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Subclinical Kidney Damage in Hypertensive Patients: A Renal Window Opened on the Cardiovascular System. Focus on Microalbuminuria

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Abstract

The kidney is one of the major target organs of hypertension.

Kidney damage represents a frequent event in the course of hypertension and arterial hypertension is one of the leading causes of end-stage renal disease (ESRD).

ESRD has long been recognized as a strong predictor of cardiovascular (CV) morbidity and mortality. However, over the past 20 years a large and consistent body of evidence has been produced suggesting that CV risk progressively increases as the estimated glomerular filtration rate (eGFR) declines and is already significantly elevated even in the earliest stages of renal damage. Data was supported by the very large collaborative meta-analysis of the Chronic Kidney Disease Prognosis Consortium, which provided undisputable evidence that there is an inverse association between eGFR and CV risk. It is important to remember that in evaluating CV disease using renal parameters, GFR should be assessed simultaneously with albuminuria.

Indeed, data from the same meta-analysis indicate that also increased urinary albumin levels or proteinuria carry an increased risk of all-cause and CV mortality. Thus, lower eGFR and higher urinary albumin values are not only predictors of progressive kidney failure, but also of

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all-cause and CV mortality, independent of each other and of traditional CV risk factors.

Although subjects with ESRD are at the highest risk of CV diseases, there will likely be more events in subjects with mil-to-moderate renal dysfunction, because of its much higher prevalence.

These findings are even more noteworthy when one considers that a mild reduction in renal function is very common in hypertensive patients.

The current European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension recommend to sought in every patient signs of subclinical (or asymptomatic) renal damage. This was defined by the detection of eGFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 or the presence of microalbuminuria (MAU), that is an amount of albumin in the urine of 30–300 mg/day or an albumin/creatinine ratio, preferentially on morning spot urine, of 30–300 mg/g.

There is clear evidence that urinary albumin excretion levels, even below the cut-off values used to define MAU, are associated with an increased risk of CV events. The relationships of MAU with a variety of risk factors, such as blood pressure, diabetes and metabolic syndrome and with several indices of subclinical organ damage, may contribute, at least in part, to explain the enhanced CV risk conferred by MAU. Nonetheless, several studies showed that the association between MAU and CV disease remains when all these risk factors are taken into account in multivariate analyses. Therefore, the exact pathophysiological mechanisms explaining the association between MAU and CV risk remain to be elucidated. The simple search for MAU and in general of subclinical renal involvement in hypertensive patients may enable the clinician to better assess absolute CV risk, and its identification may induce physicians to encourage patients to make healthy lifestyle changes and perhaps would prompt to more aggressive modification of standard CV risk factors.

Keywords

Arterial hypertension • Blood pressure • Glomerular filtration rate • Microalbuminuria • Proteinuria • Subclinical renal disease • Early kidney injury • Target organ damage • Cardiovascular disease • Cardiovascular risk assessment

1 Introduction

The kidney plays a dual role in arterial hypertension. On the one hand, even subtle renal dysfunction may cause elevation in blood pressure; on the other, systemic hypertension, whether primary or secondary, may cause renal disease or may accelerate the loss of kidney function in subjects with established parenchymal disease (Ruilope 2002).

Indeed, hypertension, along with diabetes, are the leading causes of chronic kidney disease (CKD) (Ruilope 2002; Gansevoort et al. 2013; Levin et al. 2013).

CKD is a worldwide public health problem, in view of both the number of patients and cost of

treatment involved. Globally, CKD is the 12th most common cause of death and the 17th leading cause of disability (Gansevoort et al. 2013).

End-stage renal disease (ESRD) has long been recognized as an extremely powerful predictor of serious cardiovascular (CV) sequelae and death (Ruilope 2002; Gansevoort et al. 2013; Foley et al. 2005). However, over the past 20 years a large and consistent body of evidence has been produced suggesting that people with any stage of CKD have an increased risk of developing cardiovascular diseases (CVD) (Ruilope 2002; Gansevoort et al. 2013; Levin et al. 2013; Matsushita et al. 2010). It has been also shown that middle aged and elderly patients with mild-to-moderate CKD are more likely to die due to CKD than to reach ESRD (Gansevoort et al. 2013; Levin et al. 2013). Moreover, although people with ESRD are at the highest risk of a CVD, there will be more events in subjects with early stage CKD, because of its much higher prevalence (Ruilope 2002; Gansevoort et al. 2013).

Numerous studies in recent years have provided convincing evidence that there is a quantitative association between decreased estimated glomerular filtration rate (eGFR) and CV risk (Ruilope 2002; Gansevoort et al. 2013; Levin et al. 2013; Matsushita et al. 2010; Go et al. 2004; Hemmelgarn et al. 2010; Hallan et al. 2009; The Chronic Kidney Disease Prognosis Consortium 2011).

Studies that have assessed the relation between kidney function and CV risk generally fall into three categories: investigations conducted in general population cohorts, in cohorts at high risk for chronic kidney disease, and in CKD patients (Matsushita et al. 2010; Go et al. 2004; Hemmelgarn et al. 2010; Hallan et al. 2009; 2012; The Chronic Kidney Disease Prognosis Consortium 2011; Mafham et al. 2011; O'Hare et al. 2007; Moynihan et al. 2013; van der Velde et al. 2011; Astor et al. 2011; Nitsch et al. 2013; Mahmoodi et al. 2012; Fox et al. 2012).

Despite differences in the populations studied and adjustment for confounding variables, the results are surprisingly consistent. A meta-analysis of 19 studies (including over 160,000 events) has shown that for each 20 mL/min/1.73 m^2 reduction in eGFR, the risk for major vascular events (which includes both non-fatal and fatal events) increases by approximately 50 % (hazard ratio (HR), 1.49; 95 % CI, 1.38–1.61) (Mafham et al. 2011). The Chronic Kidney Disease Prognosis Consortium has presented results from a collaborative meta-analysis of 21 general population cohorts, which included more than 1.2 million participants from 14 countries in North America, Europe, Asia, and Oceania. The meta-analysis demonstrated that, after adjustment for age, sex, ethnicity, diabetes, blood pressure (BP), total cholesterol level, smoking, and history of CVD, lower eGFR was associated with an increased risk for death from any CV cause as compared to the reference group (eGFR 90–104 mL/min/1.73 m^2). The hazard ratio for all-cause mortality at eGFRs of 60, 45, and 15 mL/min/1.73 m^2 were 1.18, 1.57, and 3.14 respectively when compared to an eGFR of 95 mL/min/1.73 m^2 (Matsushita et al. 2010).

The current threshold of eGFR $<$60 ml/min/1.73 m^2 used to define overt CKD (Levin et al. 2013) has been disputed for several reasons. Data obtained in the CKD prognosis consortium meta-analysis, about mortality and ESRD indicated that the risk of death and renal failure increased exponentially for eGFR values $<$75 ml/min per 1.73 m^2, suggesting that eGFR values in the range 60–74 ml/min per 1.73 m^2 could represent the early stages of kidney disease (Matsushita et al. 2010). On the other hand, the use of a single eGFR threshold for all age groups may potentially lead to an overdiagnosis of CKD in low-risk elderly individuals, assuming that some decline in kidney function may be regarded as a physiologic phenomenon associated with normal aging (O'Hare et al. 2007; Moynihan et al. 2013).

However, another important observation from the meta-analysis is that data were not significantly different between individuals aged $<$65 years and $\geq$65 years (Hallan et al. 2012), a finding which does not support the idea that kidney dysfunction is a physiologic change of aging.

Data from the same meta-analysis indicate that also a higher level of albuminuria carried an increased risk of all-causes and CV mortality. Albuminuria and eGFR were multiplicatively associated with all-cause mortality, without evidence for interaction. Thus, lower eGFR and higher albuminuria are risk factors for not only progressive kidney failure, but also for all-cause and CV mortality, independent of each other and of CV risk factors (Matsushita et al. 2010). Subsequently, the analysis of cohorts at risk for CKD (van der Velde et al. 2011) or with CKD (Astor et al. 2011) has demonstrated similar associations. In addition, a recent new evaluation of these cohorts assessed for the presence of a sex interaction in the associations of eGFR and urinary albumin excretion (UAE) with all-cause mortality, CV mortality, and ESRD (Nitsch et al. 2013). This study demonstrated that both sexes with reduced eGFR and increasing UAE. face an enhanced risk of all-cause mortality, CV mortality, and ESRD.

Importantly, the association of kidney disease measures with mortality or ESRD has also been consistently found in those with or without hypertension (Mahmoodi et al. 2012), diabetes (Fox et al. 2012) and also regardless of age (Hallan et al. 2012). Overall, the results of all these studies support the view that assessment of both proteinuria (and albuminuria) and eGFR level is needed in order to improve the identification of individuals at high risk of cardiovascular complications and to establish appropriate measures of prevention.

On the basis of these findings, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for evaluation and management of chronic kidney disease (Levin et al. 2013) has recommended the following: (1) the assessment of both albuminuria (or proteinuria) and eGFR in general practice and (2) the classification of CKD stages by using both kidney parameters (Fig. 1).

This because integrating both eGFR and albuminuria into CKD staging paradigms provides more precise classification and more accurate prognostic information.

Assessment of subclinical (or asymptomatic) target organ damage is a key element in the evaluation of patients with arterial hypertension (Mancia et al. 2013). Subclinical organ damage at cardiac, vascular, and renal levels often precedes and predicts the development of morbid events (Mancia et al. 2013). It has been shown that a systematic in-depth search for multiple risk factors or organ damage significantly increases the likelihood of identifying high-risk individuals. According to recent hypertension guidelines (Mancia et al. 2013) reduced eGFR, in the range 60–30 ml/min per 1.73 m^2 and microalbuminuria (MAU) have been proposed as useful integrated markers of subclinical renal damage (Mancia et al. 2013).

In the following sections we describe some epidemiological, pathophysiological, and clinical aspects regarding microalbuminuria.

2 Microalbuminuria

2.1 History

The term “microalbuminuria” was first proposed in the early 1960s, when Professor Harry Keen’s Group at Guy’s Hospital developed a radioimmunoassay technique for measuring in the urine of patients with type 1 diabetes, very low concentrations of albumin, well below the detection threshold of commonly used methods (Keen and Chlouverakis 1963). However, it was not until the 1980s, that it became an official part of the medical lexicon, when Svendsen and coll (Svendsen et al. 1981) and Viberti and coll (Viberti et al. 1982) described MAU as the presence of albuminuria below the detection limit of a standard dipstick, but at a level, revealed by using sensitive immunological methods, that was highly predictive of future overt proteinuria in diabetic patients.

It was initially defined as an albumin excretion rate between 20 and 200 μg/min. Although the lower bound was chosen because 95 % of ‘normal’ individuals had excretion rates below that limit, it was recognized that risk of

Composite ranking for relative risks by glomerular filtration rate (GFR) and albuminuria				Albuminuria stages, description and range		
				A1	A2	A3
				Normal or high normal	Increased	Severely increased and nephrotic
				< 30 mg/g	30-299 mg/g	≥ 300 mg/g
				< 30 mg/day	30-299 mg/day	≥ 300 mg/day
				< 3 mg/mmol	3-29 mg/mmol	≥ 30 mg/mmol
GFR stages, description and range (ml/min per 1.73 m2)	G1	Normal or High	≥ 90	==*	↑	↑↑
	G2	Mildly decreased	60-89	==**	↑	↑↑
	G3a	Mildly to moderate decreased	45-59	↑	↑↑	↑↑↑
	G3b	Mildly to severely decreased	30-44	↑↑	↑↑↑	↑↑↑
	G4	Severely decreased	15-29	↑↑↑	↑↑↑	↑↑↑
	G5	Kidney failure	<15	↑↑↑	↑↑↑	↑↑↑

Fig. 1 Prognosis of CKD by GFR and Albuminuria categories as identified by 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for evaluation and management of chronic kidney disease (Modified from Ref. (Levin et al. 2013), (== low risk; ↑ moderate risk; ↑↑ high risk; ↑↑↑ very high risk. * The risk may be slightly increased in subjects with ACR in the high normal range ** The risk begins to rise in subjects with estimated GFR < 75 ml/min/1.73 m^2)

progression to nephropathy was elevated among diabetics in the 'high normal' range (The Chronic Kidney Disease Prognosis Consortium 2011; Svendsen et al. 1981; Viberti et al. 1982). Mogensen was the first to describe the importance of MAU not only as a renal risk factor but also as a powerful predictor of CV mortality in patients with type 2 diabetes (Mogensen and Christensen 1984; Mogensen 1984).

In recent years, however, it has received increased attention as a prognostic marker for CV and/or renal risk even in non-diabetic subjects (Ruilope 2002; Matsushita et al. 2010; Gerstein et al. 2001; Hillege et al. 2001; 2002; Arnlov et al. 2005; Ruggenenti and Remuzzi 2006; Yuyun et al. 2004; Cirillo et al. 1998; Pontremoli et al. 1997; Pedrinelli et al. 2002; Bramlage et al. 2007; Coresh et al. 2007; Agrawal et al. 1996; Cerasola et al. 2008; 2010; Leoncini et al. 2010).

Similar to the relationship between BP and risk of CV events, mounting evidence indicates a continuous relationship between albumin excretion and risk (Matsushita et al. 2010; Gerstein et al. 2001; Hillege et al. 2001; 2002; Arnlov et al. 2005; Ruggenenti and Remuzzi 2006).

2.2 Epidemiology

European studies report a 2.2–11.8 % prevalence of MAU in the general population (Hillege et al. 2001; Yuyun et al. 2004; Cirillo

et al. 1998; Pontremoli et al. 1997; Pedrinelli et al. 2002; Bramlage et al. 2007; Coresh et al. 2007). Among the European epidemiological investigations performed in this field deserves to be mentioned the PREVEND (Prevention of Renal and Vascular End-stage Disease) study (Hillege et al. 2001) which involved 40,856 inhabitants of the city of Groningen (The Netherlands), aged 28–75 years. Microalbuminuria, defined as urinary albumin concentration 20–200 mg/L, was present in 7.2 % of population. After excluding the diabetic and hypertensive subjects MAU was still prevalent in 6.6 % of the individuals, and it was independently associated with age, gender, hypertension, diabetes, smoking, previous myocardial infarction and stroke. Cardiovascular risk factors were already elevated at levels of urinary albumin currently considered to be normal (10–20 mg/L or 15–30 mg per 24 h) (Hillege et al. 2001).

These percentages indicate that MAU is more often present in subjects with CV risk factors; however, in apparently healthy subjects MAU can frequently be encountered.

Data from the US National Health and Nutrition Examination Surveys (NHANES) showed an increase in prevalence of MAU (defined as a urinary albumin– creatinine ratio [ACR] of 30–300 mg/g) from 7.1 to 8.2 % during the survey periods 1988–1994 and 1999–2004. The increase was attributed to older age of the population, greater proportion of minority groups, prevalence of hypertension and diabetes and higher body mass index (Coresh et al. 2007).

In arterial hypertension, prevalence of MAU ranging from 5 to 60 % has been reported (Agrawal et al. 1996; Cerasola et al. 2008; 2010; Leoncini et al. 2010; Böhm et al. 2007; Meccariello et al. 2016). This wide range may be due to differences in ethnic groups, specimen collection, cut-off level of albumin excretion, analytical methods and influence of antihypertensive medications. The distribution of demographic and coexisting diseases may also contribute.

In the abovementioned large-scale population surveys, the NHANES III (Coresh et al. 2007) and the PREVEND study (Hillege et al. 2001), MAU was detected respectively in 16 % and 11.5 % of people with hypertension.

The international, observational, practice based study i-SEARCH (Survey for Evaluating Microalbuminuria Routinely by Cardiologists in patients with Hypertension) was designed to assess the frequency with which MAU occurred in a very large group of hypertensive outpatients attending a cardiologist or internist. A total of 21,050 patients from 26 countries were included in the primary analysis. Overall, this study demonstrated a very high worldwide prevalence (58.4 %) of MAU in high-risk cardiovascular patients, but with a considerable variation across countries (Böhm et al. 2007).

The use of a semi-quantitative test, which tend to overestimate urine albumin concentration, may explain to some extent the unusually high prevalence of microalbuminuria reported in this large-scale study (Böhm et al. 2007), as well as in other ones (Bramlage et al. 2007; Agrawal et al. 1996). In a very recent study conducted in 1024 unselected hypertensive patients followed by 13 Italian general practitioners MAU was detected in 35 % of the overall population (Dworkin et al. 1983).

A lower frequency of MAU (22.7 %) was observed in the REDHY (REnal Dysfunction in HYpertension) study that was conducted in 1856 non-diabetic middle-aged subjects with arterial hypertension and without cardiovascular complications and known renal diseases (Cerasola et al. 2008; 2010). Moreover, in the I-DEMAND (Italy Developing Education and awareness on Microalbuminuria in patients with hyperteNsive Disease) study, an observational, cross-sectional investigation performed in 87 centers of specialized care (Internal Medicine, Cardiology, Nephrology, Diabetology) MAU was found in 27 % of the entire population, including 3534 patients, 37 % of whom had diabetes mellitus (Leoncini et al. 2010).

2.3 Pathophysiology

The presence of microalbuminuria implies dysfunction of the glomerular filtration barrier. It

may result from haemodynamic-mediated mechanisms and/or functional or structural impairment of the glomerular barrier.

Microalbuminuria in essential hypertensive patients is the consequence of an increased transglomerular passage of albumin rather than the result of a decrease in the proximal tubule reabsorption of albumin. At least two mechanisms have been proposed for the greater albumin excretion rate (AER) in some patients with essential hypertension: increased glomerular hydrostatic pressure or increased permselectivity of the glomerular basement membrane (Mountokalakis 1997). Glomerular hydrostatic pressure is regulated by the relative vasoconstriction-vasodilatation of the afferent and efferent glomerular arterioles. The tone of these arterioles is regulated by different mechanisms, and their sensitivity to pressor/depressor substances also varies substantially (Dworkin et al. 1983).

A variety of endocrine, paracrine, and autocrine substances, as well as pharmacological agents, may influence intraglomerular hemodynamic independently of actions on systemic blood pressure (BP).

Normally, an elevation of systemic arterial pressure is associated with vasoconstriction of the glomerular afferent arterioles, which prevents transmission of the elevated hydrostatic pressure to the glomerulus and maintains the glomerular hydrostatic pressure unaltered (Hostetter et al. 1981). This protects the glomeruli from the potential damages of hypertension. If the autoregulatory adaptation of the glomerular afferent arterioles is defective, increased glomerular hydrostatic pressure may ensue. Alternatively, an exaggerated vasoconstriction of the efferent arterioles may increase intraglomerular hydrostatic pressure, even in the presence of normal systemic pressure (Hostetter et al. 1981).

A large body of experimental and clinical evidence supports the notion that derangements of these adaptive mechanisms are important determinants for the susceptibility to develop progressive renal disease (Mountokalakis 1997).

In 1992 our group, in order to verify if in essential hypertension (EH) MAU increase could be due to hemodynamic modifications or to glomerular structural changes, in a very small group of newly diagnosed essential hypertensives ($n = 30$; EHs) having 24-h AER > 16 μg/min ($n = 15$) and in 15 EHs with 24-h AER < 16 μg/min, the day- and night-time behaviour of creatinine clearance (Ccr), as well as AER clearance (AER-C) and fractional clearance (AER-FC), and behaviour of BP were evaluated (Cottone and Cerasola 1992). Patients with 24-h AER > 16 μg/min showed hyperfiltering values of both 24-h and daytime creatinine clearance than the other group of EHs, while during the night period, there were no significant differences between the two groups. On the contrary, AER and both AER-C and AER-FC resulted markedly and significantly higher in the EHs with 24-h AER > 16 μg/min not only in the 24-h evaluation, but also during the nighttime study notwithstanding the significant decrease in BP and in Ccr observed during the night. We concluded that these data, in the absence of correlations between BP and AER-FC seemed to demonstrate that among newly diagnosed essential hypertensives a subgroup of them could have early renal hemodynamic changes (Cottone and Cerasola 1992). These hemodynamic modifications, along with defects of the glomerular membrane permselectivity, led to increased microalbuminuria.

Hyperfiltration is probably mediated by abnormal transmission of systemic hypertension to the glomerulus through a disturbance in glomerular autoregulation and/or from progressive loss of functioning nephrons. Of the non-haemodynamics, functional abnormalities of the glomerular basal membrane have been claimed, although some evidence has been against this in hypertension.

More widely accepted, however, is that MAU reflects the kidney expression of a more generalised state of endothelial dysfunction (Deckert et al. 1989; Pedrinelli et al. 1994; Cottone et al. 2000; 2007).

With regard to systemic endothelial dysfunction, our group hypothesized that in EHs, plasma levels of pro-atherogenic adhesion molecules

would be increased and related with AER. Thus, we studied biochemical markers of endothelial activation ICAM-1 and VCAM-1, and their relationship with AER in a group of individuals with uncomplicated EH (Cottone et al. 2007). One hundred patients with essential hypertension and no diabetes or ultrasonographic evidence of atherosclerosis were included in the study. EHs were first studied overall, than were divided into two subgroups: those with AER >20 μg/min (MAUs) and those with AER <20 μg/min (non-MAUs). Microalbuminuric hypertensives had greater levels of adhesion molecules than non- MAUs. In multiple regression models in hypertensive persons AER was independently associated with ICAM-1, and VCAM-1. These findings showed that in EH there is a very early activation of endothelial adhesion molecules favouring atherosclerosis.

A further interesting data emerging from that study was the significant difference of plasma concentrations of adhesion molecules when comparing non-MAU hypertensives with healthy controls. Indeed, it seemed that endothelial activation expressed by adhesion molecules would be earlier than microalbuminuria, confirming that microalbuminuria could be considered a marker of systemic endothelial dysfunction (Cottone et al. 2007). A study by Klausen (Klausen et al. 2004) demonstrated that in the general population urinary albumin excretion, below the MAU definition, was associated with increased coronary heart disease risk, independently of hypertension. Thus, the Authors hypothesize that MAU emerges later in the atherosclerotic process. Our findings, showing a pro-atherogenic endothelial activation in the presence of values of AER currently considered as 'normal' seemed to be in line with this finding.

Considering the role that inflammation plays in the development of endothelial changes that lead to atherosclerosis, studies on this issue were performed (Pedrinelli et al. 2004; Festa et al. 2000; Jager et al. 2002; Kshirsagar et al. 2008).

C-Reactive Protein (CRP), a well-known marker of inflammation, was positively associated with microalbuminuria in the large data set compiled from the National Health and Nutrition Examination Surveys (NHANES) 1999 through 2004 (Kshirsagar et al. 2008). In this study, including 12,831 US men and women, the multivariate analysis showed that an increase of one milligram per liter in CRP concentration was significantly associated with a 2 % increased odds of microalbuminuria ($p = 0.0003$) (Kshirsagar et al. 2008).

2.4 Methodology and Limitations

Microalbuminuria can be revealed by several methods based on immunologic detection (immunonephelometry, immunoturbidimetry, radioimmunoassay, enzyme-linked immunosorbent assay) (Miller et al. 2009). Among these there are also a variety of semiquantitative dipsticks, such as Clinitek Microalbumin Dipsticks and Micral-Test II test strips, which can be used for MAU screening. The reported sensitivity and specificity of these tests range from 80 to 97 % and 33 to 80 %, respectively (Miller et al. 2009).

Microalbuminuria has been defined as an AER higher than the threshold value obtained from studies assessing the risk for developing nephropathy in diabetes, that is an AER between 20 and 200 μg/min. It is now clear that its significance extends beyond nephropathy and it likely mirrors a more widespread vascular injury.

It should be noted that AER may also be expressed in terms of milligrams per day (mg/day), in which case the range for microalbuminuria is 30–300 mg/day (Levin et al. 2013; Mancia et al. 2013).

Indeed, there is growing evidence, arising from several prospective studies that urinary albumin excretion levels well below the current microalbuminuria threshold ("low-grade albuminuria") are also associated with an increased risk of incident cardiovascular disease and all-cause mortality (Matsushita et al. 2010; van der Velde et al. 2011; Astor et al. 2011; Nitsch et al. 2013; Mahmoodi et al. 2012; Fox et al. 2012; Hallan et al. 2012; Klausen et al. 2004; Redon and Williams 2002). Even in

apparently healthy individuals (without diabetes or hypertension), such an association has been shown (Hillege et al. 2001). These epidemiological data prompted some authors to propose the adoption of a lower AER cut-off point for the detection of subjects with an enhanced cardiovascular risk (Redon and Williams 2002) and other ones (Ruggenenti and Remuzzi 2006) to abandon the terms of microalbuminuria and macroalbuminuria and replaced with 'urine albumin', because the use of arbitrary dichotomous categorisation does not reflect the continuously increasing risk associated with progression of urine albumin concentrations. Moreover, the term microalbuminuria may be confusing, since it should reflect small albumin molecules, and not small amounts of albumin (Ruggenenti and Remuzzi 2006).

Despite this criticism, the term microalbuminuria has become widely accepted in clinical practice.

Although 24-h urine collection is the gold standard for the detection of microalbuminuria, it has been suggested that screening can be more simply achieved by a timed urine collection or by untimed spot urine sample. In this latter case the confounding effect of variations in urine volume on the urine albumin concentration can be avoided normalizing the urinary albumin concentration to the urinary creatinine concentration (since creatinine excretion rate is considered constant) (Miller et al. 2009; Levey et al. 2009).

Indeed, the albumin/creatinine ratio (ACR) from spot urine, preferably that first voided in the morning, may be considered equivalent to the values during a 24-h urine collection (Miller et al. 2009; Levey et al. 2009).

Even if the ACR corrects for unknown urine volumes, it needs theoretically differentiation of males from females in whom creatininuria is lower because of reduced muscle mass (Miller et al. 2009; Cirillo et al. 2006; Mogensen et al. 1995), a fact not taken into account, by the KDIGO guidelines for evaluation of CKD (Levin et al. 2013) and by the 2013 ESH-ESC guidelines for management of arterial hypertension (Mancia et al. 2013), that for the definition of microalbuminuria do not recommend the use of gender-specific ACR thresholds, but a single cut-off value, that for simplicity was arbitrarily rounded to 30 mg/g (Levin et al. 2013; Mancia et al. 2013) (Fig. 1).

For the same reasons described above, albumin excretion will be underestimated in a muscular man with a high rate of creatinine excretion and overestimated in a cachectic patient in whom muscle mass and creatinine excretion are markedly reduced (Miller et al. 2009; Cirillo et al. 2006).

A number of physiologic and pathologic factors must be taken into account when interpreting AER and ACR results. Albumin excretion is normally about 25 % higher during the day, and it can vary by 10–25 or more in day-to-day measurements. In addition to age and sex, body mass index and a high-protein meal can all affect the AER. Vigorous exercise can cause a transient increase in albumin excretion. As a result, patients should refrain from vigorous exercise in the 24 h prior to the test. Measurement can be further confounded by fever, congestive heart failure, urinary tract infection, and by some drugs (Mogensen et al. 1995). Because the limited reproducibility of AER and ACR measurements, most expert committees recommend that a presumptive indication of microalbuminuria should be confirmed by quantitative measurement of urinary albumin in at least two of three, preferably nonconsecutive, specimens (Mogensen et al. 1995). Even a single determination of elevated albumin concentration, however, can predict (albeit with reduced precision) renal and cardiovascular diseases (Gerstein et al. 2001; Hillege et al. 2002).

2.5 Microalbuminuria and Cardiovascular Risk Factors

There is a strong evidence of a close relationship of microalbuminuria with a variety of cardiovascular risk factors, such as hypertension, diabetes, aging, smoking, hyperlipidemia and metabolic syndrome.

The association of microalbuminuria with all these factors is so relevant that MAU may

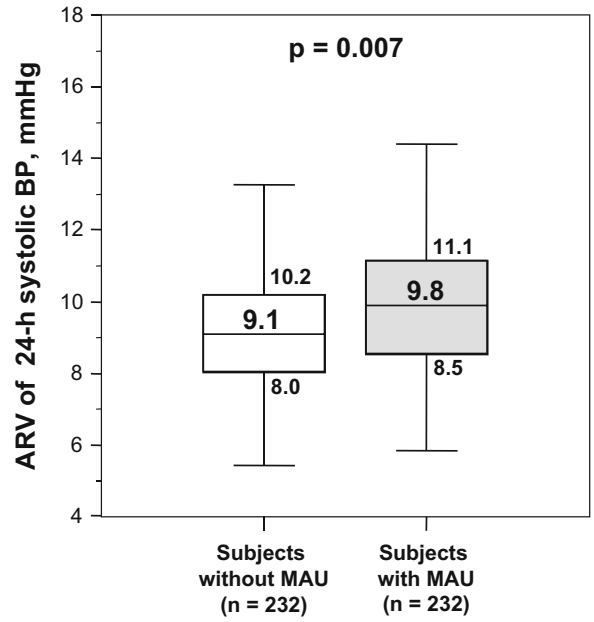

Fig. 2 Box plots showing average real variability (ARV) of 24-h systolic blood pressure (BP) in hypertensive patients with microalbuminuria and in those without it. In the Box and Whisker plots, the central boxes represent the values from the lower to upper quartile (25–75 percentile). The middle lines represent the medians. Lower and upper whiskers extend to 5th and 95th percentiles. This difference remained significant (P = 0.02), even after adjustment by ANCOVA for age, gender, average 24-h systolic BP, waist circumference, serum uric acid and diabetic status (Mulè et al. 2016)

legitimately be regarded as an integrated marker of cardiovascular risk (Pedrinelli et al. 2002).

Several studies have shown significant correlations between blood pressure values and AER (Cirillo et al. 1998; Bramlage et al. 2007; Coresh et al. 2007; Agrawal et al. 1996; Cerasola et al. 2008; 2010; Leoncini et al. 2010; Böhm et al. 2007; Cerasola et al. 1989; 1996; Hsu et al. 2009). There is also evidence that the relationship of BP with albuminuria is relatively continuous and graded, with even high-normal levels of BP associated with albuminuria (Hsu et al. 2009).

In general, the association of BP values with albuminuria becomes even closer when BP is recorded through ambulatory blood pressure monitoring (Cerasola et al. 1989; 1996; Palatini et al. 1995) which provides a more precise estimation of the real BP status. Ambulatory BP monitoring also allowed to show that there are no significant differences in AER between the white coat hypertensive and the normotensive subjects (Cerasola et al. 1995; Palatini et al. 1998) and that urinary albumin levels are higher in hypertensives in whom a blunted or absent nocturnal fall of BP occurs (non dippers) (Bianchi et al. 1994; Redon et al. 1994). In this context it is interesting to note that a clinical condition characterized by a non-dipping BP pattern, such as the obstructive sleep apnea syndrome, has been associated with microalbuminuria in patients with arterial hypertension (Tsioufis et al. 2008).

Very recently, in a group of more than 300 untreated hypertensive subjects, we reported a positive association of AER with average real variability (ARV) of 24-h systolic blood pressure (Fig. 2), a measure of short-term blood pressure variability endowed with prognostic implications (Mulè et al. 2016). This association was weakened, but still significant, taking into account the effect of the mean level of 24-h SBP and other potential confounders. Moreover, in the subset of patients with MAU and inverse relationship between ARV of 24-h SBP and eGFR was also found (Mulè et al. 2015a).

Accumulating data indicate that MAU clusters with several metabolic abnormalities

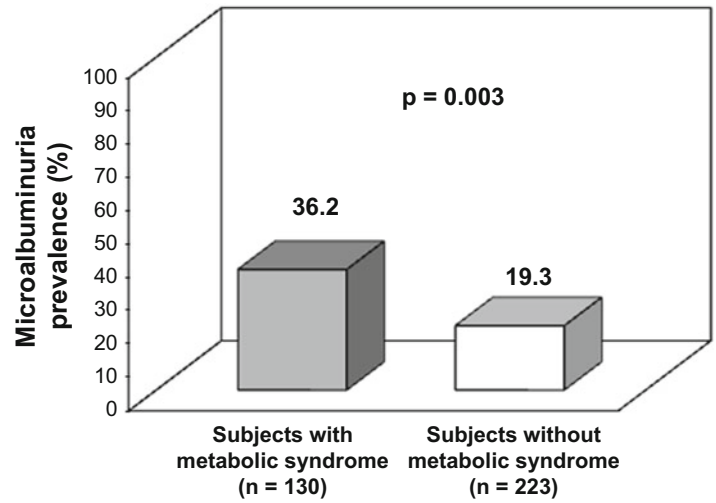

Fig. 3 Microalbuminuria prevalence in 353 non diabetic essential hypertensive patients divided on the basis of the presence or absence of metabolic syndrome, as defined by ATP III criteria (Mulè et al. 2005)

(Cirillo et al. 1998; Pontremoli et al. 1997; Cerasola et al. 2008; 2010; Leoncini et al. 2010; Campese et al. 1999; Cerasola and Cottone 1997; Pinto-Sietsma et al. 2003; Klausen et al. 2009; Mulè et al. 2006; Palaniappan et al. 2003; Andronico et al. 1998; Srinivasan et al. 2000; Alberti and Zimmet 1998; Jager et al. 1998; Chen et al. 2004; Mulè et al. 2005; Cuspidi et al. 2004; Klausen et al. 2007; Parving et al. 2006), including some phenotypes of the metabolic syndrome (MetS) and may be indeed a part of this syndrome (Alberti and Zimmet 1998).

We have previously shown, in a group of 353 essential hypertensive subjects that the prevalence of microalbuminuria and the levels of AER were higher in patients with MetS than in those without it (Mulè et al. 2005) (Fig. 3). Furthermore, although researchers have reported mixed results (Andronico et al. 1998; Srinivasan et al. 2000; Jager et al. 1998) on the association between MAU and hyperinsulinemia and insulin-resistance, multiple studies confirmed this relation (Andronico et al. 1998; Srinivasan et al. 2000). An investigation of 5659 men and women from the NHANES III, confirmed the association between MAU and the MetS, with the strongest association being with high fasting serum glucose and high BP (Palaniappan et al. 2003). A further analysis of the same study documented that the multivariate-adjusted odds ratios of microalbuminuria increased progressively with a higher number of components of the MetS, defined by the ATP III guidelines (Chen et al. 2004).

Similar results were obtained in patients with arterial hypertension (Mulè et al. 2005; Cuspidi et al. 2004).

In the general population of the Copenhagen City Heart Study not only the strong association between microalbuminuria and the MetS was confirmed, but interestingly it was also observed that MAU (even when defined by a very low cut-off value, that is > 5 μg/min) confers an increased risk of death and CV disease to a similar extent as the MetS and independently of it and of other confounding factors (Klausen et al. 2007).

A relationship between higher AER and cigarette smoking has been described in diabetic individuals (Parving et al. 2006; Gerstein et al. 2000) and in hypertensive people (Andronico et al. 2005), in subjects with increased CV risk (Gerstein et al. 2000) as well as in the general population (Pinto-Sietsma et al. 2000).

In the PREVEND study, current smokers had a higher median albumin excretion than nonsmokers and were more likely to have microalbuminuria. After adjustment for several potential confounding factors, persons who smoked 20 or fewer cigarettes/day and persons who smoked more than 20 cigarettes/day, when compared to nonsmokers, showed a relative risk of microalbuminuria of 1.92 [CI, 1.54–2.39] and

2.15 [CI, 1.52–3.03], respectively (Pinto-Sietsma et al. 2000).

However, overall, in the various studies, the link between smoking and MAU is not very strong and it seems unlikely that smoking may explain much of the excess CV risk associated with MAU.

Besides the associations reported between microalbuminuria and various conventional cardiovascular risk factors, significant correlations have been observed between increased AER and nontraditional risk factors for cardiovascular diseases.

For example, during the last decade, several cross-sectional investigations have documented that microalbuminuria is related to various inflammatory markers (Pedrinelli et al. 2004; Festa et al. 2000; Jager et al. 2002; Kshirsagar et al. 2008; Mulè et al. 2009) and to some markers of endothelial damage and dysfunction, including von Willebrand factor and adhesion molecules (sVCAM1 and sICAM1 and e-selectin) (Pedrinelli et al. 1994; Cottone et al. 2000; 2007).

2.6 Microalbuminuria and Kidney Dysfunction

The influence of glomerular filtration rate (GFR) on the microalbuminuria of hypertension merits a comment. The prevalence of microalbuminuria increases as the GFR decreases, although not always in parallel. Moreover, when GFR is < 60 ml/min/1.73 m^2, the probability of AER normalisation during antihypertensive treatment is clearly reduced (Pascual et al. 2006).

Changes in proteinuria have been suggested as a surrogate outcome for kidney disease progression to facilitate the conduct of clinical trials (Levey et al. 2009). The progression of CKD is often slow, and until late stages, it is often asymptomatic. Thus, end points for clinical trials may be long delayed from disease onset and the time that interventions may be effective. Surrogate end points may provide an opportunity to detect early evidence of effectiveness. Proteinuria is an accepted marker for kidney damage; is related to diagnosis, prognosis, and treatment in kidney disease; and has been suggested as a surrogate outcome for clinical trials of kidney disease progression (Pascual et al. 2006). A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). By definition, proteinuria and decreased GFR are biomarkers for CKD and potentially could be surrogate end points for kidney failure because in general, they precede the development of kidney failure.

An intermediate end point is a biomarker that is intermediate in the causal pathway between an intervention and a clinical end point. Decreased GFR also is an intermediate end point because it is on the causal pathway to kidney failure. Doubling of serum creatinine level is accepted as a surrogate end point because it reflects a large decrease in GFR and predicts the development of kidney failure. The increase in albumin excretion rate potentially could be a surrogate outcome for a large decrease in GFR in clinical trials.

Indeed, among the impressive number of data the PREVEND Study offered, the role of albumin excretion as a better marker than estimated GFR to identify individuals at risk for accelerated GFR loss is relevant. The 8592 patients who were included in this study were followed for a 4-year period. Among them, 134 patients with macroalbuminuria, 128 with erythrocyturia, and 103 with impaired renal function were identified. In the general population the prevalence of macroalbuminuria, erythrocyturia, and impaired renal function was calculated to be 0.6, 1.3, and 0.9 %, respectively (Halbesma et al. 2006). After a mean follow-up of 4.2 year, the macroalbuminuria group showed a -7.2 ml/min/1.73 m^2 estimated GFR loss compared with -2.3 ml/min/1.73 m^2 in the control group (difference $p < 0.001$). After exclusion of individuals with diabetes, the observed renal function decline in the macroalbuminuria group was 7.1 ml/min/1.73 m^2. It is interesting that eGFR fell by only 0.2 ml/min/1.73 m^2 (-0.4 %) in participants with impaired renal

function. Participants who at baseline had both macroalbuminuria and impaired renal function (n =18) experienced a rate of renal function decline of 9.0 ml/min/1.73 m^2 (Halbesma et al. 2006).

More recently, it was analyzed whether screening for albuminuria in the general population identifies individuals at increased risk for renal replacement therapy or accelerated loss of renal function. In a general population-based cohort of 40,854 individuals aged 28–75 year, a first morning void for measurement of urinary albumin was collected. In a subset of 6, 879 individuals, 24-h urinary albumin excretion and estimated GFR at baseline and during 6 years of follow-up were measured. Linkage with the national renal replacement therapy registry identified 45 individuals who started renal replacement therapy during 9 year of follow-up. The quantity of albuminuria was associated with increased renal risk: the higher the level of albuminuria, the higher the risk of need for renal replacement therapy and the more rapid renal function decline. A urinary albumin concentration $\geq$ 20 mg/L identified individuals who started renal replacement therapy during follow-up with 58 % sensitivity and 92 % specificity. Of the identified individuals, 39 % were previously unknown to have impaired renal function. Restricting screening to high-risk groups (e.g., known hypertension, diabetes, cardiovascular disease, and older age) reduced the sensitivity of the test only marginally but failed to identify 45 % of individuals with micro- and macroalbuminuria. Therefore, individuals with elevated levels of urinary albumin are at increased risk for RRT and accelerated loss of renal function. Screening for albuminuria identifies patients at increased risk for progressive renal disease, 40–50 % of whom were previously undiagnosed or untreated (van der Velde et al. 2009).

In arterial hypertensive subjects a retrospective cohort analysis of 141 hypertensive individuals followed up for approximately 7 years was carried out several years ago (Bigazzi et al. 1998). During follow-up, the rate of clearance of creatinine from patients with microalbuminuria decreased more than did that from those with normal urinary albumin excretion (Bigazzi et al. 1998).

Similar associations between albuminuria and renal function decline have been described by Viazzi et al in a larger cohort of patients with essential hypertension. Subjects who developed a renal event had higher baseline albumin-to-creatinine ratio compared with subjects who did not develop a renal event (5.12 vs 4.42 mg/g; $p < 0.001$) (Viazzi et al. 2010).

2.7 Microalbuminuria and Subclinical Organ Damage

According to several studies microalbuminuria correlate with various cardiac abnormalities and diseases, including left ventricular (LV) hypertrophy and dysfunction, electrocardiographic abnormalities, and coronary atherosclerosis.

There is an extensive and highly consistent body of evidence showing that microalbuminuric patients exhibited a higher prevalence of left ventricular hypertrophy (LVH), assessed either by electrocardiography or echocardiography, compared to normoalbuminurics (Cerasola et al. 1989; 1996; 2004; Palatini et al. 1995; Pontremoli et al. 1999; Wachtell et al. 2002a; b; Tsioufis et al. 2002; Ratto et al. 2008; Smilde et al. 2005; Lieb et al. 2006).

Since the first description of our group in 1989 of a close relationship between LV mass and albumin excretion rate in hypertensive patients (Cerasola et al. 1989), the vast majority of the following reports supported the view that hypertensives with elevated AER had higher cardiac mass, indicating that early renal damage and LVH occur in a parallel fashion.

It is important to note that the association between left ventricular mass and AER not only reflects an abnormal pressor overload, but remains statistically significant after accounting for blood pressure values (Cerasola et al. 1996; 2004; Palatini et al. 1995; Pontremoli et al. 1999; Wachtell et al. 2002a; 2002b; Tsioufis

et al. 2002; Ratto et al. 2008; Smilde et al. 2005). Further support to the blood pressure independent relationship of microalbuminuria with LVH arises from the observation that inappropriate left ventricular mass, that is the LV mass exceeding the compensatory needs for cardiac workload, is more strongly associated with microalbuminuria than do appropriate LV mass (Ratto et al. 2008).

Even if albumin excretion rate and LV mass are significantly and independently correlated, AER determination may add information on cardiovascular risk stratification beyond those provided by ultrasonographic detected LVH. Indeed, in a group of 312 essential hypertensive patients, we observed that a more intensive investigation for target organ damage, including ultrasound examination of the heart to detect LVH and microalbuminuria determination, beyond routine work-up alone, increases the proportion of hypertensive patients who should be classified as having a high absolute risk of cardiovascular morbidity and mortality. Overall, 26 % of patients changed risk category (mostly shifting from the medium- to high-risk stratum), a proportion that was significantly different from the percentage of patients reclassified after the addition to the routine work-up of either microalbuminuria (14 %) or echocardiography alone (16 %) (Cerasola et al. 2004). In some (Pontremoli et al. 1999), but not all studies (Wachtell et al. 2002a) microalbuminuric subjects showed a higher prevalence of concentric than eccentric LVH, being the former geometric pattern associated with a worse outcome than the latter.

Furthermore, patients with microalbuminuria showed subclinical impairment of systolic and diastolic LV (Pontremoli et al. 1999; Wachtell et al. 2002a). In the LIFE study, patients with microalbuminuria had significantly lower endocardial and midwall fractional shortening. On the other hand, patients with abnormal diastolic LV filling parameters had a significantly increased prevalence of microalbuminuria (Wachtell et al. 2002a).

Further data supporting the close association between elevated AER and cardiac abnormalities derive also from the cross-sectional relationship observed between MAU and silent myocardial ischemia, which can be evidenced by ST segment and T wave changes on an electrocardiogram (Diercks et al. 2000). Moreover, a significant and independent association between MAU and various ECG abnormalities (arrhythmias, intraventricular conduction defects, ventricular repolarization alterations and left-axis deviation) in the large observational I-DEMAND study, including 4121 hypertensive patients without overt cardiovascular disease, was found (Sciarretta et al. 2009).

Elevated AER was also directly associated with angiographic evidence of CAD. A study of 308 patients who underwent elective coronary angiography revealed that patients with angiographic evidence of CAD had significantly higher urinary albumin levels than disease-free individuals and that AER correlated with the severity of coronary atherosclerosis at angiography (Tuttle et al. 1999).

A significant association between microalbuminuria and several functional and structural changes of the arterial tree, beyond the coronary bed, has been described

Despite some conflicting results, several cross-sectional studies (Yokoyama et al. 2004; Bigazzi et al. 1995; Rodondi et al. 2007; Furtner et al. 2005; Geraci et al. 2016; Jørgensen et al. 2007), found that MAU was associated with higher thickness of the intima and media (IMT) layers of the carotid artery. In a wide population of hypertensive subjects with ($n = 183$) and without CKD ($n = 280$), we recently found greater values of carotid IMT in microalbuminuric patients when compared to normoalbuminuric ones (Geraci et al. 2016) (Fig. 4).

Moreover, in the Bruneck Study, a prospective population-based survey including 684 Caucasians adults, ACR was significantly and independently associated with the presence and severity of carotid and femoral atherosclerosis (Furtner et al. 2005). In addition, microalbuminuria predicts the development and progression of carotid atherosclerosis (Jørgensen et al. 2007).

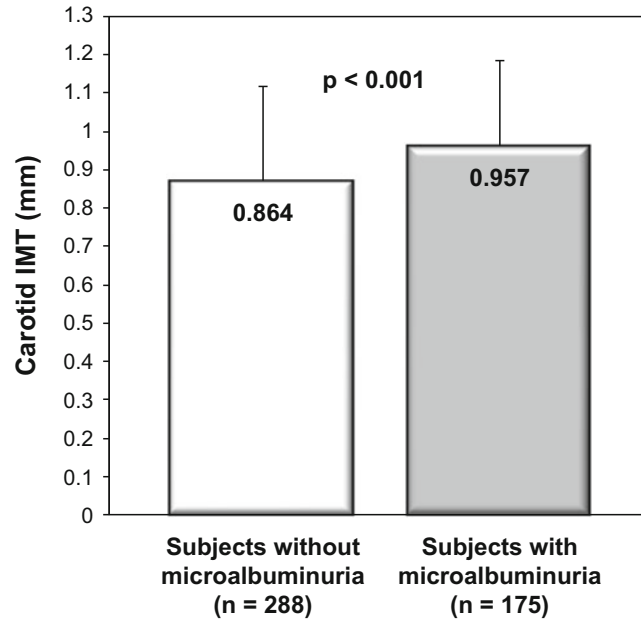

Fig. 4 Carotid intima-media thickness in hypertensive patients with and without microalbuminuria (Geraci et al. 2016). The data are given as means (the numbers inside the histograms) ± SD

Hence, it is not unexpected that microalbuminuria in several studies has been associated with a greater incidence of stroke (Gerstein et al. 2001; Hillege et al. 2002; Yuyun et al. 2004), and with cerebral small vessel disease (Ravera et al. 2002; Wada et al. 2007).

In addition, albumin excretion rate correlates with functional abnormalities of the vasculature, such as alterations of flow- and nitroglycerin-mediated brachial artery dilatation (Stehouwer et al. 2004; Malik et al. 2007) and impaired large artery elastic properties (Mulè et al. 2004; 2009; 2010; Smith et al. 2005; Hermans et al. 2007; Upadhyay et al. 2009; Munakata et al. 2009).

Large artery stiffness, especially aortic stiffness, assessed by pulse wave velocity (PWV) measurement is now well accepted as an independent predictor of cardiovascular morbidity and mortality. We demonstrated in a sample of 140 untreated nondiabetic essential hypertensive patients that microalbuminuria, was significantly associated with an augmented aortic stiffness, independently of low-grade inflammation, expressed by increased plasma level of high-sensitivity C-reactive, and of other potential confounding factors (Mulè et al. 2009). Our findings, which were replicated in a wider group of hypertensive patients (Mulè et al. 2010), are in line with previous observations of our group (Mulè et al. 2004) and of other authors (Yokoyama et al. 2004; Smith et al. 2005; Hermans et al. 2007; Upadhyay et al. 2009; Munakata et al. 2009) that reported significant relations of microalbuminuria with different indices of reduced arterial distensibility in a variety of populations. At the level of renal vasculature, microalbuminuria has been associated with increased intrarenal resistive index (RRI), a sonographic parameter, which is defined as the dimensionless ratio of the difference between maximum and minimum (end-diastolic) flow velocity to maximum flow velocity (Mulè et al. 2015b; Viazzi et al. 2015) (Fig. 5).

It is thought to indicate a greater intraparenchymal vascular impedance to blood flow and a greater risk of function worsening in the long term. However, accumulating evidence indicates that the RRI provides important information about the systemic vasculature as well (Geraci et al. 2015a; b; 2016; Mulè et al. 2015b; Viazzi et al. 2015; Morreale et al. 2016). Indeed, recent

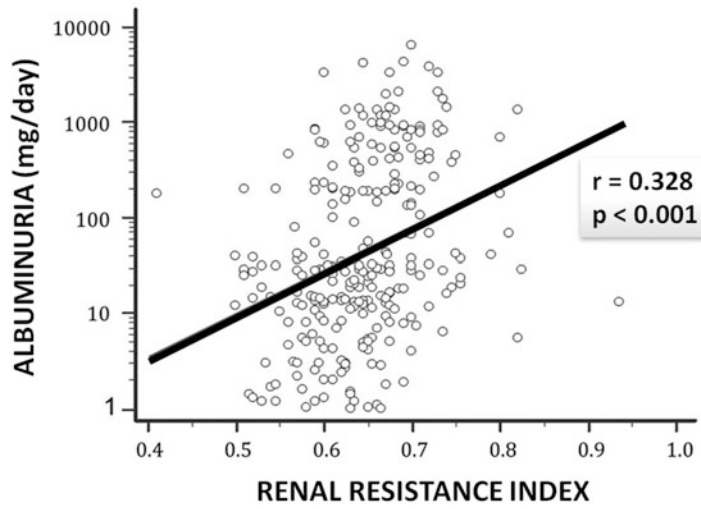

Fig. 5 Relationship between albuminuria (in logarithmic scale) and renal resistance index in hypertensive patients (Geraci et al. 2016)

data suggest that this parameter is not only expression of parenchymal perfusion, but may be also influenced by upstream vascular factors and indeed these factors appear to play a more important role than intrarenal resistance. Moreover, recent reports described significant associations of RRI with an enhanced cardiovascular risk (Mulè et al. 2015b; Viazzi et al. 2015).

Finally, an increased prevalence of retinal vascular changes has been reported in microalbuminuric hypertensive patients. Among 383 essential hypertensive subjects those with AER $>$ 20 μg/min had a prevalence of hypertensive retinopathy of 69 %, significantly higher than that observed in subjects having AER $<$ 11 μg/min (48 %) (Cerasola et al. 1996). There is also evidence, especially in type 1 diabetes, that MAU is a powerful predictor for the development of proliferative diabetic retinopathy and blindness (Newman et al. 2005).

2.8 Microalbuminuria as Predictor of Cardiovascular Morbidity and Mortality

It has long been recognised that microalbuminuria is an early sign of increased risk for developing overt nephropathy and cardiovascular disease in type 1 and type 2 diabetes (Viberti et al. 1982; Mogensen and Christensen 1984; Mogensen 1984; 2003). A meta-analysis evaluating the relationship between microalbuminuria and mortality in type 2 diabetes found that microalbuminuria doubled cardiovascular morbidity and mortality (odds ratio [OR], 2; 95 % CI, 1.4–2.7) and more than doubled the all-cause mortality rate (OR, 2.4; 95 % CI, 1.8–3.1) (Dinneen and Gerstein 1997). Subsequently, these results were confirmed in an observational analysis of the large Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, involving 10,640 type 2 diabetes patients. During an average 4.3-years follow-up, the multivariable-adjusted hazard ratio for cardiovascular events was 2.48 (95 % confidence interval 1.74–3.52) for every 10-fold increase in baseline ACR, even taking into account the level of estimated glomerular filtration rate (Ninomiya et al. 2009a).

In the past decade, a large body of evidence has been published suggesting that the value of microalbuminuria as predictor of cardiovascular events and total mortality may be extended to nondiabetic subjects and to patients with essential hypertension (Ruilope 2002; Gansevoort et al. 2013; Matsushita et al. 2010; Hallan et al. 2009; The Chronic Kidney Disease Prognosis Consortium 2011; van der Velde et al. 2011; Astor et al. 2011; Nitsch et al. 2013; Mahmoodi et al. 2012; Fox

et al. 2012; Gerstein et al. 2001; Hillege et al. 2002; Arnlov et al. 2005; Yuyun et al. 2004; Klausen et al. 2004; Brantsma et al. 2008).

In the large Netherlands cohort of the PREVEND study, after adjustment for cardiovascular risk factors, a twofold increase in urinary albumin concentration was associated with a 29 % increased risk of death from CVD (hazard ratio, 1.29; 95 % confidence interval [CI], 1.18–1.40; $p < 0.001$) (Hillege et al. 2002). Across the whole spectrum of urine albumin excretion, there was a continuous association between CVD and increasing albuminuria. The extended follow-up of the same study, limited to 8496 individuals, showed that baseline albuminuria remains a durable predictor of cardiovascular events up to 5 years after initial measurement and provides clues to determine optimal intervals between urinary albumin measurements for cardiovascular risk stratification (Brantsma et al. 2008).

Data from the NHANES III, spanning 13 years of follow-up in 14.586 adults, revealed that after adjustment for conventional CVD risk factors, C-reactive protein, and eGFR, a doubling of albuminuria was associated with a 6.3 % increase in CVD mortality and a 6.3 % increase in all-cause mortality, with similar results in patients with and without diabetes (Astor et al. 2008).

Likewise, in 1665 men and women of the Gubbio Population Study (aged 45–64 years), the highest sex-specific decile of urinary AER distribution was associated with an enhanced risk for incident cardiovascular disease, that was furtherly magnified by the concomitant presence of a high AER and a low estimated glomerular filtration rate (Cirillo et al. 2008).

The findings of these and other studies are supported by the results of two meta-analyses (Matsushita et al. 2010; Perkovic et al. 2008). The largest of these, the abovementioned Chronic Kidney Disease Prognosis Consortium study (Matsushita et al. 2010), used pooled individual data of more than 100.000 subjects with ACR measurements and 1.1 million participants with dipstick measurements from 21 general population cohorts. ACR was associated with risk of mortality linearly along its entire distribution, without threshold effects. Compared with ACR 0.6 mg/mmol, adjusted HRs for all-cause mortality were 1.20 (1.15–1.26) for ACR 1.1 mg/mmol, 1.63 (1.50–1.77) for 3.4 mg/mmol, and 2.22 (1.97–2.51) for 33.9 mg/mmol (Matsushita et al. 2010). A new recent analysis of the same data showed that there was a sex-related difference in the relationships between ACR and mortality (Nitsch et al. 2013). Compared with an ACR of 5 mg/mmol, the adjusted hazard ratio for all-cause mortality at urinary albumin-creatinine ratio 30 was higher in women [1.69 (1.54–1.84)] than in men [1.43 (1.31–1.57); p for interaction <0.01] (Nitsch et al. 2013).

On the other hand, another meta-analysis involving 24,470 participants, documented a strong independent relationship between proteinuria and cerebrovascular events. Patients with proteinuria had a 70 % greater risk of stroke compared with those without (Ninomiya et al. 2009b).

Urinary excretion of excessive amounts of albumin and cognitive impairment may be regarded as manifestations of microvascular disease, respectively of the kidney and of the brain. Therefore, these conditions may share a common pathogenesis. The results of the following study seem to be in line with this hypothesis (Barzilay et al. 2011).

In a total of 28,384 subjects with vascular disease or diabetes mellitus participating in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and in the Telmisartan Randomized Assessment Study in ACE [Angiotensin-Converting Enzyme]–Intolerant Subjects With Cardiovascular Disease (TRANSCEND) it has been demonstrated that microalbuminuria and macroalbuminuria are associated with increased odds or risk of cognitive decline (Barzilay et al. 2011). Compared with participants with normoalbuminuria, those with microalbuminuria were more likely to have a reduced Mini-Mental State Examination (MMSE) score (<24). On follow-up, participants with baseline albuminuria had increased odds of cognitive decline (decrease in MMSE score

≥3 points) compared with those with normoalbuminuria (microalbuminuria: OR, 1.22; 95 % CI, 1.07–1.38; macroalbuminuria: 1.21; 0.94–1.55). Participants with baseline macroalbuminuria treated with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker had lower odds of MMSE decline than participants treated with placebo.

Even though MAU is closely related to several traditional and non traditional CV risk factors and to a variety of indices of preclinical organ damage, the epidemiological studies above described showed that the association between microalbuminuria and cardiovascular disease remains even when all these risk factors are taken into account in multivariate analyses.

Therefore, the exact pathophysiological mechanisms explaining the association between MAU and CV disease remain uncompletely understood.

It is doubtful whether MAU causes atherothrombosis or vice versa. The most likely hypothesis is that a common pathophysiologic process, such as endothelial dysfunction, low-grade inflammation, or increased transvascular leakage of macromolecules, underlies the association between MAU and CV disease. In the STENO hypothesis put forward by Deckert et al. (Deckert et al. 1989) albumin leakage into the urine is a reflection of widespread vascular damage. The kidney thus would become a window to the vasculature; leaky renal vessels reflecting the permeability of the vasculature in general, caused by some alterations such as a reduction in the density of heparan sulfate-proteoglycan, not only of the glomerular basement membrane but also of the vascular wall. Generalized endothelial dysfunction (i.e., affecting many endothelial functions) plays an important role in both the initiation and the progression of atherosclerosis and MAU has been repeatedly shown to be accompanied by abnormalities in various markers of endothelial cell function in patients with and without diabetes (Fig. 6). However, there are some inconsistencies in the literature, and although microalbuminuria, marker of endothelial dysfunction, and low-grade inflammation are interrelated, they all are independently associated with risk for cardiovascular death.

Therefore, further studies are needed to explore the nature of the link between microalbuminuria and cardiovascular risk.

2.9 Microalbuminuria as Therapeutic Target

While there is now a very large and highly consistent amount of data showing that MAU is a strong predictor of CV risk, it is less clear whether reducing levels of MAU or limiting the progression to macroalbuminuria translates to a reduction in CV risk.

Although both ACE inhibitors and angiotensin receptors blockers (ARBs) (Redon 1998; ACE Inhibitors in Diabetic Nephropathy Trialist Group 2001; Viberti et al. 2002) have been shown to significantly reduce AER in patients with hypertension and diabetes mellitus, as well as in those with previous history of CVD, none of these clinical trials were designed to primarily study the effect of reducing microalbuminuria on CVD and renal outcomes.

In clinical trials of patients with chronic kidney disease and macroproteinuria as a result of type 2 diabetes, such as Irbesartan Diabetic Nephropathy Trial (IDNT) (Lewis et al. 2001) and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (Brenner et al. 2001), it is evident that therapeutic strategies that are associated with reduction of proteinuria are associated with fewer cardiovascular and kidney disease end points. However, whether one can extrapolate these observations to microalbuminuric patients is unknown.

The Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) is the only randomized trial to study the effect of albuminuria lowering in microalbuminuric, otherwise healthy individuals, who were not receiving antihypertensive or lipid-lowering agents (Asselbergs et al. 2004). In this clinical trial, 864 patients from the PREVEND cohort were enrolled and

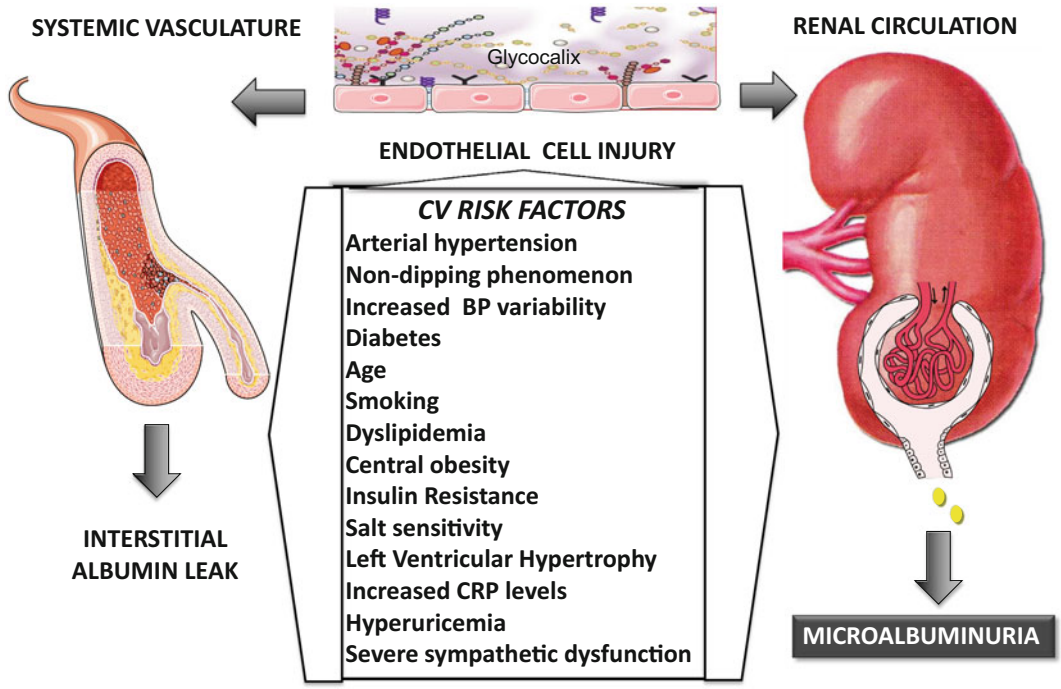

Fig. 6 Microalbuminuria as manifestation of systemic endothelial injury. Maladaptation of several endothelial functions, as a consequence of the deleterious effect of traditional and non traditional cardiovascular risk factors, is believed as an important effector mechanism in the development of albuminuria and of cardiovascular disease. A key mechanism that contributes to this process may be the loss of the glycocalyx—a proteoglycans-rich gel-like structure that lines the luminal endothelial surface. It mediates most of the regulatory functions of the endothelium and normally acts as a barrier against albumin filtration. Degradation of the glycocalyx in response to endothelial activation can lead to albuminuria and subsequent renal and vascular inflammation, thus providing a pathophysiological framework for the clinical association of albuminuria with renal and cardiovascular diseases

were randomized to receive fosinopril (20 mg/d) and/or pravastatin (40 mg/d) versus matching placebo in a 2 × 2 factorial design. The primary study end point was a composite of CVD mortality and hospitalization for nonfatal MI or myocardial ischemia, heart failure, peripheral vascular disease, or cerebrovascular accident. Participants were followed for a mean duration of 46 months. Median AER in these participants was 22.8 mg/d, and less than 5 % of participants were diabetic or had a previous CVD event. Fosinopril reduced albuminuria by 26 % ($p < 0.001$) and was associated with a 40 % reduction in the primary end point ($p = 0.098$) compared with placebo. Interestingly, a 90 % reduction ($p = 0.03$) in cerebrovascular events was observed in the group treated with fosinopril. Adjustment for the blood pressure–lowering effect of fosinopril did not significantly change the primary outcome results (Asselbergs et al. 2004). On the other hand, pravastatin did not reduce albuminuria and was associated with a non significant 13 % reduction in the primary end point.

Although this was the first study that specifically targeted reducing albuminuria, it was essentially a primary prevention trial for cardiovascular disease (only 3.4 % of the participants had a history of CVD) and had an insufficient number of patients to be followed for a sufficient period of time to have enough events, so it was underpowered to determine a change in outcomes attributable to the antialbuminuric effect of fosinopril.

In the LIFE study, 8206 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy were randomized to either losartan or atenolol and observed for a median of 4.8 years. The treatment with the angiotensin receptor blocker resulted in a greater reduction in albuminuria compared with the beta blocker, despite equivalent decreases in blood pressure. Moreover, losartan reduced the incidence of the primary composite end point (nonfatal myocardial infarction and stroke and CV death) more than atenolol did. This effect of losartan on albuminuria accounted for about one fifth of its beneficial effect on the composite end point (Ibsen et al. 2004).

A prespecified secondary analysis of the same trial noted that a decrease of albuminuria levels in the first 12 month of treatment predicted a better long-term cardiovascular outcome, independently of in-treatment level of blood pressure, suggesting that therapeutic strategies that are associated with a reduction of albuminuria may be cardioprotective (Ibsen et al. 2005).

The Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria (IRMA-2) study randomized 590 hypertensive patients with type 2 diabetes mellitus and microalbuminuria (urinary albumin excretion 20–200 μg/min) to irbesartan (150 mg/d or 300 mg/d) or placebo and observed them for a median duration of 2 years. Compared with placebo, irbesartan significantly reduced urinary albumin excretion at both doses, producing a mean reduction of 24 % with 150 mg/d and 38 % with 300 mg/d. Nonfatal CVD events tended to be slightly less frequent in the irbesartan 300 mg/d group than in the placebo group (4.5 % vs 8.7 %, $p = 0.11$) (Parving et al. 2001).

The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), in which 25,600 people were enrolled with vascular disease comparing the effects on the incidence of CV events of ramipril with telmisartan versus the combination of telmisartan along with ramipril (Investigators et al. 2008), also provides little insight on the relationships between microalbuminuria reduction and CVD outcomes. In this very large study it was observed a greater decrease in proteinuria with the combination therapy, but no additional benefit on cardiovascular disease, and a faster decrease in GFR and increased risk of kidney failure and death. In this trial, the geometric mean baseline urine albumin-creatinine ratio was approximately 10 mg/g, with microalbuminuria and macroalbuminuria in only 13 % and 4 % of participants, respectively (Mann et al. 2008). However, even if the ONTARGET was not designed and powered to evaluate the associations between AER variations and CV end-points, when the study population changes in albuminuria were assessed regardless of randomization to specific drug, a greater reduction of urinary albumin under treatment was related to a lower incidence CV events (Schmieder et al. 2011).

Similar results were obtained in post hoc analyses of Action in Diabetes Mellitus and Vascular Disease (ADVANCE) (Zoungas et al. 2009). However, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) (Bakris et al. 2010) does not confirm the potential prognostic value of AER changes. Likewise, a prospective study Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes Mellitus (ROADMAP) (Haller et al. 2011) reported no association between changes in microalbuminuria and CV events during the double-blind period, although an observational follow-up concluded that development of microalbuminuria was a marker of cardiovascular events (Menne et al. 2014).

A single-center Spanish study (Pascual et al. 2014) including 2.835 patients showed that subjects in which microalbuminuria developed during a median follow-up of 4.7 years, or persisted from the beginning, had a significantly higher rate of events than if remained normoalbuminuric.

A recent meta-regression analysis by Savarese et al showed that a successfully reduced albuminuria was associated with lower risk of myocardial infarction and stroke (Fig. 7) (Savarese et al. 2014). However, this analysis included many heterogeneous studies wherein therapeutic intervention was not primarily aimed at reducing blood pressure, had a very short follow-up time

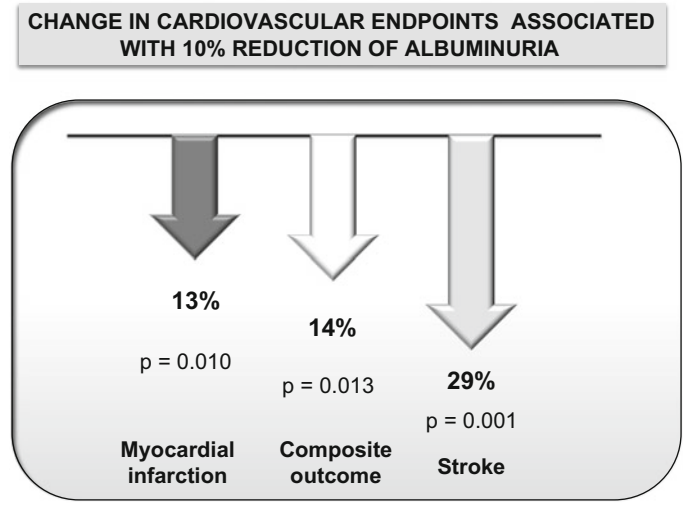

Fig. 7 Meta-regression analysis of 32 trials showing the association of albuminuria reduction with lower incidence of cardiovascular events in hypertensive and/or diabetic patients (Pascual et al. 2014) (Composite outcome: myocardial infarction, stroke, and cardiovascular death)

and did not include four trials specifically conducted on antihypertensive treatment. Similar conclusions were attained in another more recent meta-regression analysis showing a relationship between changes in albuminuria and CV risk, after adjustment for blood pressure variation under treatment. In studies reporting changes in CV events on the basis of albuminuria variations (six trials and 36,325 patients, mean follow-up 60 months, 3741 cardiovascular events), the overall adjusted relative risk of total CV events was 0.51 (95 % CI 0.38–0.59, $P < 0.000$) for albuminuria regression/no variation vs increase suggesting that urinary albumin excretion changes may be used in clinical practice as an intermediate endpoint of antihypertensive treatment (Viazzi et al. 2016). In the last European Society of Hypertension guidelines changes in albuminuria are regarded as potentially useful tool to monitor the effectiveness of treatment strategy in hypertensive patients, recognizing to this test the sensitivity to detect clinically meaningful changes over a timeframe of weeks or months (Mancia et al. 2013).

3 Conclusions

A large and highly consistent body of evidence supports the statements of recent guidelines for the management of hypertension (Mancia et al. 2013) and of KDIGO guidelines for evaluation and management of chronic kidney disease (Levin et al. 2013) that recommend to use both albuminuria and reduced GFR in all hypertensive subjects in order to provide more accurate prognostic information and therefore more precise risk stratification.

In particular, the powerful association between UAE and cardiovascular diseases, documented even below the current microalbuminuria threshold, reflects the underlying biological complexity of albumin excretion, in which subtle fluctuations signal important changes within the cardiovascular system.

In addition, it challenges our previous definition of normal, suggesting that albuminuria should be interpreted as a continuum rather than as threshold cut-off values.

Although there are some conflicting data, the great majority of studies and meta-analyses show that reducing albuminuria improves cardiovascular outcome. The simple search for subclinical renal damage in hypertensive patients may enable the clinician to better assess absolute cardiovascular.

Risk and make a more correct decision regarding therapeutic strategies. Identification of MAU and of a moderate reduction in eGFR may induce physicians to encourage patients to make healthy lifestyle changes, and perhaps would prompt to more aggressive modification of standard risk factors for cardiovascular diseases.

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