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CONTEMPORARY REVIEW

Albuminuria: An Underappreciated Risk Factor for Cardiovascular Disease

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ABSTRACT: Albuminuria, an established biomarker of the progression of chronic kidney disease, is also recognized as a biomarker for the risk of cardiovascular disease. Elevated urinary albumin excretion indicates kidney damage and systemic vascular disease, including myocardial capillary disease and arterial stiffness. Albuminuria is associated with an increased risk of coronary artery disease, stroke, heart failure, arrhythmias, and microvascular disease. There are now several therapeutic agents that can lead to albuminuria lowering and a reduction in cardiovascular risk. However, screening for albuminuria is still low. Considering the importance of multidisciplinary management of patients with cardiovascular disease, it is crucial that health care professionals managing such patients are aware of the benefits of albuminuria surveillance and management.

Key Words: albuminuria ■ cardiovascular disease ■ chronic kidney disease ■ diabetes

Cardiologists caring for people with suspected or clinical cardiovascular disease (CVD) use biomarkers to support the assessment of disease risk. Since the introduction of creatine kinase that revolutionized the diagnosis of acute myocardial ischemia, a range of biomarkers have been identified and used in clinical practice as our understanding of CVD pathophysiology continues to improve. Inflammation has been recognized as an integral component of the atherosclerotic process and can be evaluated by measuring plasma CRP (C-reactive protein) CRP levels. Patients with high-sensitivity CRP levels of ≥2 mg/L are at high risk of major adverse cardiovascular events (MACE).[1] In several clinical trials, it was also found that lowering plasma CRP levels was associated with significantly reduced coronary artery disease (CAD) outcomes and cardiovascular mortality.[2,3] Myocardial stretch, observed in various pathophysiological conditions, leads to the production of pro-B-type natriuretic peptide, which is broken down into B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide. Both proteins are routinely used as reliable cardiac biomarkers for the early diagnosis of heart failure (HF).[4] Damage to the myocardium leads to necrosis of cardiomyocytes, resulting in the release of troponin I and T, which are also routinely used in clinical practice and serve as powerful biomarkers for myocardial ischemia.[3,4]

Albuminuria, the excretion of higher than normal amounts of the protein albumin in the urine (>30 mg/L), is also a risk factor for CVD and incident chronic kidney disease (CKD).[5] Albuminuria is seen in the general population as frequently as elevated CRP levels, and its association with CVD is just as strong. In the Third National Health and Nutrition Examination Survey, elevated CRP levels (≥0.22 mg/dL) and clinically raised CRP levels (>1.00 mg/dL) were present in 27.6% and 6.7% of the population, respectively.[6] In comparison, in adults ≥65 years (the age at which most CVD presents), albuminuria is present in ~15% to 20% of the population and in ~35% to 40% of similarly aged individuals with diabetes.[7] Elevated CRP levels confer ~45% increased risk of CAD,[8] and albuminuria is associated with ~40% increased risk of clinical CAD.[9] Despite these prognostic attributes, albuminuria has been underappreciated and underused as a biomarker of disease risk by the cardiology community. In this review, we aim to make the reader aware of the cardiovascular significance

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Nonstandard Abbreviations and Acronyms

AER	albumin excretion rate
MACE	major adverse cardiovascular events
MRA	mineralocorticoid receptor antagonist
RAAS	renin–angiotensin–aldosterone system
SGLT2	sodium–glucose cotransporter 2
T2D	type 2 diabetes
UACR	urine albumin:creatinine ratio

of albuminuria. First, we discuss the physiology and pathophysiology of urinary albumin excretion, followed by the association of albuminuria with CVD (Table 1).[10-38] Last, we review the medications now available for lowering levels of albuminuria, which in turn are associated with a reduction in CVD risk and cardiorenal events.

ALBUMINURIA

Albumin is a small, negatively charged protein that represents 10% of total body protein and 50% of total plasma protein. The physiologic role of albumin is to maintain plasma oncotic pressure and to transport various endogenous and exogenous ligands through the bloodstream to target cells.[39] In healthy individuals, the endothelial layer of the glomerulus serves as a barrier that minimizes albumin movement from the blood into the urine.[39] A urine albumin level of <30 mg in a 24-hour urine sample is considered normal. Pathologic albuminuria (≥30 mg in a 24-hour urine sample) involves structural damage in the glomerulus, which is associated with an increased risk for undesirable cardiovascular and kidney outcomes.[5]

Table 1. Summary of the Associations of Albuminuria With Cardiovascular Disease

Cardiovascular disease	Association with albuminuria
CAD	Increased severity of CAD[10] High coronary artery calcium score[11] Predictor of silent ischemia[12] Underdeveloped collateral vessels in areas of CAD[13] Poor coronary artery bypass graft outcomes[14,15] Risk predictor of CAD[16]
Stroke	Stroke risk predictor[17,18]
Arterial stiffness	Predictor of arterial stiffness[19-24]
Myocardial capillary disease	Reduced myocardial flow reserve[25-27]
Heart failure	Predictor of heart failure[28,29] Predictor of systolic dysfunction[30] Predictor of diastolic dysfunction[31-33] Prognosis of heart failure[34,35]
Arrhythmia	Increased prevalence and risk of atrial fibrillation[36-38] Increased percentage of time in atrial fibrillation[36] Increased prevalence of nonsustained ventricular tachycardia[36]

CAD indicates coronary artery disease.

Cardiovascular and kidney disease share many risk factors and pathological processes that can lead to albuminuria (Figure 1). Albuminuria is often detected in hypertension and diabetes, both of which are also risk factors for CVD.[40] Although it is primarily mentioned in the context of diabetic kidney disease, albuminuria has a strong, independent association with hypertension. Among 9198 patients in a primary care setting, microalbuminuria (based on test strips that detect ≥20 mg/L urine albumin concentrations) was found in 43% of patients with hypertension only and 51% of patients with diabetes only; patients with both conditions had the highest prevalence of microalbuminuria (58%).[41]

Hemodynamic alterations induced by hyperglycemia and hypertension lead to mechanical stretch and shear stress on endothelial cells, initiating processes that damage the glomerular filtration barrier. This barrier consists of the endothelial surface layer (the glycocalyx), fenestrated endothelial cells, glomerular basement membrane, and glomerular epithelial cells (podocytes). Albuminuria reflects damage to these structures and is characterized by mesangial expansion (mesangial cell proliferation and excess production of matrix proteins in the central region of the glomerulus provide a supporting framework to the glomerular capillaries), basement membrane thickening, and podocyte apoptosis. Subsequent podocyte injury and detachment further increase albuminuria, decreasing the capillary filtration surface and ultimately leading to glomerulosclerosis.[42]

Elevated levels of inflammatory markers are also associated with the presence of albuminuria, providing another link to the association of albuminuria with CVD.[43] Many of these inflammation products are present in processes associated with the development of atherosclerosis.[39] Beyond the shared pathogenetic processes, there is also a strong interplay of the cardiovascular and renal systems where dysfunction of one system can lead to dysfunction of the other, termed cardiorenal syndromes.[44] In chronic cardiac dysfunction, compensatory mechanisms to improve cardiac output and reduce venous congestion can lead to renal hypoperfusion and kidney damage, including albuminuria.[44]

Albuminuria is classified into 1 of 3 categories, A1 to A3, depending on the severity (Figure 2).[45] There are several methods to detect albuminuria in daily clinical practice (Table 2). The gold standard is the 24-hour measurement of albumin excretion rate (AER), as albuminuria has a high short-term within-person variability.[46] However, this test is cumbersome and not convenient for routine clinical practice. The spot urine albumin:creatinine ratio (UACR) is another method of

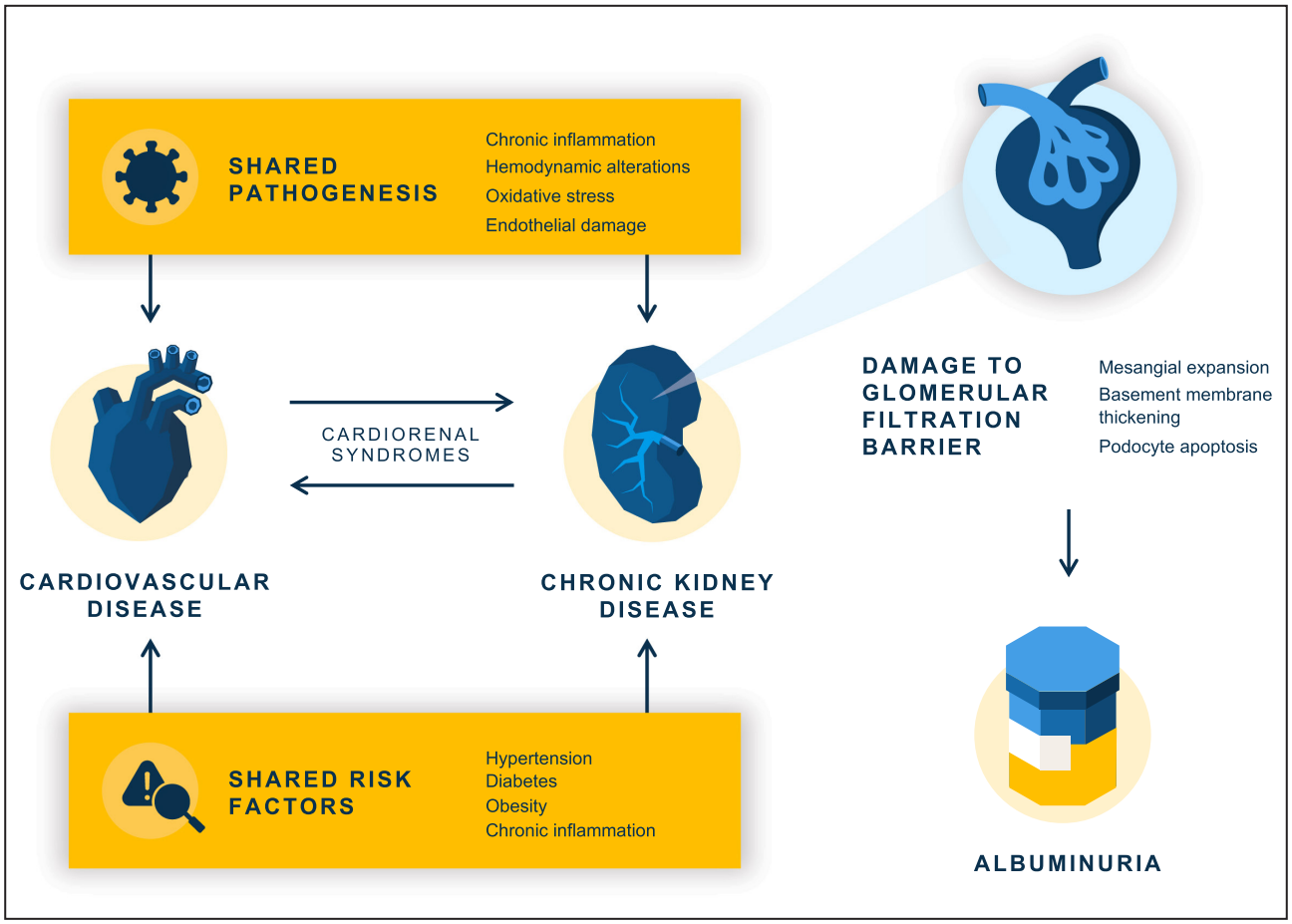

Figure 1. Reciprocal mechanisms of cardiac and renal disease leading to albuminuria
Injury to the glomerulus resulting in albuminuria is seen in cardiovascular disease because of the shared pathological processes with chronic kidney disease and because of compensatory mechanisms in chronic cardiovascular disease.

measuring albuminuria, and it quantifies the amount of urinary albumin per gram of urinary creatinine, which accounts for differences in urine concentration. The use of this ratio is based on the assumption that creatinine excretion is approximately 1 g per day. Because the amount of creatinine excreted into the urine varies, the ratio of albumin to creatinine is only an approximation of 24-hour AER.

Several factors can affect spot UACR measurements, such as muscle mass, exercise level, hydration level, and posture. Changes in creatinine generation, as seen with extremes of diet or muscle mass, can also affect UACR measurements. Dietary habits such as red meat consumption or high intake of animal fat have been associated with albuminuria, especially in diseases associated with CKD.[47,48] However, the evidence that high protein intake is cross-sectionally or prospectively associated with albuminuria is not conclusive.[49] Albuminuria is also associated with intake of food with a high acid load in various populations.[50,51] The effects of all these factors can be minimized by using a first morning urine sample. A first morning urine sample has a stronger correlation with 24-hour urine albumin excretion than a random spot sample, as the latter tends to report higher levels of UACR compared with a morning specimen.[52] Owing to the natural variability of albumin excretion, repeating the measurements is advisable. Nonetheless, studies using simultaneously collected samples for 24-hour AER and first spot morning UACR show that UACR is a good screening test for the presence of microalbuminuria, though not a good diagnostic test for quantifying 24-hour AER.[53] A conventional dipstick can be used for screening; however, it cannot sufficiently detect microalbuminuria and its sensitivity is poor relative to UACR, hence, its use for albuminuria stratification is discouraged.[54]

ASSOCIATION OF ALBUMINURIA WITH CARDIOVASCULAR DISEASE

Coronary Artery Disease

Many studies have documented a strong association of albuminuria with the presence or development of CAD.

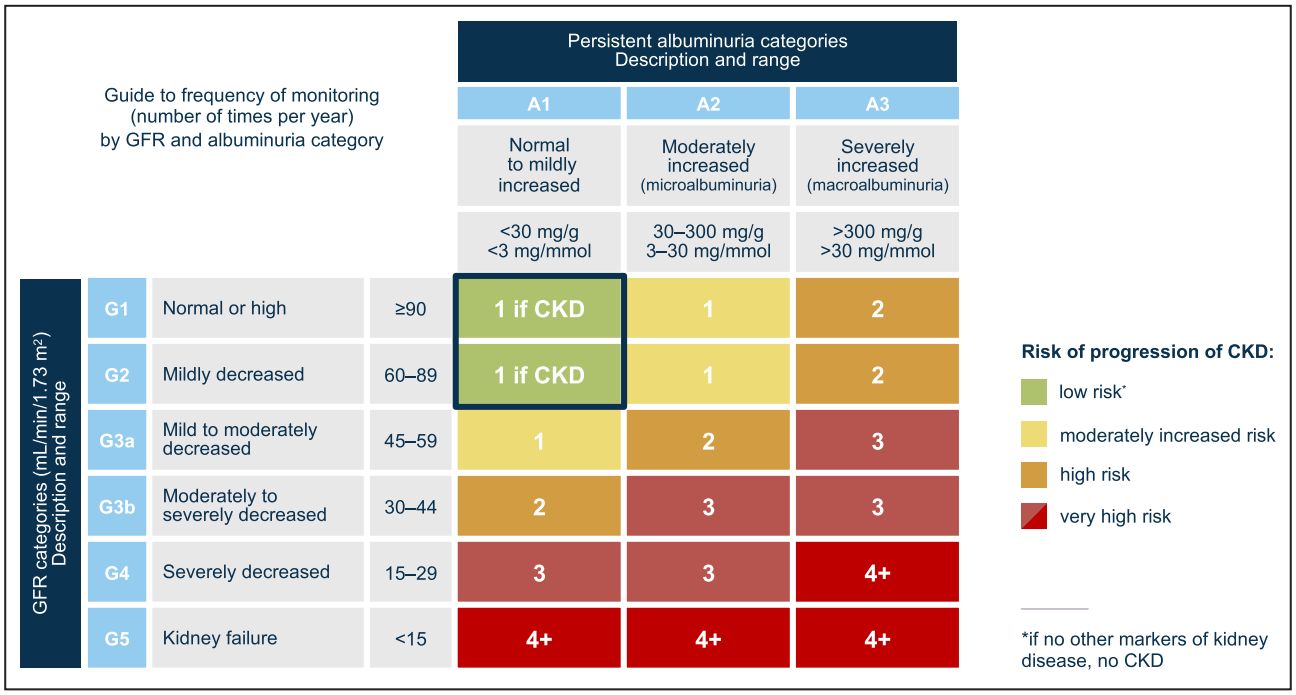

Figure 2. GFR and albuminuria grid to reflect the risk of CKD progression and requirements for monitoring
The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Albuminuria measured as urinary albumin:creatinine ratio. CKD indicates chronic kidney disease; and GFR, glomerular filtration rate. Adapted from Levin A, et al., KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease: Chapter 2: Definition, identification, and prediction of CKD progression; Kidney International Supplements, Vol 3, 63–71, Copyright (2013), with permission from Elsevier.[45]

As compared with normoalbuminuric individuals, people with albuminuria have increased severity of CAD[10]; an association with high coronary artery calcium score[11]; the presence of undetected, silent ischemia[12]; low collateral vessel development in areas of CAD[13]; and poorer outcomes after coronary artery bypass graft surgery.[14,15] One study demonstrated albuminuria to be a risk equivalent to prior myocardial infarctions.[16] In that study, patients with albuminuria and no prior history of myocardial infarction had similar rates of vascular events as patients with prior myocardial infarctions and normoalbuminuria. A meta-analysis reported the relative risk of developing clinical CAD in people with albuminuria to be 1.41 (95% CI, 1.17–1.69).[9]

In a cross-sectional study from Korea, 45 006 participants without previous CVD events underwent coronary computed tomography and a urine dipstick test as part of a health examination program. A coronary artery calcium score of >100 was clinically significant. Participants were divided into 3 groups based on urine dipstick albumin results as follows: negative (–), trace (±), and positive (+1 to +4). The participants with clinically significant coronary artery calcium score were 2.0%, 2.8%, and 4.9% for the negative, trace, and positive urine dipstick groups, respectively. Compared with the negative group, the odds ratio (OR) for significant coronary artery calcium score was 1.62 (95% CI, 1.08–2.42) in the positive group and 1.34 (95% CI,

Table 2. Overview of Urine Albumin Measurement Methods in Clinical Practice

Test	Benefits	Drawbacks	Best use
24-h AER	Accurate measurement of albuminuria excretion	Cumbersome	When accurate albuminuria diagnosis is required
Random spot UACR	Convenient, good screening test for microalbuminuria, high sensitivity	Not a good estimate of 24-h AER, variability owing to exercise, posture, hydration level, extremes of diet or muscle mass, requires retesting	Screening (if first morning spot UACR is not convenient)
First morning spot UACR	Stronger correlation with 24-h AER than random spot UACR	Affected by variability of albuminuria, requires retesting	Screening
Urine dipstick	Immediate results, convenient, low cost	Poor specificity and sensitivity to microalbuminuria	Screening (when UACR is unavailable), repeat if negative

AER indicates albumin excretion rate; and UACR, urinary albumin:creatine ratio.

1.07–1.66) in the trace group.[11] In a prospective observational study, a random sample of 760 Japanese men from the general population without CVD or other severe diseases were followed up for an average of 5 years.[55] Coronary artery calcification progression was associated with albuminuria (UACR >30 mg/g) after adjustment for diabetes, hypertension, and CRP, independent of change in estimated glomerular filtration rate (eGFR; relative risk, 1.20 [95% CI, 1.01–1.43]; P=0.04). For macroalbuminuria (UACR >300 mg/g) and coronary artery calcification, the Brazilian Longitudinal Study of Adult Health identified an even higher OR of 4.31 (95% CI, 1.27–14.64) among 4189 patients without previous CVD.[56]

The mechanisms by which albuminuria could be associated with CAD have been shown to be through impaired vasodilation[57] and increased inflammation factors.[58] In a report from the Cardiovascular Health Study, albuminuria was not associated with the risk of subclinical atherosclerosis in 3312 participants, age ≥ 65 years, without hypertension or diabetes (OR, 1.14 [95% CI, 0.59–2.23]). In contrast, it was associated with subclinical atherosclerosis in participants with hypertension (OR, 1.58 [95% CI, 1.08–2.30]) or diabetes (OR, 2.51 [95% CI, 1.27–4.94]).[59] The association between albuminuria and clinical CAD may involve destabilization of the underlying atherosclerotic vascular disease in those with hypertension and diabetes and endothelial dysfunction in those without hypertension and diabetes. More recent reports identified an association between albuminuria and subclinical atherosclerosis in the absence of diabetes,[60] so the actual pathophysiology requires further investigation.

Stroke

The association between albuminuria and the incidence of stroke has been confirmed in 2 meta-analyses. A meta-analysis of 38 studies with 1 735 390 participants concluded that any level of albuminuria was associated with greater stroke risk even after adjustments for other cardiovascular risk factors (relative risk, 1.72 [95% CI, 1.51–1.95]).[18] In a recent meta-analysis of 7 studies with 159 302 participants,[17] the risk of stroke was also increased (hazard ratio [HR], 1.84 [95% CI, 1.49–2.28]; P<0.01) with albuminuria compared with its absence. In a subgroup analysis, high levels of UACR were associated with an increased risk of ischemic stroke (HR, 1.60 [95% CI, 1.43–1.80]; P<0.01) and hemorrhagic stroke (HR, 1.76 [95% CI, 1.22–1.45]; P<0.01). High levels of UACR were not associated with higher risk of stroke in patients with either type 2 diabetes (T2D) (HR, 2.25 [95% CI, 0.55–9.17]; P=0.26) or hypertension (HR, 0.95 [95% CI, 0.28–3.22]; P=0.93). As no information on the degree of control of hyperglycemia or blood pressure was available, the absence of association between albuminuria and risk of stroke should not be considered definite in these populations.

Arterial Stiffness, Vascular Calcification, and Peripheral Arterial Disease

Cross-sectional and prospective studies suggest a statistically significant bidirectional association of albuminuria with arterial stiffness. In the Jackson Heart Study of African Americans, higher carotid-femoral pulse wave velocity was associated with prevalent albuminuria (OR, 1.66 [95% CI, 1.32–2.11]; P<0.001).[19] In the multiethnic Healthy Life in an Urban Setting Study (Amsterdam, Netherlands), aortic stiffness was associated with albuminuria in individuals with T2D (OR, 2.55 [95% CI, 1.30–4.98]) but not in those without diabetes (OR, 0.96 [95% CI, 0.63–1.45]).[20] A study from China reported UACR to be related to carotid-femoral pulse wave velocity in participants with high-normal albuminuria and macroalbuminuria.[21] Another study reported that the prevalence of microalbuminuria and macroalbuminuria increased with increasing brachial-ankle pulse wave velocity.[22] Prospectively, increased carotid-femoral pulse wave velocity was associated with incident albuminuria in the Framingham Offspring Study.[23] In the Taichung Community Health Study, baseline albuminuria was associated with the development of arterial stiffness in men (OR, 4.47 [95% CI, 1.04–19.31]), and the change in pulse wave velocity was positively associated with the change in UACR.[61] In another prospective diabetes study, arterial stiffness was more strongly associated with albuminuria than was a decrease in renal function as measured by eGFR.[24]

Vascular calcification is a common cause of arterial stiffness[62] and has been linked to albuminuria in several studies, in addition to the studies mentioned earlier in relation to coronary artery calcification. Aortic stiffness and femoral artery microcalcifications were significantly increased in patients with T2D with preserved kidney function and macroalbuminuria (UACR >300 mg/g) when compared with those without albuminuria.[63] High urinary protein-to-creatinine ratio was independently associated with high aortic arch calcification score (unstandardized coefficient β: 0.315; P=0.002) among 482 predialysis patients with CKD stages 3A to 5 (eGFR <60 mL/min/1.73 m^2).[64]

Epidemiologic studies have shown an association between peripheral arterial disease and albuminuria. In diabetes, patients with albuminuria (micro- and macroalbuminuria combined) have been shown to be 1.90 times more likely to have peripheral arterial disease (95% CI, 1.19–3.04) than those with no albuminuria.[65] The Okinawa Peripheral Arterial Disease Study also demonstrated an association between peripheral arterial disease and albuminuria, which may be a result of arterial stiffness in younger individuals.[66]

Myocardial Capillary Disease

The association of albuminuria with myocardial flow reserve (also called microvascular capillary flow) has been studied mostly in people with diabetes. Myocardial flow reserve is the ratio of stress myocardial blood flow to rest myocardial blood flow and correlates with cardiovascular outcomes. In 1 study, myocardial flow reserve decreased progressively in relation to the amount of urinary albumin excretion (normoalbuminuria: 2.9, SD 1.1; microalbuminuria: 2.3, SD 1.0; macroalbuminuria 1.8, SD 0.7; $P<0.0001$).[25] In another study, people with T2D free of overt CVD who had albuminuria had a high prevalence of coronary microvascular dysfunction.[26] Finally, in mild-to-moderate CKD, patients with albuminuria show reduced coronary vasodilator capacity.[27]

Heart Failure

In a cross-sectional analysis of 1214 adults with HF from the National Health and Nutrition Examination Survey 1999 to 2012, 22.1% had microalbuminuria and 10.4% had macroalbuminuria. In adjusted analyses, the odds of having albuminuria in those with HF (n=1214) were 1.89-fold higher than in those without HF (n=37 961).[28] Likewise, high normal UACR levels (<30 mg/g) were associated with subsequent HF among 10 975 individuals in the ARIC (Atherosclerosis Risk in Communities) study.[29] Individuals with UACR of 5–9 mg/g and 10–29 mg/g had adjusted HRs for HF of 1.54 (95% CI, 1.12–2.11) and 1.91 (95% CI, 1.38–2.66), respectively, compared with UACR of <5 mg/g. In the same study, micro- and macroalbuminuria had adjusted HR of 2.49 (95% CI, 1.77–3.50) and 3.47 (95% CI, 2.10–5.72), respectively. These estimates appeared to be independent of CAD and eGFR.

In people with HF and preserved ejection fraction, increased UACR was associated with increased right ventricular and left ventricular remodeling and with systolic dysfunction.[30] Patients with diabetes and persistent microalbuminuria have markers of diffuse cardiac and diastolic dysfunction.[31,32] Even low-grade albuminuria (<30 mg/g) is associated with left ventricular hypertrophy and left ventricular diastolic dysfunction in hypertensive patients, especially in people <70 years old.[33]

Albuminuria affects prognosis in people with HF. In 1 study, the level of UACR on admission for HF was correlated with the risk of subsequent rehospitalization for HF.[34] A meta-analysis of 11 studies of patients with HF revealed a statistically significant increased risk of all-cause mortality with microalbuminuria and macroalbuminuria.[35]

Arrhythmia

A meta-analysis of 3 major cohort studies (the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study) found a stepwise increase in the adjusted risk of incident atrial fibrillation across microalbuminuria (HR, 1.47 [95% CI, 1.20–1.79]) and macroalbuminuria (HR, 1.76 [95% CI, 1.18–2.62]).[38] More recently, in the ARIC study, albuminuria was consistently associated with higher atrial fibrillation prevalence and percentage of time in atrial fibrillation, and higher prevalence of nonsustained ventricular tachycardia.[36] In a population study from Sweden,[37] the excess risk of atrial fibrillation in individuals with T2D increased with worsening glycemic control and renal complications, including albuminuria.

Other Cardiovascular Associations

Albuminuria is also associated with other conditions of the cardiovascular system that may be encountered by different specialists in addition to cardiologists. Among patients with T2D, a cross-sectional study of 250 participants showed a definite association between urinary albumin excretion level and severity of diabetic retinopathy, a hallmark of underlying microvascular disease.[67] Even in the absence of diabetes, patients with retinopathy have higher albuminuria levels than those without, as seen in 2271 patients with hypertension.[68] The association between microvascular disease and albuminuria is also seen in relation to diabetic peripheral neuropathy, where a change in UACR ≥30% may indicate a risk for new-onset diabetic peripheral neuropathy.[69]

Several other associations between albuminuria and cardiovascular conditions are of interest. Among 8574 participants followed up for an average 8.6 years, the Prevention of Renal and Vascular End-Stage Disease study found that microalbuminuria (AER: 30–300 mg/24 h) was independently associated with an increased risk of venous thromboembolism (HR, 2.00 [95% CI, 1.34–2.98]; $P<0.001$).[70] The UACR is also a significant neurologic prognostic predictor in patients with aneurysmal subarachnoid hemorrhage; the mechanism of association between the 2 disorders is not known.[71] Microalbuminuria is also a prognostic marker of cardiopulmonary complications after major surgery. However, its independent prognostic significance remains to be established.[72]

THE IMPACT OF ALBUMINURIA LOWERING ON CARDIOVASCULAR OUTCOMES

The progression of albuminuria is strongly associated with diabetes and blood pressure control.[40,73] If either or both are not well controlled, it is unlikely that albuminuria levels will be meaningfully lowered. Weight loss,[74] lipid control,[75] and smoking cessation[76] also lower albuminuria levels and reduce renal deterioration. There are several classes of therapeutic agents that lower

albuminuria and can reduce the risk of CVD. Renin–angiotensin–aldosterone system (RAAS) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and steroidal and nonsteroidal mineralocorticoid receptor antagonists (MRAs) are of particular interest.

An early clinical trial suggested that RAAS blockade could lead to reduced CVD morbidity and mortality in high-risk patients, many of whom had albuminuria.[77] A more recently published report from the Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration examined the impact of albuminuria change in 28 cohorts with CKD (including 693 816 individuals, 80% with diabetes).[78] Most of the cohorts included in this analysis would have been treated with RAAS inhibitors such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. A 43% increase in UACR over 2 years was associated with an adjusted HR for cardiovascular mortality of 1.14 (95% CI, 1.06–1.22), whereas a 30% decrease in UACR had a statistically nonsignificant adjusted HR of 0.94 (95% CI, 0.87–1.02). In contrast, the adjusted HR for end-stage kidney disease after a 30% decrease in UACR during a baseline period of 2 years was 0.83 (95% CI, 0.74–0.94). Conversely, a 43% increase in albuminuria was associated with a 1.16 (95% CI, 1.03–1.31) increased risk of end-stage kidney disease. In sum, albuminuria lowering (mostly with RAAS blockade) was not strongly protective against CVD but was effective for renal protection. Regardless of their effect on albuminuria, a meta-analysis on patients with CKD showed that angiotensin-converting enzyme inhibitors (OR, 0.82 [95% CI, 0.71–0.92]) and angiotensin II receptor blockers (OR, 0.76 [95% CI, 0.62–0.89]) reduced the risk of MACE (defined as a composite of cardiovascular death, fatal or nonfatal myocardial infarction, stroke, or HF).[79]

SGLT2 inhibitors block mediators of glucose uptake across apical cell membranes. In the kidney, SGLT2 accounts for more than 90% of glucose reabsorption from the glomerular ultrafiltrate. SGLT2 inhibitors were initially developed for the treatment of diabetes but have been found to have cardiovascular-protective effects, derived from glucose-lowering, reduced blood volume, lowered blood pressure, and lowered weight.[80]

At present, there are 3 double-blind, randomized, placebo-controlled studies in renally impaired individuals that have reported results with the use of SGLT2 inhibitors: CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, investigating canagliflozin)[81]; DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease, investigating dapagliflozin)[82]; and EMPA-KIDNEY (Study of Heart and Kidney Protection With Empagliflozin, investigating empagliflozin).[83] In the CREDENCE study involving 4401 patients with T2D, UACR >300 to 5000 mg/g, and being treated with RAAS inhibitors, canagliflozin lowered UACR by 31% (95% CI, 27–36) and significantly increased the likelihood of achieving a 30% reduction in UACR (OR, 2.69 [95% CI, 2.35–3.07]) compared with placebo. Each 30% decrease in UACR over the first 26 weeks was independently associated with reduced risk of MACE (HR, 0.92 [95% CI, 0.88–0.96; $P<0.001$) and hospitalization for HF or cardiovascular death (HR, 0.86 [95% CI, 0.81–0.90]; $P<0.001$). In the DAPA-CKD study involving 4304 patients with UACR 200 to 5000 mg/g, CVD mortality and hospitalization for HF were reduced by 29% (HR, 0.71 [95% CI, 0.55–0.92]; $P=0.009$) following treatment with dapagliflozin. Moreover, dapagliflozin resulted in a geometric mean percentage change of albuminuria of −35.1% (95% CI, −39.4 to −30.6; $P<0.0001$) in patients with T2D and −14.8% (95% CI, −22.9 to −5.9; $P=0.0016$) in patients without T2D over the follow-up visits.[82] In the EMPA-KIDNEY study involving 6609 patients with eGFR of ≥20 to <45 mL/min/1.73 m^2, regardless of the level of albuminuria, or with an eGFR of ≥45 to <90 mL/min/1.73 m^2 and UACR ≥200 mg/g, empagliflozin reduced geometric mean UACR by 19% (95% CI, 15–23).[83] The primary composite outcome of CVD mortality or kidney disease progression was significantly lower with empagliflozin versus placebo (HR, 0.72 [95% CI, 0.64–0.82]; $P<0.001$). This benefit was primarily observed in patients with severely increased albuminuria at baseline. There was no statistically significant treatment effect on the secondary composite of hospitalization for HF or CVD mortality (HR, 0.84 [95% CI, 0.67–1.07]; $P=0.15$), possibly owing to the low number of events.[83] Nevertheless, the totality of evidence from these 3 studies suggests that lowering albuminuria with the use of SGLT2 inhibitors is associated with CVD protection. It is unknown whether this is a causal relationship and to what degree albuminuria needs to be reduced to confer CVD protection. Dapagliflozin and empagliflozin are now approved by the US Food and Drug Administration to reduce the risk of cardiovascular death and HF hospitalization in patients with HF or T2D. Canagliflozin is currently approved only for patients with T2D.

Two other classes of medications that reduce albuminuria levels and the risk of CVD are the steroidal and nonsteroidal MRAs. Overstimulation of the MR in cardiomyocytes, mesangial cells, podocytes, and endothelial and vascular smooth muscle cells leads to inflammation and fibrosis in the heart, kidneys, and blood vessels.[84] These processes are especially noticeable in HF and CKD. Blocking MRs with spironolactone (first-generation steroidal MRA) and eplerenone (second-generation steroidal MRA) has been shown to be effective in reducing cardiovascular mortality and morbidity in patients with chronic HF. Finerenone, a nonsteroidal MRA, shows a higher selectivity for the

MR than steroidal MRAs and low affinity for off-target androgen, glucocorticoid, and progesterone receptors in vitro.[85] Nonsteroidal MR antagonism with finerenone demonstrates better protective effects on cardiorenal function than spironolactone or eplerenone, possibly owing to more balanced tissue distribution in the heart and kidney, as well as a lower incidence of adverse events such as hyperkalemia and gynecomastia.[86]

In a meta-analysis of 4 randomized control studies involving 13945 patients[87] with T2D and CKD, there was significant UACR lowering from baseline in the finerenone groups compared with the placebo groups (mean difference, 30% [95% CI, −0.33 to −0.27]). The data also showed a lower risk of ≥40% decrease in eGFR from baseline in the finerenone group versus the placebo group (relative risk, 0.85 [95% CI, 0.78–0.93]). The incidence of MACE was reduced by 13% with the lowering of albuminuria (HR, 0.87 [95% CI, 0.76–0.98]; $P=0.03$), driven primarily by a lower incidence of hospitalization for HF (HR, 0.71 [95% CI, 0.56–0.90]).[88,89] Finerenone is approved by the Food and Drug Administration and the European Medicines Agency to reduce the risk of renal and cardiovascular events in patients with CKD and T2D. Using mediation analysis, a post-hoc analysis of two finerenone studies that included more than 12000 individuals with CKD and T2D showed that 84% and 37% of the reduction of renal and CVD with finerenone was due to reduction of albuminuria.[90]

There are several other therapeutic agents that lower albuminuria and reduce the risk of CVD. Thiazide diuretics are often used in addition to RAAS blockade for the management of hypertension or HF and can decrease albuminuria by >35%.[91] Statins, one of the most prescribed medications in cardiology with proven cardiovascular benefits, also decrease albuminuria and the risk for cardiovascular events in patients with CKD due to any cause, including diabetes.[92,93] Glucagon-like peptide-1 receptor agonists used in diabetes have been shown to reduce the risk of progression of albuminuria and to be associated with a lower risk of MACE compared with placebo (OR, 0.89 [95% CI, 0.84–0.94]).[94]

Need for More Albuminuria Screening

Elevated levels of urine albumin are one of the earliest signs of CKD and damage of the kidney microvasculature.[95] It follows that screening for elevated urine albumin and managing patients early on have the potential to lower the risk of end-stage kidney failure (need for dialysis or transplantation) and the risk of concomitant cardiovascular complications including ischemia, arrhythmia, and HF.[96] This is especially so today, given the availability of medications that lower albuminuria levels and provide cardiorenal protection (Figure 3). The benefit to patients seems clear but the case for an economic benefit of more albuminuria screening can also be made. In 1 retrospective analysis, the costs of care for patients with T2D with moderately and severely increased albuminuria were $3580 and $12 830 higher annually, respectively, compared with patients with normal to mildly increased albuminuria levels.[97]

Several guidelines recommend screening for albuminuria (Table 3). For patients with diagnosed CKD, the Kidney Disease: Improving Global Outcomes guidelines recommend that UACR should be tested at least annually and more often for individuals at higher risk of renal disease progression based on the eGFR categories (Figure 2).[45] For patients with diabetes, the American Diabetes Association recommends screening UACR annually in patients with type 1 diabetes ≥5 years after diagnosis and in all patients with T2D, regardless of treatment. Moreover, in patients with diabetes and urinary albumin ≥300 mg/g creatinine or an eGFR of 30 to 60 mL//min/1.73 m^2, the American Diabetes Association recommends monitoring UACR twice a year to guide therapy.[100] Albuminuria screening is also recommended for patients presenting with hypertension. Both the American College of Cardiology/American Heart Association and the International Society of Hypertension recommend routine urine dipstick testing or UACR testing to assess albuminuria.[98,99] Beyond CKD, diabetes, and hypertension, there are no guideline recommendations for albuminuria screening.

Despite the rationale and clinical evidence for the value of urine albumin screening, real-world evidence suggests that adherence to recommended testing schedules is low.[101-103] In a large US-based cohort of 1 881 446 patients with T2D, Folkerts and colleagues observed that fewer than 50% of patients were screened for albuminuria during the 1-year follow-up.[101] A US population-based study of patients with T2D showed a 1-year median testing rate of 51.6% for both ACR and eGFR and 52.9% for ACR alone.[103] Another large study spanning multiple international cohorts that included over 3 million participants reported low UACR testing rates in patients with diabetes (35.1%) and extremely low rates in patients with hypertension (4.1%).[102]

There are several reasons for this low adherence to the guidelines on albuminuria testing (Table 4). A systematic review of 13271 records screened identified only 1 study that examined drivers of nonadherence to albuminuria testing.[104] Reasons for nonadherence in patients without diabetes based on clinical scenarios in primary care (hypertension and eGFR ≥60 mL/min/1.73 m^2 and hypertension and eGFR <60 mL/min/1.73 m^2) included the perception that albuminuria test results would not significantly affect management, limited time, testing not recommended by guidelines, cost, and poor patient adherence.[105] Although specialists may be more aware of relevant guidelines,[106] primary care practitioners, who have the most patient contact, often have modest knowledge of guideline recommendations, such as those related to hypertension.[107,108] The lack of awareness of the

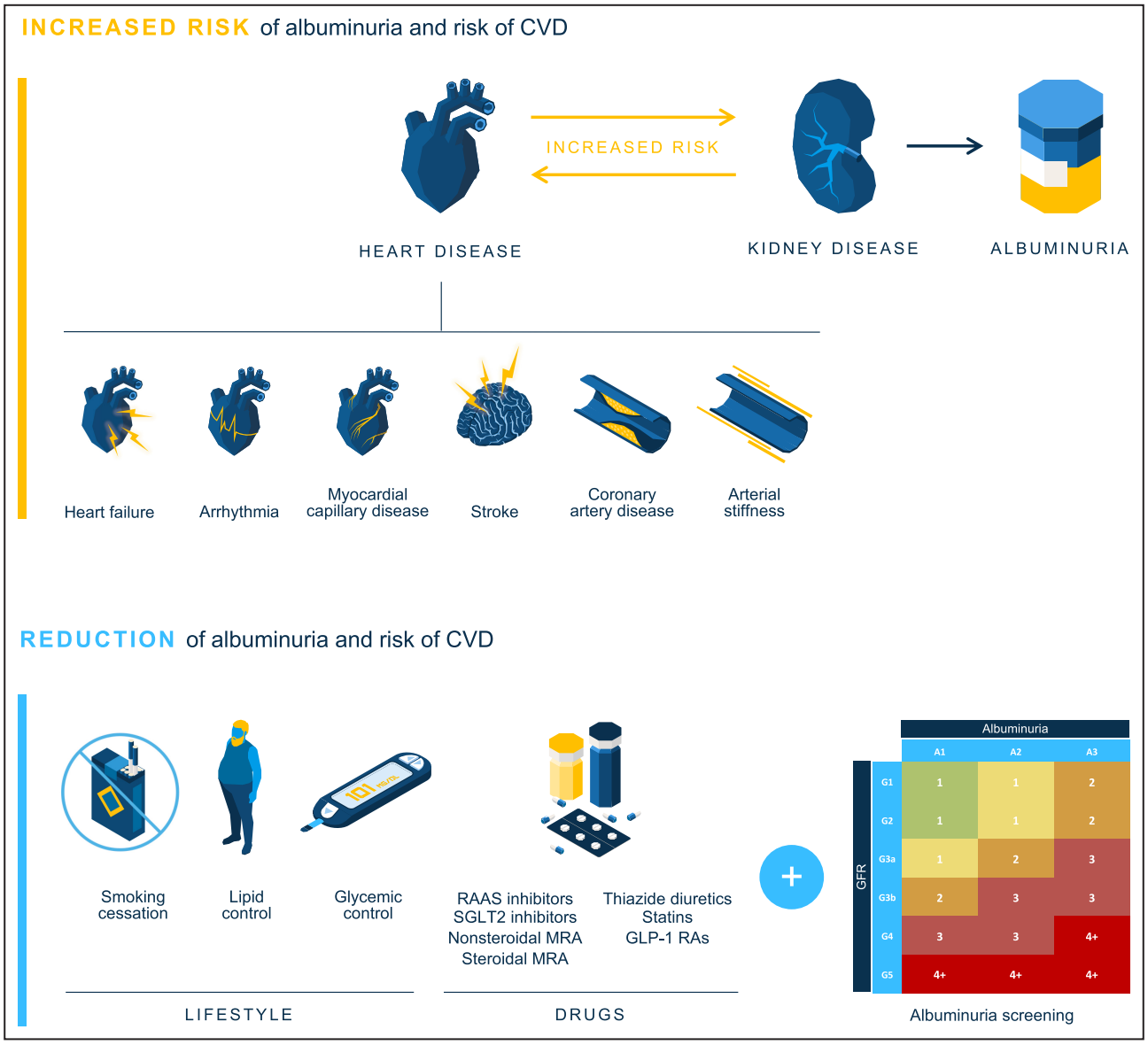

Figure 3. Importance of screening for albuminuria: a graphical abstract
Screening for albuminuria is important to identify patients at risk of CVD and CKD and to intervene early with cardiorenal-protective therapies that can help slow disease progression and improve patient outcomes. CKD indicates chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; and SGLT2, sodium–glucose cotransporter 2.

association of albuminuria with CVD and lack of awareness of the guidelines could relate to inconsistent advice from the guidelines themselves. There is currently no consensus in clinical guidelines regarding how and when to use the 2 key measures of CKD (eGFR and albuminuria) to improve CVD risk prediction, even though 1 large analysis of multiple data sets demonstrated improved cardiovascular risk prediction with the addition of measures of CKD.[109] This is a critical missed opportunity to refine personalized CVD-preventative therapies according to CKD status.

Inadequate financial incentives and fragmented health care with limited coordination/communication between providers may also affect albuminuria testing rates. Patients with limited access to health care or low disease awareness are also less likely to seek review from their clinicians and adhere to screening requests. Overcoming barriers and increasing screening rates of patients at risk are possible, especially because the ready availability and relative low cost of screening tests renders screening of populations at risk, such as those with diabetes or hypertension, very cost effective.[110] Several institutions, including primary care and secondary care, have employed simple measures such as electronic health record-based reminders and patient and clinician education to improve albuminuria screening rates.[111,112]

Table 3. Guideline Recommendations in Relation to Albuminuria Screening

Guideline	Population	Preferred testing method	Timing
Kidney Disease: Improving Global Outcomes – diabetes management in CKD[96]	At risk for and with CKD to detect progression	First morning spot UACR	Annually, and 1–4 times per year depending on the stage of CKD (see Figure 2)
American College of Cardiology/ American Heart Association – high blood pressure in adults[98]	With hypertension to detect hypertension-mediated organ damage or screening for secondary hypertension	First morning spot UACR	Optional
International Society of Hypertension – hypertension[99]	With hypertension to detect hypertension-mediated organ damage or screening for secondary hypertension	First morning spot UACR or urine dipstick	Routinely
American Diabetes Association – CKD in diabetes[100]	Anyone with diabetic kidney disease or at risk of kidney disease (type 1 diabetes with duration of >5 y; type 2 diabetes regardless of treatment) to detect progression of disease	Random spot UACR	Annually, or 1–4 times per year depending on the stage of CKD (see Figure 2)

CKD indicates chronic kidney disease; and UACR, urine albumin:creatinine ratio.

Beyond CVD and CKD

The reader of this review should be aware of the significant pervasive effects of albuminuria on health. Albuminuria is also associated with musculoskeletal, pulmonary, cerebral, endocrine, and cognitive disorders, as well as with injury (eg, falls, fractures).[113] It is also associated with a 40% increased risk of hospitalization and a 40% increased number of hospital days for a broad range of conditions.[113]

CONCLUSIONS

Albuminuria is a marker of increased physiological stress and an indicator of the need for intensive medical attention. Its recognition and treatment could lead to improved medical outcomes and reduced medical costs. It is well established that there is a strong association of albuminuria with several manifestations of CVD and CVD mortality. Despite this knowledge, rates of albuminuria screening in high-risk patients, such as those with diabetes or hypertension, are low. Health care professionals are urged to screen for albuminuria per current guidelines. Improving adherence to recommended albuminuria testing guidelines is likely to provide substantial clinical and economic benefits. Albuminuria diagnosis supports the identification of patients at risk of CVD and CKD and presents a crucial early opportunity to intervene with cardiorenal-protective therapy to slow disease progression and improve patient outcomes. Guidelines should also be more explicit in their recommendations, with clear guidance on who to screen, when to screen, and how to manage albuminuria.

Table 4. Factors That May Contribute to Low Albuminuria Testing Rates

Level	Factors
Practitioner	Lack of awareness of the association of albuminuria with cardiovascular disease
	Lack of awareness of the guidelines
	Lack of time / high workload
	Inadequate financial incentives / cost
Institutional	Fragmented health care
	Patients have limited access to health care
Patient	Low disease awareness
	Poor adherence
Guidelines	Inconsistent advice among the guidelines

ARTICLE INFORMATION

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