

# Cardiovascular implications of proteinuria: an indicator of chronic kidney disease

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**Abstract** | Proteinuria, defined as urine protein excretion greater than 300 mg over 24 h, is a strong and independent predictor of increased risk for all-cause and cardiovascular mortality in patients with and without diabetes. Proteinuria is a sign of persistent dysfunction of the glomerular barrier and often precedes any detectable decline in renal filtration function. Measurement of proteinuria is important in stratifying the risk for cardiovascular disease and chronic kidney disease progression. A variety of basic pathophysiologic mechanisms that can partially explain simultaneous renal and cardiac disease will be discussed in this Review. In addition to being a prognostic marker, proteinuria is being considered as a therapeutic target in cardiovascular medicine. Therapeutic strategies for amelioration of proteinuria by achieving blood pressure targets, glycemic control in diabetes, treatment of hyperlipidemia, and reducing dietary salt and protein intake are also reviewed in this paper. Future clinical studies are needed to assess if proteinuria reduction should be a target of treatment to reduce the burden of end-stage renal disease, cardiovascular disease, and improve survival in this high-risk population.

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### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the procedure of screening for proteinuria.
- 2 Identify the effect of inhibitors of the renin-angiotensin-aldosterone system on cardiovascular outcomes among patients with proteinuria.
- 3 Describe the relationship between proteinuria and dyslipidemia.
- 4 List treatment goals for patients with proteinuria

### Competing interests

The authors and the journal Editor, B Mearns, declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

## Introduction

AHA guidelines recommend that patients with chronic kidney disease (CKD) be considered at very high risk for cardiovascular disease (CVD).<sup>1</sup> CKD is defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>, or presence of markers of kidney damage for ≥3 months.<sup>2</sup> Proteinuria and microalbuminuria are markers of renal injury that can be detected in early stages of CKD and predict rapid decline in renal filtration function. The NHANES III (Third National Health and Nutrition Examination Survey study 1988–1994)<sup>3</sup> showed proteinuria to be present in 1% of the general population, 3.3% of patients with eGFR 30–60 ml/min/1.73 m<sup>2</sup>, and 26.0% of patients with eGFR <30 ml/min/1.73 m<sup>2</sup>. Another study found the prevalence of proteinuria to be 10.2% in patients with hypertension and eGFR <60 ml/min/1.73 m<sup>2</sup>.<sup>4</sup>

Proteinuria usually refers to the presence of an abnormal amount of protein (albumin and nonselective proteins) in the urine, owing to defects in the glomerular barrier; urine measurements that define proteinuria are described in Box 1. Macroalbuminuria is defined as more than 300 mg urine albumin over 24 h and will be referred to as proteinuria in this paper. Microalbuminuria—urine albumin secretion of 30–300 mg over 24 h—has been extensively reviewed elsewhere,<sup>5</sup> and will not be discussed in this paper unless there are inferences relevant to proteinuria.

In this Review, we will present the current data that shows an association of proteinuria with CVD, and highlight the probable mechanisms responsible for this association. Finally, we will present practical strategies for management of patients with proteinuria to decrease their risk of CVD.

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**Key points**

- Proteinuria is associated with an increased risk for all-cause and cardiovascular mortality
- Factors associating proteinuria with increased cardiovascular risk include chronic kidney disease, hypertension, hyperlipidemia, systemic inflammation, thrombotic factors, coronary artery calcification and vascular endothelial growth factor
- Identifying proteinuria in high-risk individuals allows risk stratification and initiation of therapies to reduce the risk for progression to end-stage renal disease and cardiovascular disease
- Future studies need to evaluate if proteinuria reduction should be a therapeutic target to achieve renal and cardiovascular protection

**Box 1** | Classification of proteinuria

- Proteinuria is defined as 24 h total urine protein >300 mg daily, random spot urine protein:creatinine ratio >200 mg/g, or spot urine dipstick >30 mg/dl
- Macroalbuminuria is defined as 24 h urine albumin >300 mg/day, timed urine albumin excretion >200 µg/min, or random spot urine albumin:creatinine ratio >250 mg/g in men and >355 mg/g in women<sup>a</sup>
- Persistent proteinuria, a pathological marker that reflects substantial chronic kidney disease, is defined as presence of two abnormal readings tested at least three times over 3 months

<sup>a</sup>The American Diabetes Association guidelines define macroalbuminuria as spot urine albumin:creatinine ratio >300 mg/g irrespective of sex. Microalbuminuria refers to low levels of urine albumin (30–300 mg daily).

**Measurement of proteinuria**

Measuring the amount of protein in urine allows for identification of persons at increased risk for CVD (discussed later in this Review), progression of CKD, and monitoring of the efficacy of therapy aimed at reduction of proteinuria. Routine screening for proteinuria in the general population, however, is not cost-effective.<sup>6</sup> The Kidney Disease Outcomes Quality Initiative guidelines<sup>7</sup> recommend that “individuals at increased risk of developing chronic kidney disease should undergo testing for markers of kidney damage”, such as proteinuria (Box 2).

The gold standard for measuring proteinuria is 24 h urine protein excretion; however, this measurement is cumbersome and subject to error owing to improper collection. Untimed (spot) urine sample is a more practical alternative to detect and measure proteinuria. Although first morning void specimens are preferred, random urine specimens are also acceptable. Kidney Disease Outcomes Quality Initiative guidelines<sup>7</sup> recommend screening for proteinuria with standard urine dipsticks. Urine dipstick measurements have high specificity (97–100%) but low sensitivity (32–46%), with the possibility of false negative results from dilute urine.<sup>8</sup> Patients who test positive on the dipstick should have their result confirmed with a quantitative measurement that includes spot urine protein:creatinine or albumin:creatinine ratios. These spot urine measurements correlate well with

**Box 2** | Screening for proteinuria**Clinical risk factors for proteinuria**

- Diabetes
- Hypertension
- Metabolic syndrome
- Autoimmune diseases
- Urinary tract infection
- Urinary stones
- Lower urinary tract obstruction
- Neoplasia
- Family history of chronic kidney disease
- Reduction in kidney mass
- Exposure to nephrotoxins (including NSAIDs)
- Low birth weight

**Sociodemographic risk factors for proteinuria**

- Old age
- African American, American Indian and Hispanic ethnicity
- Exposure to chemical or environmental hazards
- Low income or education

the gold-standard, 24 h protein quantitation.<sup>7</sup> Variability in the level of urine protein in an individual, from diet, activity or time of collection, is a serious limitation of the spot urine tests (standard deviation up to 40–50% of the mean).<sup>7</sup> Repeat urine studies should thus be performed when abnormal results are obtained.

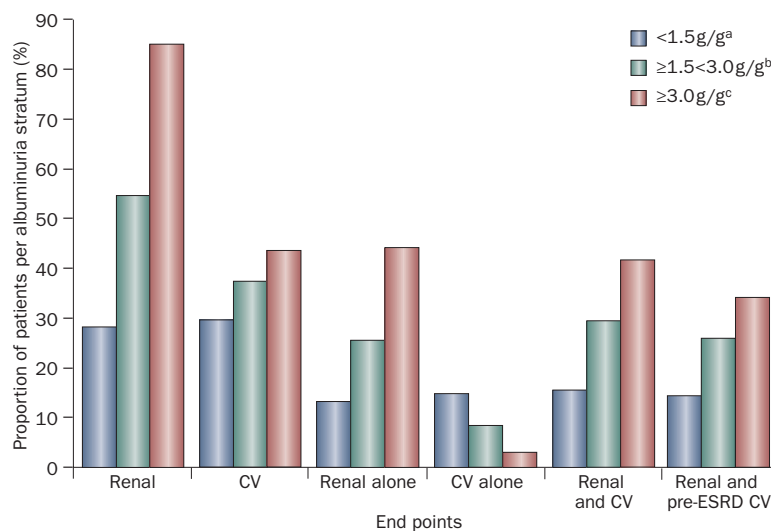
**Proteinuria and risk of CVD**

A systematic review of studies on nondialysis patients with CKD (39 studies, 1,371,990 patients) found CKD to be associated with high risk for all-cause and cardiovascular mortality outcomes regardless of the presence of confounding factors and variation in study design, study population and CKD definitions.<sup>9</sup> Indeed, patients with CKD are at greater risk for cardiovascular mortality than for progression to end-stage renal disease (ESRD). In a large, health-maintenance organization study ( $n = 27,998$ ) of patients with CKD (eGFR 15–90 ml/min/1.73 m<sup>2</sup>), the mortality rate was 24.9% and only 3.1% of patients progressed to dialysis.<sup>10</sup> An even larger community population study ( $n = 1.1$  million) demonstrated an independent graded association between reduced eGFR and increased risk of CVD outcomes and hospitalizations;<sup>11</sup> only 3,171 patients (0.28%) started dialysis at 2.84 years of follow-up compared with 51,424 deaths (4.5%) and 138,291 CVD events (12.2%). These findings show that most patients with CKD die from CVD before progressing to ESRD, with the implication that patients who have ESRD are the survivors.

As discussed earlier in this Review, proteinuria can be detected in early stages of CKD and predict rapid decline in renal filtration function. The aforementioned studies used eGFR as a measure of CKD and were limited by the absence of proteinuria measurements. Their

findings, therefore, shed no light on whether patients with proteinuria, including those with no reduction in eGFR, are more likely to die from CVD than progress to ESRD. Competing risk factor analysis of ESRD and mortality in a prospective study performed in Veterans Administration patients with CKD ( $n = 220$ , mean eGFR = 38.2 ml/min/1.73 m<sup>2</sup>), who were followed for 7 years, revealed that proteinuria had a similar effect on progression to ESRD (hazard ratio, HR 1.37) and all-cause mortality (HR 1.26).<sup>12</sup> In agreement with this study, post-hoc analysis of the RENAAL (Reduction in Endpoint in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) trial (mean baseline eGFR = 39.8 ml/min/1.73 m<sup>2</sup>) showed that proteinuria  $\geq 3$  g daily ( $n = 289$ ) was associated with a renal end point of doubling of creatinine or ESRD in 85% of patients, and with cardiovascular end point in 44% of patients. In the same analysis, proteinuria  $< 1.5$  g daily ( $n = 859$ ) was associated with renal and cardiovascular end points in 28% and 29% of patients, respectively, after adjusting for eGFR and multiple risk factors (Figure 1).<sup>13</sup> Indeed, patients with baseline urinary protein excretion  $\geq 1$ –3 g daily have been shown to benefit most from reduced CKD progression with angiotensin-converting-enzyme inhibitors (ACEIs).<sup>14,15</sup> Increased level of baseline proteinuria ( $> 1.5$  g daily) was associated with increased risk for CVD only in those patients who also progressed to a renal end point. A retrospective study of 142 non-diabetic patients with nephrotic-range proteinuria (urine protein  $> 3.5$  g/24 h) followed for 5.6 years showed that 22.5% of patients progressed to ESRD, while 4.9% of patients died from coronary heart disease.<sup>16</sup> This discrepancy in patients' outcomes might suggest different mechanisms for risk of ESRD and cardiovascular deaths in various populations with proteinuria and differing burden of endothelial dysfunction and atherosclerosis. These studies highlight the practical difficulty in differentiating whether increased renal and cardiovascular risk arises from proteinuria, reduced renal function or both.

Regardless of whether proteinuria predicts a greater risk of death from CVD or progression to ESRD, the condition has been consistently associated with increased risk for cardiovascular events and mortality in patients with and without diabetes. Patients with proteinuria had relative risks or hazard ratios for CVD events, CVD mortality and all-cause mortality of 1.6–5.5, 1.7–5.4 and 1.4–2.9, respectively (Table 1). In addition, proteinuria has been implicated in myocardial disease of the left ventricle. The Strong Heart Study showed that patients with type 2 diabetes with proteinuria (mean serum creatinine 1.63 mg/dl) had worse left ventricular systolic function and impaired diastolic left ventricular filling compared with patients with normoalbuminuria (mean serum creatinine 0.85 mg/dl) or microalbuminuria (mean serum creatinine 0.86 mg/dl).<sup>17</sup> Finally, proteinuria is also associated with increased risk for atherosclerotic events in the peripheral vasculature. Patients with proteinuria have been demonstrated to be at increased risk (relative



**Figure 1** | Relationship between CV and renal outcomes in patients with different baseline degrees of albuminuria in the RENAAL (Reduction in endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) trial.<sup>13</sup> <sup>a</sup> $n = 859$ . <sup>b</sup> $n = 365$ . <sup>c</sup> $n = 289$ . Abbreviations: CV, cardiovascular; ESRD, end-stage renal disease; g/g, g albumin/g creatinine. Permission obtained from Lippincott Williams & Wilkins © de Zeeuw, D. *et al. Circulation* **110**, 921–927 (2004).

risk 1.6–3.3) for incident stroke.<sup>18,19</sup> In aggregate, these data suggest that proteinuria might be associated with systemic vascular disease that affects the glomeruli as well as other arterial systems in the body.

### Potential mechanisms for CVD risk

Defects in the glomerular capillary endothelium, basement membrane or podocytes is manifested as proteinuria. The proteins, hormones, growth factors (insulin-like growth factor), lipoproteins and transferrin that leak into the urinary space and flow to the tubules have been postulated to cause tubulointerstitial injury and inflammation.<sup>20</sup> Eventually, this injury pathway leads to parenchymal damage, renal fibrosis and progressive decline in eGFR.<sup>21</sup> This mechanism partly explains the specific association between proteinuria and progression to ESRD and death related to renal disease, and suggests that the protein in the urinary space is a potential renoprotective treatment target.

Here, we review probable mechanisms that link proteinuria with increased CVD risk. Notably, the described mechanistic links only represent associations: they are not yet coupled with definitive data that shows a causal relationship. Indeed, patients with CKD and with eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> often have proteinuria and much of the evidence for mechanisms described in this section was found in patients with reduced renal filtration function. Numerous pathways in CKD—including extracellular fluid volume overload, hypertension, abnormal calcium and phosphorus metabolism resulting in vascular calcification, endothelial dysfunction, systemic inflammation, oxidative stress and activation of sympathetic system and renin–angiotensin–aldosterone system (RAAS)—have

**Table 1** | Studies evaluating the association between proteinuria and cardiovascular disease

Study (first author, year)	Number of patients in study (age)	Number of patients with proteinuria	Definition of proteinuria	Follow-up (years)	Atherosclerotic and cardiovascular risk factors	CV mortality risk with proteinuria	CV events risk associated with proteinuria
Anavekar (2004) <sup>70</sup>	1,715 (30–70 years)	1,715	24 h urine albumin measurement $\geq$ 900 mg	5	Diabetes (100%), previous CVD (29%), smoking (61.6%)	NR	RR 1.29/log unit ACR
Halbesma (2006) <sup>71</sup>	8,592 (28–75 years)	134	24 h urine albumin measurement $\geq$ 300 mg tested twice	4	Hypertension (46.2%), diabetes (9.7%)	HR 2.6	NR
Borch-Johnsen (1985) <sup>72</sup>	1,134 (30–60 years)	406	24 h urine protein measurement $\geq$ 500 mg in four or more measures	19	Diabetes (100%)	Increased	NR
Cardoso (2008) <sup>73</sup>	471 (35–85 years)	106	24 h urine protein measurement $\geq$ 500 mg	4.8	Hypertension (66%), diabetes (100%)	RR 4.38	RR 2.96
Kannel (1984) <sup>74</sup>	5,209 (50–62 years)	216 on first examination	Spot urine albumin measurement $\geq$ 200 mg/l	16	NR	RR 1.7 (M)	NR
Hillege (2002) <sup>76</sup>	40,548 (28–75 years)	282	Spot urine albumin measurement $>$ 200 mg/l	2.6	Diabetes 2.6%, hypertension 11.2%, hyperlipidemia 4.7%, smoking 42.2%	Increased	NR
Astor (2008) <sup>75</sup>	14,586 ( $\geq$ 20 years)	160	Spot urine albumin measurement $\geq$ 300 mg/g creatinine	13	NR	RR 2.62	NR
Howard (1999) <sup>77</sup>	4,549 (45–74 years)	464	Spot urine albumin measurement $\geq$ 300 mg/g creatinine	7	Hypertension (38.7%), diabetes (48.3%)	NR	HR 5.36 (F) HR 3.81 (M)
Xu (2005) <sup>78</sup>	1,953 (45–74 years)	410	Spot urine albumin measurement $\geq$ 300 mg/g creatinine	8.8	Hypertension (66%)	HR 3.74	NR
Zhang (2008) <sup>19</sup>	4,549 (45–74 years)	464	Spot urine albumin measurement $\geq$ 300 mg/g creatinine	13.4	Hypertension (38.7%), diabetes (48.3%)	NR	HR 3.3 stroke
Yuyun (2004) <sup>79</sup>	22,368 (40–79 years)	177	Spot urine albumin:creatinine measurement $\geq$ 250 mg/g	6.4	Hypertension (34.1%), diabetes (16.9%)	NR	HR 1.59
Wang (2005) <sup>80</sup>	870 (20–74 years)	216	Spot urine albumin:creatinine measurement $>$ 250 mg/g	9.2	Diabetes (32.9%)	NR	HR 3.4
Miettinen (1996) <sup>18</sup>	2,431 (45–64 years)	Not reported	Spot urine protein measurement $\geq$ 300 mg/l	7	Type 2 diabetes (43.4%)	NR	OR 2.8 stroke, OR 1.60 CAD, OR 2.60 PAD
Valmadrid (2000) <sup>81</sup>	840 (45–90 years)	172	Spot urine protein measurement $\geq$ 300 mg/l	12	Diabetes (100%), hypertension (71.4%), smoking (54.1%)	RR 2.61	NR
Culleton (2000) <sup>82</sup>	2,586 (50–85 years)	118	$\geq$ 1+ spot urine dipstick test	17	Hypertension (69%), diabetes (23.1%)	No association	NR
Go (2004) <sup>11</sup>	1,120,295 ( $\geq$ 20 years)	70,579	$\geq$ 1+ spot urine dipstick test	2.84	Hypertension (19.1%), diabetes (9.6%)	NR	HR 1.3
Inoue (2006) <sup>24</sup>	4,428 (19–89 years)	147	$\geq$ 1+ spot urine dipstick test	3	Hypertension (6%)	NR	Increased
Irie (2006) <sup>83</sup>	90,363 (40–79 years)	1,929	$\geq$ 1+ spot urine dipstick test	10	Hypertension (32.8%), diabetes (16.4%)	RR 2.15 (F) RR 1.38 (M)	NR
Madison (2006) <sup>84</sup>	6,252 (45–68 years)	381 (transient) 69 (persistent)	$\geq$ 1+ spot urine dipstick test on 1 or 2 occasions	27	Diabetes (24.2%), hypertension (64.3%)	NR	Transient proteinuria: RR 1.48 CHD, 1.66 stroke Persistent proteinuria: RR 3.72 CHD, 2.84 stroke
Nakayama (2007) <sup>85</sup>	1,977 ( $\geq$ 35 years)	154	$\geq$ 1+ spot urine dipstick test	7.8	NR	HR 2.8	NR

Abbreviations: ACR, albumin:creatinine ratio; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; F, female; HR, hazard ratio; M, male; NR, not reported; OR, odds ratio; PAD, peripheral arterial disease; RR, relative risk.

been implicated to increase CVD risk.<sup>22</sup> CVD risk factors associated with proteinuria are discussed below.

### Hypertension

Proteinuria is also associated with hypertension—an established cardiovascular risk factor. A study of patients with CKD (creatinine clearance <70 ml/min) in a renal clinic revealed a high prevalence of blood pressure >140/90 mmHg (60.5%), and the degree of proteinuria was found to be a significant determinant of the presence of hypertension in the study population.<sup>23</sup> Proteinuria is also a predictor for future development of hypertension among normotensive individuals.<sup>24</sup> A cross-sectional study of 232 Veterans Affairs patients with CKD (eGFR <90 ml/min/1.73 m<sup>2</sup>) showed degree of proteinuria to be the most significant correlate for systolic blood pressure.<sup>25</sup> Furthermore, increased arterial stiffness, as assessed by pulse wave velocity, was shown to be associated with presence of dipstick-positive proteinuria, creatinine clearance and systolic blood pressure in the general population of Okinawa, Japan (*n* = 3,387).<sup>26</sup>

Targeting the RAAS with ACEIs or angiotensin II receptor blockers (ARBs) is an effective strategy to reduce proteinuria (Table 2). Improvement in CVD outcomes with RAAS blockers, however, is limited. In the RENAAL trial, 1,513 patients with type 2 diabetes and nephropathy (serum creatinine 1.3–3.0 mg/dl) were randomly assigned to receive treatment with losartan or placebo for 3.4 years;<sup>27</sup> morbidity and mortality from cardiovascular causes was similar in both groups, though the rate of first hospitalization for heart failure was significantly lower in the losartan group (11.9%) than in the placebo group (16.7%, *P* = 0.005). A post-hoc analysis from the RENAAL trial showed that proteinuria reduction by 30% or more after 6 months of losartan was associated with significant adjusted relative risk reductions of 49%, 23% and 34% over the length of the study for heart failure, non-heart-failure CVD and composite CVD end points, respectively, compared with no proteinuria reduction (Figure 2).<sup>13</sup> Every 50% reduction in proteinuria reduced the risk for heart failure and CVD end points by 27% and 18%, respectively.<sup>13</sup> Given the variability in proteinuria measurements, however, it is also possible that a 30% or greater reduction in proteinuria is in part a result of regression to the mean. Furthermore, results of post-hoc analyses are well known to be far from definitive.

In the Irbesartan Diabetic Nephropathy Trial, 1,715 patients with diabetes, hypertension and proteinuria (serum creatinine 1–3 mg/dl in men and 1.2–3 mg/dl in women) were randomly assigned to treatment with irbesartan, amlodipine or placebo.<sup>28</sup> After a follow-up of 2.6 years, no significant differences in the rates of cardiovascular events (cardiovascular deaths, nonfatal myocardial infarction, heart failure, stroke, lower limb amputation) were observed between the three groups, while proteinuria was reduced by 33%, 6% and 10% in the irbesartan, amlodipine and placebo group, respectively.

A prospective cohort study in 3,773 Chinese patients with type 2 diabetes and varying degrees of albuminuria (*n* for macroalbuminuria = 634) and renal function (plasma creatinine ≥150 μmol/l in 6.8% of patients) showed reduction in all-cause mortality in the entire group (HR 0.41) with ACEI administration; however, no significant improvement in hospitalization for CVD events were seen in the various albuminuria subgroups (HR 1.21, *P* = 0.53 for patients with macroalbuminuria).<sup>29</sup> The DIABHYCAR (noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril) study included 4,912 patients with diabetes with albuminuria (*n* = 1,285 for proteinuria) and intact renal function (serum creatinine <150 μmol/l) who were randomly assigned to treatment with ramipril 1.25 mg/d or placebo.<sup>30</sup> No effect on the combined and individual CVD outcomes of death, nonfatal myocardial infarction, stroke and heart failure were observed (HR 1.03, *P* = 0.65), compared with those on placebo, while a 14% relative risk reduction in albuminuria was observed with ramipril.<sup>30</sup>

The combination of ACEI and ARB for more complete blockade of the RAAS was evaluated in the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial); the effect of combined ACEI and ARB (ramipril 10 mg/d and telmisartan 80 mg/d) on CVD events, versus ACEI or ARB monotherapy, was evaluated in patients at high cardiovascular risk (*n* = 25,620). The primary outcome of death from CVD, myocardial infarction, stroke, or hospitalization for heart failure was similar in the combination ACEI–ARB therapy versus monotherapy study groups.<sup>31</sup> Another report of the same trial revealed that combination ACEI–ARB might increase risk of renal outcomes (composite of dialysis, doubling of creatinine and death) after 56 months of follow-up;<sup>32</sup> however, the effect of these results needs to be tempered by the fact that only a small subset of the patients had proteinuria (4% had macroalbuminuria) and the ONTARGET renal end points were secondary end points of the main study. A large study that examines the long-term effect of combination ACEI and ARB on CVD and CKD progression is needed. One such study that is currently starting enrollment is the Veterans Affairs NEPHRON-D (Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy, NCT00555217) study, which is a prospective, randomized, double-blind, multicenter trial that will assess the effect of the combination of losartan 100 mg/d and lisinopril 10–40 mg/d (as tolerated), versus losartan alone, on renal end points (eGFR reduction by 50% or >30 ml/min/1.73 m<sup>2</sup> or ESRD) or CVD events in patients with type 2 diabetes and CKD (30–90 ml/min/1.73 m<sup>2</sup> and urine albumin:creatinine ratio >300 mg/g). Triple blockade of RAAS—using ACEI, ARB and the aldosterone antagonist spironolactone—is currently also being studied for more complete inhibition of the RAAS, and additional proteinuria reduction.<sup>33</sup>

**Coronary artery calcification**

Coronary artery calcification, as assessed by electron beam CT and cardiac CT angiography, identifies sub-clinical atherosclerotic plaque burden in all layers of

the vessel wall, but its reliability in patients with CKD is inadequate.<sup>34,35</sup> In the Pittsburgh Epidemiology of Diabetic Complications cohort of 302 adults with type 1 diabetes, patients with coronary artery calcification

**Table 2** | Therapeutic strategies for reduction of cardiovascular and renal risk in patients with proteinuria based on the KDOQI guidelines

Therapeutic strategy	Rationale	Recommendation
Renin-angiotensin-aldosterone-blocking agents	ACEIs or ARBs have clearly been proven to reduce proteinuria beyond their antihypertensive effect, and offer renoprotection as shown by a lower rate of decline in GFR and risk for ESRD	ACEIs or ARBs are the preferred agents in patients with CKD with proteinuria (urine PCR>200 mg/g) Target level of proteinuria=PCR<500–1,000 mg/g Greater reduction of proteinuria has been shown with combination of ACEIs and ARBs, <sup>86</sup> combination of ACEIs and nondihydropyridine calcium channel blockers, <sup>87</sup> supratherapeutic doses of ACEIs <sup>88</sup> or ARBs, <sup>89</sup> aldosterone-blocking agents, <sup>90–92</sup> and direct renin inhibitors plus ARBs. <sup>93</sup> There are no reported renal or cardiovascular outcomes resulting from combination treatment programs, and significant concern remains over hyperkalemia and other adverse events
BP control	Systemic hypertension is a major determinant of the initiation and progression of kidney injury and works synergistically with proteinuria to accelerate renal damage leading to ESRD	Goal BP <130/80 mmHg in patients with CKD but no proteinuria. Goal BP lower than systolic BP <130 mmHg (preferably <125/75 mmHg) in patients with CKD with proteinuria (>500–1,000 mg/g). ACEIs or ARBs are the preferred antihypertensive agents, followed by addition of diuretics, calcium channel blockers (nondihydropyridine) or $\beta$ -blockers if BP is not a goal
Glycemic control	High hemoglobin A <sub>1c</sub> is associated with development of proteinuria in patients with type 1 or type 2 diabetes	Target hemoglobin A <sub>1c</sub> <7% in patients with diabetes. Recommendations are extrapolated from studies in microalbuminuria as the effect of tight glycemic control on proteinuria reduction, progression to ESRD or CVD events has not been studied in large and long-term clinical trials
Lipid management	Hyperlipidemia is commonly seen in patients with CKD and proteinuria. Statins reduce LDL levels and systemic inflammation with improved cardiovascular outcomes in the general population. In addition, statins exert an inhibitory action on renal endothelin 1 and improvement of tubular function, thus reducing proteinuria. <sup>40</sup> This angiotensin-II-independent decrease in proteinuria might be additive to the antiproteinuric effect of drugs that antagonize the renin-angiotensin system <sup>41</sup>	Statin for goal LDL <2.59 mmol/l and goal non-HDL <3.37 mmol/l. Fibrate or niacin for triglyceride reduction. Notably, both fenofibrate and gemfibrozil need to have dose reductions with eGFR, and KDOQI guidelines favor the use of gemfibrozil since fenofibrate has been shown to further reduce eGFR <sup>94</sup>
Salt restriction	High salt intake (>200–250 mmol daily) has been suggested to cause proteinuria by renal hyperfiltration or alteration in the permeability of the glomerular basement membrane. <sup>95</sup> Case series of patients who switched from low salt (50 mmol daily) to high salt intake (200 mmol daily) were observed to have reduced antiproteinuric effect of diltiazem <sup>96</sup> and lisinopril <sup>97</sup> that reversed with changing to low salt intake or hydrochlorothiazide <sup>98</sup>	Dietary sodium intake <2.4 g/day in all stages of CKD and use of diuretics in most patients with CKD to reduce BP and control peripheral edema
Low protein diet	Low protein diet reduces proteinuria by reducing filtered protein load, improving glomerular permeability, and decreasing plasma renin activity; <sup>99</sup> however, a meta-analysis of randomized, controlled trials of low-protein diets in patients with diabetic nephropathy showed a significant reduction in proteinuria ( $P=0.003$ ) but no improvement in renal function. <sup>100</sup> Note that subgroup analysis of 255 patients with GFR 13–24 ml/min/1.73 m <sup>2</sup> (MDRD study B) with 10.6 years of follow-up showed that patients on a very low protein diet (0.28 g/kg daily with mixed ketoacids and amino acids) had a greater risk for death (HR 1.82) than patients on low protein diet (0.58 g/kg daily) <sup>101</sup>	Reasonable to consider implementation of low protein diet (~0.6 g/kg daily) if feasible. Monitor closely for malnutrition
Therapeutic lifestyle changes	Therapeutic lifestyle modifications are recommended as part of a comprehensive strategy to lower BP and reduce CVD risk in CKD	Smoking cessation, BMI <25 kg/m <sup>2</sup> , moderation of alcohol intake (<1–2 drinks/day) and physical activity
Antiplatelet therapy	Antiplatelet agents are indicated for primary and secondary prevention of CVD by reducing platelet activation, aggregation and thrombus formation	Aspirin 81 mg daily for men $\geq$ 45 years and women $\geq$ 65 years. Aspirin 325 mg daily for established stable patients with coronary artery disease. Aspirin 325 mg daily with clopidogrel 75 mg daily for very high risks patients post acute coronary syndrome or percutaneous intervention

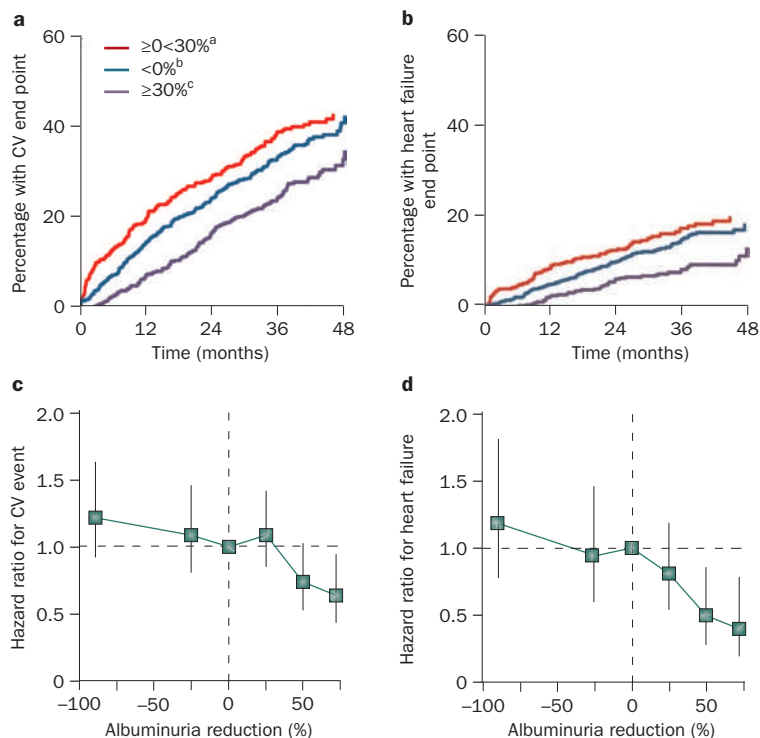
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; PCR, protein:creatinine ratio

score >400 had significantly greater prevalence of diabetic CKD (proteinuria >200 µg/min or serum creatinine >2 mg/dl).<sup>36</sup> In another study of 122 patients with type 2 diabetes (including patients with microalbuminuria and macroalbuminuria), log albumin:creatinine ratio was a significant predictor of the extent of coronary artery calcification.<sup>37</sup> A cross-sectional study that compared coronary artery calcification in 90 patients with diabetic nephropathy (urine protein:creatinine ratio >0.5 g/g), with 30 patients with diabetes and normoalbuminuria, found a greater prevalence of calcification (93% versus 63%,  $P < 0.001$ ), as well as an increased degree of calcification (calcification score 66 versus 4,  $P < 0.001$ ), in patients with proteinuria. Though the mean eGFR was  $39 \pm 4$  ml/min/1.73 m<sup>2</sup> among patients with diabetic nephropathy, no difference in the presence or extent of calcification across the various CKD stages was noted. Interestingly, greater coronary artery calcification score in patients with diabetic nephropathy was associated with the presence of severe hypertension (as studied by the number of antihypertensive medications used), female gender and age <60 years, which suggests that these factors further accelerate coronary calcification in patients with diabetic nephropathy.<sup>38</sup>

### Hyperlipidemia

Hyperlipidemia is another risk factor for increased cardiovascular mortality, and an abnormal lipid profile is commonly observed in individuals with proteinuria. Among individuals with proteinuria, the prevalence of total cholesterol >6.22 mmol/l (240 mg/dl), LDL >3.37 mmol/l (130 mg/dl), HDL <0.91 mmol/l (35 mg/dl), and triglyceride >2.26 mmol/l (200 mg/dl) has been reported to be 88%, 86%, 62%, 62%, respectively.<sup>39</sup> In addition, lipoprotein(a), a prothrombotic protein attached to apolipoprotein B100 on LDL particles, has been reported to be elevated (>1.07 µmol/l [30 mg/dl]) in 60% of patients with proteinuria.<sup>39</sup> In general, the severity of the dyslipidemia correlates with the severity of proteinuria.<sup>39</sup>

Some small studies have shown reduction in proteinuria with statin therapy over a limited follow-up period, although others have not. Furthermore, clear evidence for improved CVD and CKD outcomes with use of statins in patients with proteinuria is lacking. In a prospective, double-blind study of 63 patients with proteinuria (with serum creatinine <1.5 mg/dl), normolipemia (total cholesterol <6.22 mmol/l) and controlled hypertension (<140/90 mmHg), participants were randomly assigned to treatment with pravastatin or placebo;<sup>40</sup> after 6 months of treatment, patients on statin therapy demonstrated reduced proteinuria that correlated with reduction in urinary endothelin 1, but not with change in lipid profile, and creatinine clearance remained stable. In a similar study, the research group reported further improvement in proteinuria in patients on statins and losartan therapy, which was lost with withdrawal of statin.<sup>41</sup> Another prospective, controlled, open-label study in 56 patients with



**Figure 2** | Relationship between change in albuminuria after 6 months of losartan therapy and CV and heart failure end points in the RENAAL (Reduction in endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) trial.<sup>13</sup> Kaplan–Meier curves stratified by the change in albuminuria after 6 months of losartan are shown for **a** | CV and **b** | heart failure end points. Hazard ratios as functions of percentage change in albuminuria after 6 months of losartan therapy are also shown for **c** | CV and **d** | heart failure end points. The relationship is corrected for multiple risk factors (history of cardiovascular disease and heart failure, age, sex, ethnicity, hemoglobin, sitting diastolic and systolic blood pressure, estimated glomerular filtration rate, weight and hemoglobin A<sub>1c</sub>) at baseline and 6-month changes and log-changes in sitting diastolic and systolic blood pressure, estimated glomerular filtration rate, weight and hemoglobin A<sub>1c</sub> from baseline. <sup>a</sup>n=393. <sup>b</sup>n=631. <sup>c</sup>n=489. Abbreviation: CV, cardiovascular. Permission obtained from Lippincott Williams & Wilkins © de Zeeuw, D. *et al. Circulation*. **110**, 921–927 (2004).

proteinuria (secondary to idiopathic glomerulonephritis, baseline creatinine clearance 50 ml/min) and hyperlipidemia, demonstrated significant proteinuria reduction and slower decline in creatinine clearance with atorvastatin after one year of ACEI–ARB antihypertensive therapy.<sup>42</sup> However, these effects on albuminuria and GFR were not seen in three other studies, which included 26 patients with type 1 diabetes with nephropathy who were treated with simvastatin,<sup>43</sup> 30 adults with nephrotic syndrome or proteinuria >1 g daily who were randomly assigned to simvastatin or placebo,<sup>44</sup> and, despite improvement in hyperlipidemia, in 10 patients with nephrotic syndrome who were treated with simvastatin and cholestyramine.<sup>45</sup> A meta-analysis of randomized, placebo-controlled trials of statins in patients with CKD (presence of proteinuria or eGFR <60 ml/min/1.73 m<sup>2</sup>) showed an overall significant reduction in proteinuria (n = 311 patients, 6 studies), unchanged GFR, and an interesting significant reduction in CVD events.<sup>46</sup>

Questions still remain as to whether there is a dose-dependent response of statin therapy on urine protein and if different statins cause varying beneficial effect on proteinuria. It is also unclear if the tubular proteinuria from reduced receptor mediated endocytosis at the proximal tubule observed with use of statin (rosuvastatin 80 mg daily) is injurious or protective to the kidney.<sup>47</sup>

Nevertheless, the National Cholesterol Education Project Adult Treatment Panel 4 guideline recommendations on use of statins for goal LDL <1.81 mmol/l and non-HDL <2.59 mmol/l should be adhered to in patients with CKD (proteinuria or eGFR <60 ml/min/1.73 m<sup>2</sup>) (Table 2). American Diabetic Association/ACC recommendations published in 2008<sup>48</sup> include a third lipid goal—an apolipoprotein B100 level <0.8 g/l—which addresses the problem of residual risk related to increases in LDL particle number in the setting of low HDL and high triglycerides.

### Inflammation

Inflammatory biomarkers of vascular changes and endothelial dysfunction are being actively studied to define their role as markers of atherosclerotic burden, mediators of vascular damage, or both. C-reactive protein (CRP) is a large pentameric protein produced by the liver in response to adipokine signals from intra-abdominal fat stores; this protein is probably not pathogenic itself, but has been associated with impaired endothelial function.<sup>49</sup> CRP measured by high sensitivity CRP (hs-CRP) testing correlates with the degree of global cardiometabolic risk associated with adipose tissue.<sup>49</sup> Hs-CRP measures are elevated in asymptomatic patients with nephrotic-range proteinuria and are associated with impaired microvascular endothelial function as assessed by acetylcholine iontophoresis.<sup>25</sup> Moreover, significant correlation between the severity of proteinuria and level of hs-CRP has been demonstrated.<sup>50</sup> Proteinuria is also associated with asymmetric dimethylarginine, another inflammatory biomarker that inhibits production of nitric oxide (NO), and thus causes endothelial dysfunction and atherosclerosis.<sup>51</sup>

### Thrombotic mechanisms

Thrombogenic factors and blood viscosity might predict CVD events in patients with proteinuria. In a prospective study of 328 individuals, von Willebrand factor, tissue type plasminogen activator, soluble vascular cell adhesion molecule, soluble E-selectin and fibrinogen were found to correlate with increased urinary albumin excretion.<sup>52</sup> Plasma prekallikrein, a modulator of vascular tone and structure, was found to be high in patients with diabetes with macroalbuminuria.<sup>53</sup> Monocyte chemoattractant protein 1, a chemokine that recruits monocytes into atherosclerotic plaques and produces a local inflammatory response, was also found to be elevated in patients with diabetes with macroalbuminuria.<sup>54</sup> Finally, elevated factor VII, plasminogen activator inhibitor type 1, platelet adhesiveness, and erythrocyte aggregability in patients

with diabetes and proteinuria<sup>55,56</sup> could be indicative of high thrombosis risk in the setting of plaque rupture, and the development of thrombi as a result of stasis in the arterial system.

### Endothelial dysfunction and nitric oxide

Proteinuria might reflect not only renal injury but also a systemic increase in endothelial permeability, though clear evidence is lacking for this hypothesis. The vascular endothelium has an important role in regulating transport of proteins across microvascular walls through intercellular clefts,<sup>57</sup> transcellular holes,<sup>58</sup> and, possibly, caveolae.<sup>59</sup> Endothelial dysfunction is an attractive mechanism that might link proteinuria with the pathogenesis of atherosclerosis, as endothelial dysfunction, in response to shear stress and the deposition of lipoproteins in the subendothelial space, is an early event in atherogenesis and is hypothesized to accelerate atherosclerotic plaque formation.<sup>60</sup> Increased transvascular leakage as a result of endothelial permeability could allow the gradient-dependent entry of apolipoprotein B100 containing lipoproteins into the vessel wall, where they would become trapped. In addition, injury to the endothelium results in increased cell and platelet adhesiveness, greater permeability to proteins and inflammatory cells, and altered production of vasoactive mediators, specifically NO.

Against the hypothesis that proteinuria is a marker of increased systemic permeability, transcapillary escape rate of albumin was observed to be increased among patients with diabetes, compared with control participants, to a similar extent in patients with and without proteinuria (urine albumin >300 mg/day).<sup>61</sup> However, macrovascular endothelial function, as assessed by flow-associated dilation, has been shown to be impaired in individuals with nephrotic-range proteinuria.<sup>62</sup> This process is thought to occur though the loss of vasoregulatory effects of NO. In addition to maintaining vasodilatory tone, NO also prevents platelet adhesion and aggregation, inhibits vascular smooth muscle proliferation and leukocyte adhesion, antagonizes lipoprotein flux into the subendothelium, and attenuates the oxidative modification of the trapped cholesterol. Indeed, decreased NO activity in individuals with nephrotic syndrome is thought to be responsible for their atherosclerosis.<sup>63</sup>

Nephrotic-range proteinuria is associated with deranged NO activity through indirect mechanisms. Dyslipidemia is commonly seen in individuals with nephrotic syndrome, and increases in very low-density lipoprotein, and LDL is believed to further worsen NO-mediated vasodilation (endothelial dysfunction).<sup>64</sup> An interesting hypothesis to explain this link involves lysophosphatidylcholine. In patients with nephrotic syndrome, abnormally low serum albumin levels results in diminished binding of lysophosphatidylcholine to albumin, thus leading to sequestration and increased levels of lysophosphatidylcholine in LDL cholesterol.<sup>65</sup> The lysophosphatidylcholine probably affects endothelial function through NO dependent and independent

pathways, in addition to its proinflammatory and oxidative effects.<sup>66</sup> There is a lack of evidence for endothelial dysfunction in patients with milder degree of proteinuria, but it is possible that the aforementioned mechanism occurs in non-nephrotic proteinuria.

### Vascular endothelial growth factor

Another interesting potential mechanism that links proteinuria and hypertension is being studied in patients receiving vascular endothelial growth factor (VEGF) inhibitors for treatment of cancer. In a meta-analysis of 7 trials (1,850 patients), use of a VEGF antagonist (bevacizumab) was associated with an increased incidence of proteinuria and hypertension.<sup>67</sup> These adverse effects were reversed when the anti-VEGF therapy was stopped.<sup>68</sup> The pathogenesis of proteinuria that results from VEGF antagonism is not clear, but endothelial dysfunction is a potential cause. VEGF is expressed by the podocytes and is important in glomerular development (angiogenesis), maintenance of endothelial function and endothelial repair after injury.<sup>69</sup> Increased hemodynamic stress from the associated hypertension might also be implicated in the proteinuria. Studies have not assessed whether anti-VEGF-associated endothelial dysfunction occurs only at the glomerular level, or also at a systemic level to result in increased atherosclerosis and cardiovascular risk.

### Management of patients

In patients with proteinuria, reduction of cardiovascular risk is aimed at both the reduction in degree of proteinuria and control of associated clinical risk factors including hypertension, diabetes, hyperlipidemia, obesity and smoking. This multifactorial intervention offers benefit in reducing the global cardiovascular risk. A summary of therapeutic strategies is presented in Table 2.

Is proteinuria a target for cardiovascular protection? Despite an approach aimed at reduction in degree of proteinuria often being included in the therapeutic strategy for the reduction of cardiovascular risk in patients with proteinuria, to date no completed, randomized, controlled trials have proved that reducing urinary protein excretion lowers CVD risk. Clearly, the presence of proteinuria is associated with an increased risk for CVD mortality, and its presence is as good a predictor of CVD mortality as CKD or previous myocardial

infarction.<sup>56</sup> CKD itself is a cardiovascular risk marker owing to a high prevalence of traditional and non-traditional cardiovascular risk factors, including proteinuria; the concurrent presence of proteinuria might further amplify the increased cardiovascular risk observed with decreased GFR. Clear dissociation of the exaggerated cardiovascular risk imposed by the concurrent presence of these two important risk factors is challenging. Clinical trials studying the effect of different proteinuria targets on cardiovascular outcomes are strongly needed, but are difficult to plan and implement for a variety of practical reasons—including variability in measures of proteinuria, difference among class and dosage of medications that reduce proteinuria, baseline levels of proteinuria that predict varying outcomes and responses to RAAS blockade, difficulty achieving target blood pressure, patient adherence to diet and therapy, careful monitoring of medication complications, and long term follow-up needed to demonstrate benefit in clinical outcomes.

### Conclusions

Proteinuria is clearly associated with increased risk for CVD and mortality. Traditional and nontraditional cardiovascular risk factors increase this risk in patients with proteinuria. Furthermore, the presence of proteinuria accelerates the progression of CKD, thus amplifying the CVD risk. Attempts towards early detection, and aggressive therapies directed at reduction of proteinuria might help reduce the risk of cardiovascular disease, ESRD requiring dialysis, and all-cause mortality.

#### Review criteria

We performed a MEDLINE search of full-text articles published from 1975 to September 2008 that studied the association between proteinuria and cardiovascular disease. We used the search terms “cardiovascular disease”, “coronary artery disease”, “proteinuria” and “macroalbuminuria”. We also looked into the reference citations of each paper to find additional studies. Abstracts presented at scientific meetings were excluded. Prospective studies selected for discussion had a minimum of 100 patients with proteinuria and a minimum of 1-year follow-up. We excluded retrospective studies and did not include any studies or any data on microalbuminuria.

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