New Definition of Microalbuminuria in Hypertensive Subjects

Association With Incident Coronary Heart Disease and Death

Klaus Peder Klausen, Henrik Scharling, Gorm Jensen, Jan Skov Jensen

Abstract—Microalbuminuria has so far been defined as urinary albumin excretion between 20 and 200 μg/min (or 15 to 150 μg/min overnight). In a recent report, an overnight urinary albumin excretion >5 μg/min was strongly predictive of coronary heart disease and death in the general population. The aim of the present study was to confirm this observation in a population of hypertensive individuals. In The Third Copenhagen City Heart Study in 1992 to 1994, 1734 men and women aged 30 to 70 years with hypertension, but no history of coronary heat disease, delivered a timed overnight urine sample. They were followed-up prospectively by registers until 2000 with respect to coronary heart disease, and until 2004 with respect to death. During follow-up, 123 incident cases of coronary heart disease and 308 deaths were traced. Incident coronary heart disease occurred in 11% of subjects with urinary albumin excretion ≥5 μg/min compared with 5% in subjects with urinary albumin excretion <5 μg/min ($P<0.001$). Similarly, the cumulative mortality was 28% versus 13% ($P<0.001$). The relative risks of coronary heart disease and death associated with urinary albumin excretion ≥5 μg/min were 2.0 (1.4 to 2.9; $P<0.001$) and 1.9 (1.5 to 2.3; $P<0.001$), respectively, after adjustment for age, sex, blood pressure level, antihypertensive drugs, diabetes, creatinine clearance, smoking, lipoproteins, and body mass index. In conclusion, our study supports the new definition of microalbuminuria as urinary albumin excretion >5 μg/min. In future risk assessment in hypertensive individuals, measurement of microalbuminuria has to be included. **(*Hypertension*. 2005;46:33-37.)**

Key Words: albuminuria ■ coronary disease ■ diabetes mellitus ■ hypertension, arterial ■ mortality

Microalbuminuria has become a prognostic marker for cardiovascular risk in diabetic and nondiabetic subjects.[1–15] It is also associated with increased risk of death in patients with myocardial infarction.[16,17] Essential hypertension and microalbuminuria in nondiabetic individuals was first associated in 1974[18] and later confirmed in subsequent studies.[1,10,19–21] Measurement of microalbuminuria is in some guidelines recommended for risk stratification in people with hypertension.[22]

Originally, microalbuminuria was defined in diabetes as 20 to 200 μg albumin excreted per minute in urine collected over 24 hours, or 15 to 150 μg/min in urine collected overnight.[23] Initially it was found to be associated with increased risk of chronic renal failure.[12,24] In subjects without diabetes, the excretion of albumin in the urine is much lower than the level seen in diabetes.[9,25,26] However, recent studies have challenged the original definition of microalbuminuria when looking on the risk of coronary heart disease (CHD) or death.[6]

In a recent study,[11] we assessed the level of urinary albumin excretion (UAE) above which the risk of CHD and death is increased in the general population. We found that microalbuminuria defined as a urinary albumin excretion ≥4.8 μg/min is a strong independent determinant of CHD and death. The purpose of the present study was to determine whether this threshold value also could be relevant in hypertensive subjects by assessing the predictive impact of microalbuminuria on subsequent development of CHD and death. We also aimed to see whether renal function as measured by creatinine clearance could affect this possible association.

Methods

The study was performed as a substudy of the Third Copenhagen City Heart Study in 1992 to 1994.[27] Approximately 16 000 subjects were randomly drawn by the Copenhagen Population Register. Out of these, 10 200 attended (64%), and all the participants between 30 and 70 years were asked to collect timed overnight urine sample. A total of 3645 urine samples were received. In the present report we included those with hypertension if a total set of data were obtained, and no history of CHD was reported (n=1734). All subjects gave their informed consent to participate. The study was approved by the regional ethics committee and performed in accordance with the Second Helsinki Declaration.

Baseline Variables

Hypertension was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥85 mm Hg, and/or use of antihyperten-

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TABLE 1. Baseline Characteristics of Hypertensive Subjects From the Third Copenhagen City Heart Study in 1992 to 1994 Divided Into Individuals With CHD and/or Who Died During Follow-Up and Controls

Characteristics	Controls for CHD (n=1611)	CHD (n=123)	Controls for Death (n=1426)	Death (n=308)
Men, %	51	61	50	60§
Age, years	56.8 (56.3–57.2)	62.0 (61.0–63.0)*	56.1 (55.6–56.6)	61.9 (61.2–62.5)*
Systolic blood pressure, mm Hg	146 (145–147)	154 (150–158)*	145 (144–146)	152 (150–154)*
Diastolic blood pressure, mm Hg	92 (91–93)	93 (91–95)	92 (91–93)	93 (92–94)
Antihypertensive medicine instituted, %	13	29‡	13	22‡
Smokers, %	47	57¶	43	66‡
Body mass index, kg/m^2	26.7 (26.5–26.9)	27.0 (26.3–27.7)	26.7 (26.5–26.9)	26.8 (26.4–27.3)
Diabetics, %	4.0	8.9‖	3.2	9.7‡
Plasma total cholesterol, mmol/L	6.4 (6.3–6.5)	6.8 (6.6–7.0)†	6.4 (6.3–6.5)	6.4 (6.2–6.5)
Plasma HDL cholesterol, mmol/L	1.55 (1.53–1.57)	1.43 (1.35–1.51)‖	1.54 (1.52–1.57)	1.51 (1.44–1.57)
Renal creatinine clearance, mL/(min×m^2)	43 (42–44)	42 (38–46)	43 (42–44)	42 (39–44)
Urine albumin excretion, μg/min	3.8 (3.6–3.9)	5.5 (4.4–7.0)*	3.5 (3.4–3.7)	5.6 (5.1–6.8)*

Parentheses indicate 95% confidence intervals.
Continuous variables are means, except from urinary albumin excretion, which are geometric means.
CHD indicates coronary heart disease; HDL, high-density lipoprotein.
*$P<0.0001$; †$P<0.0005$; ‡$P<0.001$; §$P<0.005$; ¶$P<0.05$; ‖$P<0.01$, compared with controls.

sive drugs. Blood pressure was measured in sitting position on the left upper arm after a 5-minute rest. A London School of Hygiene sphygmomanometer was used.

Urinary albumin concentration was measured by an enzyme-linked immunosorbent assay technique[28] and the urinary albumin excretion (UAE) was calculated as urinary albumin concentration multiplied by the diureses (μg/min). Urinary creatinine concentration was measured by a colorimetric method, and renal clearance of creatinine was calculated as the ratio of urine to serum concentration multiplied by the diuresis, and adjusted for body surface area as calculated by the formula: $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$ [mL/(min×m^2)], and was taken as an index of glomerular filtration rate.

Data regarding smoking, medication, and self-reported disease were recorded. Body mass index was calculated as weight divided by height squared (kg/m^2). Diabetes was defined as nonfasting plasma glucose ≥11.1 mmol/L (colorimetric enzymatic method), or use of antidiabetic medicine or self-reported disease. Plasma total and high-density lipoprotein cholesterol and serum creatinine were measured by enzymatic colorimetric methods.

End Points

All participants were followed-up until December 31, 2000, with respect to development of CHD (ICD-10 codes I20.0 through I25.9), and until March 1, 2004, with respect to death and emigration by means of the National Patient Register, the National Register of Causes of Death, and the Civil Registration System. The completeness of case finding from the sample was >95%.[29]

Statistical Analysis

Differences in baseline characteristics between groups were compared by Student *t* test and χ^2 test. Relative risks were calculated as hazard ratios by Cox proportional hazards regression analyses with age as the underlying time scale and stratified by gender, thus assuming similar effects of covariates but allowing for different baseline hazards in the 2 sexes. Blood pressure, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, renal creatinine clearance, smoking, and body mass index were included in multivariate analyses. $P<5\%$ was taken as significant.

Results

During 12 259 person-years of follow-up, 123 incident cases of CHD were identified, and during 17 216 person-years 308 deaths were identified. The cases were at baseline characterized by higher levels of the conventional atherosclerotic risk factors than the controls, whereas creatinine clearance was similar in cases and controls (Table 1). Subjects in whom CHD developed during follow-up had higher baseline UAE than control subjects [geometric mean, 5.5 (95% CI, 4.4 to 7.0) versus 3.8 (3.6 to 3.9) μg/min; $P<0.0001$] (Table 1). This was also the case among subjects who died [geometric mean, 5.6 (95% CI, 5.1 to 6.8) versus 3.5 (3.4 to 3.7 μg/min; $P<0.0001$] (Table 1).

Table 2 shows the baseline characteristics of the 1734 hypertensive subjects divided into 2 groups: microalbuminuria, ie, UAE ≥4.8 μg/min (n=522, ≈30%) and normoalbuminuria, ie, UAE <4.8 μg/min (n=1212, ≈70%). During follow-up, incident CHD occurred among 11% of subjects with microalbuminuria compared with 5% of subjects with normoalbuminuria ($P<0.001$), and death occurred in 28% versus 13% ($P<0.001$). The subjects with microalbuminuria had higher levels of the conventional risk factors and creatinine clearance.

The age- and sex-adjusted relative risks of incident CHD and death for hypertensive subjects with microalbuminuria compared with hypertensive subjects with normoalbuminuria were 2.1 (Table 3). Adjustment for other risk factors (blood pressure, use of antihypertensive drugs, diabetes, lipoproteins, renal creatinine clearance, smoking, and body mass index) did not significantly alter the relative risks of CHD and death (Table 3). Because there was no interaction between microalbuminuria and sex for development of CHD ($P=0.5$) or death ($P=0.2$), sex-stratified relative risks are not given. Furthermore, there was no interactions between microalbuminuria and any of the other atherosclerotic risk factors, ie, age, blood pressure, smoking, body mass index, diabetes, total or high-density lipoprotein cholesterol, or creatinine clearance.

The age-adjusted relative risks of CHD and death are shown in Figure 1. These are significantly increased for UAE >5 μg/min.

TABLE 2. Characteristics of Hypertensive Subjects From the 3rd Copenhagen City Heart Study in 1992 to1994 Divided Into Individuals Who Exhibited Microalbuminuria (UAE ≥4.8 μg/min) or Normoalbuminuria (UAE <4.8 μg/min)

Characteristics	Normoalbuminuria (n=1212)	Microalbuminuria (n=522)
Men, %	47	61‡
Age, years	56.8 (56.3–57.3)	58.0 (57.2–58.7)‖
Systolic blood pressure, mm Hg	144 (143–145)	151 (149–153)*
Diastolic blood pressure, mm Hg	92 (91–93)	94 (93–95)*
Antihypertensive medicine instituted, %	13	18¶
Smokers, %	44	55‡
Body mass index, kg/m^2	26.4 (26.2–26.6)	27.4 (27.0–27.8)*
Diabetics, %	2.6	8.4‡
Plasma total cholesterol, mmol/L	6.4 (6.3–6.5)	6.3 (6.2–6.4)
Plasma HDL cholesterol, mmol/L	1.57 (1.54–1.60)	1.46 (1.42–1.50)*
Renal creatinine clearance, mL/(min × m^2)	41 (40–42)	47 (44–50)*
Incident CHD during follow-up, %	5	11‡
Deaths during follow-up, %	13	28‡

Continuous variables are means with 95% confidence intervals in parentheses.
UAE indicates urinary albumin excretion.
*$P<0.0001$; †$P<0.0005$; ‡$P<0.001$; §$P<0.005$; ¶$P<0.05$; ‖$P<0.01$.

Figures 2 and 3 show the curves of the cumulative incidence of CHD and mortality, respectively, for hypertensive subjects having microalbuminuria or normoalbuminuria.

Discussion

Microalbuminuria was originally defined as excretion of 20 to 200 μg albumin per minute in the urine (15 to 150 μg/min in urine samples collected overnight) among patients with diabetes mellitus.[23] It was found to be associated with increased risk of chronic renal failure.[12,24] This original definition is of limited clinical relevance as a risk factor for CHD and death in subjects without diabetes. Studies have shown that the risk increases at much lower values.[2,6,11] Data from the HOPE study suggested that a 0.4 mg/mmol increase in the ratio of urinary albumin to creatinine concentration led to a 5.9% higher age- and sex-adjusted risk of CHD.[6] This risk increased well below the usually defined level of microalbuminuria. This was confirmed in our recent publication based on UAE in a general population.[11] We found that risk of CHD and death increased remarkably when the UAE was higher than the upper quartile in the entire population, ie, 4.8 μg/min. We therefore also used UAE ≥4.8 μg/min in this study for the definition of microalbuminuria among hypertensive subjects. Stratification of this population according to different levels of UAE showed that such definition is also useful among hypertensive subjects (Figure 1).

Using this definition we found that hypertensive subjects with microalbuminuria as a group exhibit a worse risk profile when looking at the conventional cardiovascular risk factors (male sex, age, blood pressure, smoking, body mass index, cholesterol, diabetes). However, inclusion of all these risk factors in the Cox proportional hazards regression analysis did not abolish the strong predictive effect of microalbuminuria on CHD and death.

A recent study has shown that even mild renal insufficiency diagnosed by the estimated glomerular filtration rate should be considered a major risk factor for cardiovascular complications after myocardial infarction.[30] Another study has shown that reduced glomerular filtration rate also is an independent predictor of CHD in middle-aged subjects.[31] However, adjusting the associations between microalbuminuria and CHD, and microalbuminuria

TABLE 3. Relative Risks With 95% Confidence Intervals in Parentheses of Incident CHD and Death in 1734 Hypertensive Individuals With Microalbuminuria (UAE ≥4.8 μg/min)

	CHD (n=123)		Death (n=308)	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Microalbuminuria vs normoalbuminuria (adjusted for age and sex)	2.1 (1.5–3.0)	<0.001	2.1 (1.6–2.6)	<0.001
Microalbuminuria vs normoalbuminuria (multivariate-adjusted*)	2.0 (1.4–2.9)	<0.001	1.9 (1.5–2.3)	<0.001

*Adjusted for age, sex, blood pressure, use of antihypertensive drugs, diabetes, lipoproteins, renal creatinine clearance, smoking, and body mass index.
Hypertensive individuals with normoalbuminuria (UAE <4.8 μg/min) serve as reference.
CI indicates confidence interval; RR, relative risk.

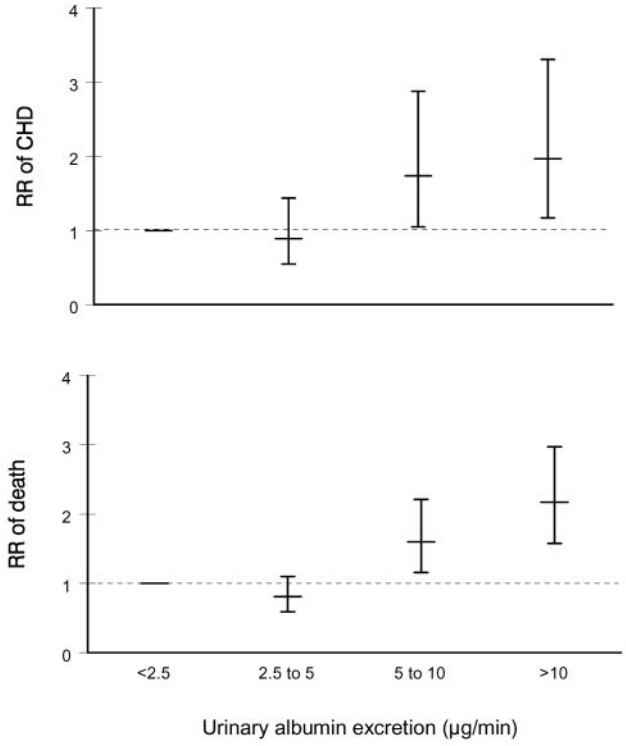

Figure 1. Age-adjusted relative risks (RR) of CHD and death associated with different levels of urinary albumin excretion (UAE) in 1734 hypertensive subjects.

and death for renal creatinine clearance, had no influence on the associations.

Our results are consistent with a similar study in another population[10] in which microalbuminuria was the strongest predictor for CHD in untreated hypertensive subjects. In that study, the relative risk of CHD was 3.5 after adjustment for the conventional atherosclerotic risk factors was made. A limitation of that study was that spot urine samples were used, and thus UAE and creatinine clearance could not be measured.

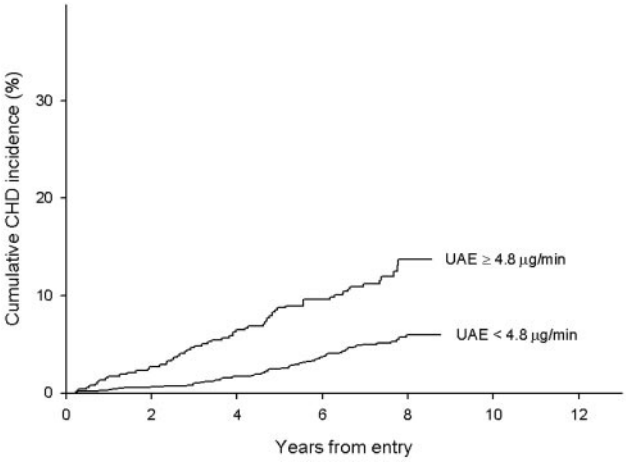

Figure 2. Cox-estimated age-adjusted curves of cumulative incidence of coronary heart disease (CHD) for a 60-year-old person based on 1734 hypertensive subjects with microalbuminuria (UAE ≥4.8 µg/min; n=522) and normoalbuminuria (UAE <4.8 µg/min; n=1212; $P<0.001$).

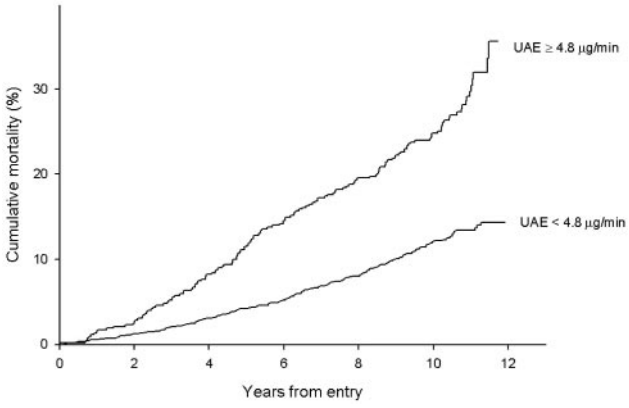

Figure 3. Cox-estimated age-adjusted curves of cumulative mortality for a 60-year-old person based on 1734 hypertensive subjects with microalbuminuria (UAE ≥4.8 µg/min; n=522) and normoalbuminuria (UAE <4.8 µg/min; n=1212; $P<0.001$).

The pathophysiological mechanism linking microalbuminuria to atherosclerosis and CHD is uncertain. It has been hypothesized that microalbuminuria reflects diffuse endothelial dysfunction,[32] leading to generalized transendothelial sieving of albumin.[33] However, in recent experiments this hypothesis could not be extended to include increased transendothelial sieving of lipoproteins.[34] It is likely that microalbuminuria emerges later in the atherosclerotic process.[35–37]

We recognize that many factors potentially influence the UAE in a population study such as urine collection, laboratory methods, urinary tract infection, size of population, response rate, and age range. Despite this, the presence of UAE ≥4.8 µg/min in a single urine sample seems to increase the risk. Furthermore, it is known that there is considerable intraindividual variability of UAE and therefore regression dilution.[38] The observed risk of CHD and death associated with microalbuminuria may thus be underestimated.

Perspectives

In future trials of hypertensive patients it may be of relevance to measure UAE before and after intervention in order to see whether reduction of UAE decreases the risk of CHD and death. There is scarce evidence on this field, but recent data from the LIFE study shows that a reduction in UAE could explain 20% of the benefits of losartan versus atenolol.[39]

In conclusion, our study shows that hypertensive subjects with microalbuminuria defined as UAE ≥4.8 µg/min have 100% higher risk of incident CHD and death than hypertensive subjects with UAE <4.8 µg/min. This increased risk is independent of age, sex, level of blood pressure, diabetes mellitus, renal function, lipoproteins, body mass index, and smoking.

The study supports the need for redefining microalbuminuria, from UAE >15 µg/min (in nocturnal collections) to ≥5 µg/min (or urinary albumin-to-creatinine ratio ≥0.7 mg/mmol). We suggest a future risk assessment of CHD or death in hypertensive individuals to include measurement of microalbuminuria.

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