21 (0.55–2.67)
HbA1c, % of hemoglobin	1.08 (0.84–1.38)	1.15 (0.98–1.34)
Fasting insulin, pmol/L	0.88 (0.35–2.26)	1.24 (0.68–2.24)
Preexistent IHD, %¶	3.14 (1.36–7.24)	2.05 (1.16–3.64)
Stroke, %#	not applicable	0.35 (0.05–2.51)

LDL indicates low density lipoprotein; HDL, high density lipoprotein; HbA1c, glycated hemoglobin; IHD, ischemic heart disease.

\*Relative risk (95% CI) by Cox regression analyses of 5-year cardiovascular and all-cause mortality of continuous or dichotomous variables after adjusting for age, gender, impaired glucose tolerance, and NIDDM, except when this was the variable under consideration.

†Per 5-year increase, with 50 to 55 years as reference.

‡ $>vs\leq 27$  kg/m<sup>2</sup> for men and  $>vs\leq 26$  kg/m<sup>2</sup> for women.

§ $<vs\geq 0.9$  mmol/L.

||Log-transformed.

¶Minnesota code, 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on the ECG, coronary bypass operation, or angioplasty.

#Stroke or transient ischemic attack according to the WHO questionnaire.

Age, obesity, current smoking, hypertension, levels of total and HDL-cholesterol and triglyceride, NIDDM, and preexistent IHD showed no significant interaction with MA or PAD (all  $P>0.2$ , data not shown). Subgroup analyses in nondiabetic and diabetic subjects separately showed higher RRs associated with MA and PAD among diabetic compared with nondiabetic subjects (Table 3). In a forward stepwise regression model, including all variables shown in Table 2, age, current smoking, low level of HDL-cholesterol, NIDDM, preexistent IHD, and MA were significantly associated with cardiovascular mortality (Table 4).

Four subjects died of sudden death. When sudden death was enclosed in the definition, the RRs of cardiovascular mortality were 3.66 (1.59 to 8.39) for MA and 3.52 (1.52 to 7.72) for PAD in analyses similar to model 1 in Table 3.

Inclusion of serum creatinine or creatinine clearance (Ccr) calculated from the Cockcroft and Gault formula<sup>28</sup> in the analyses above slightly decreased the RRs for MA and PAD. Further analyses showed that this was entirely due to subjects with moderate renal failure (Ccr $<51$  mL/min;  $n=22$ ); after exclusion of these subjects, the respective RRs were similar to those in the initial analyses (data not shown).

### All-Cause mortality

MA and PAD were both associated with an about 2-fold increased risk of all-cause mortality after adjusting for age,

gender, IGT, and NIDDM (Table 5). Further adjustment for current smoking, low level of HDL-cholesterol, level of triglyceride, and preexistent IHD slightly decreased the RRs associated with MA and PAD (to 1.85 and 1.64, respectively). These RRs were similar after further adjustment for obesity, hypertension, and total cholesterol level (Table 5). Additional analyses indicated that the risk estimates for MA and PAD were markedly (about 5- and 4-fold) higher in the presence of hypertension than in its absence ( $P$  for interaction=0.15 and 0.08, respectively; Table 5). The RR of mortality associated with MA among hypertensive nondiabetic subjects ( $n=150$ ) was 2.63 (0.64 to 10.83) in an analysis analogous to model 1 in Table 5. Age, obesity, current smoking, level of total and HDL-cholesterol and triglyceride, NIDDM, and preexisting IHD showed no interaction with MA or PAD with regard to risk of mortality (data not shown).

The RRs associated with MA and PAD, after adjusting for age, gender, IGT, and NIDDM, were not importantly affected by mutual adjustment; both remained about 2.0 (data not shown). After further adjustment for current smoking, low level of HDL-cholesterol, triglyceride level, and preexistent IHD, the RRs (95% CIs) were 1.73 (0.89 to 3.38) for MA and 1.46 (0.73 to 2.91) for PAD. These RRs were similar after further adjustment for obesity, hypertension, and total cholesterol level (data not shown).

Inclusion of serum creatinine or creatinine clearance (Ccr) calculated from the Cockcroft and Gault formula<sup>28</sup> in the analyses above slightly decreased the RRs for MA and PAD. Further analyses showed that this was entirely due to subjects with moderate renal failure (Ccr $<51$  mL/min;  $n=22$ ); after exclusion of these subjects, the respective RRs were similar to those in the initial analyses (data not shown).

Twenty-six subjects (45%) died of cancer. Neither MA nor PAD were significantly associated with cancer mortality [RRs 0.96 (0.28 to 3.27) and 1.05 (0.36 to 3.07), respectively].

Finally, we examined whether changing the definitions of PAD and MA would affect our results. Lowering the ABPI criterion from 0.9 to 0.8 or 0.7 did not materially affect the results (data not shown). MA defined as ACR  $>3.0$  mg/mmol somewhat increased the RRs among diabetic subjects: for example, the RR for all-cause mortality adjusted for age and sex was 3.01 (1.34 to 6.75) versus 2.22 (1.01 to 4.87) when MA was defined as ACR  $>2.0$  mg/mmol. Other risk estimates showed only minor changes (data not shown). Excluding subjects with macroalbuminuria (ACR  $>30$  mg/mmol;  $n=6$ ) gave similar results (data not shown). When MA was defined on the basis of 1 overnight urine sample in all subjects, the results were also similar (data not shown). Other definitions of a low HDL-cholesterol and obesity also gave similar results.

### Discussion

This study shows that both MA and PAD are strongly associated with 5-year risk of cardiovascular death. Mutual adjustment did not markedly affect the relative risk estimates, which argues against the idea that MA is a marker of generalized atherosclerosis. Both MA and PAD are useful measurements in estimating individual cardiovascular risk, respectively, in the presence of IHD. In addition, our data

**TABLE 3. Relative Risk of 5-Year Cardiovascular Mortality Associated with Presence of MA or PAD after Adjusting for Potential Confounding Risk Factors**

Model	Added Variables	RR (95% CI)*					
		MA (ACR >2.0 mg/mmol)			PAD (ABPI <0.90)†		
		Nondiabetic Subjects (n=458)	Diabetic Subjects (n=173)	All Subjects (n=631)	Nondiabetic Subjects (n=458)	Diabetic Subjects (n=173)	All Subjects (n=631)
1	Age, sex, IGT, NIDDM	1.85 (0.21–16.61)	5.70 (2.00–16.26)	4.58 (1.91–11.00)	2.24 (0.42–11.79)	4.35 (1.57–12.03)	3.75 (1.62–8.68)
2	Model 1 and hypertension, low HDL-cholesterol level,‡ triglyceride level,§ and preexistent IHD	2.99 (0.23–40.00)	5.60 (1.81–17.31)	3.33 (1.37–8.09)	2.80 (0.48–16.34)	4.21 (1.41–12.59)	3.58 (1.50–8.58)
3	Model 2 and obesity,¶ current smoking and cholesterol level	1.38 (0.06–34.46)	5.68 (1.74–18.52)	3.22 (1.28–8.06)	3.13 (0.48–20.35)	2.56 (0.74–8.83)	2.36 (0.92–6.09)
4	Model 1 and MA or PAD#	1.84 (0.20–16.52)	5.50 (1.91–15.84)	4.31 (1.79–10.36)	1.58 (0.17–14.85)	3.34 (1.17–9.56)	2.98 (1.20–7.40)
5	Model 2 and MA or PAD#	2.30 (0.15–34.56)	5.23 (1.66–16.48)	2.87 (1.15–7.16)	2.84 (0.21–37.81)	3.17 (0.95–10.62)	2.74 (1.02–7.39)
6	Model 3 and MA or PAD#	0.99 (0.04–26.57)	5.20 (1.57–12.03)	2.86 (1.11–7.34)	5.93 (0.37–96.19)	1.85 (0.48–7.06)	1.99 (0.69–5.74)

\*Relative risk (95% confidence interval) of 5-year cardiovascular mortality analyzed by Cox multiple regression analyses. Model 1, stratification variables; model 2, as model 1, plus all risk factors significantly associated with cardiovascular mortality (shown in Table 2, left column); model 3, as model 2, plus major risk factors that were nonsignificant (Table 2).

†And/or peripheral arterial bypass or amputation.

‡HDL-cholesterol level, <0.9 mmol/L.

§Log-transformed triglyceride levels.

||Minnesota code 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on ECG, coronary bypass operation, or angioplasty.

¶Body mass index >vs≤27.0 kg/m<sup>2</sup> for men and >vs≤26.0 kg/m<sup>2</sup> for women.

#With the variable added which was not in the model already.

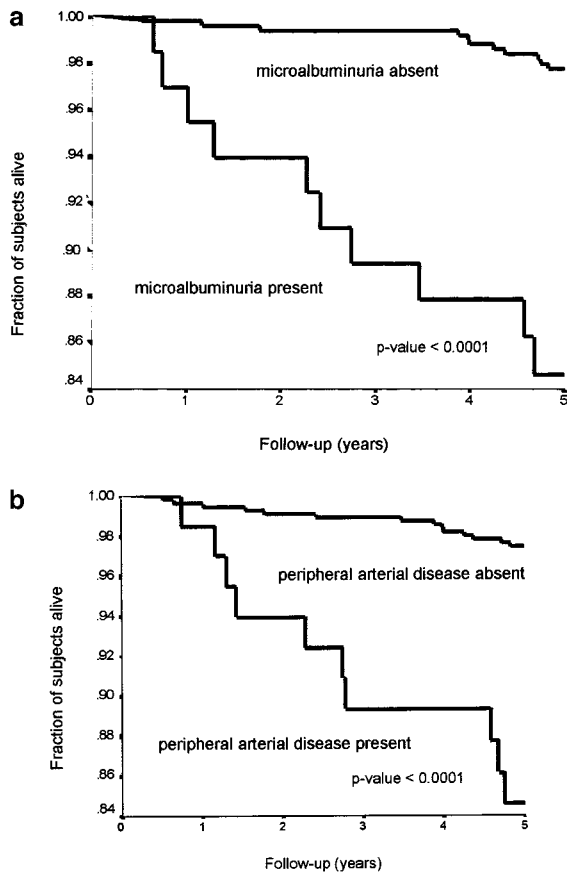
suggest that MA and PAD are particularly strong risk indicators among subjects with hypertension.

Our study confirms that MA and PAD are strong indicators of an increased risk of cardiovascular mortality, independent of the presence of important cardiovascular risk factors such as hypercholesterolemia, smoking, and hypertension.<sup>1–8</sup> PAD is thought to be a marker of generalized atherosclerotic disease, which is a plausible explanation for the increased risk of mortality in subjects with PAD.<sup>14–16</sup> In contrast, it is unclear why MA is associated with an increased mortality risk.<sup>1,2,4,6,8</sup> It has been suggested that MA, like PAD, is a marker of generalized atherosclerosis.<sup>31–36</sup> Two findings of the present study argue against this idea. First, only about 25% of subjects with MA also had PAD and vice versa. Second, the increased risk of mortality conferred by the presence of MA was not materially lowered by including PAD in the multivariate regression model, which would have been expected if MA affected risk through generalized atherosclerosis.

How, then, can the association between MA and mortality be explained? First, MA is associated with increased levels of von Willebrand factor, thrombomodulin, fibrinogen, thrombin–antithrombin III complexes and impaired fibrinolytic activity and may thus be a marker of a prothrombotic state.<sup>37–39</sup> Second, MA may reflect a specific type of endothelial dysfunction from distinct from

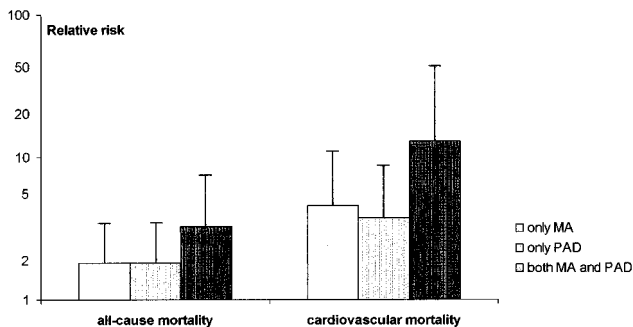
atherosclerosis per se. Finally, MA in part may be a marker of a low-grade chronic inflammatory state,<sup>41</sup> which itself is associated with an increased risk of cardiovascular disease.<sup>42,43</sup> Taken together, these data and the present study support the hypothesis that MA and PAD affect risk through different pathways. Further studies are needed to address the mechanisms by which MA increases the risk of cardiovascular disease in more detail.

We found that both MA and PAD were associated more strongly with all-cause mortality among hypertensive than among normotensive subjects (Table 5), although the confidence intervals of the risk estimates clearly do not exclude the possibility of significant associations of MA and PAD with mortality among normotensive subjects. In previous studies, the mortality risk associated with MA or PAD has usually been adjusted for the presence of hypertension<sup>1,2,4</sup> or systolic or diastolic blood pressure.<sup>3,5,8</sup> However, this does not necessarily rule out the presence of an interaction with hypertension, as suggested by our results. The explanation for these findings is not clear, but it is noteworthy that, in the same population, we found the presence of hypertension (and NIDDM) to be the strongest determinants of MA.<sup>22</sup> This, together with the present results, raises the possibility that, in the presence of hypertension, the pathogenetic backgrounds of MA and PAD and of their link with mortality are distinct from those in the absence of hypertension. These issues require



**Figure 1.** (a) Cardiovascular survival (Kaplan-Meier) according to the absence versus the presence of microalbuminuria. (b) Cardiovascular survival (Kaplan-Meier) according to the absence versus the presence of peripheral arterial disease.

MA was thus significantly associated with all-cause mortality among hypertensive subjects, which is in agreement with some,<sup>44,45</sup> but not all<sup>34</sup> previous studies, whereas other studies<sup>2,4,6,8</sup> did not specifically examine this issue. This result, however, has to be interpreted with caution, because our study was not specifically designed to answer this question and lacked information about duration and type of hypertension. Nevertheless, our data add to accumulating evidence that, among hypertensive subjects, both overt proteinuria<sup>46,47</sup> and MA<sup>44,45</sup> may be markers of a poor prognosis.



**Figure 2.** Relative risks of all-cause and cardiovascular mortality associated with microalbuminuria (MA) and/or peripheral arterial disease (PAD), after adjusting for age, gender, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus (stratification variables, see Methods).

**TABLE 4. Relative Risk of 5-Year Cardiovascular Mortality: Forward Cox Regression Analysis**

Variable	Cardiovascular Mortality RR (95% CI)*
Age, per 5-year increase	1.12 (1.03–1.21)
Current smoking	2.76 (1.07–7.10)
HDL-cholesterol, <0.9 mmol/L	4.48 (1.78–11.25)
NIDDM	3.67 (1.36–9.95)
Preexistent IHD†	3.64 (1.46–9.05)
MA‡	3.27 (1.31–8.17)

\*Relative risk (95% confidence interval) analyzed by forward Cox regression analyses with all potential risk factors (Table 2) in the model.

†Minnesota code 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on the ECG, coronary bypass operation, or angioplasty.

‡Albumin-to-creatinine ratio >2.0 mg/mmol.

The clinical implication of our findings is that both measurement of the ankle-brachial blood pressure index and of the urinary albumin excretion is useful to estimate individual risk (Tables 3 to 5). Both measurements are easy to obtain. All-cause and cardiovascular mortality risk are increased about 3-fold and 15-fold, respectively, when both PAD and MA are present, compared with when both are absent (Figure 2). It is especially noteworthy that the association of MA with cardiovascular mortality is of the same order of magnitude as those of NIDDM and preexistent ischemic heart disease (Table 4).

Our study had several limitations. In the majority of subjects, MA was estimated from 1 urine sample, which may have increased nondifferential misclassification, leading to an underestimation of the association with mortality. The study was too small to establish definitively whether MA and PAD are significantly stronger risk markers in hypertensive than in normotensive subjects. The study was also too small to investigate whether the increased mortality risk associated with MA among hypertensive subjects varied with the mode of treatment of hypertension or its duration, or with the level of blood pressure. Although we found evidence against the concept that MA is a marker of generalized atherosclerosis, we did not address alternative mechanisms linking MA to mortality. Finally, our study lacked the power to exclude with confidence the presence of interaction between glucose tolerance status and MA (or PAD) with respect to cardiovascular mortality. Both MA and PAD were in fact more strongly associated with cardiovascular mortality in diabetic than in nondiabetic subjects, although this was not significant (Table 3). However, it appears unlikely that such an interaction, if present, would affect our main conclusion, ie, that MA and PAD are mutually independent risk indicators.

In conclusion, we have shown that both MA and PAD are independently associated with cardiovascular mortality and so may affect risk through different pathways. Measurement of the urinary albumin excretion and the ankle-brachial pressure index are therefore useful to estimate individual risk (Figure 2 and Table 4). Such information is clinically useful, because it can help to individualize decisions on, for example, cholesterol- and blood pressure-lowering treatment. Furthermore, the associations of MA and PAD with mortality were more pronounced in hyper-



**TABLE 5. Relative Risk of 5-Year All-Cause Mortality Associated with the Presence of MA or PAD after Adjusting for Potential Confounding Risk Factors**

Model	Added Variables	RR (95% CI)*	
		MA (ACR >2.0 mg/mmol)	PAD (ABPI <0.90)†
All subjects (n=631)			
1	Age, sex, IGT, NIDDM	1.92 (1.01–3.64)	2.06 (1.14–3.71)
2	Model 1 and current smoking, low HDL-cholesterol level,‡ triglyceride level,§ and preexistent IHD	1.85 (0.96–3.55)	1.64 (0.87–3.06)
3	Model 2 and obesity,# hypertension and cholesterol level	1.70 (0.86–3.34)	1.50 (0.79–2.84)
Only hypertensive subjects (n=247)			
1	Age, sex, impaired glucose tolerance, non-insulin-dependent diabetes mellitus	2.48 (1.14–5.37)	2.97 (1.46–6.05)
2	Model 1 and current smoking, low HDL-cholesterol level,‡ triglyceride level,§ and preexistent ischemic heart disease	2.92 (1.31–6.49)	2.38 (1.10–5.16)
3	Model 2 and obesity,# hypertension, and cholesterol level	2.78 (1.22–6.33)	2.21 (1.00–4.87)
Only normotensive subjects (n=384)			
1	Age, sex, IGT, and NIDDM	0.44 (0.06–3.31)**	0.62 (0.14–2.65)**

\*Relative risk (95% CI) of 5-year cardiovascular mortality analyzed by Cox multiple regression analyses. Model 1, stratification variables; model 2, as model 1, plus all risk factors significantly associated with all-cause mortality (shown in Table 2, right column); model 3, as model 2, plus major risk factors that were nonsignificant (Table 2).

†And/or peripheral arterial bypass or amputation.

‡HDL cholesterol level <0.9 mmol/L.

§Log-transformed triglyceride levels.

||Minnesota code, 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on ECG, coronary bypass operation, or angioplasty.

#Body mass index >vs≤27.0 kg/m<sup>2</sup> for men and >vs≤26.0 kg/m<sup>2</sup> for women.

\*\*Further adjustment for other risk factors gave similar results.

tensive than in normotensive subjects. Further studies are needed to clarify the underlying pathophysiologic mechanism linking MA to (cardiovascular) mortality, as this may have additional therapeutic implications.

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