

# The association of microalbuminuria with mortality in patients with acute myocardial infarction. A ten-year follow-up study

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## Abstract

Our study evaluates the long-term effect of microalbuminuria on mortality among patients with acute myocardial infarction. We followed 151 patients from 1996 to 2007 to investigate if microalbuminuria is a risk factor in coronary heart disease. All patients admitted with acute myocardial infarction in 1996 were included. At baseline, we recorded urinary albumin/creatinine concentration ratio, body mass index, blood pressure, left ventricle ejection fraction by echocardiography, smoking status, medication, diabetes, age, and gender. Deaths were traced in 2007 by means of the Danish Personal Identification Register. Microalbuminuria, defined as a urinary albumin/creatinine concentration ratio above 0.65 mg/mmol, occurred in 50% of the patients and was associated with increased all-cause mortality. Thus, 68% of the patients with microalbuminuria versus 48% of the patients without microalbuminuria had died during the 10 years of follow-up ( $P=0.04$ ). The crude hazard ratio for death associated with microalbuminuria was 1.78 (CI: 1.18-2.68) ( $P=0.006$ ), whereas the gender- and age-adjusted hazard ratio was 1.71 (CI: 1.03-2.83) ( $P=0.04$ ). We concluded that microalbuminuria in hospital-

ized patients with acute myocardial infarction is prognostic for increased long-term mortality. We recommend measurement of microalbuminuria to be included as a baseline risk factor in patients with acute myocardial infarction and in future trials in patients with coronary heart disease.

## Introduction

A subclinical elevation of urinary albumin excretion, that is, microalbuminuria, has been associated with an increased risk of cardiac morbidity and mortality in reported population studies.<sup>1,5</sup> Microalbuminuria was first introduced as a risk factor for chronic renal failure among patients with diabetes,<sup>6,7</sup> and later was found to reflect systemic vascular damage.<sup>8,9</sup> Furthermore, microalbuminuria was correlated with left ventricular wall thickness independent of blood pressure.<sup>10</sup> Previously we reported an increased prevalence of microalbuminuria in patients with acute myocardial infarction.<sup>10</sup> In the present report we have analyzed 10-year follow-up results in the previously studied cohort in order to further evaluate the association between the risk of death in patients with acute myocardial infarction and microalbuminuria.

whom gave informed consent. The study was in accordance with the Helsinki II Declaration and approved by the local ethics committee.

On the day of discharge (about one week after admission), the patients provided an early morning urine specimen. Urinary albumin concentration was measured using an enzyme-linked immunosorbent assay (ELISA).<sup>11</sup> Urinary creatinine concentration was measured using an enzymatic colorimetric method. The albumin/creatinine concentration ratio was taken as an index of the albumin excretion rate in urine.<sup>12</sup> In accordance with previous studies, microalbuminuria was defined as a urinary albumin/creatinine concentration ratio above 0.65 mg/mmol.<sup>2</sup> The left ventricle ejection fraction was estimated as a percentage by the wall motion index using the nine-segment model multiplied by 30.<sup>13</sup> A Vingmed echocardiograph model CFM 750 (Norway) was used. Blood pressures were measured using a standard mercury sphygmomanometer and an appropriately sized cuff. The body mass index was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Information about smoking status, presence of diabetes, and medication at discharge were obtained from patient records. In 2007, the patients were traced by means of the Danish Personal Identification Register. Data are given as means, geometric means, or proportions with 95% confidence intervals. Differences in mean values between the groups were tested using the t-test for unpaired comparisons. The effect of microalbuminuria and other baseline variables on mortality was analyzed by the Cox proportional hazards regression analysis and expressed as a hazard ratio. All analyses were performed with the SPSS 14.0 computer package. A value of  $P<0.05$  was considered significant.

## Materials and Methods

In 1996, 250 Caucasian individuals were admitted to Hvidovre University Hospital, Department of Cardiology, with acute myocardial infarction. The diagnosis was based on the presence of chest pain, electrocardiographic alterations, and significant elevations of coronary enzymes. Patients who died during admission were excluded as were patients who underwent acute percutaneous coronary intervention or coronary artery bypass grafting, as such interventions would probably overrule any prognostic effect of microalbuminuria. In addition, patients with known renal or urinary tract disease were excluded. In total, 151 of the eligible patients could be included in the primary study,<sup>10</sup> all of

## Results

The baseline characteristics of patients with acute myocardial infarction with or without microalbuminuria are given in Table 1. The patients with microalbuminuria were older and had a lower body mass index. There were no statistically significant differences

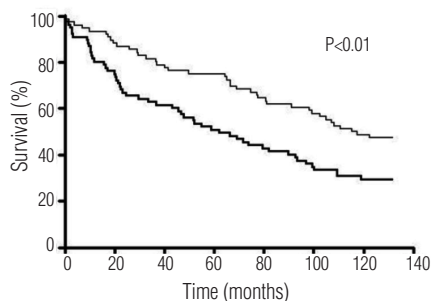
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**Figure 1. Unadjusted survival curves for patients with acute myocardial infarction and microalbuminuria (bold) or normoalbuminuria (thin). Relative risk of death associated with microalbuminuria versus normoalbuminuria = 1.78 (95 % CI, 1.18-2.68); P<0.01.**

found in gender, systolic or diastolic blood pressure, left ventricle ejection fraction, smoking status, or diabetes. After a 10-year follow-up, 52% of the patients with normoalbuminuria were still alive, whereas only 32% of the patients with microalbuminuria were (Figure 1). The hazard ratio for death associated with microalbuminuria was 1.78 (1.18-2.68) (P=0.006). Adjusted for age and gender, microalbuminuria was associated with mortality with a hazard ratio of 1.71 (1.03-2.83) (P=0.04). As shown in Table 2, microalbuminuria was associated with a similar risk of death as a left ventricle ejection fraction below 40%. Conversely, diabetes, hypertension, smoking, or male gender had no impact on mortality, and high body mass index was associated with enhanced survival.

## Discussion

Microalbuminuria is an established predictor of coronary heart disease in diabetic patients as well as in non-diabetic healthy persons.<sup>2,4,11,14-19</sup> In this study we confirm that microalbuminuria is strongly associated with an increased hazard of mortality in patients with acute myocardial infarction. Even though the study population consisted of 151 patients only, we were able to show that microalbuminuria significantly increases the risk of death, independently of age and gender. Thus, microalbuminuria is a very strong and robust risk indicator among patients with acute myocardial infarction. This observation confirms and extends previous observations by our group.<sup>20</sup>

The finding in our present study could likely be explained by more extensive vascular disease, for example, atherosclerosis, in patients with microalbuminuria. This is supported by other studies in which the severity of carotid

**Table 1. Baseline characteristics in 151 patients with acute myocardial infarction with or without microalbuminuria (urine albumin/creatinine concentration ratio >0.65 mg/mmoL).**

	Normoalbuminuria (n=76)	Microalbuminuria (n=75)	P
Age (years)	65 (63-68)	73 (70-76)	<0.001
Men <sup>†</sup> (%)	70 (60-80)	60 (49-71)	0.24
Systolic blood pressure (mmHg)	129 (125-133)	131 (127-135)	0.51
Diastolic blood pressure (mmHg)	78 (75-81)	76 (74-78)	0.42
Left ventricle ejection fraction <sup>‡</sup> (%)	50 (20-60)	47 (20-60)	0.19
Body mass index (kg/m <sup>2</sup> )	26.7 (25.7-27.7)	24.6 (23.8-25.4)	0.002
Smokers <sup>†</sup> (%)	42 (31-53)	44 (33-55)	1.00
Diabetes patients <sup>†</sup> (%)	11 (4-18)	13 (5-21)	0.63
Urine albumin/creatinine* (mg/mmoL)	0.35 (0.30-0.40)	2.31 (1.73-3.08)	<0.001

Data are means, \*geometric means or †proportions with 95% confidence intervals. Left ventricle ejection fraction is shown by ‡medians with interquartile ranges.

**Table 2. Relative risks of ten-year mortality associated with risk factors measured during baseline admission in 151 patients with acute myocardial infarction.**

Baseline variable	Relative risk (hazard ratio)	P
Age >65 years	3.06 (1.82-5.12)	<0.001
Left ventricle ejection fraction <40%	1.80 (1.12-2.89)	0.02
Microalbuminuria	1.78 (1.18-2.68)	0.006
Microalbuminuria*	1.71 (1.03-2.83)	0.04
Diabetes	1.22 (0.66-2.23)	0.52
Hypertension	0.89 (0.55-1.44)	0.64
Smoking	0.87 (0.58-1.32)	0.51
Male	0.86 (0.57-1.31)	0.49
Obesity	0.63 (0.42-0.96)	0.03

Microalbuminuria, urine albumin/creatinine concentration ratio >0.65 mg/mmoL; hypertension, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; obesity, body mass index >25 kg/m<sup>2</sup>. \*Adjusted for age and sex. Relative risks are shown with 95% confidence intervals in parentheses.

atherosclerosis, measured ultrasonographically, was correlated with urinary albumin excretion.<sup>21-23</sup> Moreover, the link between microalbuminuria and atherosclerosis is confirmed by the fact that half of the patients included in our study had microalbuminuria, as defined by a urinary albumin excretion above the upper 10% range in the background population.<sup>2</sup> In our study we used spot urines, not timed urine collections. However, calculation of the albumin/creatinine ratio yields an acceptable measure of the urinary albumin excretion rate in terms of specificity and sensitivity when screening for microalbuminuria.<sup>12</sup>

The definition of microalbuminuria in diabetes was based originally on the level of urinary albumin excretion above which the risk of chronic renal failure, but not of atherosclerotic cardiovascular disease, was increased,<sup>24</sup> that is, an albumin excretion rate above 30 mg/day or an albumin/creatinine ratio above 2 mg/mmoL. In addition, it has become evident that the risk of atherosclerotic cardiovascular disease is increased at even

lower levels of urinary albumin excretion in diabetic as well as non-diabetic subjects.<sup>17,25-27</sup> We used our previous definition of microalbuminuria, for example, a urinary albumin/creatinine ratio above 0.65 mg/mmoL, which in non-diabetic subjects independently increases the risk of atherosclerotic cardiovascular disease without additional gain in risk with increasing values.<sup>2,28</sup>

We concluded that microalbuminuria is associated with impaired survival in patients hospitalized with myocardial infarction. Microalbuminuria may be useful for risk stratification in these patients and, moreover, should be included as a baseline variable in intervention trials.

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