Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease

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The earlier observations on the association between renal failure and increased rates for cardiovascular (CV) complications and death date back several decades [1,2]. Similarly, it has long been noted that subclinical elevations of urinary albumin excretion (UAE) are related to higher risk of subsequent development of clinical nephropathy in patients with diabetes mellitus [3,4], and that increased UAE was associated with higher risk for CV events and mortality in both diabetic and non-diabetic individuals [4–7]. Since then, a substantial amount of data have accumulated, providing solid evidence that both the decline in renal function and the elevation in UAE are independently associated with increased risk for cardiovascular disease (CVD). This article reviews the roles of microalbuminuria (MA) and chronic kidney disease (CKD) as risk factors for CVD, discussing the progress of the epidemiological and clinical evidence on the field.

Definitions of microalbuminuria and chronic kidney disease

In the first description of MA as a predictor of nephropathy in patients with type 1 diabetes in 1982, Viberti et al. [3] defined MA as the overnight UAE rate between 30 and 140 mg/min and clinical nephropathy as an ‘Albustix’ stick positive for proteinuria. Since then, the definition of MA has been refined to include all the possible methods of UAE measurement. Currently, MA is defined as UAE between 30 and 300 mg/day, if measured in a 24 h urine collection, 20–200 µg/min, if measured in a timed urine collection or 30–300 mg/g, if measured with the use of urinary albumin to creatinine ratio (UACR) in a spot urine collection. Any urinary albumin value below these limits is considered as normal UAE, whereas any value above them reflects the presence of macroalbuminuria or clinical proteinuria [8,9].

CKD is defined either as kidney damage, as confirmed by kidney biopsy or markers of damage, or as the presence of glomerular filtration rate (GFR) under the level of 60 ml/min/1.73 m², each for a period greater than 3 months [10]. The clinical syndrome of CKD is divided in terms of severity in five stages, which are based on the level of GFR, irrespective of the cause of kidney damage. Decreased kidney function starts at a GFR below 89 ml/min/1.73 m² and is considered to be pronounced if the GFR is <60 ml/min/1.73 m² for more than 3 months [10]. In clinical terms, the latter is reflected in an elevation of serum creatinine levels above the normal range [≥1.5 mg/dl (133 µmol/l) in men and ≥1.3 mg/dl (115 µmol/l) in women].

Prevalence and natural course of microalbuminuria and chronic kidney disease

Early observations suggested a high prevalence of MA in patients with diabetes, but later and larger studies failed to confirm these results [11–16]. These variations in prevalence can be attributed to differences in the populations studied in terms of age, race, blood pressure (BP) or renal function levels, as well as the techiques used for detection of MA. The prevalence of MA in patients with type 2 diabetes is estimated at about 20%, and about 30% in those subjects >55 years of age [11,17,18]. Without specific intervention, the rate of progression to diabetic nephropathy (i.e. development of macroalbuminuria) in patients with type 2 diabetes and MA would be 5% per year,
Factors known to influence the development of microalbuminuria in subjects without diabetes

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<tr>
<th>Factor</th>
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<td>1. Elevated blood pressure (systolic, diastolic, mean)</td>
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<td>2. Increased body mass index</td>
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<td>3. Endothelial dysfunction</td>
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<td>4. Decrease in high density lipoprotein levels</td>
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Measurement of urinary albumin excretion and renal function

Twenty-four hour or other timed collections were the traditional way to measure UAE but measuring UACR in a spot collection of morning urine in the fasting state is currently recommended as a simple, quick and comparatively accurate way of determining albuminuria [8,10,30,31]. The use of this approach, however, requires knowledge of the factors that can affect spot UACR measurement (Table 2). It is important to note that the range of UAE is about 25% lower during sleep than while awake and MA can exhibit a daily intra-individual variation between 40 and 100% [32–34]. This can be largely attributed to biological variations due to inflammation associated with small injury, toothaches, etc. as well as changes in dietary sodium and protein intake [35]. Caution is required when interpreting the UACR in patients with higher muscle mass, i.e. males or African-Americans, as these populations have higher levels of creatinine excretion [36]. That is why different levels for MA in males and females have been proposed [9]. The imprecise nature of MA and creatinine measurements require at least three measures to be made over a period of 2–3 months before determining the actual UACR for a particular individual [30]. Ideally, these measurements should be obtained in the fasting state and collected from the first morning void, to avoid the effect of any physical activity during the day [37].

Serum creatinine has been long considered an imprecise index of renal function, since it is affected by various factors, apart from creatinine filtration; patients with mild renal impairment can thus have normal or near normal levels [38,39]. This is why stages of CKD are defined with the use of GFR levels, which is considered the best index of renal function in both health and disease [10]. Most accurate estimations of GFR require the measurement of renal clearance of inulin, which is cumbersome and time-consuming, so is the use of various radioactive substances, which also gives accurate results [40], but seems difficult for everyday clinical practice. To overcome these limitations, a number of equations using serum creatinine and demographic variables have been developed to estimate GFR through creatinine clearance, such as the Cockcroft–Gault formula, the Modification of Diet in Renal Disease (MDRD) study formula and others [41,42]. The MDRD study formula seems to provide a much more accurate estimate of GFR than other commonly used equations [42] and therefore it is currently recommended for GFR determination [10,31].
Microalbuminuria and cardiovascular disease

Microalbuminuria and the risk for cardiovascular outcomes

Yudkin et al. [43] were the first to report cross-sectional associations between MA and the prevalence of coronary artery disease (CHD) and peripheral vascular disease (PVD). Since then, several studies, either in the general population or in high-risk individuals, have reported the associations of MA with established CV risk factors (age, hypertension, hyperglycaemia, obesity, high-total and LDL-cholesterol, high triglycerides, low HDL-cholesterol, smoking) as well as emerging CV risk factors and other unfavourable conditions (high C-reactive protein, insulin resistance, hyperinsulinaemia, endothelial dysfunction, hyperhomocysteinaemia, high-fibrinogen levels and others) [14,16,17,44–60]. Furthermore, MA has been long suggested to be an independent risk factor for CV morbidity and mortality in various populations, either with or without diabetes mellitus. In patients with type 1 or type 2 diabetes, early observations in small cohorts of subjects followed for periods up to many years linked the presence of MA with increased risk of CV events and overall or CV death, in parallel to an enormous elevation of the risk for future development of clinical proteinuria [4,6,7]. Subsequent prospective cohort studies further supported these findings, showing independent associations between MA and CV or total mortality [11,61,62]. Similarly, in non-diabetic individuals, MA was found to be a strong predictor of future CV morbidity and mortality, independent of major CV risk factors of 3.5 [63,64]. However, the best evidence of the association between MA and the risk for CVD comes from post-hoc analyses of long-term clinical trials, as well as from recent large prospective cohort studies. In individuals with a history of CVD or diabetes of the Heart Outcomes Prevention Evaluation (HOPE) trial, MA was associated with an adjusted relative risk of 1.83 for major CV events, 2.09 for all-cause mortality and 3.23 for hospitalization for congestive heart failure [65], with similar relative risks in subjects with or without diabetes. Notably, the risk for the primary endpoint started from UACR levels well below the cut-off for MA and increased continuously. For every 0.4 mg/mmol increase in the UACR level, the adjusted hazard of major CV events increased by 5.9%. Similarly, in a post-hoc analysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [66], the risk for the primary composite endpoint (CV death, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction) increased continuously from very low levels of UAE. In non-diabetic patients, for every 10-fold increase in UACR, hazard ratios for the composite endpoint increased by 57%, for CV mortality by 97.7%, for all-cause mortality by 75.2%, for stroke by 51.0% and for myocardial infarction by 45%. The results for diabetic patients were similar, with the exception of myocardial infarction, which was not significant.

In addition to the above, in a subpopulation of the NHANES II study, examined between 1976 and 1980 and followed for 16 years, the adjusted relative hazards for CV and all-cause mortality were 1.57 and 1.64 for subjects with urinary protein levels of 30–299 mg/dl and 1.77 and 2.00, respectively, in subjects with urinary protein levels ≥300 mg/dl, compared with the individuals with levels of <30 mg/dl [67]. A series of studies on subpopulations of 20,000–23,600 individuals from the population-based European Prospective Investigation into Cancer and Nutrition study, Norfolk, UK (the EPIC-Norfolk Study) further support the above. In these studies, after mean follow-up of 6.2–7.2 years, the presence of MA at baseline was independently associated with a significantly greater risk of 36% for incident CHD [68], 49% for stroke [69], 103% for CV mortality and 48% for all-cause mortality [70]. Notably, the risk for CV events associated with the presence of macroalbuminuria was again even higher [68,69]. In a very recent prospective study, MA at baseline was also independently associated with future CV events after an average follow-up of 42.5 months [71].

In contrast to the above, it is still uncertain whether the reduction of MA is linked to a reduction in CV endpoints. In the LIFE trial, the group of subjects with the lowest CV event rate also had the greatest reduction in UAE from baseline and one-fifth of the difference in favour of Losartan on the primary composite endpoint was attributed to the greater reduction in albuminuria on Losartan [72]. In the Prevention of Renal and Vascular End-stage Disease Intervention Trial (PREVEND IT), subjects with MA were randomized to fosinopril 20 mg/day or matching placebo and pravastatin 40 mg/day or matching placebo. During a mean follow-up of 46 months, fosinopril reduced UAE by 26% but the reduction in CV mortality or CV hospitalization in patients treated with this agent showed only a trend towards statistical significance [73]. This study, however, was limited by the low overall number of CV events, as well as submaximal doses of fosinopril.

Microalbuminuria as a marker of target organ damage and disease severity

It has been hypothesized that MA can also serve as a marker for subclinical CV organ damage. In various previous studies, MA has been associated with larger left ventricular mass and higher degrees of left-ventricular hypertrophy [14,74–77]. Even among hypertensive patients who are normoalbuminuric, those with higher absolute levels of UAE have greater left ventricular wall thickness and more frequent concentric left-ventricular hypertrophy [78]. In the LIFE study, UAE was correlated with left-ventricular hypertrophy at baseline and after 1 year of treatment independently of systolic BP, plasma glucose and age,
and the changes in these parameters during the 1 year period were also correlated independent of systolic BP and glucose changes [79]. MA has also been associated with the degree of atherosclerotic disease, evaluated with the use of ultrasound imaging of the intima-media thickness in the carotid artery [14,76,77,80,81] or the prevalence of vascular retinal changes [14,82]. Overall, as most patients with diabetes, hypertension or other risk factors for CVD progress to major CV events through an asymptomatic phase that is characterized by the presence of subclinical organ damage (left-ventricular hypertrophy, peripheral atherosclerosis, etc.) and this asymptomatic phase not only precedes but also predicts the occurrence of major events [83], screening for MA can be an invaluable tool for identifying high-risk individuals.

Measurement of UAE is also considered a very sensitive tool for assessment of the severity of any inflammatory condition, including CVD. The level of UAE is proportional to the severity of many acute inflammatory processes such as trauma, sepsis and surgery [84]. The severity of conditions like ischaemic and reperfusion injuries is also associated with the level of UAE. For example, MA was found to be an early response in patients with acute myocardial infarction and proportional to the severity of the infarct [85], whereas in patients with PVD and claudication, the level of UACR after exercise was related to the severity of muscle ischaemia during exercise [86].

**Chronic kidney disease as cardiovascular risk factor**

Historically, the earlier observations that patients with ESRD had elevated rates for CV complications and death, were made more than 30 years ago [1,2] as aforementioned. Among patients in the Medicare database in the US, 80% of those with CKD submitted CVD claims over a 2-year period compared with only 45% of those without CKD, and the prevalence of heart failure was four times higher in CKD patients compared with those without CKD [26]. In ESRD patients treated by dialysis, the risk of CVD was enormously elevated, with CV mortality rates in various studies being ~15 times higher than age- and sex-matched controls in the general population [87]. Needless to say, CVD is by far the principal cause of death in ESRD patients on both sides of the Atlantic [26,88].

In several of the above studies linking MA with CVD risk, there was a continuous association between the level of UAE and the risk for CVD and, thus, macroalbuminuria or clinical proteinuria was associated with a higher risk for CV morbidity and mortality than MA [61,65–69]. Since the presence of macroalbuminuria is a clear manifestation of overt nephropathy and is associated with faster deterioration of kidney function [9,10,89], the underlying mechanisms for the increase in CV risk in macroalbuminuric patients could be somehow different from those in patients with MA; the excess CV risk in patients with macroalbuminuria could be attributed not only to the presence of a generalized vascular injury, as in the case of MA, but also to the appearance of a number of uraemia-related factors which can also promote CVD.

In parallel to the common presence of many of the traditional (hypertension, diabetes, obesity, etc.) or non-traditional (i.e. hyperhomocysteinaemia) CV risk factors in patients with CKD [9], as GFR falls below 60 ml/min/1.73 m² and most physiological functions of the kidney start to wane, a number of factors related to impaired renal function and which can further contribute to CVD also appear [90,91], providing explanations for the independent connection between renal function loss and CV risk. These factors become obvious clinically when the GFR falls below 45 ml/min/1.73 m² and blatant at a GFR of 30 ml/min/1.73 m². The most important of these uraemia-related factors seem to be alterations in calcium/phosphorus and related hormones homoeostasis and anaemia resulting from reduced production of erythropoietin. Changes in calcium, phosphorus and parathyroid hormone (PTH) metabolism have been associated with increased vascular calcification, arteriosclerosis and CV risk, while recent evidence suggests that reduced levels of vitamin D also contribute to increased CV mortality in CKD patients [92]. On the other hand, anaemia through various effects on the CV system, mainly left-ventricular hypertrophy, is also associated with adverse CV outcomes in CKD patients [93]. Moreover, preliminary evidence suggests that both vitamin D supplementation and partial correction of haemoglobin levels are associated with reduction of CV events [92,93].

Since the very first observations in ESRD patients [1,2], numerous studies have investigated the association between renal function and CV outcomes or overall mortality in populations with or without CVD. Most of these studies suggested that mild to moderate elevations in serum creatinine levels were associated with increased risk of CV events or death [94–98], as well as of death from any cause [5,94,95,97–102], whereas a few did not confirm these results [103]. A major limitation of these studies was the use of only serum creatinine levels to assess the level of renal function [5,94–97,99–103] with different cut-off values to define the presence or the stages of CKD [5,94–96,99–103], as well as the use of dichotomous groups of estimated kidney function [5,94,95,98–101,103]. Several were also characterized by relatively small numbers of individuals with CKD [5,94,95,97–101,103] and others were restricted to the study of selected populations (elderly subjects, patients with CVD, etc.) [96–99,102].

Thus, it is only very recently that studies performed either on the general population [67,104,105] or in patients with pre-existing CVD [106,107] evaluated the association between the continuum of kidney function loss and CV risk using the level of GFR and gave more...
precise information. In the aforementioned study in the subcohort of the NHANES II population [67], CVD-related mortality rates were 4.1, 8.6 and 20.5 deaths/1000 person-years of follow-up among participants with estimated GFR of ≥90, 70–89 and <70 ml/min, respectively. In addition, individuals with estimated GFR of <70 ml/min had a higher risk of 68% for death from CVD and 51% for overall mortality compared with subjects having GFR ≥90 ml/min. In the population-based Atherosclerosis Risk In Communities (ARIC) study [104], subjects with GFR of 15–59 ml/min/1.73 m² had a 38% adjusted higher risk for CV events and subjects with GFR of 60–89 ml/min/1.73 m² had a 16% higher risk compared with subjects with GFR of 90–150 ml/min/1.73 m², after 6.2 years of follow-up. Further, each 10 ml/min/1.73 m² lower GFR was associated with a significant adjusted hazard ratio of 1.05, 1.07 and 1.06 for CVD, de novo CVD and recurrent CVD, respectively. Similarly, in a cohort of almost 5000 subjects over 65 years of age, followed for 5 years, each 10 ml/min/1.73 m² lower GFR was independently associated with a hazard ratio of 1.05 for CVD, 1.07 for de novo CVD, 1.04 for recurrent CVD and 1.06 for all-cause mortality [108].

A recent prospective cohort study on more than 1 million individuals in the US seems to provide the best evidence on the field [105]. After a median follow-up of 2.84 years, which amounts to over 3 million person-years of follow-up, the adjusted hazard ratio for CV events was 1.4 for individuals with a GFR 45–59 ml/min/1.73 m², 2.0 for those with GFR 30–44 ml/min/1.73 m², 2.8 for those with GFR 15–29 ml/min/1.73 m² and 3.4 for individuals with GFR <15 ml/min/1.73 m² compared with the subjects with GFR ≥60 ml/min/1.73 m², who were used as the reference group. The adjusted risk of overall mortality and hospitalization followed the same pattern. Notably, the confidence intervals for the calculated adjusted risks were very small, obviously due to the enormous sample size, thus the results provide very accurate estimates of the actual risks.

Recent studies extended these findings on independent associations between the declining GFR estimated with the MDRD formula and increasing CV risk also in patients with pre-existing CVD [106,107]. In 14 527 patients with acute myocardial infarction complicated by heart failure, left-ventricular dysfunction, or both, from the population of Valsartan in Acute Myocardial Infarction Trial (VALIANT), the adjusted hazard ratio for the composite endpoint (death from CV, congestive heart failure, recurrent myocardial infarction, resuscitation after cardiac arrest and stroke) was 1.10 for individuals with GFR 60–74.9 ml/min/1.73 m², 1.26 for those with GFR 45–59.9 ml/min/1.73 m² and 1.49 for those with GFR <45 ml/min/1.73 m², respectively, compared with subjects of the reference group with GFR ≥75 ml/min/1.73 m². The adjusted risk from overall death was also progressively increasing with decreasing GFR, while for baseline-estimated GFR values below a considerably higher renal function level (81.0 ml/min/1.73 m²), each 10-unit decrease was associated with a 10% increase in the risk of death and non-fatal CV outcomes. Similarly, a recent analysis examined the association of kidney function with CVD in patients with chronic heart failure, from the population of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme [107]. After a median follow-up of 34.4 months, the adjusted hazard ratio for the primary outcome of CV death or hospitalization for worsening congestive heart failure was 1.54 for patients with GFR 45–60 ml/min/1.73 m² and 1.86 for those with GFR <45 ml/min/1.73 m² compared with patients with GFR >60 ml/min/1.73 m² and similar was the association between GFR and all-cause mortality. Notably, this effect of GFR was not related to the level of left-ventricular ejection fraction, which was also found to be an independent predictor of worse outcomes.

Studies that examined the prognostic importance of renal dysfunction after coronary artery bypass graft (CABG) surgery in patients with coronary artery disease-yielded comparable results. Previous studies on the field have shown that both ESRD [109,110] and severe renal dysfunction not requiring renal replacement therapy [111–113] are associated with increased morbidity and mortality after CABG. However, the latter studies also identified patients with renal dysfunction by splitting the examined populations into dichotomized groups on the basis of serum creatinine level and not measuring renal function as a continuous variable [91]. Again, recent studies that used GFR as a measure of renal function, estimated either with the Cockcroft–Gault [114], or the MDRD formula [115,116], have clearly shown that reduced GFR was independently associated with elevated operative morbidity and mortality as well as post-operative mortality. Interestingly, as in the general population, in the latter studies the relation between renal dysfunction and mortality risk was not linear but presented a steep increase when GFR fell below a threshold of about 60 ml/min/1.73 m² [115,116].

Conclusions

Recently accumulated evidence allows a better understanding of the longitudinal relationships between MA or CKD and the risk for CVD. Both MA and CKD are independently associated with a higher risk for CV events, as well as CV and overall mortality in the general population and in patients with other CV risk factors or prevalent CVD. While the pathophysiology and clinical significance of these associations remain to be fully established, these findings suggest that determination of UAE and renal function levels should be implemented in clinical practice for overall risk evaluation, at least in individuals with high CVD risk. The rationale for routine assessments of these variables is further supported by the fact that
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determination of both, MA with the use of UACR and level of renal function with estimation of GFR are
inexpensive, easy to obtain in the clinical setting and the results are rapidly available. Further research
should define in detail the populations that would benefit from these routine measurements and future
guidelines should provide clear recommendations for their clinical use.

Conflict of interest statement. None declared.

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