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Prevalence of microalbuminuria and its associated cardiovascular risk: German and Swiss results of the recent global i-SEARCH survey

A sub-analysis of a survey of 21,050 patients in 26 countries worldwide

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Summary

Question under study: The aim of this study was to determine the prevalence of microalbuminuria (MAU) in hypertensive patients attending an office or hospital based cardiologist or internist. An additional aim was to describe associations between MAU and cardiovascular risk factors as well as to investigate the role of pharmacotherapy.

Methods: International, observational, cross-sectional study of 22 282 patients with 5605 attendees in Germany and Switzerland at 444 cardiology centers. Inclusion criteria were male and female outpatients, aged ≥18 years with currently treated or newly diagnosed hypertension (≥140/90 mm Hg at rest on the day of the study visit) and no reasons for false positive dip stick tests. The main outcome measures were the prevalence of MAU, co-morbid cardiovascular risk factors or disease and their association with the presence of MAU, and the role of pharmacotherapy in modulating prevalence of MAU.

Results: Prevalence of MAU in Germany and Switzerland (53.1%) was high, but lower when compared to the prevalence in "other countries" (OC, 60.2%). Routine MAU measurement was performed in 52.9% of the practices only (32.9% OC), although physicians regarded MAU to be important for risk assessment and therapeutic decisions. MAU is highly correlated with a wide variety of cardiovascular risk factors and co-morbid cardiovascular conditions including high waist circumference (55.1% [95%CI 56.0; 59.7]), diabetes (59.1% [56.8; 61.3]), atrial fibrillation (62.3% [57.4; 66.9]) and peripheral arterial disease (67.1% [61.6; 72.2]). Angiotensin receptor blockers (ARBs) appeared to be associated with the lowest risk of MAU (52.1%). Calcium channel blockers (CCBs) were used more frequent in patients with MAU (28.7%) than without (23.4%).

Conclusions: Patients with MAU are common in clinical cardiology and its presence is associated with a wide variety of cardiovascular risk factors and co-morbid cardiovascular conditions. A more aggressive multi-factorial treatment might help to reduce this risk constellation.

Key words: microalbuminuria; prevalence; cardiology; hypertension; irbesartan; risk factors

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Introduction

The transgression of albumin into the urine demarcates a disturbance in the barrier function of endothelial glomerular cells (podocytes) [1, 2]. A common measurement category is mg/24 h and albuminuria is frequently standardised for the urinary volume using simultaneous determination of urinary creatinine. While every excretion of albumin into the urine has to be regarded as pathologic, a range has been identified at which a progression to advanced renal disease becomes likely (30 and 300 mg/24 h). The threshold was termed microalbuminuria (MAU) and is correlated with an increased incidence of clinical proteinuria, an increase in serum creatinine, the more frequent development of terminal renal insufficiency, but also associated with an increased cardiovascular risk [3].

The transgression of albumin into the urine is frequently regarded as a kidney problem. However, there is often a simultaneous transgression of albumin into the retinal bed (cotton wool spots) [4]. Moreover, preclinical studies have shown that, using labelled albumin, transgression seems to be also present in the whole vascular system, including the myocardium [5]. Consequently, albuminuria reflects a generalised endothelial disturbance and is frequently seen within the context of endothelial dysfunction. Interestingly, an improvement in endothelial function is reflected in a decrease of albuminuria [6].

Also for cardiologists, albuminuria seems to be of critical importance to determine the prognosis of patients with cardiovascular disease. Patients with myocardial infarction, for example, have a worse prognosis if albuminuria is present compared to patients without albuminuria [7]. Furthermore, for patients with angiographically normal coronary arteries, the extent of endothelial dysfunction has been shown to correlate to the extent of albumin excretion [8]. Consequently the prognosis of patients with CAD and MAU is worse when compared to patients without [9, 10]. Overall it has been shown that MAU seems to be more relevant than many established cardiovascular risk factors [11]. A recent multivariate analysis of the HOPE trial has shown that the probability of stroke, myocardial infarction and cardiovascular death was higher for patients with MAU as compared to those with PAD, diabetes or the impact of male gender. The analyses further support the notion that, for cardiovascular risk assessment, not only MAU but albumin excretion below the threshold (low grade albuminuria) is already reflected in a higher probability of cardiovascular disease (for a recent review see [12]).

Although there is sound evidence for the importance of MAU in clinical cardiology, there are no epidemiological data documenting the prevalence of this risk marker in clinical cardiology settings and its association with other cardiovascular risk factors and disease. Therefore the "International Survey Evaluating microAlbuminuria Routinely by Cardiologists in patients with Hypertension" (i-SEARCH) was undertaken to answer the following questions: 1) Prevalence of MAU and its importance for therapeutic decisions. 2) Associations with established cardiovascular risk markers and disease. 3) Relation between coronary artery disease and MAU. 4) Subsumption of national data into a global context aiming to compare cardiovascular risk and quality of care with other countries. The present manuscript therefore reports the data for Germany and Switzerland, from global data which have been recently published [13, 14].

Methods

Two step epidemiological design

The current investigation was an international, observational, cross-sectional study in which participants were evaluated during a single clinic visit to office and hospital based cardiologists (methods have been published previously [13]). To allow extrapolation of results to the broadest possible population, the physician selection procedure in each country took account of geographical (west/east, south/north, urban/suburban/rural) and physician (office/hospital) profiles. In a first step, prior to patient recruitment, participating physicians completed a site questionnaire that documented practice location (urban, suburban or rural) and type (community or hospital-based), as well as duration of service, and degree of awareness and experience of MAU detection and its clinical relevance. In a second step at each site, consecutive patients fulfilling eligibility criteria (10, max. 15 per physician) were invited to participate in the study. Institutional and ethical review board approval for the study was granted for all participating centres, and all patients gave written informed consent for study participation. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki and was consistent with the International Conference on Harmonization Good Clinical Practice (ICH GCP).

Abbreviations

ARB	angiotensin receptor blocker
CAD	coronary artery disease
CABG	coronary artery bypass graft
CCB	calcium channel blocker
MAU	microalbuminuria
PAD	peripheral arterial disease
PTCA	percutaneous transluminal coronary angiography
RAS	renin angiotensin system

Study population

Inclusion criteria were male and female outpatients, aged 18 years or older, with currently treated or newly diagnosed arterial hypertension, defined as a seated systolic/diastolic blood pressure of ≥140/90 mm Hg at rest on the day of the study visit. Patients with acute fever (>38 °C), renal disease (serum creatinine >20 mg/L), concomitant urinary tract infection, receiving treatment with cimetidine, or having undertaken strenuous physical activity in the preceding 24 hours, as well as female subjects who were pregnant or menstruating were ineligible to participate due to the likely presence of false positive results for MAU.

Data acquisition

Once enrolled, the following measurements were carried out on each patient: heart rate, urinary albumin and creatinine concentration, and waist and hip circumference. To ensure consistency between study sites, all centres performed dipstick screening for MAU with sponsor-provided reagent strips (Microalbustix®), which have a sensivity of 82.6% [15]), and followed a standardised sample collection and testing procedure. Demographic data, cardiovascular history and presence of cardiovascular risk factors, co-morbidities, symptoms and signs of cardiovascular disease, and current chronic drug therapy were documented on the case report form.

Objectives

The primary objective of this study was to define the prevalence of MAU in hypertensive outpatients attending a cardiologist (i-SEARCH A) and to compare prevalence in hypertensive outpatients with or without coronary artery disease (i-SEARCH B). Secondary objectives were to establish a correlation between the prevalence of MAU and known cardiovascular risk factors in the study population, and to increase physicians' awareness for the importance of MAU screening to identify "at risk patients".

Statistical analyses

In the present analysis Germany and Switzerland were compared to other countries [OC] which included Vietnam, Indonesia, Thailand, Morocco, Australia, Turkey, Mexico, Taiwan, Sweden, Italy, Spain, Greece, Belgium, Peru, Colombia, Canada and countries from the Middle East [13]. Population characteristics were summarised into counts of non-missing data, means, and standard deviations (SD) together with 95% confidence intervals (CI) of the mean for quantitative variables, and count and percentage with 95% CI of the population for categorical data. Outcomes included prevalence of MAU with 95% CIs, taking into account the cluster design effect using the Proc SURVEYMEANS in SAS for categorical variables. The association between high levels of MAU and cardiovascular risk factors and co-morbid conditions (for example history of MI, documented CAD, diabetes, dyslipidaemia, a lack of physical exercise and a history of smoking) was studied using multiple logistic regression models and prevalence rates were displayed together with 95% confidence intervals. Since the amount of data missing was low, the data provided is without respective sensivity analyses. For the calculations SAS, version 8.2 was used [16].

Results

Baseline Characteristics

In 444 practices in Germany and Switzerland 5605 patients were screened, from which 80 did not sign informed consent and 237 did not meet the pre-specified inclusion and exclusion criteria, or either coronary artery disease status, albumin or creatinine was not documented (Primary analysis population: 5288 patients).

Patients were 64.1 [SD 11.3] years old, 52.3% were male, had a history of hypertension of 9.0 [SD 8.4] years and a mean blood pressure of 152.6 [SD 19.7] / 89.0 [SD 11.7] mm Hg on the study day. For details on the cardiovascular risk profile see table 1.

From the study population, 17.6% had evidence of coronary artery disease, 46.8% of which had a history of myocardial infarction. Only 33.2% had ever had a revascularisation (55.6% OC) with most patients receiving PTCA only (63.5%) or CABG only (31.9%). From the sample, 75.4% of participants had a history of angina pectoris.

Physicians estimated prevalence and importance of MAU

Physicians stated that MAU was routinely measured in about half of the practices in Germany and Switzerland (52.9% [95%CI 47.9; 57.8] compared to 32.9% [30.4; 35.5] in OC). Most physicians (25.3%) estimated the frequency of MAU in hypertensive patients, to lie between 11 and 20% (28.3 % OC, for details see fig. 1).

In contrast, 91.9% of treatment decisions and 97.3% of decisions relating to treatment of blood pressure were said to be influenced by the presence of MAU. Furthermore 85.4% of physicians said that MAU also influenced decisions relating to achieving glycemic control. The vast majority (98.7%) of physicians linked the presence of MAU to a worse patient's prognosis, while 93.1% also felt that a diagnosis of MAU was relevant to improving the management of other cardiovascular risk factors. These attitudes were highly comparable with the colleagues in the OC.

Prevalence of MAU

Within the primary analysis population, only few patients had impaired renal function and 8.95% [95%CI 8.2; 9.8] had previously identified MAU (5.98% [95%CI 5.6; 6.4] OC). However, urine analysis with a one time dipstick test revealed that 53.1% [95%CI 51.1; 55.0] of the study population had evidence of MAU (60.2% [59.0; 61.4] OC), with prevalence rates higher in men (57.0%) than women (43.0%).

Cardiovascular risk factors associated with the presence of MAU

Several cardiovascular risk factors were tested to determine whether they were associated with the presence of MAU. Male gender, high waist circumference, systolic blood pressure ≥180 mm

Table 1

Cardiovascular risk profile (Primary analysis population).

	Parameter (mean ± SD or %)	Germany / Switzerland (n = 5288)	Other countries (n = 15 762)
Demographics	Age (years)	64.1 ± 11.3	61.8 ± 11.8
	<Gender (male, %)	52.3	52.3
	BMI (kg/m^2)	29.8 ± 6.8	28.5 ± 5.3
Hypertension	Duration (years)	9.0 ± 8.4	7.8 ± 7.5
	SBP (mm Hg)	152.6 ± 19.7	148.1 ± 20.2
	DBP (mm Hg)	89.0 ± 11.7	86.9 ± 11.8
	Uncontrolled (≥140/90 mm Hg)	84.7	74.2
Heart Rate / Sinus Rhythm	Heart rate (bpm)	72.9 ± 11.5	73.9 ± 11.8
	Sinus rhythm yes (%)	94.6	94.9
Behavioural risk factors for CVD	Family history MI/CAD (%)	28.7	27.6
	Regular physical exercise (%)	39.8	33.3
	Current/former smoker (%)	12.6 / 21.5	14.7 / 20.1
Additional risk factors	Total cholesterol (mmol/L)	5.5 ± 1.1	5.3 ± 1.1
	HDL Chol. (mmol/L)	1.5 ± 0.5	1.3 ± 0.4
	LDL Chol. (mmol/L)	3.3 ± 1.0	3.2 ± 1.0
	Triglycerides (mmol/L)	1.9 ± 1.1	1.8 ± 1.0
	CRP (mg/dL)	1.18 ± 1.04	0.8 ± 0.9
	Current diabetic (%)	35.1	25.0
	Type 1 / Type 2 diabetes (%)	4.1 / 96.0	5.3 / 94.7
	Duration of diabetes (years)	8.2 ± 8.6	7.8 ± 7.2
	Serum creatinine (µmol/L)	86.9 ± 22.2	90.9 ± 24.3
	Creatinine clearance (mL/min)	93.6 ± 33.9	85.8 ± 33.9
	<30 mL/min (%)	0.3	0.8
	30–60 mL/min (%)	12.9	21.5
	60–80 mL/min (%)	25.2	26.9
	80–120 mL/min (%)	43.8	37.0
	>120 mL/min (%)	17.8	13.7
Co-morbidities	CAD (%)	17.6	24.7
	Congestive heart failure (%)	5.6	5.9
	Atrial fibrillation (%)	7.8	8.5
	History of ischemic stroke (%)	4.1	5.1
	History of TIA (%)	2.9	4.0
	Peripheral artery disease (%)	5.7	3.7
	Carotid endarterectomy (%)	22.5	18.4
Other cardiovascular disease	LVH (Sokolow mm)	21.0 ± 9.6 (n = 1609)	25.7 ± 9.7 (n = 6702)
	Ejection fraction ≤40% (%)	3.8	5.0
	Carotid stenosis (%)	3.8	2.6
	Aortic aneurysm (%)	1.2	1.4

SD – standard deviation; CAD – coronary artery disease, LVH – left ventricular hypertrophy, TIA – transitory ischemic attack, CRP – C-reactive protein, MI – myocardial infarction

Hg, pulse pressure ≥80 mm Hg, high triglycerides and diabetes were derived as significantly associated from multivariate analyses and were significantly associated with a higher prevalence of MAU (table 2). In contrast, patients participating in regular physical exercise and patients with high HDL cholesterol had a lower risk of MAU. Figure 2 aggregates these values and shows the number of present cardiovascular risk factors compared with the presence of MAU.

Cardiovascular disease associated with the presence of MAU

It was also tested whether MAU was associated with the presence of cardiovascular disease. While the presence of an aortic aneurysm was not associated with the presence of MAU, positive associations were found with congestive heart failure, atrial fibrillation, coronary artery disease, a history of cerebral pathology and peripheral arterial disease (table 2). Figure 3 aggregates these

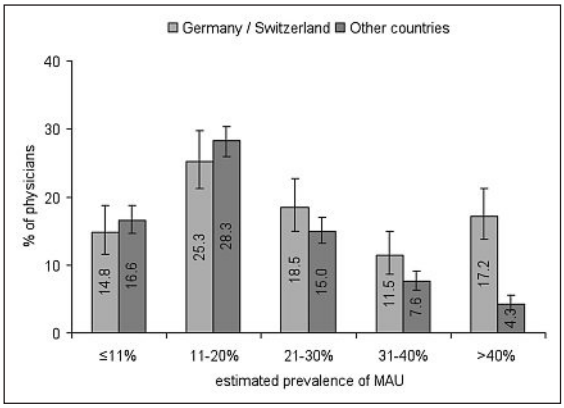


Figure 1

Mean prevalence estimates [95% CI].

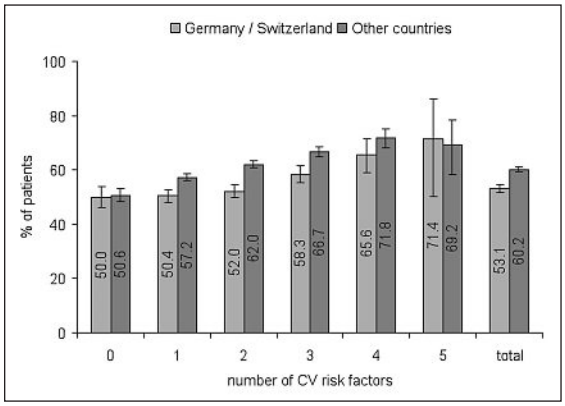


Figure 2

Mean prevalence estimates [95% CI]; the risk factors considered are: no regular exercise, current smoking, known dyslipidemia, family history of myocardial infarction or documented CAD and Diabetes.

numbers and displays the number of risk factors present in a patient in relation to the presence of MAU.

Pharmacotherapy and prevalence of MAU

Use of antihypertensive pharmacotherapy was more intense in patients with the presence of MAU. CCBs (+5.3%), ACE Inhibitors (+3.8%), thiazide diuretics (+1.8%) and beta-blocker (+2.7%) were more frequently prescribed in patients with MAU compared to patients without (fig. 4). The number of patients showing MAU when receiving pharmacotherapy was in the order CCBs > ACE Inhibitors > thiazides diuretics > beta blockers > ARBs (fig. 5).

Table 2

Prevalence of MAU in patients with and without respective risk factors or co-morbid disease (identified from multiple regression analyses).

Risk factor	Prevalence of MAU in pts with risk factor (% [95%CI])	Prevalence of MAU in pts without risk factor (% [95%CI])
Gender	Male 57.8% [56.0; 59.7]	Female 47.8% [45.8; 49.7]
Waist circumference	High 55.1% [53.5; 56.7]	Normal 48.0% [45.5; 50.5]
Systolic blood pressure	≥180 mm Hg 60.8% [56.7; 78.6]	120–130 mm Hg 49.1% [43.4; 54.9]
Pulse pressure	≥80 mm Hg 58.3% [54.3; 62.2]	between 50 and 60 mm Hg 50.9% [48.3; 53.4]
Triglycerides	High 55.5% [53.2; 57.7]	Low 50.7% [48.4; 52.9]
Diabetes	Present 59.1% [56.8; 61.3]	Absent 50.0% [48.3; 51.7]
Physical exercise	None 54.6% [52.9; 56.4]	Regular 50.7% [48.6; 52.9]
HDL-Cholesterol	Low 61.9% [58.5; 65.2]	High 50.5% [48.6; 52.3]
Co-morbid disease		
CHF	Yes 60.1% [95%CI 54.4; 65.5]	No 52.6% [51.2; 54.0]
Atrial Fibrillation	Yes 62.3% [57.4; 66.9]	No 52.4% [51.0; 53.9]
CAD	Yes 57.9% [54.7; 61.0]	No 52.0 [50.6; 53.5]
Stroke / TIA	Yes 61.8% [57.9; 65.5]	No 51.9% [50.5; 54.4]
PAD	Yes 67.1% [61.6; 72.2]	No 52.4% [51.0; 53.8]

MAU, microalbuminuria; CI, confidence interval; CHF, congestive heart failure; CAD, coronary artery disease; TIA, transitory ischemic attack; PAD, peripheral arterial disease

Figure 3

Mean prevalence estimates [95% CI]; cardiovascular disease considered were: History of myocardial infarction (MI) or CABG or PTCA, history of ischemic stroke or carotid endarterectomy or carotid angioplasty, peripheral arterial disease (PAD).

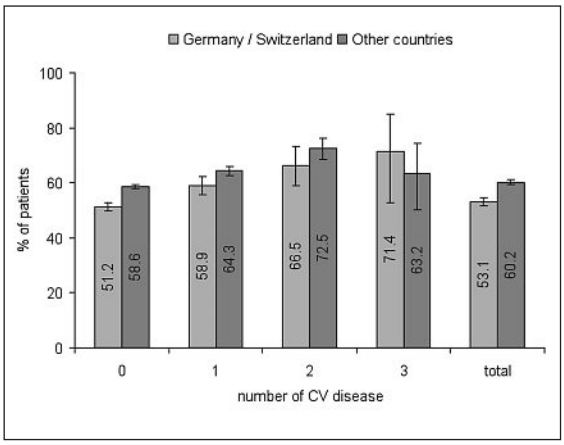
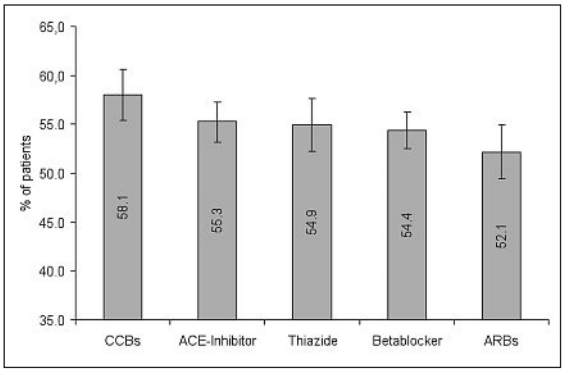


Figure 5

Mean prevalence estimates [95% CI] of MAU in patients receiving specific antihypertensive drug classes; ARBs – Angiotensin receptor blockers; ACE – Angiotensin Converting Enzyme; CCBs – Calcium Channel Blockers.



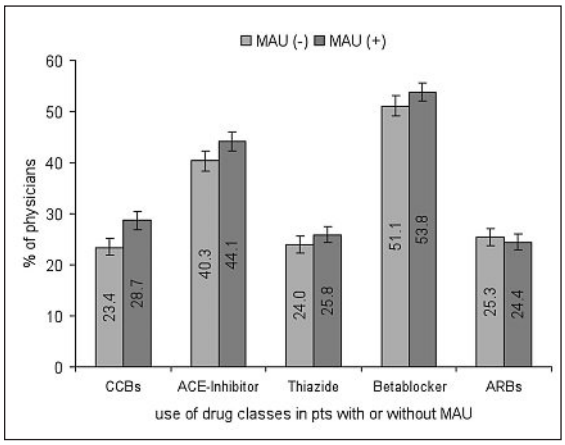


Figure 4

Use of antihypertensive drug classes in patients with (+) or without (–) microalbuminuria. Mean prevalence estimates [95% CI] are provided. ARBs – Angiotensin receptor blockers; ACE – Angiotensin Converting Enzyme; CCBs – Calcium Channel Blockers.

Discussion

The demographic characteristics of the present sample indicate that high risk patients are common in a hypertensive population seen by cardiologists. The population were mostly elderly with a substantial cardiovascular risk factor profile and a considerable burden of co-morbidity. Therefore, as MAU is not only a risk marker for diabetic nephropathy but also indicates a considerable increase in cardiovascular risk, the investigation of the interdependence of cardiovascular risk and MAU is of particular value in this patient population. The present subanalysis of the Swiss and German centres of the global i-SEARCH survey generated the following key results: 1) Patients in Germany and Switzerland were highly comparable to the OC patient population, except that higher rates of diabetes and uncontrolled blood pressure were present in Germany and Switzerland. 2) The prevalence of MAU in clinical cardiology (53.1%) exceeds the one found in most of the previous studies in similar populations, specifically in primary care, and physicians regard MAU as a cardiovascular risk marker. 3) MAU is associated with a number of cardiovascular risk factors and co-morbidities. 4) CCBs are more frequently used in MAU positive patients as compared to ARBs.

Microalbuminuria is frequent, but is underestimated

The prevalence of MAU found in the present sample of hypertensive patients in a cardiologic outpatient setting indicates that this cardiovascular risk marker is very common in clinical cardiology (53.1%). Furthermore it was higher than found in studies on unselected persons in the general population [17–19] and patients in primary care [20, 21]. The HYDRA study in primary care for example [20] has documented a prevalence of 21.2% of patients with hypertension and 37.8% of patients with both hypertension and diabetes. The global DEMAND Study has documented a prevalence of 51.8% in patients of general practitioners in Germany (sub-analysis of [21], unpublished). Explanations for this difference may be as follows: In i-SEARCH, the study population was older than in most previous studies. Additionally 35% of the enrolled hypertensive patients were diabetic, whereas in other studies [22–24] diabetic subjects were excluded. Patients with known MAU were also not excluded as they were in the DEMAND study [21]. These factors and the cardiovascular high risk population attending a cardiologist, in comparison to primary care, may account for the observed differences and the somewhat higher prevalence reported in the present study.

Comparing the German and Swiss results to the results obtained in the OC prevalence it is apparent, that the OC prevalence of MAU (60.2%) is higher than reported for Germany (53.1%). Furthermore physicians estimated prevalence and awareness of MAU as a cardiovascular risk marker is higher than in other countries. Methodological differences between countries are unlikely to have resulted in this discrepancy because the question-

naires were standardised and a Microalbustix® dip stick test kit for MAU provided to the participating physician. Given that this test corrects for urine volume by urine creatinine determination differences between countries are more likely related to differences in co-morbidity, and patient care between more advance health care systems and those of "third world" countries. Although the prevalence is high, the estimated prevalence of MAU, the knowledge about the true prevalence in their patient cohort and the use of this marker for day to day decisions on how to proceed with therapy is low. This finding has also been documented for general practitioners (HYDRA) [20]. This finding reflects an important gap that exists between physician awareness of the prognostic importance of MAU and actual screening for MAU in cardiology practices.

MAU is associated with a considerable cardiovascular risk and disease

MAU was associated with a number of cardiovascular risk factors and disease in the present study. This observation is in agreement with previous data from population based studies [17] and primary care [20]. This indicates that MAU is common in patients who are referred to a cardiologist and is associated with a number of other cardiovascular risk factors. This association has been previously described in clinical studies for male gender [25] and older age [26], diabetes [27], obesity [28], smoking [29], insulin resistance syndrome [30], left ventricular hypertrophy (LVH) [31], left ventricular dysfunction [32] and CRP [33] (not significant in the present study). While not all parameters could be confirmed in the present study, the strong association of MAU with a variety of cardiovascular risk markers is evident.

Interestingly the prevalence of MAU was particularly low in patients participating in more than four hours per week of regular exercise or having high HDL cholesterol. The former finding, which has been also confirmed in the overall i-SEARCH-population, is in line with a previous report that showed MAU is low in physically active patients and can even be reversed when patients are motivated to perform regular exercise [34].

Therapeutic implications

A wide spectrum of treatments including statins, ACE inhibitors and ARBs has been shown to improve endothelial dysfunction, MAU and proteinuria. In the IDNT study [35], for example, the ARB Irbesartan has been shown to prevent the further deterioriation of proteinuria in comparison to the CCB Amlodipine or standard therapy (beta-blockers, diuretics, certain CCBs). In the IRMA-2 study it was even shown that an early intervention results in a reversal and normalisation of albumin excretion [36]. Therefore it was of particular interest to test whether there are differences between antihypertensive classes with respect to MAU. The analyses are difficult to interpret because of unknown confounding variables and the cross-sectional character of the study but have shown that CCBs are more widely prescribed in MAU positive patients than ARBs (which would be reasonable in combination with RAS blocking agents but usually not as monotherapy). In contrast, MAU is more frequently present in patients on CCBs. This may be a question of what occurred first, MAU or treatment with a CCB, but choice of the substance class is at least not in agreement with recent study results discussed previously. Furthermore analyses presented in the global analysis of the i-SEARCH survey [13] indicated by using multiple regression analyses that, while ARBs are at least neutral or even nominally beneficial in these patients, CCBs (and beta-blockers) were not. Evidence for favouring ARBs over beta-blockers comes from a subanalysis of the LIFE trial. Ibsen and colleagues compared Atenolol and Losartan with respect to the cardiovascular outcomes in patients with MAU and showed that a reduction in MAU was associated with a significantly reduced risk of non-fatal myocardial infarction, stroke and cardiovascular death [37].

MAU is also an established target for primary prevention, which has been shown in the PREVENT-IT study [38]. Healthy individuals with MAU, but without hypertension or hypercholesterolemia, were treated either with placebo or RAS blockade. At four-years follow-up, MAU was effectively reduced, which was associated with a 44 % reduction in cardiovascular events.

Strength and limitations

The main strengths of this cross-sectional study included a large, referred cohort of hypertensive patients attending a cardiologist or internist, with validation of predefined primary and secondary end points. However, two limitations should be noted. Firstly, MAU could only be assessed on a single occasion although guidelines recommend triple testing (2 out of 3 tests need to be positive). Therefore the present data may not allow an exact quantification of how many patients would be positive or negative on a second occasion. However, other data suggest that this requirement will only reduce the point prevalence by one-fifth up [39] to a maximum of one third [40]. Secondly, a follow up would allow the closer investigation of the relation between ARB use and the development or regression of MAU. This was not done in the present study but will be part of i-SEARCH Plus, the design of which has been published recently [41].

Conclusions

A high prevalence of MAU was detected in consecutive patients attending a cardiology outpatient setting, indicating that cardiovascular high risk is common and possibly underestimated. Early detection, a more aggressive multifactorial treatment to reduce blood pressure as well as to control other cardiovascular risk factors is warranted to facilitate not only secondary but also primary prevention.

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References

1 Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, et al. Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest. 1997;99(2):342–8.
2 Deckert T, Feldt-Rasmussen B, Djurup R, Deckert M. Glomerular size and charge selectivity in insulin-dependent diabetes mellitus. Kidney Int. 1988;33(1):100–6.
3 Diercks GF, van Boven AJ, Hillege HL, Janssen WM, Kors JA, de Jong PE, et al. Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population. The PREVEND (Prevention of REnal and Vascular ENdstage Disease) study. Eur Heart J. 2000;21(23):1922–7.
4 Cuspidi C, Meani S, Valerio C, Fusi V, Catini E, Sala C, et al. Prevalence and correlates of advanced retinopathy in a large selected hypertensive population. The Evaluation of Target Organ Damage in Hypertension (ETODH) study. Blood Press. 2005;14(1):25–31.
5 Yamaji T, Fukuhara T, Kinoshita M. Increased capillary permeability to albumin in diabetic rat myocardium. Circ Res. 1993;72(5):947–57.
6 Schmieder RE. Endothelial dysfunction: how can one intervene at the beginning of the cardiovascular continuum? J Hypertens Suppl. 2006;24(2):S31–5.
7 Berton G, Cordiano R, Palmieri R, Cucchini F, De Toni R, Palatini P. Microalbuminuria during acute myocardial infarction; a strong predictor for 1-year mortality. Eur Heart J. 2001;22(16):1466–75.
8 Cosson E, Pham I, Valensi P, Paries J, Attali JR, Nitenberg A. Impaired coronary endothelium-dependent vasodilation is associated with microalbuminuria in patients with type 2 diabetes and angiographically normal coronary arteries. Diabetes Care. 2006;29(1):107–12.
9 Lekatsas I, Kranidis A, Ioannidis G, Kalofoutis C, Tavernarakis A, Thalassinos N, et al. Comparison of the extent and severity of coronary artery disease in patients with acute myocardial infarction with and without microalbuminuria. Am J Cardiol. 2004;94(3):334–7.
10 Klausen KP, Scharling H, Jensen G, Jensen JS. New definition of microalbuminuria in hypertensive subjects: association with incident coronary heart disease and death. Hypertension. 2005;46(1):33–7.
11 Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134(8):629–36.
12 Schmieder RE, Schrader J, Zidek W, Tebbe U, Paar WD, Bramlage P, et al. Low-grade albuminuria and cardiovascular risk: What is the evidence? Clin Res Cardiol. 2007;96(5):247–57.
13 Böhm M, Thoenes M, Danchin N, Bramlage P, La Puerta P, Volpe M. Association of cardiovascular risk factors with microalbuminuria in hypertensive individuals: the i-SEARCH global study. J Hypertens. 2007;25(11):2317–24.
14 Böhm M, Reil J, Danchin N, Thoenes M, Bramlage P, Volpe M. Association of Heart Rate to Microalbuminuria in Cardiovascular High Risk Patients – Data from I-SEARCH. J Hypertens. 2008;26:18–25.
15 Comper WD, Jerums G, Osicka TM. Deficiency in the detection of microalbuminuria by urinary dipstick in diabetic patients. Diabetes Care. 2003;26(11):3195–6.
16 SAS8.2. SAS® software In. Release 8.2 ed. Cary NC: SAS Institute Inc.; 2001
17 Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001;249(6):519–26.
18 Jones CA, Francis ME, Eberhardt MS, Chavers B, Coresh J, Engelgau M, et al. Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2002;39(3):445–59.
19 Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. Kidney Int. 2002;61(6):2165–75.
20 Bramlage P, Pittrow D, Lehnert H, Höfler M, Kirch W, Ritz E, et al. Frequency of Albuminuria in Primary Care: a cross sectional study. Eur J Cardiovasc Prev Rehabil. 2007;14:107–13.
21 Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int. 2006;69(11):2057–63.
22 Gatzka CD, Reid CM, Lux A, Dart AM, Jennings GL. Left ventricular mass and microalbuminuria: relation to ambulatory blood pressure. Hypertension Diagnostic Service Investigators. Clin Exp Pharmacol Physiol. 1999;26(7):514–6.
23 Agrawal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. J Hypertens. 1996;14(2):223–8.
24 Summerson JH, Bell RA, Konen JC. Racial differences in the prevalence of microalbuminuria in hypertension. Am J Kidney Dis. 1995;26(4):577–9.
25 Gould MM, Mohamed-Ali V, Goubet SA, Yudkin JS, Haines AP. Microalbuminuria: associations with height and sex in non-diabetic subjects. BMJ. 1993;306(6872):240–2.
26 Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. BMJ. 1990;300(6720):297–300.
27 Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982;1(8287):1430–2.
28 Valensi P, Assayag M, Busby M, Paries J, Lormeau B, Attali JR. Microalbuminuria in obese patients with or without hypertension. Int J Obes Relat Metab Disord. 1996;20(6):574–9.
29 Cirillo M, Senigalliesi L, Laurenzi M, Alfieri R, Stamler J, Stamler R, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Arch Intern Med. 1998;158(17):1933–9.
30 Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the insulin resistance atherosclerosis study. Diabetes. 1998;47(5):793–800.
31 Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlof B, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Losartan Intervention for Endpoint Reduction. Am Heart J. 2002;143(2):319–26.
32 Liu JE, Robbins DC, Palmieri V, Bella JN, Roman MJ, Fabsitz R, et al. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the Strong Heart Study. J Am Coll Cardiol. 2003;41(11):2022–8.
33 Barzilay JI, Peterson D, Cushman M, Heckbert SR, Cao JJ, Blaum C, et al. The relationship of cardiovascular risk factors to microalbuminuria in older adults with or without diabetes mellitus or hypertension: the cardiovascular health study. Am J Kidney Dis. 2004;44(1):25–34.
34 Fredrickson SK, Ferro TJ, Schutrumpf AC. Disappearance of microalbuminuria in a patient with type 2 diabetes and the metabolic syndrome in the setting of an intense exercise and dietary program with sustained weight reduction. Diabetes Care. 2004;27(7):1754–5.
35 Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–60.
36 Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870–8.
37 Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension. 2005;45(2):198–202.
38 Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110(18):2809–16.
39 Kalter-Leibovici O, Van Dyk DJ, Leibovici L, Loya N, Erman A, Kremer I, et al. Risk factors for development of diabetic nephropathy and retinopathy in Jewish IDDM patients. Diabetes. 1991;40(2):204–10.
40 Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41(1):1–12.
41 Tebbe U, Lüders S, de Haan F, Bramlage P, Böhm M, Paar WD, et al. Langzeitverlauf kardiovaskulärer Risikomarker bei Patienten mit Hypertonie: Rationale, Design und Ausgangscharakteristika des i-SEARCH Plus Registers. Med Klin. (München) 2007;102(10):824–32.