

may not be appreciated otherwise. This would primarily help prevention of the disease but also enhance early detection.

Albuminuria

■ Definition & assessment

Under normal circumstances, urine contains protein that is composed of low-molecular-weight proteins (20%), Tamm–Horsfall mucoprotein (40%) and albumin (40%) [13]. Albumin, however, is the predominant form of protein once the levels increase and when the albumin:creatinine ratio exceeds 30 mg/g the term high albuminuria applies. Even though the terms proteinuria and albuminuria are used interchangeably, it is more accurate to use the latter since only albuminuria has been shown to be an indicator of progressive kidney damage and worsening cardiovascular outcomes. In this regard, measurement of total urinary protein requires additional studies to discern the protein type (i.e., albumin, light-chain proteins or β 2-microglobulin). Elevated light-chain proteins and β 2-microglobulin are also associated with particular kidney diseases, but these are not addressed in this article.

Current practice guidelines recommend urinary albumin determination in the assessment of kidney function decline [14]. The American Diabetic Association (ADA) recommends at least two nonconsecutive morning specimens be obtained within 3 months. Note there is as much as a 25% variation in daily albuminuria in any given normal person, hence spot collection at varying times will ensure greater accuracy [15]. This relates to many things that affect albumin excretion including circadian rhythm, exercise, food intake, ongoing infection and pediatric population [10,16]. The screening should be performed in all at-risk patient populations, primarily patients with hypertension, diabetes mellitus and early CKD [12,13,17].

The gold standard for measuring urinary albumin excretion is a 24 h urine collection. This may be inaccurate, however, if proper timed collection is not performed. Measurement of total creatinine over the same period provides information regarding accuracy of collection. More acceptable and validated against a 24 h urine collection is a spot albumin:creatinine ratio obtained from the first morning urine specimen obtained on two to three different days over a week reflecting night-time albumin excretion [18,19].

The cutoff values differ in men and women since females excrete less creatinine and this is outlined in TABLE 1. This categorization is

important since the clinical evidence implies that adverse cardiovascular outcomes occur starting at a range slightly below normal and increasing linearly [15,20,21]. The most current recommended definitions of the albuminuria spectrum includes normal to high normal (<29 mg/g), high (30–299 mg/g), very high (>300 mg/g) and nephrotic (\geq 2000 mg/g) [22].

■ Prevalence

Data derived from the National Health and Nutrition Survey (NHANES) 1999–2004 estimated the prevalence of high albuminuria to be 8.2% and very high albuminuria to be 1.3% through all ranges of estimated GFR [23]. Similar results were derived from European cohort studies [24]. Estimates for those with diabetes mellitus, hypertension or elderly are much higher [25]. Specifically, the rates of high albuminuria are higher in diabetic compared to nondiabetic patients with otherwise high cardiovascular risk burden to 32.2 and 14.7%, respectively [26]. Moreover, the transition from high to very high levels of albuminuria dramatically increases in patients with uncontrolled diabetes mellitus to 80% and 20–40% in Type 1 and Type 2, respectively [27].

Pathogenesis of albuminuria

In the setting of hypertension without diabetes, high pressure as well as increased oxidant stress injures the endothelium making it susceptible to increased fluxes of atherogenic lipoproteins and inflammatory cells with simultaneous initiation of various signaling cascades of prothrombotic and inflammatory potentials [28]. This results in altered permeability of the vessels including the glomerular capillaries. In obesity-related conditions such as diabetes, production of reactive oxygen species and advanced glycation products more aggressively affects functioning of the vasculature, which includes the most vascular organ in the body, the kidney [8]. This initiating process induces the renin angiotensin aldosterone system (RAAS) with inflammatory cytokines and growth factor production. Subsequently, the damage ensues within glomeruli by glomerular basement membrane changes and podocyte dysfunction. This accentuates albumin excretion, which in turn induces inflammatory changes in tubular interstitium further advancing the disease. Moreover, the tubular injury resulting in impaired albumin absorption could be responsible for increased urinary secretion [29].

Albuminuria & cardiovascular risk

■ Hypertension

Evaluation of 1041 individuals aged 18–45 years who were never treated for stage 1 hypertension had an 8% prevalence of high albuminuria that was not associated with any other cardiovascular risk factors. This study did not find any correlation between albuminuria presence and the development of sustained hypertension and offered evidence that glomerular hyperfiltration is the likely cause [30]. Moreover, in the Nurses' Health Study participants without diabetes mellitus who had normoalbuminuria in the higher range (between 3.68 and 24.17 mg/g) were more likely to develop hypertension compared with their counterparts with no or lower levels of albuminuria [31]. This suggests that microalbuminuria might also have a predictive value for the occurrence of hypertension.

Additional clinical studies demonstrate that nocturnal hypertension, specifically nondipping, is a significant contributor to the prevalence of microalbuminuria in hypertensive patients. Ambulatory blood pressure monitoring in 63 hypertensive individuals revealed a significant increase in microalbuminuria among patients whose night-time blood pressures fell by less than 10/5 mmHg over the daytime blood pressure [32]. More recently, work carried out in patients with resistant hypertension demonstrated that high night-time systolic blood pressures were closely associated with a higher urinary albumin excretion rate [33]. Data by Tsioufis *et al.* suggests that nocturnal hypertension is a better determinant of chronic kidney disease progression [34].

The level of albuminuria also correlates with the level of blood pressure elevation. The data from the MAGIC study demonstrate that higher diastolic and mean blood pressure readings were associated with higher ranges of albuminuria [35]. Similarly, analysis of data collected from a cohort of men and women aged 45–64 years-old without diabetes revealed higher relative risk for microalbuminuria in the group that had a 18 mmHg higher systolic blood pressures compared with the other subjects [36].

■ Metabolic disorders

Insulin resistance is associated with hyperglycemia, hyperinsulinemia and low high-density lipoproteins (HDLs) and high triglycerides. This is commonly seen in patients with obesity and diabetes [37,38]. Evaluation of individuals diagnosed with the metabolic syndrome noted an increased in prevalence of microalbuminuria

Table 1. Definitions of albuminuria.

Definition	Gender	Albumin:creatinine ratio (mg/g)
Optimal	Male	<10
	Female	<15
High normal	Male	10 to <20
	Female	15 to <30
High	Male	20 to <200
	Female	30 to <300
Very high	Male	>200
	Female	>300

and CKD [39]. Recent assessment of individuals with hypertension who also have metabolic syndrome manifest higher urinary albumin creatinine ratios (20 vs 12.3 mg/g) in spite of similar blood pressure control [40]. In particular, there is evidence to suggest a reciprocal relationship between the level of microalbuminuria and number of components of metabolic disarray [41].

Additionally, in the Multi-Ethnic Study of Atherosclerosis (MESA), patients with microalbuminuria and the metabolic syndrome were at greater risk for negative cardiovascular outcomes than patients without microalbuminuria, suggesting that microalbuminuria might be predictive of at-risk patients. The former group also had a higher incidence of insulin resistance [42]. This is consistent with the observation that higher levels of insulin coexist in hypertensive, albuminuric patients [43,44]. The Australian Diabetes, Obesity and Lifestyle Study confirmed that worsening glycemic control, even in individuals without diabetes mellitus, negatively affects albuminuric level [45]. Not all studies, however, confirm this finding. For example, the Hoorn study did not find any relation between microalbuminuria and components of the metabolic syndrome [46].

■ Endothelial dysfunction

Vascular injury is a multifactorial process. Atheromatous transformation is dependent on abnormal lipoprotein utilization. The lipid profile of hypertensive patients is oftentimes negatively affected and is recognized as a part of the definition of the metabolic syndrome. Microalbuminuria occurrence has been associated with increased low-density lipoproteins and triglyceride levels and decreased HDL levels [47]. In a prospective follow-up of 574 patients, development of microalbuminuria in Type 2 diabetics was found to be directly correlated to total cholesterol levels [48]. A prospective cohort study of 2304 adults demonstrated that increases in triacylglycerol, ApoB, ApoA-II and HDL – cholesterol

levels are associated with development of microalbuminuria in Type 1 diabetic patients [49]. Similarly, adolescent diabetics with Type 1 diabetes mellitus had higher non-HDL levels if they were microalbuminuric [50]. Taken together, available data establish a rather strong connection between lipid utilization patterns and microalbuminuria. This is, in part, responsible for the elevated cardiovascular risk in this patient group.

Endothelial dysfunction is reflective in vascular function throughout the body; hence, it contributes to hemodynamic changes within the kidney and predisposes to changes associated with progressive increases in albuminuria as well as the development of atherosclerosis. The initiating factor leading to increased membrane permeability of the endothelium and vasculature relates to oxidant stress and advanced glycation products in diabetic states, as well as lipid abnormalities and impairment that results in the deposition of atherogenic lipoproteins that further promote altered molecular physiology of the vessel wall [51]. These factors all contribute to a reduction in NO that decreases affinity for platelet aggregation and inflammatory cell influx leading to more progressive vascular damage [52]. People with these diseases also have an increased incidence of microalbuminuria [53,54]. Additionally, experimental evidence suggests that high levels of angiotensin II in the vessel wall, frequently associated with the above conditions, also increase the production of reactive oxygen species [55]. Hyperinsulinemia and hyperglycemia also have the same effect.

A potential biomarker for endothelial injury, von Willebrand factor, was found to be elevated in hypertensive patients with microalbuminuria when compared with patients without hypertension, and was one of the predictors of nephropathic development in microalbuminuric diabetic patients during the IRMA II trial [56,57]. In this study higher asymmetric dimethyl arginine levels were also noted, which is another potential biomarker implicated in decreased NO production, in patients with hypertension and diabetes mellitus, and correlated with increased levels of microalbuminuria [58,59]. In addition, serum levels of the cytokine TNF- α and acute phase reactant C-reactive protein, both involved in inflammatory pathways of endothelial damage, correlate significantly with the presence of microalbuminuria in hypertensive and diabetic subjects [60,61].

Taken together, these observations imply that vascular impairment on the cellular and molecular level is closely related to the presence of high

albuminuria. These changes translate into a high risk of cardiovascular disease and potentially impaired kidney function in those genetically susceptible. Moreover, it was found that patients with high albuminuria have increased carotid artery intimal thickness when compared with patients without protein in their urine, confirming that the damage is diffuse [56]. Albuminuria was also shown to be associated with increased arterial stiffness and left ventricular mass [62,63].

Prognostic implications

■ Cardiovascular outcomes

The presence of albumin in the urine even at low levels (i.e., <200 mg/day), as reviewed above, signifies vascular damage manifested as increased endothelial inflammation and permeability. Even though it is not specific enough to distinguish between different diseases, it does represent a sensitive marker.

The pathophysiology of cardiovascular disease development correlates with the mechanisms of vascular inflammation described earlier. The notion that high albuminuria might present a new clinical marker for the prediction of cardiovascular risk has been evaluated extensively. Levels of albuminuria, even below the current threshold for a diagnosis, correlate with increased risk of myocardial infarction, stroke, cardiovascular mortality and all-cause mortality [64]. Yudkin and colleagues first reported an association between albuminuria and a higher risk of coronary artery disease and peripheral artery disease in diabetic patient populations [65]. Since then numerous studies have provided evidence in support of high albuminuria being a predictor of morbidity and mortality in different patient populations [36,66,67].

Hypertension and diabetes are major risk factors for cardiovascular morbidity and mortality. In this regard, one would expect that high albuminuria development in these patients would also be associated with an increased cardiovascular risk. This was corroborated by the assessment of 9795 low risk diabetic patients in the FIELD study, which found that the risk of cardiovascular events, cardiovascular death or death from all causes was inversely linearly related to a 5 mg/mmol urinary albumin increase, being 1, 3 and 3% higher over a period of 5 years, respectively [68]. Similarly, data from the LIFE study reported that the primary composite outcomes of cardiovascular deaths, MIs and strokes were increased significantly in hypertensive and diabetic populations over the different ranges of microalbuminuria and

even at levels lower than the currently proposed cutoffs for the definition of pathologic urinary albumin excretion [69]. Moreover, results of the HOPE study demonstrate that individuals with microalbuminuria have an increased relative risk of cardiovascular outcomes, with the highest risk being a 3.2-fold greater risk for heart failure development [70].

Even if diabetes mellitus is not present, high albuminuria in hypertensive patients alone seems to have a predictive value of the rate of cardiovascular outcome occurrence. During a 4.5-year follow-up of 10,881 hypertensive only patients, high albuminuria was an independent prognostic factor for the primary end point of fatal and nonfatal MI and stroke as well as other related cardiovascular death. Risk of declining kidney function also increased [71]. In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, urinary albumin levels were consistent with a four fold higher risk in a nondiabetic population with untreated or borderline hypertension [72].

High albuminuria alone, without risk factors such as hypertension or hyperglycemia, correlates well with the risk for cardiovascular morbidity as shown in several epidemiological studies. The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study, which assessed the general population and had 23,964 participants, demonstrated that there was an independent association with microalbuminuria and cardiovascular risk with an odds ratio of 1.3 after adjustment for other risk factors [73]. Similar conclusions have emerged from the analysis of data provided from the Prevention of Renal and Vascular End Stage Disease general population cohort. In this population, higher albuminuria levels significantly increased the likelihood of death caused by a cardiovascular event [15]. Likewise, data obtained after analysis of a cohort of postmenopausal women in the general population revealed increased cardiovascular mortality in women with higher urinary albumin concentrations [74]. In the Framingham cohort participants without diabetes mellitus, hypertension or cardiovascular diseases who had increasing levels of microalbuminuria had a threefold elevated risk of cardiovascular morbidity. This was noted even at levels of 3.9 mcg/mg, which is well below the current cutoff value for high albuminuria [75]. There is an ongoing debate regarding the need for the establishment of a lower threshold value for the diagnosis of high albuminuria [15,69]. While this lower level needs to be explored further, it is clear that some prospective outcome

trials differ relative to changes in albuminuria level compared with those observed in epidemiological studies. Specifically, the ACCOMPLISH, ONTARGET and ROADMAP trials all demonstrate reductions in high albuminuria development. Unfortunately, none of these trials showed that a reduction in high albuminuria development correlated with a lower cardiovascular event rate [76–78].

■ Progression of CKD (outcome trials)

The kidney is a highly vascular organ and it is reasonable to assume that any injury to the endothelium manifests as a protein leak in the urine. Undeniably, different ranges of albuminuria signify different types of kidney pathology. The definition of CKD and its relationship with albuminuria levels for predicting cardiovascular and kidney disease risk has recently been revised. The Kidney Disease: Improving Global Outcomes (KDIGO) workgroup analyzed data from 45 cohorts including 1,555,332 people divided into the following groups: general population and high-risk populations (hypertension, diabetes mellitus or cardiovascular disease and CKD) [22]. Three levels of albuminuria have also been integrated over all GFR categories for better risk assessment (FIGURE 1).

Despite this change it should be noted that the recommendation from the scientific workshop, sponsored by National Kidney Foundation and US FDA is that albuminuria change is not a surrogate for kidney outcomes across all stages of kidney disease [79]. Likewise, high albuminuria has been evaluated in clinical trials and the same is true for this early marker of endothelial dysfunction and inflammation. The latest data from the KDIGO suggests that albuminuria levels signal progression of nephropathy when the estimated GFR is <60 and the levels of albuminuria are >300 mg day [80]. Only in the, The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was the true progression to kidney failure in the presence of high albuminuria evaluated among patients with Type 2 diabetes [81]. There was no relationship found between the level of albuminuria and kidney outcomes since blood pressure was well-controlled in both groups [81]. Moreover, recent data did not support the connection between microalbuminuria and progression of CKD in Type 1 diabetics [82,83].

In one study albuminuria levels of >300 mg/day were highly predictive of kidney disease progression [84]. This is supported by results from the AASK trial where patients with

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)				Albuminuria stages, description and range (mg/g)				
				A1		A2	A3	
				Optimal and high-normal		High	Very high and nephrotic	
				<10	10–29	30–299	300–1999	>2000
GFR stages, description and range (ml/min per 1.73 m ²)	G1	High and optimal	>105					
			90–104					
	G2	Mild	75–89					
			60–74					
	G3a	Mild–moderate	45–59					
	G3b	Moderate–severe	30–44					
	G4	Severe	15–29					
	G5	Kidney failure	<15					

Figure 1. Composite ranking for relative risks by glomerular filtration rate and albuminuria. Colors reflect the ranking of adjusted relative risk. The ranking assigned were averaged across all five outcomes for the 28 glomerular filtration rate and albuminuria categories. The categories with mean rank numbers 1–8 are green, mean rank numbers 9–14 are yellow, mean rank numbers 15–21 are orange and mean rank numbers 22–28 are red. Color for 12 additional cells in purple is extrapolated based on results from meta-analysis of chronic kidney disease cohorts. The highest level of albuminuria is termed ‘nephrotic’ to correspond with nephrotic range albuminuria and is expressed here as 2000 mg/day. GFR: Glomerular filtration rate. Reproduced with permission from [99].

hypertensive kidney disease and very high albuminuria, had a greater GFR decline [85]. More recent evidence, however, potentially disputes the necessity of microalbuminuric advancement to very high albuminuria as a factor in the development of kidney failure. This study was carried out in Type 1 diabetics and had a 12-year follow-up, and suggested that microalbuminuria and the development of advanced kidney failure are in fact two separate processes [86].

Therapeutic interventions

Therapeutic modalities aimed at risk reduction differ. Initially, it is important to consider all factors that reduce risk of nephropathy and cardiovascular disease since their control would prevent albuminuria or if one is already present, possibly reverse it. These modifiable factors include a low salt diet (sodium <3000 mg/day), physical activity and reduced dietary protein intake to 0.8 g/kg. More importantly, tight blood pressure control and aggressive glycemic management to a HgA1c level of <7 is of utmost importance.

Further tailoring of the therapeutic approach is dependant on the level of albuminuria. Blood pressure control is one of the most important

targets in the therapeutic approach for reduction of adverse cardiovascular and kidney events in patients with very high albuminuria. The recommended target blood pressure for those with very high albuminuria is <130/80 mmHg and is not dependent on the presence of diabetes mellitus [87]. More recently, a systematic review of trials evaluating blood pressure targets in individuals with CKD with and without very high albuminuria emphasized that strict blood pressure control to the above level offers clear benefits in patients with albuminuria levels of >200 mg/day but not in patients within lower levels of urinary albumin excretion [88]. Moreover, the benefits of renoprotection were seen when albuminuria levels decreased by >30% within 6 months of treatment and if the treatment given included angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or renin inhibitors. This is true not only for the reduction in albuminuria in relation to the target blood pressure but also for the additional effect of RAAS blockade [89,90]. In hypertensive nondiabetic patients with kidney impairment and very high albuminuria in the AASK cohort (mean urinary protein:creatinine ratio >0.22), this lower blood pressure target was associated with improved outcomes defined as doubling of serum creatinine, end-stage renal disease or death [91].

There is little evidence to suggest that a combination regimen including ARBs and ACEIs would provide patients with greater protection from kidney disease than either agent alone even with a further reduction in albuminuria levels, as seen in the ONTARGET trial [92]. However, the ONTARGET trial did not have this as a primary end point and so this has not been adequately tested; the ongoing VA NEPHRON D study will fully address the relationship between further albuminuria reduction and CKD progression in patients with diabetes [93]. The study will finish in 2014.

Aside from RAAS blockers, nondihydropyridine calcium channel blockers (diltiazem, verapamil) have a 25–30% greater reduction in very high albuminuria levels when combined with a RAAS blocker [94]. The effects of reducing high albuminuria on CKD progression has not been properly assessed in a prospective controlled trial. The closest attempt was the ABCD trial and the results of that trial do not show that a reduction in high albuminuria levels affects CKD progression independent of blood pressure reduction [81]. Data from the ONTARGET trial was driven by results obtained from patients

with very high albuminuria rather than high or normoalbuminuria. The IRMA II trial, which evaluated irbesartan's impact on the progression of high albuminuria to very high albuminuria did find statistical significance in reaching its end point, but blood pressure control was better in the experimental group [95]. Therefore, in this clinical scenario, the best approach is improved control of risk factors (i.e., hypertension, diabetes and hyperlipidemia).

High albuminuria has been shown to affect prognosis of cardiovascular outcomes. The Microalbuminuria, Cardiovascular and Renal outcomes (MICRO)-HOPE study found that a reduction in the albumin:creatinine ratio led to improved cardiovascular outcomes in 1140 patients with high cardiovascular risk treated with ramipril. A 20% reduction in microalbuminuria levels was associated with a reduction in cardiovascular outcomes of 21% [96]. Furthermore, the LIFE study assessed the effect of the angiotensin receptor blocker losartan, on cardiovascular morbidity occurrence, and showed similar findings with a 20% reduction in cardiovascular outcomes related to a decrease in albuminuria [97]. More recently, the BENEDICT-B trial demonstrated a similar relationship between the reduction of high albuminuria levels and a decreased incidence of fatal or nonfatal major cardiovascular events (i.e., myocardial infarction, cerebrovascular accident and arterial revascularization). However, this study did not find any beneficial effect when ramipril was combined with verapamil [98]. Review of the available data presented provides rationale for the use of ACEIs and ARBs in individuals with high cardiovascular risk in addition to meticulous management of blood pressure and diabetes.

Conclusion

At present, the data available regarding the etiology, pathophysiology and significance of albuminuria allows us to better use this marker in terms of prognosis and management of many conditions, in particular kidney and cardiovascular diseases. The most important finding from the clinical evidence evaluating albuminuria and its relationship with kidney disease is that high albuminuria in concert with adequate blood pressure and glycemic control does not predict kidney failure unless it is progressively increasing to very high albuminuria levels. The observed association between the two cannot be established as causal with the available data and certainly can be significantly confounded by

other variables such as obesity, hyperlipidemia, smoking or genotype. Thus, the presence of high albuminuria should be viewed as a cardiovascular risk marker and should be assessed in all people that have a propensity for this risk. Treatment should focus on improvement of blood pressure control, controlling hyperlipidemia and diabetes as well as considering implementation of RAAS blockers in the treatment plan.

Conversely, very high albuminuria is a sign of CKD. This marker is a target for therapeutic approach, however, it does not necessarily translate into improved outcomes and more data are certainly needed for clarification. RAAS antagonists are preferred agents in this setting, and have been shown to improve outcomes beyond the improvement attributed to blood pressure control alone.

Future perspective

Considering the significance that urinary albumin concentration has in terms of cardiovascular and renal disease, this type of laboratory testing is likely to remain highly important. Current methods used for albuminuria detection are not standardized and are frequently being replaced by total urine protein measurement. Therefore, the use of standardized point-of-care testing for albuminuria is available and needed. This approach should be clearly defined and easily applied but also needs to provide accurate assessment of urinary albumin concentration.

In addition, the abundance of data, as explored in this article demonstrates that the degree of albuminuria correlates and predicts the level of cardiovascular risk. Recently, the presence or absence of CKD has been added to cardiovascular risk predictor calculators as an important variable. Considering the role of albuminuria in the same context, it would be important to explore its value in helping to predict cardiovascular risk.

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Executive summary

Albuminuria

- Albuminuria is an indicator of worsening cardiovascular outcomes and progressive kidney damage.
- The currently recommended definition of the albuminuria spectrum includes normal to high normal (<29 mg/g), high (30–299 mg/g), very high (>300 mg/g) and nephrotic (≥2000 mg/g).
- Most recent data estimate the prevalence of high albuminuria (previously microalbuminuria) to be 8.2% and very high albuminuria (previously macroalbuminuria) to be 1.3% for the general population, with rates being higher for people with high cardiovascular risk burden and diabetes.
- Patients with hypertension, diabetes mellitus and early chronic kidney disease should be screened for the presence of urinary albumin with at least two morning specimens obtained within 2 months since there is a significant daily variation.
- Screening is performed with urinary albumin collection over 24 h or with a spot albumin:creatinine ratio.

Pathogenesis of albuminuria

- High pressure and formation of reactive oxygen species injures endothelium and increases permeability of albumin through the glomerulus.
- Initiation of inflammatory cascades and growth factor production damages the glomerular basement membrane and podocytes leading to increased albumin leak.
- Impairment of tubular albumin reabsorption further aggravates urinary albumin loss.

Albuminuria & cardiovascular risk

- Uncontrolled hypertension is associated with higher levels of albuminuria, with night-time elevations correlating with occurrence of higher albumin excretion rate.
- Individuals with higher ranges of albuminuria seem to be more likely to develop hypertension.
- Metabolic derangements including hyperinsulinemia, hyperglycemia and dyslipidemia affect albuminuria development and are independent of hypertensive control.
- Endothelial dysfunction predisposes to changes associated with progressive increases in albuminuria through increased oxidant stress and diminished nitric oxide dysfunction, ultimately leading to progressive vascular damage.
- These changes additionally translate into a higher risk for cardiovascular disease and renal impairment, particularly in those who are genetically susceptible, with microalbuminuria being correlated with increased left ventricular mass and arterial stiffness.

Prognostic implications

- High albuminuria is associated with an increased risk for cardiovascular morbidity in the general population with and without risk factors such as hypertension and diabetes mellitus.
- Rate of undesirable cardiovascular outcomes increases over a different spectrum of albuminuria.
- Most recent recommendations for risk assessment include three levels of albuminuria integrated over different ranges of glomerular filtration rate.
- Albuminuria change is not a surrogate for kidney outcomes across all stages of kidney disease as presented by the FDA.
- High levels of albuminuria (<200 mg/day) do not signify the progression of chronic kidney disease; however, very high levels of albuminuria (>200 mg/day) represent renal injury and progression of nephropathy when glomerular filtration rate is <60.
- Strict hypertensive control to goals of <130/80 mmHg is imperative for patients with very high albuminuria levels and is associated with improved kidney outcomes.

Therapeutic interventions

- Control of risk factors that contribute to development of nephropathy and cardiovascular risk is beneficial for the reduction of risk.
- Blood pressure control represents a cornerstone for therapeutic approach and should be targeted to <130/80 mmHg in individuals with albuminuria levels of >200 mg/day regardless of glycemic status.
- Renin–angiotensin–aldosterone system (RAAS) blockers offer improved renoprotection in albuminuria treatment in addition to targeting blood pressure; however, data does not suggest improved outcomes when angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are combined.
- RAAS antagonists when paired with nondihydropyridine calcium channel blockers further reduce albuminuria by an additional 25–30% in patients with very high albuminuria.
- There is no evidence that treatment of high albuminuria translates into decreased kidney disease progression and in this scenario risk factor control remains the most important factor.
- Cardiovascular outcomes decrease with reduction of high albuminuria levels, and RAAS blockade in patients with high cardiovascular burden is effective.

Bibliography

- Collins R, Peto R, MacMahon S *et al.* Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 335(8693), 827–838 (1990).
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* 351(13), 1296–1305 (2004).
- Heidenreich PA, Trogon JG, Khavjou OA *et al.* Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 123(8), 933–944 (2011).
- Sarafidis PA, Li S, Chen SC *et al.* Hypertension awareness, treatment, and control in chronic kidney disease. *Am. J. Med.* 121(4), 332–340 (2008).

- 5 MacIsaac RJ, Jerums G, Cooper ME. New insights into the significance of microalbuminuria. *Curr. Opin. Nephrol. Hypertens.* 13(1), 83–91 (2004).
- 6 Lee ET, Howard BV, Wang W *et al.* Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. *Circulation* 113(25), 2897–2905 (2006).
- 7 Hemmelgarn BR, Manns BJ, Lloyd A *et al.* Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303(5), 423–429 (2010).
- 8 Vallon V. The proximal tubule in the pathophysiology of the diabetic kidney. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 300(5), R1009–R1022 (2011).
- 9 Mundel P, Reiser J. Proteinuria: an enzymatic disease of the podocyte? *Kidney Int.* 77(7), 571–580 (2010).
- 10 Karalliedde J, Viberti G. Proteinuria in diabetes: bystander or pathway to cardiorenal disease? *J. Am. Soc. Nephrol.* 21(12), 2020–2027 (2010).
- 11 Danziger J. Importance of low-grade albuminuria. *Mayo Clin. Proc.* 83(7), 806–812 (2008).
- 12 Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am. J. Kidney Dis.* 50(2), 169–180 (2007).
- 13 Mansia G, De BG, Dominiczak A *et al.* 2007 ESH–ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press.* 16(3), 135–232 (2007).
- 14 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am. J. Kidney Dis.* 39(2 Suppl. 1), S1–S266 (2002).
- 15 Hillege HL, Fidler V, Diercks GF *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106(14), 1777–1782 (2002).
- 16 Tsioufis C, Mazaraki A, Dimitriadis K, Stefanidis CJ, Stefanadis C. Microalbuminuria in the paediatric age: current knowledge and emerging questions. *Acta Paediatr.* (2011).
- 17 Nelson RG, Tuttle KR. The new KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and CKD. *Blood Purif.* 25(1), 112–114 (2007).
- 18 Ewald B, Attia J. Which test to detect microalbuminuria in diabetic patients? A systematic review. *Aust. Fam. Phys.* 33(7), 565–567 (2004).
- 19 Witte EC, Lambers Heerspink HJ, de Zeeuw D, Bakker SJ, de Jong PE, Gansevoort R. First morning voids are more reliable than spot urine samples to assess microalbuminuria. *J. Am. Soc. Nephrol.* 20(2), 436–443 (2009).
- 20 Ruggenenti P, Remuzzi G. Time to abandon microalbuminuria? *Kidney Int.* 70(7), 1214–1222 (2006).
- 21 Solomon SD, Lin J, Solomon CG *et al.* Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. *Circulation* 116(23), 2687–2693 (2007).
- 22 Levey AS, de Jong PE, Coresh J *et al.* The definition, classification and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int.* 80(1), 17–28 (2010).
- 23 Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 298(17), 2038–2047 (2007).
- 24 Hillege HL, Janssen WM, Bak AA *et al.* Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J. Intern. Med.* 249(6), 519–526 (2001).
- 25 Atkins RC, Polkinghorne KR, Briganti EM, Shaw JE, Zimmet PZ, Chadban SJ. Prevalence of albuminuria in Australia: the AusDiab Kidney Study. *Kidney Int.* (Suppl. 92), S22–S24 (2004).
- 26 Gerstein HC, Mann JF, Pogue J *et al.* Prevalence and determinants of microalbuminuria in high-risk diabetic and nondiabetic patients in the heart outcomes prevention evaluation study. The HOPE study investigators. *Diabet. Care* 23(Suppl. 2), B35–B39 (2000).
- 27 Kalaitzidis RG, Roa M, Bakris GL. Changes in albuminuria/proteinuria – a prognostic marker of kidney disease progression. *US Nephrol.* 3, 59–64 (2009).
- 28 Khosla N, Sarafidis PA, Bakris GL. Microalbuminuria. *Clin. Lab. Med.* 26(3), 635–653, vi–vii (2006).
- 29 Tojo A, Endou H. Intrarenal handling of proteins in rats using fractional micropuncture technique. *Am. J. Physiol.* 263(4 Pt 2), F601–F606 (1992).
- 30 Palatini P, Mormino P, Mos L *et al.* Microalbuminuria, renal function and development of sustained hypertension: a longitudinal study in the early stage of hypertension. *J. Hypertens.* 23(1), 175–182 (2005).
- 31 Forman JP, Fisher ND, Schopick EL, Curhan GC. Higher levels of albuminuria within the normal range predict incident hypertension. *J. Am. Soc. Nephrol.* 19(10), 1983–1988 (2008).
- 32 Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am. J. Hypertens.* 7(1), 23–29 (1994).
- 33 Oliveras A, Armario P, Martell-Claros N, Ruilope LM, de la Sierra A. Urinary albumin excretion is associated with nocturnal systolic blood pressure in resistant hypertensives. *Hypertension* 57(3), 556–560 (2011).
- 34 Tsioufis C, Andrikou I, Thomopoulos C, Petras D, Manolis A, Stefanadis C. Comparative prognostic role of nighttime blood pressure and nondipping profile on renal outcomes. *Am. J. Nephrol.* 33(3), 277–288 (2011).
- 35 Pontremoli R, Sofia A, Ravera M *et al.* Prevalence and clinical correlates of microalbuminuria in essential hypertension: the MAGIC study. Microalbuminuria: a Genoa investigation on complications. *Hypertension* 30(5), 1135–1143 (1997).
- 36 Cirillo M, Senigalliesi L, Laurenzi M *et al.* Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: the Gubbio population study. *Arch. Intern. Med.* 158(17), 1933–1939 (1998).
- 37 Lakka HM, Laaksonen DE, Lakka TA *et al.* The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288(21), 2709–2716 (2002).
- 38 Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52(5), 1210–1214 (2003).
- 39 Chen J, Muntner P, Hamm LL *et al.* The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann. Intern. Med.* 140(3), 167–174 (2004).
- 40 Shishido T, Konta T, Nishiyama S *et al.* Suppressive effects of valsartan on microalbuminuria and CRP in patients with metabolic syndrome (Val-Mets). *Clin. Exp. Hypertens.* 33(2), 117–123 (2011).
- 41 Vyssoulis G, Karpanou E, Spanos P, Kyvelou SM, Adamopoulos D, Stefanadis C. Urine albumin excretion, within normal range, reflects increasing prevalence of metabolic syndrome in patients with essential hypertension. *J. Clin. Hypertens. (Greenwich)* 12(8), 597–602 (2010).

- 42 Afonso L, Hari P, Kondur A *et al.* Usefulness of microalbuminuria in patients with the metabolic syndrome to predict subclinical atherosclerosis and cardiovascular disease outcomes. *Am. J. Cardiol.* 106(7), 976–983 (2010).
- 43 Bianchi S, Bigazzi R, Valtriani C *et al.* Elevated serum insulin levels in patients with essential hypertension and microalbuminuria. *Hypertension* 23(6 Pt 1), 681–687 (1994).
- 44 Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the insulin resistance atherosclerosis study. *Diabetes* 47(5), 793–800 (1998).
- 45 Tapp RJ, Shaw JE, Zimmet PZ *et al.* Albuminuria is evident in the early stages of diabetes onset: results from the Australian diabetes, obesity, and lifestyle study (AusDiab). *Am. J. Kidney Dis.* 44(5), 792–798 (2004).
- 46 Jager A, Kostense PJ, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: the HOORN Study. *Diabetologia* 41(6), 694–700 (1998).
- 47 Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. *Diabet. Metab.* 26(4), 254–264 (2000).
- 48 Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in Type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch. Intern. Med.* 158(9), 998–1004 (1998).
- 49 Tolonen N, Forsblom C, Thorn L *et al.* Lipid abnormalities predict progression of renal disease in patients with Type 1 diabetes. *Diabetologia* 52(12), 2522–2530 (2009).
- 50 Marcovecchio ML, Dalton RN, Prevost AT *et al.* Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with Type 1 diabetes. *Diabet. Care* 32(4), 658–663 (2009).
- 51 Stocker R, Keaney JF Jr. Role of oxidative modifications in atherosclerosis. *Physiol. Rev.* 84(4), 1381–1478 (2004).
- 52 Munzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann. Med.* 40(3), 180–196 (2008).
- 53 Duffy SJ, Gokce N, Holbrook M *et al.* Effect of ascorbic acid treatment on conduit vessel endothelial dysfunction in patients with hypertension. *Am. J. Physiol. Heart Circ. Physiol.* 280(2), H528–H534 (2001).
- 54 Ting HH, Timimi FK, Boles KS, Creager SJ, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* 97(1), 22–28 (1996).
- 55 Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ. Res.* 86(5), 494–501 (2000).
- 56 Sarafidis PA, Bakris GL. Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. *Nephrol. Dial. Transplant.* 21(9), 2366–2374 (2006).
- 57 Persson F, Rossing P, Hovind P *et al.* Endothelial dysfunction and inflammation predict development of diabetic nephropathy in the Irbesartan in patients with Type 2 diabetes and Microalbuminuria (IRMA 2) study. *Scand. J. Clin. Lab. Invest.* 68(8), 731–738 (2008).
- 58 Das UN, Repositi G, Dain A, Eynard AR. L-arginine, NO and asymmetrical dimethylarginine in hypertension and Type 2 diabetes. *Front Biosci.* 16, 13–20 (2011).
- 59 Tsioufis C, Dimitriadis K, Andrikou E *et al.* ADMA, C-reactive protein, and albuminuria in untreated essential hypertension: a cross-sectional study. *Am. J. Kidney Dis.* 55(6), 1050–1059 (2010).
- 60 Navarro-Gonzalez JF, Mora C, Muros M, Jarque A, Herrera H, Garcia J. Association of tumor necrosis factor- α with early target organ damage in newly diagnosed patients with essential hypertension. *J. Hypertens.* 26(11), 2168–2175 (2008).
- 61 Navarro JF, Mora C, Gomez M, Muros M, Lopez-Aguilar C, Garcia J. Influence of renal involvement on peripheral blood mononuclear cell expression behaviour of tumour necrosis factor- α and interleukin-6 in Type 2 diabetic patients. *Nephrol. Dial. Transplant.* 23(3), 919–926 (2008).
- 62 Andrikou E, Tsioufis C, Dimitriadis K *et al.* Parallel deterioration of albuminuria, arterial stiffness and left ventricular mass in essential hypertension: integrating target organ damage. *Nephron. Clin. Pract.* 119(1), C27–C34 (2011).
- 63 Schutte R, Schutte AE, Huisman HW *et al.* Arterial stiffness, ambulatory blood pressure and low-grade albuminuria in non-diabetic African and Caucasian men: the SABPA study. *Hypertens. Res.* 34(7), 862–868. (2011).
- 64 Zamora CR, Cubeddu LX. Microalbuminuria: do we need a new threshold? *J. Hum. Hypertens.* 23(2), 146–149 (2009).
- 65 Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington diabetes survey. *Lancet* 2(8610), 530–533 (1988).
- 66 Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch. Intern. Med.* 157(13), 1413–1418 (1997).
- 67 Stephenson JM, Kenny S, Stevens LK, Fuller JH, Lee E. Proteinuria and mortality in diabetes: the WHO multinational study of vascular disease in diabetes. *Diabet. Med.* 12(2), 149–155 (1995).
- 68 Drury PL, Ting R, Zannino D *et al.* Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in Type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* 54(1), 32–43 (2011).
- 69 Ibsen H, Olsen MH, Wachtell K *et al.* Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. *Diabetes Care* 29(3), 595–600 (2006).
- 70 Gerstein HC, Mann JF, Yi Q *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286(4), 421–426 (2001).
- 71 Farbotm P, Wahlstrand B, Almgren P *et al.* Interaction between renal function and microalbuminuria for cardiovascular risk in hypertension: The Nordic Diltiazem Study. *Hypertension* 52(1), 115–122 (2008).
- 72 Jensen JS, Feldt-Rasmussen BF, Strandgaard S, Schroll M, Borch-Johnsen K. [Microalbuminuria is associated with a fourfold increased risk of ischemic heart disease among hypertensive patients]. *Ugeskr Laeger* 164(32), 3773–3777 (2002).
- 73 Yuyun MF, Khaw KT, Luben R *et al.* Microalbuminuria, cardiovascular risk factors and cardiovascular morbidity in a British population: the EPIC-Norfolk population-based study. *Eur. J. Cardiovasc. Prev. Rehabil.* 11(3), 207–213 (2004).
- 74 Roest M, Banga JD, Janssen WM *et al.* Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. *Circulation* 103(25), 3057–3061 (2001).
- 75 Arnlov J, Evans JC, Meigs JB *et al.* Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham heart study. *Circulation* 112(7), 969–975 (2005).
- 76 Jamerson K, Weber MA, Bakris GL *et al.* Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N. Engl. J. Med.* 359(23), 2417–2428 (2008).

- 77 Haller H, Ito S, Izzo JL Jr *et al.* Olmesartan for the delay or prevention of microalbuminuria in Type 2 diabetes. *N. Engl. J. Med.* 364(10), 907–917 (2011).
- 78 Yusuf S, Teo KK, Pogue J *et al.* Telmisartan, ramipril, or both in patients at high risk for vascular events. *N. Engl. J. Med.* 358(15), 1547–1559 (2008).
- 79 Levey AS, Cattran D, Friedman A *et al.* Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National kidney foundation and the US food and drug administration. *Am. J. Kidney Dis.* 54(2), 205–226 (2009).
- 80 Astor BC, Matsushita K, Gansevoort RT *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int.* 79(12), 1331–1340 (2011).
- 81 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and Type 2 diabetes. *Diabetes Care* 23(Suppl. 2), B54–B64 (2000).
- 82 Mauer M, Zinman B, Gardiner R *et al.* Renal and retinal effects of enalapril and losartan in Type 1 diabetes. *N. Engl. J. Med.* 361(1), 40–51 (2009).
- 83 Steinke JM, Sinaiko AR, Kramer MS, Suissa S, Chavers BM, Mauer M. The early natural history of nephropathy in Type 1 diabetes: III. Predictors of 5-year urinary albumin excretion rate patterns in initially normoalbuminuric patients. *Diabetes* 54(7), 2164–2171 (2005).
- 84 So WY, Kong AP, Ma RC *et al.* Glomerular filtration rate, cardiorenal end points, and all-cause mortality in Type 2 diabetic patients. *Diabetes Care* 29(9), 2046–2052 (2006).
- 85 Wright JT Jr, Bakris G, Greene T *et al.* Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 288(19), 2421–2431 (2002).
- 86 Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS. In patients with Type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. *Kidney Int.* 77(1), 57–64 (2010).
- 87 Khosla N, Bakris G. Lessons learned from recent hypertension trials about kidney disease. *Clin. J. Am. Soc. Nephrol.* 1(2), 229–235 (2006).
- 88 Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann. Intern. Med.* 154(8), 541–548 (2011).
- 89 Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann. Intern. Med.* 148(1), 30–48 (2008).
- 90 Sarafidis PA, Khosla N, Bakris GL. Antihypertensive therapy in the presence of proteinuria. *Am. J. Kidney Dis.* 49(1), 12–26 (2007).
- 91 Appel LJ, Wright JT Jr, Greene T *et al.* Intensive blood-pressure control in hypertensive chronic kidney disease. *N. Engl. J. Med.* 363(10), 918–929 (2010).
- 92 Mann JF, Schmieder RE, McQueen M *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 372(9638), 547–553 (2008).
- 93 Fried LF, Duckworth W, Zhang JH *et al.* Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). *Clin. J. Am. Soc. Nephrol.* 4(2), 361–368 (2009).
- 94 Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int.* 65(6), 1991–2002 (2004).
- 95 Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with Type 2 diabetes. *N. Engl. J. Med.* 345(12), 870–878 (2001).
- 96 Heart Outcomes Prevention Evaluation Study. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* (355), 253–259 (2000).
- 97 Ibsen H, Wachtell K, Olsen MH *et al.* Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. *J. Hypertens.* 22(9), 1805–1811 (2004).
- 98 Ruggenenti P, Fassi A, Ilieva AP *et al.* Effects of verapamil added-on trandolapril therapy in hypertensive Type 2 diabetes patients with microalbuminuria: the BENEDECT-B randomized trial. *J. Hypertens.* 29(2), 207–216 (2011).
- 99 Levey AS, de Jong PE, Coresh J *et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int.* 80(1), 17–28 (2011).

■ Websites

- 101 Ostchega Y, Yoon SS, Hughes J, Louis T. Hypertension awareness, treatment, and control – continued disparities in adults: United States, 2005–2006. Hyattsville MD. National Center for Health Statistics (2008) www.cdc.gov/nchs/data/databriefs/db72.htm
- 102 United States Renal Data System. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease. Bethesda, MD; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (2009) www.usrds.org/2010/slides/indiv/v1index.html