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STATE OF THE ART REVIEW
Hypertension

Prevention of cardiorenal damage: importance of albuminuria

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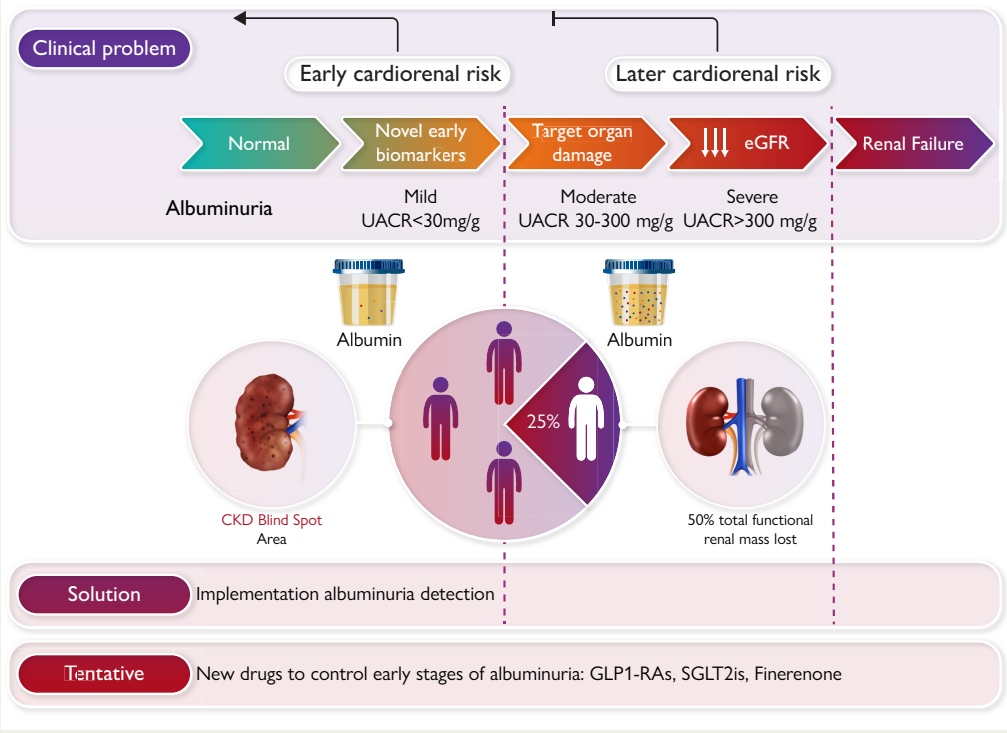
Graphical Abstract



The chronic kidney disease (CKD) 'blind spot' concept establishes that most patients with CKD and mild albuminuria preceding an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 are not recognized nor treated. CKD will progress and 50% of functional kidney mass will be lost before diagnosis. Albuminuria is a major risk factor for the progression of cardiovascular disease (CVD), starting from values not yet considered as defining CKD. The key point is early diagnosis of CKD as a risk factor for CVD and the widespread implementation of albuminuria screening, the assessment

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of early biomarkers and new therapies application to control early stages of albuminuria will diminish the cardiovascular burden related to CKD. GLP1-RAs, glucagon-like peptide 1 receptor agonists; SGLT2is, sodium-glucose cotransporter-2 inhibitors; UACR, urinary albumin/creatinine ratio.

Abstract

Chronic kidney disease (CKD) is projected to become a leading global cause of death by 2040, and its early detection is critical for effective and timely management. The current definition of CKD identifies only advanced stages, when kidney injury has already destroyed >50% of functioning kidney mass as reflected by an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or a urinary albumin/creatinine ratio >six-fold higher than physiological levels (i.e. > 30 mg/g). An elevated urinary albumin-excretion rate is a known early predictor of future cardiovascular events. There is thus a 'blind spot' in the detection of CKD, when kidney injury is present but is undetectable by current diagnostic criteria, and no intervention is made before renal and cardiovascular damage occurs. The present review discusses the CKD 'blind spot' concept and how it may facilitate a holistic approach to CKD and cardiovascular disease prevention and implement the call for albuminuria screening implicit in current guidelines. Cardiorenal risk associated with albuminuria in the high-normal range, novel genetic and biochemical markers of elevated cardiorenal risk, and the role of heart and kidney protective drugs evaluated in recent clinical trials are also discussed. As albuminuria is a major risk factor for cardiovascular and renal disease, starting from levels not yet considered in the definition of CKD, the implementation of opportunistic or systematic albuminuria screening and therapy, possibly complemented with novel early biomarkers, has the potential to improve cardiorenal outcomes and mitigate the dismal 2040 projections for CKD and related cardiovascular burden.

Keywords Albuminuria • Chronic kidney disease • Cardiovascular disease • CKD blind spot • Cardiorenal disease

Introduction

According to the Global Burden of Disease Study, chronic kidney disease (CKD) was the 16th and 10th global cause of death in 2016 and 2019, respectively, and it is likely to climb higher by 2040.[1–3] CKD thus ranks among the fastest-growing disease burdens and preventive initiatives are urgently needed to minimize its impact on cardiovascular outcomes and healthcare costs.

CKD is diagnosed when abnormalities of kidney structure or function with negative consequences for health are present for more than 3 months. Currently, the most commonly used criteria to categorize CKD are albuminuria (>30 mg/24 h or >30 mg/g urinary creatinine) or a significant fall (<60 mL/min/1.73 m^2) in the estimated glomerular filtration rate (eGFR).[1] The cut-off level for albuminuria is more than six-fold greater than physiological levels, and the association between the urinary albumin/creatinine ratio (UACR) and cardiovascular disease (CVD) risk is linear from levels of 1 mg/g.[4] Indeed, the Losartan Intervention For Endpoint reduction study identified UACR thresholds ranging from 6.45 to 9.37 mg/g (depending on sex and type of analysis) that were already associated with increased CVD risk.[5,6] Additionally, meeting the definition of CKD following the eGFR threshold implies that >50% of the functional kidney mass has already been lost,[7] indicating that these diagnostic criteria and thresholds distinguish only late-stage disease.

The global prevalence of CKD oscillates between 11 and 13%,[8,9] and the majority of patients are in the G3 stage (eGFR 30–59 mL/min/1.73 m^2).[10] This distribution pattern further highlights a major shortcoming in the current conceptualization of CKD, namely that early-stage disease is often overlooked. In the majority of clinical conditions, milder early stages are generally more prevalent than the more severe later stages. In this sense, CKD stages G1 and G2—evidence of kidney injury (UACR >30 mg/g) in the presence of normal (≥90) or mildly decreased (60–90 mL/min/1.73 m^2) eGFR—should theoretically be more common than G3, but we lack diagnostic tools to identify them. This has been described as the *blind spot* in CKD, namely that kidney injury is already present with a progressive loss of eGFR from normal values of ~120 to <60 mL/min/1.73 m^2.[7,11] This unmet need is clearly illustrated in the case of autosomal dominant polycystic kidney disease (ADPKD), a condition where sonography strongly supports the diagnosis of CKD decades before the current eGFR and UACR thresholds are met.[7,11] Additional diagnostic tests are thus needed for early identification of the disease (*Table 1*). Notably, the currently available eGFR and albuminuria indicators are not typically assessed in most patients, contributing to the invisibility (and late diagnosis) of CKD. Moreover, physicians' unawareness of the concept of CKD adds to the high cardiovascular burden even when eGFR and albuminuria measures are available.[12] Thus, CKD may progress untreated until diagnosed at more advanced stages, at which time the impact of treatment is likely to be suboptimal.[13] This inevitably increases the risk of adverse cardiorenal outcomes, as no regenerative therapy is available for CKD, and it does not typically regress.[13]

Albuminuria and low eGFR are independent predictors for a higher risk of CVD-related death that, in patients with CKD, is greater than the risk of needing kidney replacement therapy,[14,15] and a high UACR clearly increases renal and CVD risk even against a background of preserved eGFR.[16,17] Furthermore, patients presenting with both albuminuria and diminished eGFR are at high cardiorenal risk, with major consequences for CVD-related morbidity and mortality. Based on these premises, the 2021 guidelines of the European Society of Cardiology (ESC) on cardiovascular prevention[18] recommend measuring albuminuria and eGFR as part of routine assessment. UACR or eGFR values indicative of moderate or severe CKD automatically place the individual at high or very-high CVD risk, respectively, regardless of the presence or not of traditional cardiovascular risk factors.[19] Correspondingly, adding albuminuria to the Systematic Coronary Risk Estimation[19] scale increases the prevalence of high or very-high CVD risk in patients with CKD.[18] Controlling albuminuria through therapeutic intervention is associated with a lower risk of renal and cardiovascular outcomes independent of eGFR values.[20,21] Former guidelines proposed that albuminuria should be routinely measured in patients at high risk of CVD owing to the presence of arterial hypertension, Type 2 diabetes mellitus (T2DM), obesity, heart failure (HF), coronary artery disease, or hyperlipidaemia.[22] However, given the high cost associated with CKD, which in Europe exceeds that of cancer and T2DM,[1] and the low cost of measuring albuminuria, in addition to the need for identifying previously undetected patients at high CVD risk, the 2021 ESC cardiovascular prevention

Table 1 Current issues in the early diagnosis of CKD that should be addressed to optimise cardiovascular risk reduction, and proposed research

Issue	Plain language summary	Needed research
CKD 'blind spot'. Current diagnostic tests and thresholds for those tests allow most causes of CKD to progress undiagnosed (and untreated) for decades, with some exceptions (e.g. ADPKD where imaging allows diagnosis of CKD decades earlier than eGFR or UACR thresholds)	Lack of tools for earlier diagnosis of CKD and treatment of CVD risk	Develop novel diagnostic tests that, alone or in combination with subclinical albuminuria (e.g. UACR 10–30 mg/g), allow for an earlier diagnosis (and treatment) of CKD. Potential tools include imaging and systems biology of urine and/or plasma
Poor implementation. Suboptimal uptake of albuminuria testing	Tools for earlier diagnosis of CKD and treatment of cardiovascular risk are available but not used	How to implement current 2021 ESC CVD prevention guidelines in which eGFR and UACR testing are entry level steps, similar to serum glucose and cholesterol, for CVD risk management
Poor awareness. Suboptimal translation into routine clinical practice from eGFR and UACR values to a chart diagnosis of CKD	Tools for earlier diagnosis of CKD and treatment of cardiovascular risk are available and implemented but are not translated into clinical diagnosis or therapeutic decisions	How to improve awareness of the therapeutic impact of a CKD diagnosis at all healthcare levels, from primary to specialised care

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.

guidelines propose that opportunistic or systematic assessment of albuminuria should be considered in all men above the age of 40 and in all women above the age of 50 (or post-menopausal).[19] Unfortunately, albuminuria is assessed in only 35% of patients with T2DM and in 4% of those with hypertension in the best of circumstances.[23] A similar situation exists for individuals with normoalbuminuria in the normal-high blood pressure (BP) range who are already at increased risk but for whom no intervention is recommended through guidelines for hypertension, T2DM, or HF.[24] The low implementation of albuminuria assessment has been partly attributed to the lack of effective and safe treatments; however, a recent wave of clinical trials and scientific guidelines now emphasize the actionability of high albuminuria or low eGFR to diagnose CKD. This might promote the prescription of new drugs such as sodium-glucose cotransporter-2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP1-RAs), and novel mineralocorticoid receptor antagonists (MRAs) such as finerenone (see later). While the kidney and cardiovascular protective effects of these drugs were first demonstrated in T2DM, the indications are rapidly expanding to non-diabetic populations who are also at high CVD risk, including the SGLT2i dapagliflozin for CKD or HF or the GLP1-RAs semaglutide for overweight or obesity.[25,26]

Here, we review the current status of albuminuria as a cardiorenal risk factor, including novel factors and biomarkers that promote albuminuria and facilitate the early induction of cardiorenal injury, together with shortcomings in their implementation and awareness. We also discuss novel approaches regarding the CKD 'blind spot' (*Figure 1* and *Graphical Abstract*). Finally, we review recently available therapeutic strategies for patients with CKD that can improve cardiorenal outcomes.

Current status of albuminuria as a cardiorenal risk factor

The cardiorenal risk accompanying CKD begins under normal UACR with preserved eGFR,[24,27] and endothelial dysfunction is evident at these early stages.[28] Several other factors are known to increase the risk of developing albuminuria, including genetic background, peripartum-related factors, hypertension, T2DM, obesity, metabolic syndrome, smoking, and older age. The development of associated CVD develops in conjunction with progression of albuminuria and low eGFR.

Genetic background

Genetic diseases are typically under-represented in kidney disease registries. While ADPKD is considered as a single entity, others are grouped into a miscellaneous section or remain undiagnosed.[29,30] Interestingly, the mean age at kidney failure in ADPKD is 60 years, reflecting that inheritance may also influence the risk of CKD in older age. Most cases of hypertensive nephropathy in African Americans—who have the highest incidence of hypertensive nephropathy—are known to be associated with a genetic variant in the apolipoprotein A-I gene that pre-disposes to CKD triggered by diverse stimuli such as viruses.[31,32] Genetic background promotes additional mechanisms pre-disposing to albuminuria. For instance, variants in genes encoding for transporters that recover filtered albumin in the proximal tubular cells are associated with albuminuria.[33] Also, other genetic kidney diseases associated with albuminuria with or without concomitant haematuria, such as Alport syndrome, are more common than previously thought.[29] Thus, family history of albuminuria or CKD is a key risk factor.

Preterm and low birth weight

Optimal cardiovascular health during pregnancy prevents the development of lifelong CVD in offspring, as maternal cardiovascular health influences future cardiovascular health in children during early adolescence.[34] Preterm birth (born before 37 weeks) and low birth weight (<2500 g) are associated with a lower number of nephrons, which has been considered as the initial factor for the early development of hypertension, albuminuria, proteinuria, obesity, and CKD.[35] Although total nephron number can vary considerably in normal

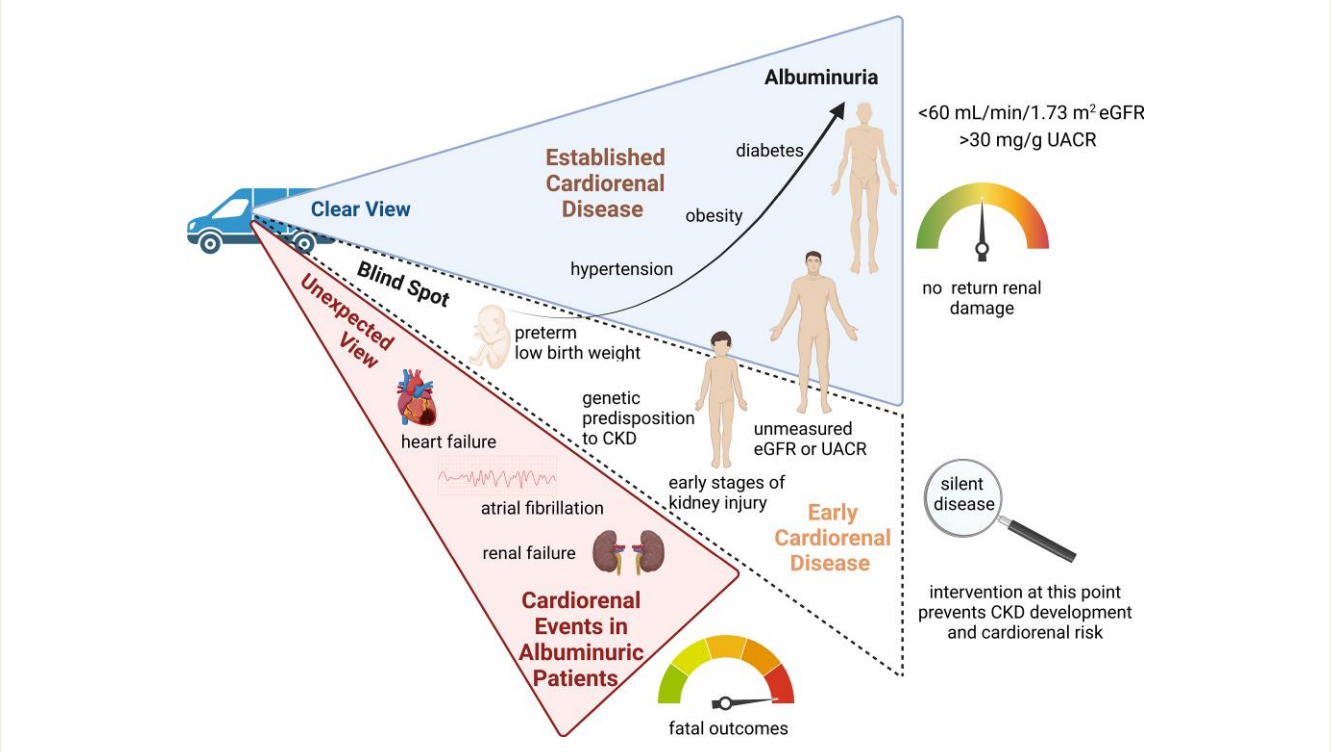

Figure 1 Illustration of CKD 'blind spot' concept and the different clinical settings in which measurement of albuminuria is mandatory to manage cardiorenal disease and prevent CVD outcomes.

kidneys,[36] a seminal study by Keller *et al.* demonstrated that nephron number is typically lower in patients with hypertension than in peers with normal BP.[37] Preterm birth is a risk factor for CKD from childhood into mid-adulthood and smaller body size at birth is associated with an increased risk for developing CKD in men, while preterm delivery can also be associated with an increased risk in women.[38,39] Low birth weight is associated with childhood proteinuria,[40] but clinical manifestations appear predominantly in adolescence, particularly obesity and reduced kidney volume.[41,42] Beyond elevated BP and albuminuria, left ventricular remodelling and arterial stiffness may develop at this stage of life or later.[43–45]

Hypertension

Arterial hypertension increases the risk of albuminuria, starting from the stage of high-normal BP,[46] particularly when isolated diastolic hypertension is present.[47,48] Minor and continuous increases in systolic BP are associated with a higher risk of CVD, even when they remain within the so-called normal range (i.e. non-hypertension), and in the absence of other traditional risk factors.[49] In addition, up to 25% of patients with sustained and treated hypertension develop albuminuria, indicating the progression of cardiorenal disease.[50] Indeed, risk phenotypes identified with ambulatory BP monitoring are associated with the development of albuminuria, and a close relationship between night-time BP and development of albuminuria was described 20 years ago.[51] Moreover, CKD is accompanied by increased visit-to-visit BP variability, which facilitates the progression of albuminuria.[52] The impact of different antihypertensive drugs on the regression of albuminuria to normal (or near-normal) levels is variable and the management of patients with elevated albuminuria requires the use of specific drug combinations that are essentially coincidental with hypertension guidelines.[53,54] Among first-line antihypertensive agents, those blocking the renin-angiotensin-aldosterone system and calcium channel blockers have been better documented in preventing or reducing albuminuria in clinical trials.[54] Yet, new drugs that were initially conceived for the treatment of T2DM have recently been shown to simultaneously decrease BP and albuminuria (see new drugs in section 4).

Because primary aldosteronism is a more common cause of essential hypertension than previously believed,[55] appropriate screening in hypertensive and diabetic populations is mandatory for the diagnosis and targeted treatment of this highly modifiable cardiorenal risk factor.[56] Masked uncontrolled hypertension is accompanied by increased out-of-clinic aldosterone secretion;[57] although evidence is lacking from prospective clinical studies of albuminuria, this indicates that plasma aldosterone concentration and the aldosterone/renin ratio may serve as potential therapeutic targets for the early prevention of cardiorenal disease.[58] In young individuals, however, elevated BP is usually accompanied by elevated pulse pressure and early vascular stiffness, both predicting later development and progression of cardiorenal disease.[59,60]

Women with peri- or post-partum hypertension represent a special category because exposure to adverse pregnancy outcomes, including hypertensive disorders of pregnancy, gestational T2DM, and preterm delivery, is associated with a higher risk of long-term CKD, with the risk of kidney failure greatest among women who experience pre-eclampsia [adjusted risk ratio 4.90; 95% confidence interval (CI) 3.56–6.74].[29]

Diabetes, obesity, and metabolic syndrome

T2DM is the principal cause of kidney failure. It is frequently preceded by a pre-diabetic state or metabolic syndrome and is often

accompanied by overweight or visceral obesity. Renal risk starts early in metabolic syndrome and pre-diabetes, when pre-hypertension and albuminuria often also develop.[61] Increases in systolic BP within the normal range are associated with body mass index and waist circumference values in the overweight range, as well as with increasing levels of fasting glycaemia, preceding the appearance of metabolic syndrome and pre-diabetes.[49] Elevated aldosterone levels are frequently present in this early stage of cardiorenal disease in people with obesity and T2DM, facilitating the development of arterial hypertension, CKD, and HF.[62] Expansion of visceral fat is tightly linked to CKD. Indeed, kidney failure is often accompanied by visceral obesity and treatments to protect the cardiorenal system must also include reduction of overweight.[63]

Impact of albuminuria on the heart

Elevated urinary albumin excretion seems especially predictive of HF, particularly in patients with T2DM, renal dysfunction, or both. Albuminuria is associated with the two phenotypes of HF, with preserved or reduced ejection fraction (HFpEF or HFrEF, respectively),[64] but it is preferentially associated with the former.[65] Albuminuria has been shown to reflect endothelial dysfunction, which is in line with the contemporary hypothesis that HFpEF is characterized by widespread microvascular dysfunction and chronic underlying inflammation.[66] Interestingly, albuminuria is associated with atrial fibrillation, the most prevalent sustained arrhythmia in CKD.[67] The underlying mechanisms potentially linking albuminuria and atrial fibrillation are a subject of intense investigation.

Smoking

Smoking has been associated with both the magnitude of albuminuria and the risk of CKD.[68,69] The risk persists even after smoking cessation and the odds of CKD are higher in current and former smokers than in never smokers.[68]

Suboptimal implementation of clinical assessment of early chronic kidney disease

An unresolved issue in the diagnosis/management of CKD is the lack of implementation. With respect to eGFR, although serum creatinine is frequently determined whenever serum biochemistry is assessed, data from eGFR do not lead to a diagnosis of CKD when eGFR values are >60 mL/min/1.73 m^2. Recent data from Sweden illustrate the seriousness of this issue. Among over 50 000 patients who fulfilled bona fide criteria for CKD diagnosis (i.e. eGFR <60 mL/min/1.73 m^2 on at least two occasions separated for longer than 3 months), only 23% had a diagnosis of CKD in their electronic health records.[12,70] Among those with CKD, the diagnosis was less common than a diagnosis of cancer, diabetes, or HF, among others. There were, unfortunately, consequences of this misdiagnosis for patient care. The use of nephrotoxic drugs was indeed more common among patients with CKD without a diagnosis of CKD. With respect to albuminuria, the key issue is that this index is not frequently assessed in everyday clinical practice (i.e. less often than recommended by clinical guidelines), even in high-risk populations. Importantly, both indicators, particularly albuminuria, should be assessed at least in those patients presenting with the classical risk factors for CVD and other facilitators (the new predictive biomarkers reviewed below) and should ideally be measured in all men above the age of 40 and all women above the age of 50, as indicated in the 2021 ESC cardiovascular prevention guidelines.[19]

Assessing the chronic kidney disease 'blind spot': new predictive biomarkers of albuminuria

Individuals not meeting the Kidney Disease Improving Global Outcomes (KDIGO) criteria for CKD (i.e. with both UACR <30 mg/g and eGFR >60 mL/min/1.73 m^2) have been traditionally considered to be essentially not at risk for cardiorenal disease. However, retrospective clinical studies seem to support the opposite, demonstrating a continuous association between albuminuria levels and cardiorenal risk that starts within the normal range of albuminuria values.[71,72] In terms of early prevention, novel clues are needed to identify those people who, despite having eGFR and albuminuria values within the normal range, already show subclinical kidney disease and are in the CKD *blind spot* (*Figure 1*). An obvious approach would be to lower the UACR threshold to diagnose CKD and, thereby, promote earlier treatment. As an alternative, UACR values may be combined with (or replaced by) other biomarkers. This will require a more thorough understanding of the molecular mechanisms involved in the early and subclinical stages of albuminuria progression.[24,73]

Metabolome and proteome biomarkers

Among normoalbuminuric hypertensive subjects under chronic renin-angiotensin system (RAS) blockade, the molecular profile of urine differs between those below or within the high-normal UACR range (<10 mg/g or 10–30 mg/g, respectively). Protein and metabolic markers identified include those involved in inflammatory response, immune system, lipid metabolism and energy metabolism, among others, pointing to defective tubular reabsorption and vascular injury already in the early subclinical condition of normal albuminuria.[74,75] In particular, the levels of several metabolites previously associated with CVD and renal risk have been shown to be altered in people who are in the high-normal albuminuria range, supporting the vascular component of albuminuria progression beyond the kidney and/or the presence of subclinical kidney injury.[76] Urine and plasma molecular profiles have also highlighted a cluster of biomarkers associated with moderately increased albuminuria that could predict cardiorenal damage. The evident molecular disparities are related to alterations in several processes: inflammation and immune cell response; blood coagulation; vascular remodelling; apoptosis, particularly that associated with endoplasmic reticulum stress; oxidative stress; endothelial damage and vascular stiffness; and blood/immune cell adhesion, among others.[77–84] Thus, an early increase in the circulating levels of one or more of these factors might help to identify patients at risk of target organ damage and albuminuria. For instance, in patients with hypertension and high-normal albuminuria, increased plasma levels of the acute phase proteins are associated with different albuminuria outcomes.[85,86] Indeed, several of these biomarkers are elevated in patients who have progressed in their level of albuminuria during RAS blockade, and are also associated with resistant albuminuria. Overall, the molecular findings might reflect a systemic pro-oxidative and inflammatory state that could be a mechanistic link between early albuminuria, even within the 'normal' range, and cardiorenal disease. Analysis of the urine peptidome is another systems biology approach that has aided in the assessment of cardiorenal risk in the pre-albuminuric stages.[7,87] For example, the multipeptide classifier, CKD273 (composed of 173 peptides), predicts the future development of albuminuria in patients with T2DM,[88] and variants of this classifier predict the future decrease of eGFR better than albuminuria in individuals with normal eGFR.[89] Interestingly, the CKD273 classifier is

characterized by reduced levels of collagen fragments in urine and is associated with kidney fibrosis, suggesting that it reflects the pathophysiological process of diminished collagen degradation leading to kidney fibrosis.[90] In turn, a 150-peptide classifier, also mostly composed of collagen fragments, identifies individuals with obesity and with early-stage obesity-related nephropathy.[91]

Genetic biomarkers

Available data support the genetic pre-disposition to CKD suggested by family studies beyond Mendelian kidney disease.[92] The relevance of genetics for cardiorenal disease has been mainly demonstrated through polygenic risk scores (PRS) for kidney function, and their association with circulating markers and incident kidney disease.[93] While a genetic association between albuminuria, cardiometabolic disease, and BP has been previously described,[94] there is scarce information on the integrated genetic background-risk for CKD in the form of PRS. In patients with T2DM, PRS have been associated with risk of CKD.[95] PRS are also available for other prevalent conditions (e.g. ischaemic heart disease), although generally these are based on genome-wide association studies (GWAS). It is clear from these studies that the current paradigms for primary CVD prevention incompletely capture the polygenic susceptibility to coronary artery disease,[96] which might also be true for CKD. Indeed, the prevalence of high PRS was 10-fold greater than Mendelian defects in patients with early-onset myocardial infarction.[97] Extrapolation of these data to patients with kidney disease suggests a polygenic genetic background in most cases of CKD with an unknown cause, as well as for many cases currently misdiagnosed as hypertensive or even diabetic CKD (i.e. having T2DM does not negate the risk of also having CKD due to genetic causes). Several GWAS have identified loci associated with higher risk of low GFR, higher albuminuria or rapid loss of eGFR, and although the number of identified loci continues to increase, none have yet been incorporated into a holistic approach to CKD or validated in routine clinical practice.[98–100] It is likely that PRS based on deep genomic sequencing might offer more relevant information, but their eventual clinical use must await further investigation and advances in technology.

Current management of cardiorenal disease targeting albuminuria as a primary outcome

Most of the evidence on the management of cardiorenal disease derives from patients with eGFR <60 mL/min/1.73 m^2 and albuminuria. Patients with albuminuria accompanied by preserved eGFR undergo similar therapy to their peers with eGFR <60 mL/min/1.73 m^2. Yet, only widespread albuminuria assessment will identify patients with early CKD, thereby allowing fast intervention measures. Early diagnosis of CKD before irreversible renal damage is of particular importance in view of the evidence discussed above. Treatments based on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prevent the development and progression of cardiorenal disease in patients with T2DM and/or CKD. Yet, despite the broad use of these drugs, the incidence of CKD continues to rise, reflecting the need to consider additional strategies to prevent its development and progression before irreversible changes ensue. Along this line, several new classes of drugs have been shown to suppress albuminuria and/or prevent progression to kidney failure in patients with CKD and/or T2DM, including SGLT2is and MRAs. GLP1-RAs can also attenuate albuminuria, but their impact on loss of GFR is still under evaluation. In addition to pharmacological treatments, lifestyle interventions [particularly, regular physical activity (PA)] might also help to prevent CKD or attenuate its progression.

Physical activity

Recent meta-analytic evidence points to a dose–response association between PA levels and risk of CKD, with each 10 metabolic equivalents of task (MET)-hour/week associated with a 2% lower risk.[101] Likewise, a recent meta-analysis concluded that exercise not only improves kidney function in patients with CKD, but also improves several CVD risk factors (notably by reducing BP and body mass).[102] Indeed, PA is inversely associated with the prevalence of several comorbidities linked to CKD progression, including obesity, T2DM and hypertension.[103,104] Martens *et al.* studied the association of PA and sedentary behaviour with eGFR and albuminuria in 2258 participants of the Maastricht Study, and found that each extra daily hour of total PA or sedentary behaviour was associated with a more favourable or more adverse kidney function, respectively, with a mean increase or decrease in eGFR of 2.30 mL/min/1.73 m^2 and −0.71 mL/min/1.73 m^2.[105] They also found that, compared with individuals with the lowest levels of total PA, those with the highest levels had less kidney damage, with an odds ratio of having albuminuria levels of 15–30 mg/24 h or ≥30 mg/24 h of 0.63 and 0.84, respectively, whereas the opposite pattern was seen for a more sedentary behaviour.[105] Likewise, Böhm *et al.* assessed the association between self-reported PA and renal outcomes in high-risk patients over a median follow-up of 56 months, finding that PA was inversely associated with renal outcomes such as doubling of creatinine or kidney failure, whereas performing PA ≥2 times/week was associated with lower risk of renal outcomes and lower incidence of new albuminuria compared with lower PA levels.[106] There is also evidence of the benefits of PA on renal function in people at high-risk based on randomized controlled trials (RCTs). For instance, Hellberg *et al.* performed a single-centre RCT in patients with CKD with eGFR ~22 mL/min/1.73 m^2 randomized to either aerobic plus balance exercise or aerobic plus strength exercise, during 12 months of training intervention.[107] The authors found a significant treatment difference for albuminuria, which decreased by 33% in the strength-training group. Similarly, in patients with T2DM, a 4-month interval of walking-training reduced albuminuria by 45% vs. the opposite trend in controls.[108] Overall, PA appears to be an important component in the prevention and treatment of CKD and CVD, reducing the healthcare burden and costs imposed by this condition.[109]

New cardiorenal drugs

Sodium-glucose cotransporter-2 inhibitors

SGLT2is reduce the UACR and prevent kidney failure progression in patients both with and without T2DM.[110,111] These agents also prevent the development of HFrEF and HFpEF, and reduce cardiovascular outcomes across HF phenotypes with and without T2DM.[112] SGLT1 and SGLT2 are expressed in the proximal renal tubule where they promote glucose absorption, and inhibition of their function results in an increase in urinary glucose and sodium excretion in patients with normal or moderately reduced renal function. Kidney and cardiovascular protective mechanisms associated with SGLT2is in the kidney have been reviewed elsewhere[113] and include diminished delivery of sodium chloride to the macula densa with a consequential effect on tubule-glomerular feedback and a reduction in proinflammatory cytokines, oxidative stress, uric acid, renal fibrosis, and sympathetic nervous activity, together

with release of sirtuins. Nonetheless, their individual contribution to preventing the progression of renal disease and cardiovascular outcomes remains controversial. While the relative efficacy and safety of SGLT2is in preventing renal disease in patients with UACR of 10–30 mg/g remains to be evaluated in a specifically designed RCT, in *post-hoc* analyses, the SGLT2i empagliflozin improved cardiovascular and kidney outcomes in all risk categories determined as per the two-dimensional KDIGO classification framework, with no evidence of heterogeneity across risk categories.[114] Specifically, in low-risk patients (eGFR >60 mL/mL/min/1.73 m^2 and UACR <30 mg/g), the hazard ratio (HR) for all-cause mortality was 0.68 (95% CI 0.49–0.94) and the HR for doubling of serum creatinine, kidney failure or renal death was 0.31 (95% CI 0.16–0.63) among SGLT2i-treated patients. Similar data, with no evidence of heterogeneity across risk categories for the primary outcome and for other cardiovascular and kidney outcomes, were reported for canagliflozin.[115] Both studies were, however, conducted in populations with T2DM and pre-existing high cardiovascular risk. As pointed out above, while SGLT2is have been shown to be efficacious in patients with T2DM and either HFrEF or HFpEF, there is recent evidence from the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial that SGLT1 inhibition may add to the benefits of SGLT2is in patients with T2DM.[116,117] Data from patients with T2DM and CKD suggest that the SGLT1/2 inhibitor sotagliflozin significantly reduces the occurrence of non-fatal and fatal stroke as well as non-fatal and fatal myocardial infarction by around 30%.[18] In contrast, a meta-analysis[118] of SGLT2is in patients with T2DM failed to reveal a significant reduction in stroke, despite a reduction in BP and an 11% reduction in myocardial infarction, likely due to a reduction in pre-load and myocardial oxygen demands in patients with pre-existent ischaemic heart disease. Further studies are needed to determine the efficacy and safety of sotagliflozin in patients with T2DM, as well as RCTs comparing sotagliflozin to more selective SGLT2is such as empagliflozin.

Glucagon-like peptide 1 receptor agonists

GLP1-RAs reduce UACR and have been suggested to prevent the progression of renal disease in patients with T2DM independently of their glucose lowering effects, which is associated with their anti-inflammatory, antioxidant, antifibrotic, and renal natriuretic effects.[119] In addition, they help to prevent the development of non-fatal and fatal stroke and myocardial infarction, likely related to the effect of GLP1 on platelet activation and atherosclerotic plaque stability.[120] In the Dulaglutide and cardiovascular outcomes in Type 2 diabetes (REWIND) trial, in which 68% of the participants did not have known CVD, the GLP1-RA dulaglutide reduced major adverse cardiovascular events both in patients with and without prior CVD.[121] GLP1-RAs also reduce appetite and body weight, and semaglutide reduces weight independently of the presence of T2DM.[122] Thus, GLP1-RAs appear effective both in the prevention and treatment of T2DM and of obesity. Indeed, their effects on UACR and body weight point to important roles in patients with T2DM, hypertension and visceral obesity with albuminuria during the early stages of renal disease before the development of potentially irreversible changes in renal function and decreases in eGFR. More recently, tirzepatide, a dual GIP/GLP-1 receptor co-agonist approved for the treatment of T2DM in the USA and Europe,[123] was superior to semaglutide with respect to the mean change in the glycated haemoglobin level from baseline to 40 weeks in T2DM and caused a larger decrease in body weight and systolic BP and had a better impact on lipid levels.[124] This overall improved profile may result in improved cardiovascular and renal outcomes, which are being explored in large phase 3 RCTs expected to be completed by 2024 (NCT04847557 and NCT04255433). Tirzepatide once weekly also provided substantial and sustained reductions in body weight in obese patients or overweight patients at high cardiovascular risk that were also associated with lower BP, triglycerides, and LDL cholesterol, and increased HDL cholesterol vs. placebo.[125] In addition, the comparison of SGLT2is and GLP1-RAs presented a similar risk of HF and less risk of renal events, on the contrary, the comparison of GLP1-RAs vs. SGLT2is was associated with a slightly lower risk of major adverse cardiovascular events.[126] Thus indicating that both classes of drugs differ by their cardiorenal effects.

Mineralocorticoid receptor antagonists

The steroidal MRAs spironolactone and eplerenone reduce UACR but are contraindicated in patients with severe renal disease (eGFR <30 mL/min/1.73 m^2) owing to the risk of hyperkalaemia. The underlying mechanisms associated with their effects on UACR and CKD progression have been recently reviewed and include reductions in renal inflammation, oxidative stress, and renal fibrosis.[127] However, while they also reduce BP in patients with resistant hypertension and cardiovascular outcomes in patients with HFrEF, and likely HFpEF, their use remains suboptimal even in patients with normal renal function due to the fear of hyperkalaemia. The development and clinical use of non-steroidal MRAs such as finerenone has, however, been associated with a lower incidence of hyperkalaemia and a slower progression to kidney failure, as well as a reduction in cardiovascular outcomes in patients with diabetic nephropathy.[128–131] The non-steroidal MRAs have a different mode of binding to the mineralocorticoid receptor than the steroidal MRAs, interfering with a different panel of transcription coactivator partners, and they also have a different distribution between the kidney and heart.[127] The steroidal MRAs are mainly distributed in the kidneys and less in the heart whereas the non-steroidal MRAs are more evenly distributed between kidneys and heart, which may, in part, account for the lower incidence of hyperkalaemia. Of particular interest is the finding of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO) trial, in which 62% of patients showed UACR levels >30 mg but eGFR >60 mL/min/1.73 m^2, and in whom finerenone reduced cardiovascular outcomes (mainly hospitalization for HF) and progression to kidney failure.[130] While there was twice the incidence of hyperkalaemia in patients randomized to finerenone in the FIGARO trial, the percentage of patients who discontinued finerenone due to hyperkalaemia was only around 1%.[131] Thus, in CKD Stages 1–3, finerenone appears to be well tolerated and prevents disease progression in patients with and without an SGLT2i and with and without a GLP1-Ra.[130,131] Potentially of even greater importance is the recent finding that high serum aldosterone levels in patients with CKD are independently associated with an increased risk for kidney disease progression, irrespective of the presence of T2DM.[132] Thus, in view of the recent findings that primary aldosteronism can occur in patients without hypertension, has a higher prevalence than previously thought in essential hypertension (being present in >20% of patients with resistant hypertension[133]), and that high aldosterone levels predict kidney disease progression, screening for albuminuria and the use of MRAs in patients with hypertension is a promising strategy for the prevention of cardiorenal disease.

The use of SGLT2is, GLP1-RAs and MRAs alone or in combination with RAS blockers is promising for the prevention of cardiorenal

Table 2 Take-home messages

1. Children with preterm delivery or low birth weight should be monitored regularly for hypertension, excessive weight gain, hyperglycaemia, and albuminuria throughout life
2. In adolescents with obesity, control of body weight gain is needed to diminish cardiorenal risk
3. eGFR and albuminuria should be ideally estimated in all adults visiting primary health centres, and certainly in those with any condition associated with increased renal or cardiovascular risk. This is the only way to avoid the 'blind spot' of albuminuria and preserved renal function
4. Early and regular detection of albuminuria represents a scalable and cost-effective tool to predict and prevent cardiorenal outcomes
5. New drugs such as SGLT2is, GLP1-RAs, and non-steroidal MRAs should be considered from the earliest stages of cardiovascular and renal disease to prevent the occurrence of irreversible renal disease
6. The American Diabetes Association and the 2022 Kidney Disease Improving Global Outcomes Guidelines include recommendations for the use of these new drugs to prevent cardiovascular and renal disease
7. Further advances in predictive molecular biomarkers and their integration into clinical practice will facilitate the early identification of patients at increased cardiorenal risk

eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; GLP1-RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

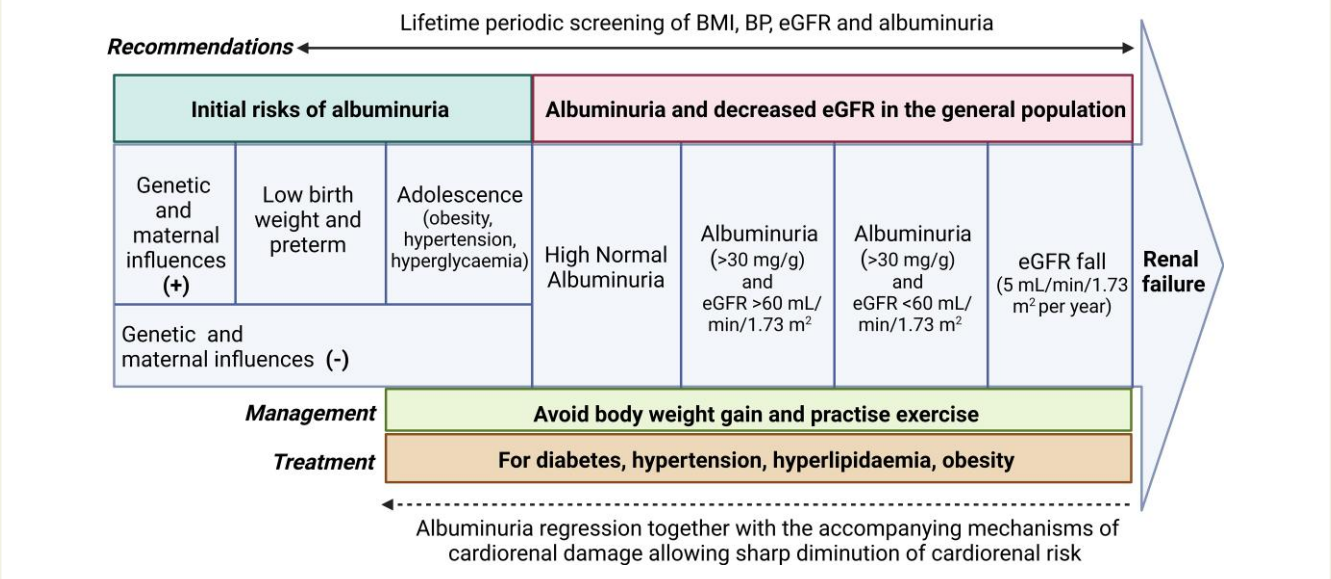

Figure 2 Different clinical settings linked to albuminuria development and evolution, and its adequate management.

outcomes in patients with albuminuria, including those with UACR <30 mg/g and eGFR >60 mL/min/1.73 m^2. Moreover, current data suggesting that the combination of a low dose of the SGLT2i empagliflozin and the non-steroidal MRA finerenone is additive in reducing mortality.[128] Further studies will be needed to evaluate the efficacy, safety, and cost effectiveness of the aforementioned drugs to prevent the development of CKD in patients with early albuminuria (UACR 10–30 mg/g) and an eGFR >60 mL/min/1.73 m^2.

Conclusions

The incorporation of albuminuria into the definition of CKD has proven its value as a major risk factor for the progression of cardiorenal disease, and represents a scalable and drug-actionable clinical biomarker and target. However, implementation and awareness issues limit its value in routine clinical practice. Additionally, there is an unmet clinical need for biomarkers that identify earlier stages of CKD-associated cardiovascular risk. Importantly, beyond the CKD-defining UACR threshold of 30 mg/g, values of albuminuria of 10–30 mg/g—and even lower—are also associated with increased cardiorenal risk. Lower UACR thresholds or novel biomarkers, or a combination of both, should be assessed for the initiation of cardiorenal-protective interventions at earlier stages (*Table 2*). Adequate management needs to start ideally in adolescence and be maintained over the lifespan using strategies to stratify individual cardiorenal risk and guide interventions. These may range from PA to drugs recently approved to mitigate cardiorenal risk in patients with albuminuria and/or decreased eGFR in diabetics and/or non-diabetics, such as SGLT2is, GLP1-Ras, and MRAs, on top of other CVD prevention strategies (*Figure 2*). Widespread implementation of opportunistic or systematic albuminuria screening and therapy to reduce albuminuria may, in fact, prevent or delay cardiorenal

outcomes and challenge the dismal projections for the burden of cardiorenal disease by 2040.

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Data availability

No new data were generated or analysed in support of this research.

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