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REVIEW

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Low-grade albuminuria and cardiovascular risk

What is the evidence?

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Abstract Microalbuminuria (MA), conventionally defined as a urinary albumin excretion (UAE) of 30–300 mg/day, is recognised as a marker of endothelial dysfunction. Furthermore, it represents an established risk factor for cardiovascular morbidity and mortality and for end-stage renal disease in individuals with an adverse cardiovascular risk profile. It is common in the general population, particularly in patients with diabetes mellitus or arterial hypertension. There is growing evidence from prospective observational trials that UAE levels well below the current MA threshold ("low-grade MA") are also associated with an increased risk of incident cardiovascular disease and all-cause mortality. Even in apparently healthy individuals (without diabetes or hypertension), such an association has been shown. As albuminuria screening assays that are reliable even in the lower ranges are commercially available, there may be an important clinical role for MA in disease screening, comparable to the role of blood pressure and lipid screening. MA is modifiable, and the inhibition of the renin-angiotensin system by ACE inhibitors and AT_1 receptor antagonists has been shown to result in a lower incidence of cardiovascular events.

Key words microalbuminuria – endothelial dysfunction – cardiovascular risk – renin angiotensin system – urinary albumin excretion – urinary albumin creatinine ratio – scrennning – prevention

Background

The thresholds for proteinuria are variously defined (Table 1) [1] Conventionally, microalbuminuria (MA) is characterized by an urinary albumin excretion (UAE) of 20–200 μg/min (equivalent to 30–300 mg/day) [1]. In order to avoid unpractical timed measurements, the urinary albumin-to-creatinine ratio (UACR) in spot samples is recommended by the National Kidney Foundation [1], and applied in the majority of the respective epidemiological studies. Using this convention, an UACR of 30–300 mg/g defines the microalbuminuric range [1]; however, a somewhat higher UACR range has been proposed for women to account for their less muscle mass and lower urinary creatinine excretion [2].

MA is a common condition in the community or in primary care, respectively. The US American community-based NHANES-III study showed that 29% of individuals with diabetes mellitus, 16% of patients with arterial hypertension, and 5% apparently healthy individuals (without diabetes, hypertension, cardiovascular disease or increased serum creatinine) had MA [3]. The respective MA prevalence rates in the general population in Groningen/The Netherlands were 16% (diabetes), 12% (hypertension) and 7% (no diabetes, no hypertension) [4], and in primary care in Germany 38% (diabetes plus hypertension), 30% (diabetes alone), 21% (hypertension alone), and 15% (no diabetes, no hypertension) [5]. In a referred cohort of 24151 type-2 diabetic patients from 33 countries in the *Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes study* (DEMAND), the overall global prevalence of normo-, micro-, and macroalbuminuria was 51%, 39%, and 10%, respectively [6].

Differences between individuals in their level of UAE rate are already seen at a very early age (just after birth). Actually, the interindividual variability seems to be relatively constant in the first five decades of life, indicating that microalbuminuria is not necessarily a consequence of vascular damage at later age [7]. The precise pathophysiology associated with MA is unknown, but various mechanisms seem to be involved. Principally, the condition may simply represent the consequence of increased intraglomerular pressure, e.g. due to systemic hypertension [8]. Further, leakage of albumin may reflect the renal manifestation of a global abnormality of endothelial function, and represent a generalised arterial disease not only affecting the glomeruli, but also the retina, and the intima of large vessels at the same time [9, 10]. Thus, a pathophysiologic link between microalbuminuria and (preclinical) atherosclerosis mediated through an increased generalized transvascular leakage of albumin, is likely [11]. The systemic transvascular leakiness – due to hemodynamic factors or structural or functional perturbations of the endothelium or the intracellular matrix beneath – may also include lipoproteins, and allow for increased lipid penetration into the vessel walls [12].

MA has been extensively studied as a risk factor for cardiovascular outcomes, primarily in subjects with diabetes mellitus. Table 2 (top) shows that in populations of patients with prevalent type-1 or type-2 diabetes, considered as highest-risk patients, almost all prospective studies showed an association between MA and cardiovascular disease and/or all-cause mortality [13]. Similarly, in patients with a history of vascular diseases [14,] electrocardiographic ST-T segment changes [15], in the upper 15% of ischemic heart disease risk [16] or those with hypertension [17–19], a clear association between MA or proteinuria and cardiovascular outcomes was shown (Table 2, bottom).

The concept of *low-grade* albuminuria is less known, although lower degrees of UAE (< 30 mg/d)

[1] To convert UACR in μg/mg to mg/mmol, multiply by 0.113. To convert UACR in mg/mmol to mg/g, multiply by 8.84

Table 1 Definitions of proteinuria

Urine collection method	Normal	Micro-albuminuria	Albuminuria or clinical proteinuria
Total protein			
24 h excretion[†]	<300 mg/d	NA	≥300 mg/d
Spot urine dipstick	<300 mg/dl	NA	≥300 mg/l
Spot urine protein-to-creatinine ratio [†]	<200 mg/g	NA	≥200 mg/g
Albumin			
24 h excretion	< 30 mg/day	30–300 mg/day	> 300 mg/day
Spot urine albumin-specific dipstick	< 3 mg/dl	> 3 mg/dl	NA
Spot urine protein-to-creatinine ratio	< 17 mg/g (M) <25 mg/g (F)	17–250 mg/g (M) 25–355 mg/g (F)	> 250 mg/g (M) > 355 mg/g (F)

[†] Varies with method; *F* females; *M* men; *NA* not applicable. Source: National Kidney Foundation [1]

Table 2 Microalbuminuria or albuminuria as a risk factor for CVD outcomes or all-cause death in prospective studies

Author, year	Inclusion criteria	n	Definition of CVD	Association with CVD	Association with all-cause mortality
Diabetes mellitus					
Stehouwer, 2002 [46]	Type 2 DM; age < 66 y	363	NA	NA	+
Gerstein, 2001 [14]	DM plus another CVD risk factor	3498	Composite: MI, stroke, CVD death	+	+
Agewall, 1997 [19]	DM and treated hypertension	94	CVD mortality	+	+
Stephenson, 1995 [47]	Type 1 DM	1188	CVD mortality	+	+
Stephenson, 1995 [47]	Type 2 DM	3234	CVD mortality	+	+
Dinneen, 1997 [48]	Type 2 DM: pooled odds ratios of 11 cohort studies	2138	Composite: CVD morbidity and mortality	+	+
Mogensen, 1984 [49]	Type 2 DM; age 50–75 y	76	NA	NA	+
Valmadrid, 2000 [50]	Type 2 DM; mean age 68 y	840	CVD mortality	+	+
Miettinen, 1996 [51]	Type 2 DM	1056	Composite: stroke, IHD, and PAD	+	NA
Messent, 1992 [52]	Type 1 DM	63	CVD mortality	+	–
Rossing, 1996 [53]	Type 1 DM	939	CVD mortality	+	+
Gall, 1995 [54]	White with type 2 DM	328	CVD mortality	albuminuria only	+
Uusitupa, 1993 [55]	Incident type 2 DM	133	CVD mortality	–	NA
ECG changes					
Gerstein, 2001 [14]	Vascular disease	5545	Composite: MI, stroke, CVD mortality	+	+
Diercks, 2002 [15]	Subjects with ST-T wave changes	7330	CVD mortality	+	+
Grimm, 1997 [16]	Men in the upper 15% of coronary heart disease risk	12866	CVD mortality	+	+
Hypertension					
De Leeuw, 2002 [17]	Systolic hypertension and age ≥60 y	4695	Composite: fatal and nonfatal CVD (stroke and IHD)	+	+
Ljungman, 1996 [18]	Hypertensive and nonhypertensive men	120	Composite: IHD, stroke, and PVD	+	NA
Agewall, 1997 [19]	Treated hypertension	345	CVD mortality	–	–

CVD cardiovascular disease; *DM* diabetes mellitus, *NA* not applicable, the outcome was not evaluated in the study; *MI* myocardial infarction; *IHD* ischemic heart disease; *PAD* peripheral arterial factors; +, MA (in diabetics) or proteinuria (ECG changes, vascular disease, hypertension) was an independent risk factor for the outcome after adjustment for all other CVD risk-factors (author conclusion); –, MA (in diabetics) or proteinuria (ECG changes, vascular disease, hypertension) was *not* an independent risk factor for the outcome after adjustment for all other CVD risk factors (author conclusion). Adapted from: Sarnak et al. [13]

frequently may be found. Thus, in recent years a focus of research has shifted towards the prognostic value of low-grade albuminuria, i.e., UAE in the high "normoalbuminuric" range. In the following the current evidence from prospective, observational cohort studies (almost all community based) investigating a wide range of patients but also normal individuals is summarized (see also Table 3).

Morbidity

Arterial hypertension Wang et al. recently hypothesized that elevated UAE may predict the development of hypertension, what previously had not been tested in humans [20]. They found in a large cohort of middle-aged non-diabetic, non-hypertensive individuals from the Framingham Offspring Study that very low degrees of UAE are clinically important, as they were associated with blood pressure progression and incident hypertension. UACR values as low as 1.7–3.8 mg/g for men and 3.4–7.5 mg/g for women, corresponding to the second quartile, were associated with a statistically significant 71% increase in the risk of incident hypertension compared with lower values. The authors reported that UACR in their study had a sensitivity of 31% and a specificity of 76% for detecting the development of hypertension over the next three years. Thus measurement of UACR, alone or in combination with other biomarkers, could aid in the primary prevention of hypertension by identifying those at higher risk.

Mortality in high risk patients

High risk patients with acute myocardial infarction In a prospective cohort study in 3 coronary care units, Berton et al. showed that the incidence of 1-year mortality of patients with acute myocardial infarction was related to the baseline UACR [21]. The best cut-off for total mortality approximated to be

Table 3 Studies investigating *low-grade* microalbuminuria as a risk factor for CVD outcomes or all-cause death in prospective population-based studies

Author, year	Inclusion criteria	Follow-up	Definition of CVD	Association with CVD	Association with all-cause mortality	Risk increase (details)
Borch-Johnson, Denmark, 1999 [22] WHO MONICA	2085 individuals without IHD, renal disease, urinary tract infection, or DM	up to 10 yrs	IHD	+	NA	UACR > 90th percentile (> 0.65 mg/mmol = 5.75 mg/g): Adjusted RR for IHD 2.3 (95%: 1.3–3.9, p = 0.002) 10-yr disease-free survival decreased from 97% to 91%, p < 0.0001
Hillege, Groningen/ NL, 2002 [24]	40458 individuals from general population	2.6 yrs	not detailed	+	+	Crude incidence rates of CV death for 0-10/ 20-20/20-200/> 200 mg/l: 1.2 (1.0–1.5)/1.3 (0.8–2.0)/4.7 (3.2–6.6)/16.6 (8.9–29.1), p for trend: 0.001
Romundstadt, Norway, 2003 [23]	2089 apparently healthy individuals (many hypertensives)	4.4 yrs	NA	NA	+	Lowest UACR level associated with increased RR for mortality was the 60th percentile (≥ 6.7 mg/g = 0.76 mg/mmol; RR 2.4; 95% CI: 1.1–5.2)
Romundstadt, Norway, 2003 [56]	5369 individuals with treated hypertension (partially suboptimal)	4.3 yrs	NA	NA	+	In men, UACR in the fourth quartile (1.70 mg/mmol = 15.0 mg/g) was associated with increased RR of all-cause mortality, 1.6 (95% CI: 1.0–2.6), compared with UACR in the first quartile. The lowest UACR level associated with mortality in men was 0.86 mg/mmol = 7.60 mg/g, RR 1.6 (95% CI: 1.1–2.4)
Yuyun, Norfolk/UK, 2004 [11] EPIC-Norfolk	22368 individuals aged 40–79 yrs without baseline IHD and 1596 with baseline IHD	6.4 yrs	IHD	+ for MA	+ for MA*	Age-adjusted incidence of IHD trended to increase (n.s.) across tertiles of normo-albuminuria (up to UACR < 2.5 mg/mmol = 22.1 mg/g). The multivariate HR for incident primary IHD was 1.36, 95% CI: 1.12–1.64 for MA and 1.59; 95% CI: 1.10–2.37 for MA
Ärnlöv, US, 2005 [25] Framingham	1568 individuals without hypertension and without diabetes	6 yrs	Composite: IHD, stroke, TIA, CHF, IC	+	+ (borderline)	Participants with UACR greater than or equal to the sex-specific median (3.9 mg/g for men, 7.5 mg/g for women) experienced a nearly 3-fold risk of CVD (adjusted HR 2.92; 95% CI: 1.57–5.44; p < 0.001)

(Legend, also see Table 2) CHF congestive heart failure; *CI* confidence interval; *CV* cardiovascular; *IC* intermittent claudication; *n.s.* not significant; *MA* microalbuminuria; *RR* risk reduction; *TIA* transitory ischemic attack. * Only in patients with baseline IHD

50 mg/g on the first day after myocardial infarction, 30 mg/g on the third day, and 20 mg/g on the seventh day. At multivariable Cox analysis, the UACR was the strongest among several independent predictors of mortality (including age, left ventricular ejection, peak creatine phosphokinase-MB isoenzyme, and thrombolysis) at day 1, 3 and 7 after admission. Patients with a high UACR had a significant 3.4 to 5.0-fold increased risk of cardiovascular mortality and 3.6 to 4.9-fold increased risk of total mortality for the three UACR measurements.

High risk patients with cardiovascular disease or diabetes mellitus with at least one additional risk factor In a retrospective analysis of the HOPE and MICRO-HOPE studies, there was a continuous association between albuminuria and cardiovascular events starting at 4.4 mg/g (corresponding to 0.5 mg/mmol) and thus well below the conventional MA cut-off, when men and women were analyzed combined [14].

Mortality in low risk individuals

WHO MONICA cohort in healthy individuals Borch-Johnsen et al. observed 2085 individuals without ischemic heart disease, renal disease or diabetes mellitus in the Danish WHO MONICA cohort over 10 years [22]. They found a slightly increased UACR (> 0.65 mg/mmol, corresponding to 5.8 mg/g) to be a potent and clinically relevant risk marker for the development of ischemic heart disease, independent of other established atherosclerotic risk factors such as male sex, arterial hypertension, dyslipidemia, smoking, old age, and obesity. When adjusted for these risk factors, the relative risk of ischemic heart disease associated with MA above this threshold was

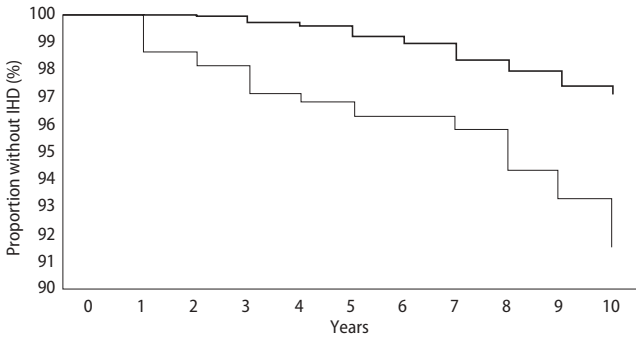

Fig. 1 Incident ischemic fatal or non-fatal heart disease (IHD) in a population of individuals without IHD, diabetes mellitus or renal disease over 10 years. The Kaplan-Meier estimate shows that the crude survival free from IHD during 10-year follow-up in participants with normoalbuminuria was 97% (bold curve) and 91% with microalbuminuria (thin curve, $p < 0.0001$). Microalbuminuria was defined as the upper 10% of the distribution of UACR, corresponding to >0.65 mg/mmol, corresponding to 5.75 mg/g. Data from the Danish WHO MONICA cohort. Reprinted with permission from Borch-Johnsen et al. [22]

2.3; 95% CI: 1.3–3.9, $p = 0.002$, and the 10-year disease-free survival decreased from 97% to 91% ($p < 0.0001$) when microalbuminuria was present (Fig. 1). The presence of microalbuminuria more than doubled the predictive effect of the conventional atherosclerotic risk factors for development of ischemic heart disease. The authors concluded that microalbuminuria is not only an independent predictor of ischemic heart disease but also substantially increases the risk associated with other established risk factors.

HUNT study in "apparently healthy" individuals This population-based study in Norway followed 2089 non-diabetic subjects, who were not drug treated for hypertension, over 4.4 years [23]. Notably, many patients were hypertensive (e.g. SBP ≥140 mmHg in men with UACR <22 mg/g: 41%, with UACR ≥22 mg/g: 69%). Patients with existing ischemic heart disease were excluded in the main analysis. The study did not assess CV events, but found a positive association between all-cause mortality and albumin excretion. The lowest UACR level associated with increased RR for mortality was the 60th percentile (≥6.7 mg/g, corresponding to 0.76 mg/mmol; RR 2.4; 95% CI: 1.1–5.2).

EPIC-Norfolk Study in healthy individuals and patients with IHD The British population-based study in 22 368 individuals without IHD at baseline followed over 6.4 years confirmed these findings [11]. When the normalbuminuria range was divided into three tertiles, the age-adjusted incidence of IHD increased in the upper tertile (0.91–2.49 mg/mmol, corresponding to 8.0–22.0 mg/g) compared to lower (0.0–0.40 mg/mmol, corresponding to 0–3.5 mg/g) was increased by 30% (hazard ratio, HR 1.30; 95% CI: 0.86–1.47). The risk further significantly increased in the ranges defined as microalbuminuric (2.5–25 mg/mmol, corresponding to 22.1–221 mg/g); HR: 1.86; 95% CI: 1.24–1.92) and macroalbuminuric (>25 mg/mmol, corresponding to 221 mg/g, HR 2.84; 95% CI: 1.80–4.46). Age-adjusted incidence of IHD increased significantly across categories of baseline albuminuria. Albuminuria even in the low so far defined normal range and proteinuria predicted primary IHD events independently of other established cardiovascular disease risk factors. Both were equally predictive of recurrent events among participants with prevalent baseline IHD, in whom the absolute level of risk was much higher.

PREVEND study in unselected individuals Hillege et al. aimed to generate more generalizable findings in that they investigated a less selected population and not only used cardiovascular death, but also all-cause mortality as an endpoint [24]. In their Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort, a total of 40 548 individuals (11% with hypertension, 3% with diabetes mellitus, 4% with previous myocardial infarction or stroke) were followed up over a mean of 2.6 years. They found a positive dose-response relationship between increasing UAE and mortality. The relationship was already apparent at levels of albuminuria currently considered to be normal (Fig. 2). After adjustment for other well-recognized cardiovascular risk factors, a twofold increase in UAE was associated with an additional risk of 29% for CV mortality (1.29; 95% CI: 1.18–1.40) and 12% for non-cardiovascular mortality (1.12; 95% CI: 1.04–1.21). A major strength of that study was that the study used the full range of UAE instead of using predefined categories in studying the relationship with mortality, and thus could show that the risk increase was continuous, already beginning at UAC concentrations of 10–20 mg/l.

Framingham Heart Study in healthy individuals Similary to the above observation, Ärnlöv et al. showed in a community-based sample of middle-aged non-hypertensive, non-diabetic individuals that low levels of UAE well below the current microalbuminuria threshold predicted the development of cardiovascular disease [25]. The increased cardiovascular disease risk associated with UACR at or above the median remained robust in analyses restricted to individuals without microalbuminuria and in subgroups with intermediate and low pre-test probabilities of cardiovascular disease. The observations add to the growing body of evidence that challenges the

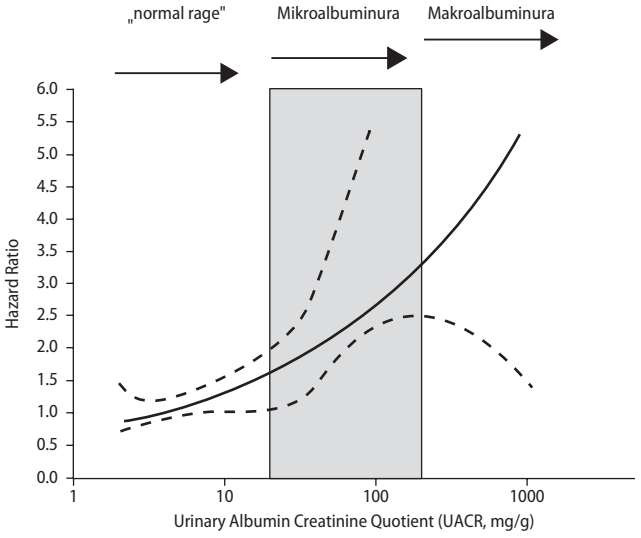

Fig. 2 Association between urinary albumin exretion and fatal cardiovascular events. Figure shows the cardiovascular risk increase (hazard ratio) with increased UACR. The solid line indicates the mean, the dotted lines the 95% confidence intervals. The range conventionally defined as "microalbuminuria" (30–300 mg/g) is shaded. Cardiovascular risk increases already in UACR values which are in the "normal range". Reprinted with permission from: PREVEND Study [24]

notion that UACR < 30 μg/mg indicates "normal" albumin excretion.

When considering the five major prospective community-based studies together it is of note that four studies (Danish WHO MONICA, EPIC-Norfolk, PREVEND, HUNT) included patients with hypertension [11, 22–24], two studies also included patients with diabetes (EPIC-Norfolk, PREVEND) [11, 24], and one study (PREVEND) also included patients with prior myocardial infarction or stroke [24]. These conditions might confound the outcomes of the studies, as high-risk individuals will be submerged in a pool of lower-risk patients which might dilute the size effect, or, despite statistical adjustment for these conditions in multivariate analyses, residual confounding may exist as albuminuria may be a marker of target organ damage and chronicity of blood pressure elevation or diabetes [25]. Against this background, the recent study data from the Framingham Offspring cohort in "healthy individuals" [25] is of particular interest.

The individual studies were not entirely consistent about the prognostic significance of low-grade MA. For example, in the EPIC-Norfolk study the risk increase in the three tertiles of low-grade albuminuria ("normoalbuminuria") showed a trend, but did not achieve statistical significance [11]. In the HUNT study, the association of low-grade MA (defined as > 6.7 mg/l) with all-cause mortality was attenuated but not lost after exclusion of hypertensive individuals [23]. These studies together with both the PREVEND study (which did not cluster UACR levels into categories), and the Framingham Offspring study with low cut-offs (sex-specific medians of 3.9 mg/g for men and 7.7 mg/g for women) well below the conventional threshold for MA (UACR 30 mg/g) do support the risk increase associated with low-grade albuminuria.

Intervention in individuals with increased UAE

At present, no studies exist that show whether non-pharmacological or pharmacological approaches to *low-grade* albuminuria improve the prognosis of individuals. Such studies do exist, however, in patients with microalbuminuria or macroalbuminuria. Angiotensin converting enzyme (ACE) inhibitors and angiotensin-1 (AT_1) receptor antagonists, which both inhibit the renin-angiotensin system, play an important role. They not only reduce UAE and delay progression of renal disease, but also seem to favorably improve cardiovascular outcomes. Table 4 summarizes important outcome studies in this area.

Slowed progression of renal disease

A number of large-scale trials with the ACE inhibitors captopril [26], ramipril [27], fosinopril [28], trandolapril [29] and the AT_1-receptor antagonists irbesartan [30, 31], and losartan [32, 33] found a favorable effect of long-term drug treatment on the progression of renal disease. For example, in the IRMA-2 study irbesartan was found to be renoprotective independently of its blood pressure lowering effect in patients with type-2 diabetes and microalbuminuria (Fig. 3) [34]. Regarding the primary outcome (time to onset of diabetic nephropathy) the Kaplan-Meier curves for the placebo group and the 300 mg irbesartan group separated already at the three-month visit and continued to diverge. The risk for progressive diabetic nephropathy defined as development of overt proteinuria was reduced by 39% (unadjusted hazard ratio 0.61, $p = 0.08$) in the 150-mg group and by 70% in the 300-mg group (HR 0.30, $p < 0.001$). Thus, irbesartan reduced the level of UAE throughout the study in a dose-dependent manner.

The Irbesartan Diabetic Nephropathy Trial (IDNT) in patients with *type-2 diabetes* and overt nephropathy investigated as the primary endpoint a composite of doubling of serum creatinine levels, end-stage renal disease, and death from any cause [31]. After a mean duration of follow-up of 2.6 years, the primary composite end point was 20% lower in

Table 4 Effect of the inhibition of the RAS on cardiovascular outcomes or mortality in patients with (micro-)albuminuria: randomized, prospective studies

Author, year	N	Inclusion criteria	Follow-up	Intervention	Endpoint(s)	Outcomes
Lewis, 1993 [26]	409	Type-1 diabetes with nephropathy	3 yrs	Captopril 25 mg t.i.d. vs. placebo	1) Doubling of baseline serum creatinine, 2) Death/Dialysis/Tx	1) 48% RR vs. Placebo, 2) 50% RR vs. Placebo
Yusuf , 2000 [27] HOPE	9297	High-risk patients due to vascular disease or DM	5 yrs	Ramipril 10 mg/d vs placebo	Myocardial infarction/stroke/ cardiovascular death	Primary endpoint 14.0% ramipril vs 17.8% placebo
Parving, 2001 [30] IRMA-2	590	Type-2 diabetes with hypertension and microalbuminuria	2 yrs	Irbesartan 150 mg/d or 300 mg/d vs. placebo	1) Time to manifest diabetic nephropathy, 2) Change in UAE	1) Overt nephropathy: adjusted HR 0.56 (150 mg) and 0.32 (300 mg), both significant 2) ↓24% (150 mg), ↓38% (300 mg), ↓2% (Pla) Normoalbuminuria in 24% (150 mg), 34% (300 mg), 21% (Pla)
Lewis, 2001 [31]	1715	Type-2 diabetes with hypertension and diabetic nephropathy	2.6 yrs	Irbesartan 300 mg/d vs. amlodipine vs. placebo	1) Time to doubling of serum creatinine or end-stage renal disease, or death, 2) Doubling of serum creatinine, 3) Cardiovascular death/heart failure/cerebrovascular events	1) Composite endpoint 20% ↓ vs. placebo ($p=0.02$) and 23% ↓ vs amlodipine ($P=0.006$), 2) 33% ↓ vs placebo, and 37% vs. amlodipine. End-stage renal disease: ↓23% vs. placebo/amlodipine, 3) no signif. differences in total mortality/events
Brenner, 2001 [33] RENAAL	1513	Type-2 diabetes with diabetic nephropathy	3.4 yrs	losartan 50–100 mg/d vs. placebo	1) Doubling of serum creatinine, end-stage renal failure or death, 2) End-stage renal disease, 3) CV mortality/morbidity	1) 25% ↓ losartan vs placebo, 2) 28% ↓ losartan vs placebo, 3) no difference in CV morbidity and mortality
De Zeeuw, 2004 [57] RENAAL post-hoc	1513	Type-2 diabetes with diabetic nephropathy	3.4 yrs	losartan 50-100 mg/d	Cardiovasc. events (MI, Stroke, Hospitalisation for heart failure or instable angina)	Reduction of MA in the first 6 months was the only predictor for CV events (per 50% reduction of albuminuria 18% reduction of CV risk)
Asselbergs, 2004 [28] PREVEND-Substudy	1439	General population with MA	3.8 yrs	Fosinopril 20 mg/d Pravastatin Placebo	CV mortality and morbidity	MA ↓26% CV mortality and morbidity 40% ↓ vs placebo
Marre, 2004 [58] DIABHYCAR	4912	Type-2 diabetes and MA or albuminuria	4 yrs	Ramipril low dose 1.25 mg/d	Combined: CV death/MI/stroke, heart failure/end stage renal failure	None of the endpoints was significantly reduced
Ibsen, 2005 [32] LIFE-Substudy	8206	Hypertension with left ventricular hypertrophy	4.8 yrs	Losartan	CV death, non-fatal MI or stroke	Correlation of CV risk with UAE. Benefit in patients with UAE reduction vs. baseline
Schrader, 2006 [41] MARPLE	3529	Essential hypertension without DM	3.5 yrs	Ramipril-based	CV events (MI, stroke)	MA and proteinuria increase CV risk Ramipril reduces cerebrovascular events

the irbesartan compared to the placebo group ($p=0.02$) and 23% lower than that in the amlodipine group ($p=0.006$). These differences were not explained by differences in the blood pressures that were achieved. Similar results were observed in the Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study in patients with *type-2 diabetes* and nephropathy [33].

Cardiovascular events

The majority of the studies described in Table 4 evaluated cardiovascular morbidity or mortality as a secondary endpoint. Lewis et al. in 1993 were the first to show a reduction of cardiovascular morbidity and mortality [26]. In patients with *type-1 diabetes* and diabetic nephropathy, captopril treatment was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation (secondary endpoint) that seemed to be was independent of the small disparity in blood pressure between the groups.

In the IDNT study there were numerical, but no significant differences in the rates of death from any cause or in the cardiovascular composite end point [35]. Yet, a statistically significant protective effect of irbesartan compared to amlodipine or placebo was demonstrated on the development of congestive heart failure, a finding that agrees with results of trials using ACE inhibitors [36], the RENAAL trial

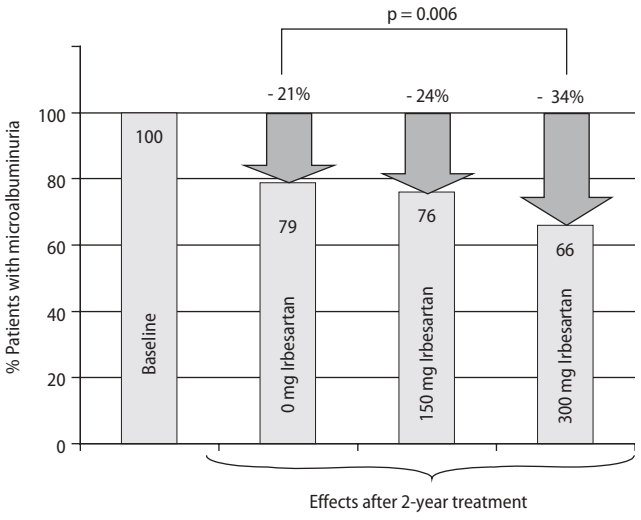

Fig. 3 Favorable effect of RAS inhibition on urinary albumin excretion: rate of patients with the diagnosis "microalbuminuria" after long-term treatment with irbesartan or control drugs. Values in indicate changes of the rate of patients with microalbuminuria after 2-year treatment with a) control drugs (no RAS inhibitors, 0 mg irbesartan), or b) irbesartan 150 mg or c) irbesartan 300 mg. Arrows indicate risk reduction. Irbesartan was renoprotective independently of its blood-pressure-lowering effect in patients with type 2 diabetes and microalbuminuria. Source: IRMA-2 study [34]

with losartan [33], the analysis of the subgroup of patients with diabetes in the LIFE trial [37], and a study of valsartan in a cohort of patients with heart failure [38].

In the post-hoc analysis of RENAAL by de Zeeuw et al. among all available baseline risk markers, albuminuria was the strongest predictor of cardiovascular outcome [39]. Furthermore, reduction of albuminuria was the strongest predictor of long-term protection from cardiovascular events (18% reduction in cardiovascular risk and a 27% reduction in heart failure, respectively, for every 50% reduction in albuminuria).

The IRMA-2, IDNT and RENAAL studies were midsized and not powered to detect differences in cardiovascular events. In a metaanalysis of these studies, the incidence of cardiovascular events was significantly reduced with AT_1-receptor antagonists by 15% (odds ratio 0.85; 95% CI: 0.73–0.98, $p = 0.03$); however the reduction of all-cause mortality did not reach significance (odds ratio 0.89; 95% CI: 0.74–1.07; $p = 0.22$) [40].

In the MARPLE study including *non-diabetic hypertensive* patients, the presence of MA was associated with the incidence of cardiovascular events. Normalization of MA with ramipril-based treatment correlated with a reduction of cardiovascular events [41].

PREVEND IT was the first study specifically designed to target UAE and to address the question whether primary prevention is indicated in MA subjects (UAE 15–300 mg/day) without any other reason for primary prevention [28]. There was a direct relation between the level of UAE and long-term clinical outcome. Treatment with the ACE inhibitor fosinopril had a significant rapid and long-lasting effect on UAE. In addition, fosinopril treatment was associated with a trend in reducing the primary combined endpoint of cardiovascular deaths and hospitalizations. Subjects treated with fosinopril showed a 40% lower incidence of the primary end point (hazard ratio 0.60; 95% CI: 0.33–1.10). This was in contrast to pravastatin treatment which did not result in a significant reduction in UAE or cardiovascular events.

Further studies have indicated that an adequate dosage of drugs is mandatory to achieve suppression of the renin angiotensin system. The DIABHYCARE study showed that in patients with type-2 diabetes and elevated UAE low-dose ramipril led to a small blood pressure reduction, but not to a reduction of any of the cardiovascular or renal endpoints. Conversely, it was demonstrated that very high doses of AT_1-receptor antagonists (irbesartan 900 mg) in patients with hypertension and albuminuria were generally safe and offered additional renoprotection independent of changes in systemic blood pressure and glomerular filtration rate in comparison to the currently recommended dose used in hypertensive patients [42].

These findings can be explained by the fact that dose-response curves for blood pressure and albuminuria appear to be different in both diabetic [43] and non-diabetic patients [44]. Thus, it is likely that therapy aimed at reducing albuminuria could result in additional benefit beyond that achieved with blood pressure lowering alone. High doses of AT_1-receptor antagonists seem to be required to achieve additional reduction in albuminuria and thereby offering additional reno- and cardioprotective effects.

However, there is an obvious need for prospective trials to determine whether low grade albuminuria should be addressed in therapeutic strategies and which cut-off threshold should be used in clinical practice in a cost-effective manner.

Implications and perspective

The present observational studies have shown in cohorts of patients with high cardiovascular risk (diabetes, existing vascular disease, hypertension, etc.) as well as in apparently healthy individuals that the presence of elevated UAE is associated with an increased rate of cardiovascular events and mortality.

The presence of increased albumin excretion is associated with a number of conventional risk factors (they may well share common pathways), but is in the multivariate analyses independently associated with cardiovascular risk, i.e., it carries prognostic information beyond that of the other risk factors. The risk increase operates on a continuum and UAE levels well below the conventional microalbuminuria threshold (30 mg/g or 30 mg/day) are associated with a risk increase. Important prognostic information is missed if patients are categorized according to the conventional dichotomous "normal/pathological" classification of albuminuria. Based on data from the Framingham study patients with a UACR greater than or equal to the sex-specific median (≥3.9 mg/g for men, ≥7.5 mg/g for women) should be regarded as abnormal with regard to the urinary albumin excretion since they experience a nearly 3-fold risk of cardiovascular disease compared with those with UACR below the median.

There may be an important clinical role for albuminuria in cardiovascular disease screening that is analogous to the role of blood pressure and lipid screening [4]. Such a test might be valuable for clinicians to aid in the decision whether a hypertensive patient should receive drug treatment: the presence of (low-grade) microalbuminuria indicates target organ damage and thus an indication for treatment. This might be also applicable for the prehypertensive stage or in patients at risk for type 2 diabetes. Like hypertension or dyslipidemia, albuminuria is a modifiable risk marker. A series of studies of secondary prevention have shown that blood pressure-lowering drugs effectively reduce the UAE rate, and inhibitors of the RAS system seem to be particularly effective. Therefore, ACE inhibitors or AT_1 blockers are preferable to other agents which do not have proven organ protective properties [45].

In conclusion, the current notion of "normal" urine albumin excretion is challenged by the current studies on "low-grade" albuminuria, as it may be a marker for subclinical vascular damage that predisposes to future cardiovascular disease and death, not only patients with risk factors (such as hypertension and diabetes mellitus), but also apparently healthy individuals [25]. The current observation may lead to new therapeutic strategies in the prevention of cardiovascular disease, which will have to be tested prospectively in randomized controlled studies.

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