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# Non-diabetic microalbuminuria, endothelial dysfunction and cardiovascular disease

**Roberto Pedrinelli[a], Giulia Dell'Omo[a], Giuseppe Penno[b] and Mario Mariani[a]**

**Abstract:** Subclinical increases in albuminuria (microalbuminuria) predict morbid events, but the reasons for that are still not understood in full. This paper reviews the existing evidence regarding the relationships of non-diabetic microalbuminuria and cardiovascular disease, the underlying assumption being that endothelial dysfunction contributes both to atherosclerotic macrovascular disease and renal microvascular disease of which albuminuria is a marker. Much data support that concept, and suggest a preferential link with endothelial activation in response to acute and subclinical inflammatory stimulation, although further studies are needed to establish the exact cause–effect mechanisms. Epidemiological studies also show associations with cardiovascular events, and some recent prospective results also indicate the power of microalbuminuria to predict risk independently from conventional atherogenic factors. Thus, microalbuminuria might be considered as an integrated marker of cardiovascular risk sensitive to systemic vascular status in addition to other parameters such as blood pressure levels, glucose metabolism, smoking habits, a profile rather unique among the prognostic predictors available to stratify risk in hypertensive patients.

**Key words:** albuminuria; cardiovascular risk factors; essential hypertension; inflammation; vascular endothelium

## Introduction

Since the first description in 1974,[1] the presence of subclinical increases in urinary albumin excretion (UAE) has attracted attention, but much remains to be understood about the role of microalbuminuria (MA) in non-diabetic individuals. Exaggerated morbidity and mortality heralded by greater amounts of urine albumin was reported several decades ago,[2] a phenomenon still elusive in its determinants despite the growing number of publications (see Table 1). An interesting hypothesis postulates that more albumin leaks through glomeruli which are made more permeant by the same endothelial pathology that promotes and/or accelerates the atherogenic process. According to that concept, originated from diabetology (see ref. 3 for an updated review) and extended to essential hypertension and the general population, clinical events due to atherosclerosis share common determinants with renal microvascular disease of which albuminuria is a marker.

The specific aims of this work are:

1. to review and interpret the available evidence – direct, inferential or circumstantial – about non-diabetic MA as a marker of endothelial dysfunction, and its possible links with inflammation and widespread vascular damage;
2. to review the overall set of the available cross-sectional and prospective epidemiological studies (see Table 1 for a synopsis), focusing on the independent effect of MA as a marker and/or predictor of clinical events.[4]

The discussion will focus on essential hypertension and non-diabetic populations. As a general caveat, the reader should take into account that the presence and extent of vascular disease in humans can only be inferred by surrogate measures – clinical, biochemical and instrumental – and are prone to some error. When pertinent, other diseases will be considered, although data obtained in one category may not necessarily extend to the other. Because of the overlap with hypertension, data relative to diabetes will frequently be quoted, although this clinical condition should rather be considered as a separate disease with specific characteristics. Unless strictly relevant to the point, the implications of macroalbuminuria or proteinuria will not be covered.

### Methodological considerations

Following Viberti et al,[5] the term MA has taken hold, although the so-called microalbuminuric levels are an artificial category carved out of a continuum of values. Normal limits vary frequently from author to author, and changing cut-offs influence the sensitivity, specificity and predictive value of a positive test.

Urine albumin can be collected through several procedures such as daily, overnight or early morning collections, but, independent of sampling modalities, the measurement is affected by huge variability.[6] Repeated measures do not resolve the problem because even with most careful collections albuminuria is still twice as variable as creatininuria (Figure 1). The matter is also complicated by heterogeneous measurement units expressed as rates (μg/min or mg/24 h), concentrations (mg/l) or albumin/creatinine ratios (ACR; mg/mg or mg/mmol). Urine albumin measurements on timed collections, when

[a]Dipartimento Cardio Toracico and [b]Malattie Metaboliche, Università di Pisa, Pisa, Italy

Address for correspondence: Roberto Pedrinelli, Dipartimento Cardio Toracico, Università di Pisa, 56100 Pisa, Italy. Tel: +39 050 996712; Fax: +39 050 540522; E-mail: r.pedrinelli@int.med.unipi.it



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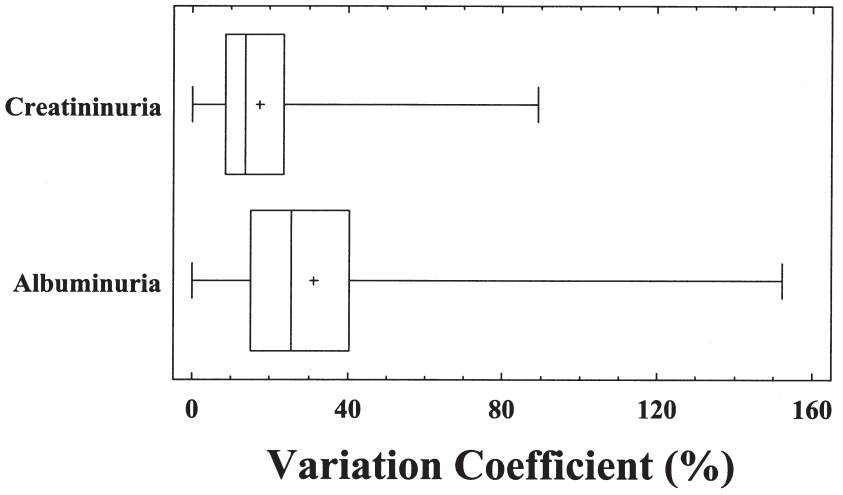


**Figure 1** Variability (variation coefficient, SD/mean %) of albuminuria (triplicate overnight collections) compared with creatininuria from a database of 274 non-diabetic male, hypertensive subjects with UAE less than 200 μg/min. (*Box-and-Whisker plot*: The *central box* encloses the middle 50% of the data; the *horizontal line* inside the box represents the median and the mean is plotted as a cross; *vertical lines (whiskers)* extend from each end of the box and cover four interquartile ranges.)

feasible, should be preferred since concentrations and ACRs (frequently used in the epidemiological field to correct for incomplete collections) may be strongly biased by variable hydration and skeletal muscle mass. To facilitate comparisons, one might roughly approximate the conventional boundaries of MA (20 and 200 μg/min or 30–300 mg/24 h) to 20/25–200/250 mg/l or 20/25–200/250 mg/g and 2/2.5–20/25 mg/mmol creatinine.

## MA and endothelial dysfunction

The concept that atherosclerosis arises in response to endothelial injury was proposed more than 20 years ago.[7] Since then, a consistent body of evidence has shown that risk factors, such as smoking, diabetes, hyperlipidemia, hypertension, mechanical stress and inflammation, perturb endothelial function, and, in turn, endothelial dysfunction accelerates the propagation of vascular lesions.[8] The proposal of MA as a marker of endothelial dysfunction stemmed from studies in type I and type II diabetes[9] in which subclinical increments in UAE represent an established marker of cardiovascular risk.[10,11] In both subtypes, endothelial dysfunction appears to precede the appearance of MA, suggesting a cause–effect relationship.[9] In essential hypertensive individuals, Pedrinelli et al were the first to show an association between albuminuria and von Willebrand Factor (vWF),[12] a hemostatic factor released in greater amount by a perturbed and/or damaged endothelium,[13] a predictor of cardiovascular events[14] elevated in frank atherosclerotic vascular disease and in the presence of all major risk factors of atherosclerosis.[15] Those results, confirmed by other reports,[16–19] including longitudinal observations of individuals with high vWF at baseline,[20] are consistent with the notion of MA as a covariate of endothelial dysfunction as assessed through endothelial-derived circulating proteins. The recently reported reduction of both endothelium-dependent and independent components of flow-mediated dilation of the brachial artery[21] agrees only partially with that concept, however. Previous studies also showed no differences between micro- and normoalbuminuric individuals as regards nitric-oxide-mediated vasomotion tested through local acetylcholine infusion[22] or endothelial-mediated release of tissue-plasminogen activator, the key fibrinolytic factor in man.[23] To try to reconcile the discrepancy, one might consider that vascular endothelium, besides controlling specific functions such as vasomotion and fibrinolysis,[24] is also a prime target for any inflammatory substance reaching the circulation.[8,25] Therefore, MA might rather reflect a non-specific endothelial perturbation, a possibility that needs further articulation.

### MA, inflammation and capillary permeability

Short-lived and reversible increments in urine albumin in the absence of functional or structural renal impairment characterize the early phases of myocardial infarction,[26,27] the same time course followed by interleukin-6, C-reactive protein and serum amyloid, i.e. the inflammatory components of the acute phase reaction triggered by myocardial cell necrosis.[28] The amount of albuminuria triggered by acute myocardial infarction, similar to other acute phase reactants,[29] yielded prognostic information independent of the degree of left ventricular performance[27] or history of hypertension.[30] Acute limb ischemia also increased UAE in parallel with indices of neutrophil activation in arteriopaths[31] or exaggerated vascular albumin permeability in rats.[32] Inflammation is persistent even in stroke survivors,[33] in whom MA is highly prevalent during the early phase of recovery along with hypoalbuminemia,[34] in itself an inflammatory marker.[35]

'Acute phase' conditions stimulate oxygen free radical production, activation of the complement system, adhesion molecule expression, neutrophil adherence, and increased circulating levels of inflammatory cytokines.[23] In turn, circulating inflammatory molecules damage the parenchymal function of several organs,[25] in particular the kidneys whose glomeruli are provided with a wide endothelial surface area. The capability of MA to respond to an 'acute phase reaction' is also shown by the increased UAE reported in non-cardiovascular conditions characterized by

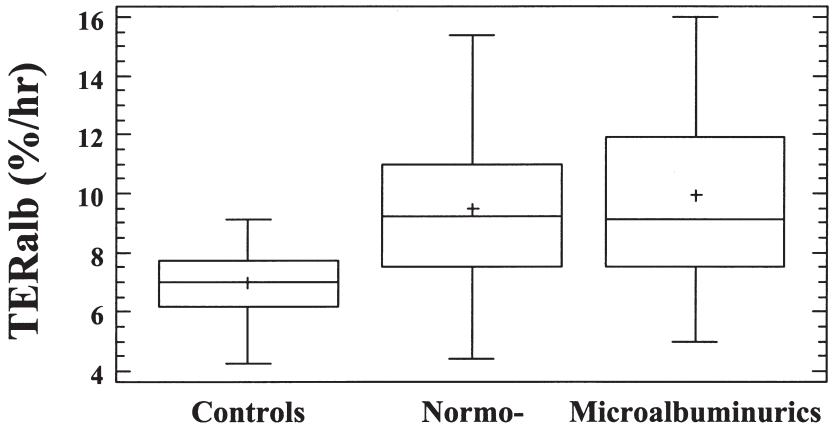


**Figure 2** Comparable $^{125}$I-albumin transcapillary escape rate (TERalb) between normo- ($n$=53) and micro- ($n$=20, UAE > 15 μg/min) albuminuric essential hypertensive patients. Data of age- and sex-matched controls are also reported ($n$=21). (*Box-and-Whisker plot*: The *central box* encloses the middle 50% of the data; the *horizontal line* inside the box represents the median and the mean is plotted as a cross; *vertical lines (whiskers)* extend from each end of the box and cover four interquartile ranges.) (Reproduced with permission from ref. 50.)

a prominent inflammatory response, including acquired immuno-mediated syndrome,[36] rheumatoid arthritis,[37] bowel inflammatory syndrome,[38] surgery,[17] adult respiratory distress syndrome[39] and many other not listed here.

The above concepts, pioneered by Gosling,[40] might extend also to chronic subclinical inflammation whose contribution to atherosclerosis development has only recently been recognized.[28,29] Thus, MA might behave as other inflammatory-derived cardiovascular predictors such as fibrinogen[41,42] and C-reactive protein.[43] This hypothesis is consistent with recently reported positive correlations with C-reactive protein,[44] cytokines,[20,45] fibrinogen[46] and vascular cell adhesion molecule-1 (VCAM-1) levels,[47] a main mediator of endothelial activation.[8,28,29] A chronic subclinical inflammatory stimulus might also sustain the constitutive secretion of vWF levels,[13] and, by damaging systemic endothelial-mediated permeability to macromolecules, allow more albumin to leak from renal glomeruli, as reported in some infectious diseases,[48] stressful conditions[49] and diabetes.[3] Still, some pieces of the puzzle do not fit. In fact, systemic capillary permeability, at least as tested through the $^{125}$I-albumin escape rate measurement, was altered both in essential hypertensive patients[50] (Figure 2) and in normotensive arteriopaths[51] (Figure 3) in spite of UAE levels well within normal limits. This negative conclusion is supported by studies in patients with peripheral vascular disease[52] and chronic renal failure,[53] although the reader should also be aware of some discordant data.[54,55]

## MA and cardiovascular events in the general population

### Cross-sectional studies (Table 1)

Yudkin et al[56] were the first to report a cross-sectional association of MA (2-h daytime UAE >20 μg/min) with coronary and peripheral vascular disease risk independently from other risk factors in a sample of 187 subjects (59 diabetic or glucose intolerant) from the Islington Diabetes Survey. The data delineated a role of MA as a risk marker in non-diabetic individuals, although a later analysis of 913 non-diabetic individuals from the same cohort did not confirm those results.[57] In the prospective section of the study, Yudkin et al[56] also showed a strong independent association of MA with all-cause mortality (6/18 (33.33%) micro- versus 3/149 (2.01%) normoalbuminuric individuals) in 167 subjects after a mean 3.6 years follow-up. The odds ratio (OR) for death was 180.3 but the 95% CI was extremely

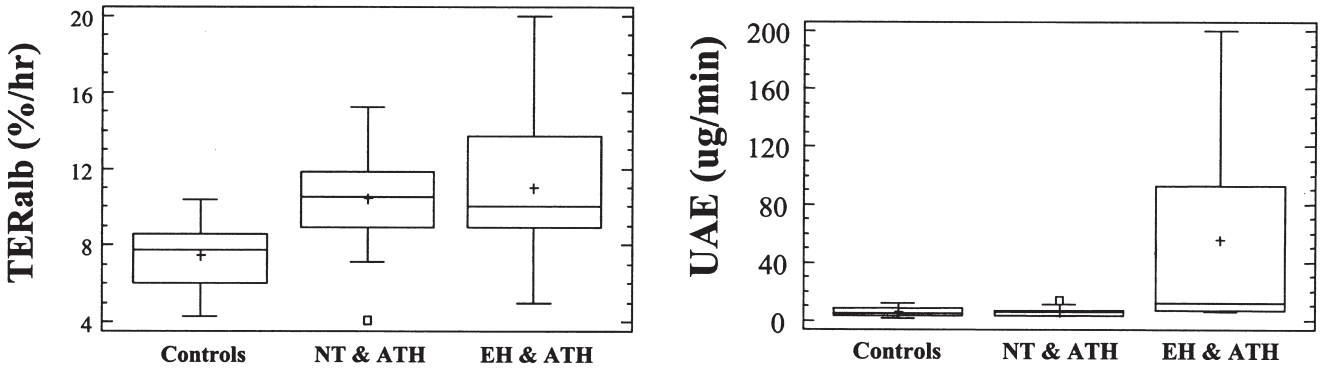


**Figure 3** Increased $^{125}$I-albumin transcapillary escape rate (TERalb) in normo- (NT & ATH, $n$=18) and hypertensive (EH & ATH, $n$=12) arteriopathic patients compared with age- and sex-matched controls (CON, $n$=11, $p$<0.01 for both) (left panel), in comparison with elevated ($p$<0.004) UAE only in hypertensive patients (right panel). (*Box-and-Whisker plot*: The *central box* encloses the middle 50% of the data; the *horizontal line* inside the box represents the median and the mean is plotted as a cross; *vertical lines (whiskers)* extend from each end of the box and cover four interquartile ranges.) (Reproduced with permission from ref. 51.)

**Table 1** List of the available cross-sectional (C) and prospective (P) studies reporting data about non-diabetic microalbuminuria and/or urinary albumin excretion as a covariate and/or predictor of cardiovascular events.

| No. | Author/ref. | Date | *n* | Design | End-point | Population |
|---|---|---|---|---|---|---|
| 1 | Yudkin[56] | 1988 | 187 | C/P | Major, minor ECG changes, history of MI and angina, peripheral vascular disease | Diabetic, glucose-intolerant and non-diabetic subjects |
| 2 | Haffner[58] | 1990 | 316 | C | Self-reported MI | Non-diabetic subjects |
| 3 | Damsgaard[70] | 1990 | 216 | P | Total mortality | Non-diabetic subjects |
| 4 | Winocour[60] | 1992 | 447 | C | ECG abnormalities | Diabetic and non-diabetic subjects |
| 5 | Damsgaard[71] | 1992 | 216 | P | Total abnormality | Non-diabetic subjects |
| 6 | Damsgaard[72] | 1993 | 216 | P | Total mortality | Non-diabetic subjects |
| 7 | Gould[57] | 1994 | 959 | C | MI, angina, peripheral vascular disease | Non-diabetic subjects |
| 8 | Howard[63] | 1995 | 4 549 | C | Definite MI and ischemic heart disease | Diabetic and non-diabetic American Indians |
| 9 | Kuusisto[66] | 1995 | 1 069 | P | Fatal and non-fatal coronary heart disease | Non-diabetic subjects |
| 10 | Gorgels[69] | 1995 | 233 | P | MI and angina | Diabetic and non-diabetic women |
| 11 | Agewall[89] | 1995 | 119 | C | Subclinical carotid atherosclerosis | 94 essential hypertensive and 25 NIDDM diabetic |
| 12 | Bigazzi[91] | 1995 | 90 | C | Subclinical carotid atherosclerosis | Hyper- and normotensive subjects |
| 13 | Ljungman[77] | 1996 | 120 | P | MI, angina, stroke, peripheral vascular disease | Hyper- and normotensives |
| 14 | Agrawal[79] | 1996 | 11 343 | C | Previous MI, angina, stroke, peripheral vascular disease | Hypertensive subjects |
| 15 | Jensen[59] | 1997 | 2 613 | C | History of MI | Hyper- and normotensives |
| 16 | Agewall[78] | 1997 | 439 | P | Total and cardiovascular mortality (MI, sudden death, fatal stroke, cardiac failure, aortic aneurysm) | 94 diabetic and 345 non-diabetic hypertensive subjects |
| 17 | Jensen[82] | 1997 | 1 254 | C | Previous MI | Hypertensive subjects |
| 18 | Mykkanen[93] | 1997 | 1 441 | C | Subclinical carotid atherosclerosis | 991 non-diabetic, 450 diabetic |
| 19 | Bigazzi[83] | 1998 | 141 | Retrospective cohort study | Fatal and non-fatal MI, angina, TIA, intermittent claudication | Hypertensive subjects |
| 20 | Pontremoli[92] | 1998 | 53 | C | Subclinical carotid atherosclerosis | Hyper- and normotensive subjects |
| 21 | Fabsitz[64] | 1999 | 4 276 | C | Ankle/brachial index $<0.9$ | Diabetic and non-diabetic American Indians |
| 22 | Howard[65] | 1999 | 4 549 | P | Fatal and non-fatal coronary and cerebrovascular events | As above |
| 23 | Borch-Johnsen[73] | 1999 | 2 085 | P | Fatal and non-fatal MI, angina pectoris, ischemic heart disease | Subjects healthy at baseline |
| 24 | Jager[74] | 1999 | 631 | P | Total and cardiovascular mortality | Diabetic and non-diabetic subjects |
| 25 | Beamer[34] | 1999 | 121 | P | Stroke, MI, vascular death | Diabetic and non-diabetic patients with ischemic stroke |
| 26 | Diercks[61] | 2000 | 7 579 | C | ECG changes | Non-diabetic subjects |
| 27 | Gerstein[62] | 2000 | 5 708 | C | Peripheral vascular disease | Non-diabetic with cardiovascular disease |
| 28 | Jensen[84] | 2000 | 204 | P | Fatal and non-fatal MI, angina, ischemic heart disease | Uncomplicated hypertensive subjects |
| 29 | Pedrinelli[90] | 2000 | 136 | C | Subclinical carotid atherosclerosis | Uncomplicated hypertensive men |
| 30 | Roest[75] | 2001 | 1 118 | P | Cardiovascular mortality | Postmenopausal women |
| 31 | Gerstein[76] | 2001 | 5 545 | P | MI, stroke, CV death, all-cause mortality, CHF hospitalization | Non-diabetic with cardiovascular disease |

ECG, electrocardiogram; MI, myocardial infarction; TIA, transient ischemic attack; NIDDM, non-insulin-dependent diabetes mellitus; CHF, congestive heart failure.

wide (7.41–4393), given the small percentage of people with MA. Following that suggestive report, other reports confirmed a higher prevalence of myocardial infarction[58,59] and abnormal ECG tracings[60] in non-diabetic individuals with MA, although adjustment for hypertension abolished statistical significance.[58,60] That criticism does not apply, however, to the recent PREVEND study in which MA (30–300 mg/24 h) was strongly and independently linked with ECG evidence of either myocardial infarction or ischemia in 7579 non-diabetic individuals.[61] The HOPE study also showed that MA (MA:ACR≥2 mg/mmol) was a significant and independent predictor among 5708 non-diabetic individuals with established vascular disease.[62]

**Prospective studies (Table 1)**

In the non-diabetic American Indians of the Strong Heart Study, the prevalence of coronary heart disease, peripheral vascular disease and stroke was associated with MA (ACR between 30 and 300 mg/g) independent of age, diabetes, systolic blood pressure, cholesterol and fibrinogen.[63,64] Furthermore, both micro- (ACR>30 mg/g) and macroalbuminuria (ACR>300 mg/g) predicted incident cardiovascular disease (CVD) mortality, although only the latter remained significant after statistical adjustment.[65] In 1069 non-diabetic Finns from the Kuopio community[66] followed-up for 3.5 years, incident cardiac mortality and coronary events more than doubled in the presence of an ACR ≥3.22 mg/mmol. Adjustment for several potential confounders, including hypertension, weakened the association (cardiac mortality: OR: 2.29, 95% CI: 0.99–5.27, $p = 0.053$; fatal+non-fatal coronary events: OR: 1.76, 95% CI: 1.01–3.76, $p = 0.047$), though. The sample also included an undefined number of macroalbuminuric individuals whose contribution was not analyzed. In addition, both the Strong Heart and the Kuopio studies were carried out in communities with extremely high prevalences of MA,[63–65,67] difficult to extrapolate to Caucasian individuals in whom that figure is probably less than 5%.[68] In 121 patients with previous ischemic stroke, albuminuria predicted recurrent cerebrovascular disease, myocardial infarction and vascular death independent of diabetes, hypertension and smoking status, but that series also pooled 31 micro- (UAE in early morning collections between 20 and 200 mg/l) with 10 macroalbuminuric (UAE >200 mg/l) individuals.[33] In the nested case–control study of the Diagnostisch Onderzoek Mammacarcinoom Cohort,[69] higher ACR adjusted for smoking and postmenopausal state (OR: 2.4, 95% CI: 1.1–5.0) was predictive of acute myocardial infarction or angina pectoris, but exclusion of diabetic individuals reduced the OR below the formal limits of significance, and data were not adjusted for coexisting hypertension.

Stronger evidence for MA as an independent risk marker was produced by Damsgaard et al[70] who showed prospectively a threefold higher death rate in normoglycemic individuals whose albuminuria was equal to or above the median (>7.52 μg/min; four macroalbuminuric) compared with those below (23/109 vs 8/107). Urinary albumin explained all-cause mortality independent of serum creatinine, male sex, hypertension, fasting blood glucose, triglycerides and ischemic heart disease, although the study had only 31 outcomes, insufficient to assess cardiovascular disease risk. In a longer follow-up accumulating 15 additional deaths, the independent predicting power of urine albumin was only borderline significant (15/107 vs 26/109, $p = 0.048$).[71] In a next report,[72] the prognostic value of albuminuria on total mortality disappeared when excluding individuals who died within the first 5 years, suggesting that albuminuria tends to predict more accurately short-term mortality. In the Copenhagen City Heart Study, 79 out of 2085 screenees developed a cardiovascular event over a 11–12-year follow-up, and baseline MA (defined as the upper decile of the distribution; ACR>0.65 mg/mmol) carried an independent 2.3-fold higher risk. After adjustment for several confounders, the 10-year disease-free survival was 99% vs 97% in normo- vs microalbuminuric individuals, a small but still highly significant difference.[73] In the 631 components of the Hoorn study, MA (ACR>2 mg/mmol) was independently associated with about a fourfold increased risk of cardiovascular death.[74] In that study, mutual adjustment for MA and atherosclerotic vascular disease did not markedly affect the relative risk estimates, suggesting that the factor promoting albuminuria is not atherosclerotic disease *per se* as much as the associated endothelial damage. A recent cohort study carried out according to a nested case–control reported similar findings in postmenopausal women drawn from a general Dutch population, and the risk was significantly greater starting from ACR greater than 1 mg/mmol.[75] On the same line, prospective data from the 5545 non-diabetic individuals of the HOPE cohort[76] reported the independent predictive power of MA (ACR≥ 2 mg/mmol) for a composite endpoint including myocardial infarction, stroke or cardiovascular death (relative risk (RR): 1.61, 95% CI: 1.36–1.9) as well as all-cause mortality (RR: 2.00, 95% CI: 1.65–2.41) and congestive heart failure hospitalization (RR: 2.20, 95% CI: 1.40–3.26). Interestingly, the study also confirmed the existence of a continuous relationship between albuminuria and cardiovascular events, not restricted to the microalbuminuric range but extending at least as low as 0.5 mg/mmol.

## MA and cardiovascular events in hypertensive patients (Table 1)

Ljungman et al[77] were the first to study prospectively a cohort mainly composed of essential hypertensive individuals in whom albuminuria predicted fatal and non-fatal events (myocardial infarction, angina pectoris, stroke and intermittent claudication) independently from several covariates, including hypertension. However, that series included five (4.1% of the total sample) macroalbuminuric patients (UAE >300 mg/24 h on at least two out of three 24-h collections) who might have influenced the outcome. In fact, exclusion of eight (2.3%) patients with macroalbuminuria (overnight UAE>200 μg/min) from a total number of 345 abolished the predicting power of UAE for incident total and cardiovascular mortality. In that same series, the difference in mortality between normo- and microalbuminuric patients (overnight UAE between 20 and 200 μg/min) was not significant.[78]

In 11 343 non-diabetic hypertensive patients recruited among German medical practices, MA (at least two out of three spot morning UAE levels between 20 and 200 mg/l with a qualitative assay) was a strong, independent covariate of stroke, myocardial infarction and peripheral occlus-

ive vascular disease.[79] The 30% MA prevalence reported in that population, however, contrasts with the three to sixfold lower figures expected in mild–moderate hypertensive individuals,[80–82] and is still twofold higher than in patients with coronary heart disease,[62] suggesting some bias with the assay technique. Jensen et al reported, against those results, no difference in myocardial infarctions in 1195 normo- compared with 59 microalbuminuric (overnight UAE 15 μg/min) hypertensive patients.[82] Those same authors, however, recently reported, in agreement with a retrospective cohort study,[83] an independent and elevated risk (OR: 5.4, 95% CI: 1.8–15.7) for incident cardiac events (fatal and non-fatal myocardial infarction, angina, ischemic heart disease) in apparently uncomplicated, non-diabetic hypertensive patients with MA.[84] That study also introduced the important possibility of UAE as a risk marker even at lower than previously suggested levels (ACR>1.07 mg/mmol, the upper decile of the distribution). This interesting possibility, confirmed by recent large-scale population studies,[85] might lead in the future to the adoption of lower thresholds for non-diabetic and perhaps even diabetic[86] MA.

## MA and subclinical atherosclerosis

High resolution carotid ultrasonography has provided quantitative and reproducible predictors of morbid events,[87] and end-points to gauge progression and regression of vascular disease.[88] The common carotid artery (CCA) intima media thickness (IMT) complex used as a surrogate measure of subclinical atherosclerosis was dissociated from MA (UAE>15 μg/min in triplicate overnight collections) in either high-risk or uncomplicated essential hypertensive subjects.[89,90] Although not completely consistent,[91,92] that evidence tends to confirm the view of urine albumin as an index of functional abnormalities rather than of overt or subclinical atherosclerosis *per se*. In our study,[90] systolic blood pressure also emerged as the stronger covariate of the CCA IMT, in agreement with population studies in which the difference in carotid thickness between micro- (ACR ≥2.0 mg/mmol on a morning urine spot sample) and normoalbuminuric non-diabetic individuals was by and large a function of hypertension.[93]

## Conclusions

Strong associations with blood pressure levels, metabolic status, lipids and smoking habits[4] make MA an integrated marker of cardiovascular risk in hypertensive, non-diabetic individuals. That profile is rather unique and could add to the several predictors that we used to stratify risk. Ongoing, large-scale clinical trials using statins to reverse endothelial dysfunction in non-hypertensive, non-hypercholesterolemic individuals with MA will hopefully clarify this issue.[94] As an added value, MA also carries information about the functional status of vascular endothelium, possibly because of a relationship with subclinical inflammation. A critical and detailed review of the recent and less recent epidemiological studies accumulated during the last decade supports unequivocally an independent association between MA and cardiovascular risk. This important finding should not be overlooked, although the reasons for the predictive power of MA are still controversial, partly because of entangled and confounding relationships with cardiovascular risk factors and primarily elevated blood pressure levels (see ref. 4 for a review).

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