

# PERSPECTIVES

## OPINION

### Does cardiovascular protection translate into renal protection?

Gema Ruiz-Hurtado and Luis M. Ruilope

**Abstract** | Cardiovascular and renal disease often have similar origins and shared risk factors. With the progression of chronic kidney disease (CKD), additional risk factors develop, contributing to the evolution of both diseases. Progression of CKD has been primarily investigated in patients with established diabetic nephropathy and severely increased albuminuria, in cohorts smaller than those necessary for studies of cardiovascular outcomes. Consequently, simultaneous cardiovascular and renal protection was not demonstrated clearly in these studies. Nevertheless, data from some clinical trials in the field of arterial hypertension have demonstrated that cardiovascular and renal protection can be attained using the same therapy. Further investigation on factors that promote rapid progression of cardiovascular disease and CKD should result in new therapies to improve the outcome of patients presenting with both diseases.

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#### Introduction

A large body of clinical evidence demonstrates that cardiovascular disease (CVD) often runs in parallel along a continuum with chronic kidney disease (CKD; Figure 1), and the presence of both diseases results in a fourfold to sixfold increase in the risk of cardiovascular events and death when adjusted for traditional cardiovascular risk factors.<sup>1,2</sup> Moreover, progression of established CVD can contribute to a continuous decline in renal function.<sup>1,2</sup>

The origin of CVD is multifactorial and is associated with the presence of a series of risk factors, among which diabetes mellitus, arterial hypertension, lipid disorders, and smoking are the most prevalent and confer the highest risk. These factors are also frequently present in the origin of CKD, with diabetes and arterial hypertension among the most common causes of end-stage renal disease (ESRD).<sup>1</sup> The pathological mechanisms underlying the cross-talk between cardiovascular and renal systems involve the effects of these risk factors, as well as the ageing process, albuminuria, anaemia, vitamin D deficiency, and alterations

in calcium and phosphate levels.<sup>1</sup> Moreover, as CKD progresses, new risk factors (Box 1) develop and contribute simultaneously to the progression of atherosclerosis and renal dysfunction.<sup>1,2</sup> In 1985, the predictive value of proteinuria for the development of cardiovascular events or death was described.<sup>3</sup> Subsequently, in 1989, an analysis of the Hypertension Detection and Follow-up Program<sup>4</sup> revealed that an increased level of serum creatinine predicted the development of cardiovascular events and death in patients with hypertension.

CKD is defined as the presence of moderately increased (30–300 mg/g of creatinine) or severely increased (>300 mg/g of creatinine) albumin concentration, or a diminished estimated glomerular filtration rate (eGFR; <60 ml/min/1.73 m<sup>2</sup>), and is divided into five stages (Box 2) according to the Kidney Disease Outcomes Quality Initiative (KDOQI®; National Kidney Foundation, USA) guidelines.<sup>5</sup> Both albuminuria and diminished eGFR are independent and additive risk factors for the prediction of cardiovascular events and death.<sup>2</sup> In fact, a 2012 report in *The Lancet* indicated that eGFR <60 ml/min/1.73 m<sup>2</sup> should be considered to be one of the five most-potent promoters of acute coronary syndrome.<sup>6</sup> The relationship

between the various stages of CKD and the level of cardiovascular risk is illustrated in Figure 2. The lower the eGFR and the more severe the albuminuria, the greater the risk of cardiovascular events or death.<sup>7</sup> The cardiovascular risk associated with CKD is similar in men and women,<sup>8</sup> and low eGFR and moderately or severely increased albuminuria have been shown to predict ESRD and death at any age,<sup>9</sup> even though low eGFR and albuminuria can also be signs of ageing rather than of disease.

The close relationship between cardiovascular and renal diseases is not reflected in the vast majority of cardiovascular clinical trials, including comparisons of antihypertensive therapies or those in which various therapies for patients at high cardiovascular risk are tested. In such trials, the presence of stage 3 or 4 CKD is frequently an exclusion criterion. Patients with stage 3 or 4 CKD and those with severely increased albuminuria have been included only in studies on the evolution of renal function, which are characterized by short-term follow-up and small sample size that impede conclusions about cardiovascular outcomes being drawn.

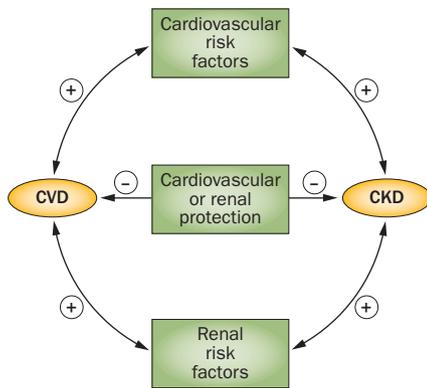
We believe that simultaneous protection for both cardiovascular and renal disease can be achieved with the same therapy. In this Perspectives article, we review the evidence from clinical trials supporting this theory, and discuss strategies to prevent both CVD and CKD.

#### Evidence base

Studies with the primary objective of elucidating the evolution of renal function have generally been performed in patients with diabetic nephropathy and severely increased albuminuria. The simultaneous control of blood pressure (BP) and reduction in albuminuria obtained with an angiotensin-receptor blocker (ARB) compared with placebo, slowed the progression of renal failure in the RENAAL<sup>10</sup> (with losartan) and IDNT<sup>11</sup> (with irbesartan) trials. In these studies, the sample size required to obtain a sufficiently high number of renal events to demonstrate the primary aim was relatively small compared with that required in trials of cardiovascular outcomes. As a consequence, the prevalence of cardiovascular events was low, with a ratio of renal events

#### Competing interests

The authors declare no competing interests.



**Figure 1** | Cross-talk between CVD and CKD. Cardiovascular risk factors (for example, increasing age, diabetes mellitus, obesity, hypertension, and hyperlipidaemia) and renal risk factors (for example, stage 3–5 CKD and albuminuria) predispose the individual to CVD, CKD, or both. Protection of the cardiovascular and renal systems through control of blood pressure and lipid levels and adoption of a healthy lifestyle help to prevent the development of CVD and CKD. Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease.

(defined as doubling of serum creatinine or increased decline in eGFR and ESRD) to death of around 1:0.51.<sup>10,11</sup>

The interest in evaluating renal function in trials of cardiovascular outcomes began with the demonstration in the HOT<sup>12</sup> and HOPE<sup>13</sup> trials that reduced eGFR and the presence of albuminuria were powerful predictors of the primary combined cardiovascular end point. These studies and others, including ALLHAT<sup>14</sup> and ONTARGET,<sup>15</sup> also showed that the number of renal events was small compared with studies that had progression of renal disease as the primary end point (ratio of renal events to death 1:4.47).<sup>10,11</sup> These trials<sup>12–15</sup> included very few patients with albuminuria in the range relevant for the deterioration of renal function. Although ONTARGET<sup>15</sup> was not primarily focused on hypertension, BP levels could have had a role in the occurrence of cardiovascular events and death. Moreover, CVD and CKD can be promoted by BP within the range of prehypertension (>120–139 mmHg systolic and >80–89 mmHg diastolic). Indeed, 50% of the burden of CVD attributable to BP occurs in individuals with prehypertension,<sup>16</sup> and CKD can also develop in individuals with prehypertension.<sup>17</sup> Importantly, a substantial number of patients presenting with BP levels within the range of prehypertension, either treated or untreated, have masked hypertension (office BP <140/90 mmHg, but 24 h ambulatory

or home BP  $\geq$ 140/90 mmHg).<sup>18</sup> In other words, these patients actually have elevated BP that requires antihypertensive treatment as recognized by the 2013 European Society of Hypertension/European Society of Cardiology guidelines.<sup>19</sup>

Three studies have been published, in which various antihypertensive therapies were investigated and simultaneous reductions in cardiovascular and renal events were reported (Table 1).<sup>20–24</sup> These studies were conducted in patients with arterial hypertension and diabetes, high cardiovascular risk (three or more cardiovascular risk factors), or both. These three trials confirm that, with sufficient sample size and duration of follow-up, the incidence of the renal end point could be sufficiently high to prove that therapies targeted towards providing cardiovascular protection could also have a similar capacity to reduce the number of renal events. Subtle differences between the groups compared in these trials could have accounted, at least in part, for the simultaneous positive effects independently of the type of therapy. However, small differences in BP have been shown not to be associated with different cardiovascular outcomes.<sup>25</sup>

The ONTARGET study<sup>15,26</sup> of monotherapy with ramipril or telmisartan showed similar cardiovascular and renal protective capacities for both drugs. However, dual blockade with these two inhibitors of the renin–angiotensin system (RAS) was shown not to reduce cardiovascular risk, but to result in subtle worsening of renal function.<sup>15,26</sup> In 2009, the question was raised of whether renal and cardiovascular events deserved similar consideration in trials of patients with high cardiovascular risk, and in particular those with type 2 diabetes.<sup>27</sup> The ALTITUDE trial<sup>28</sup> of patients with type 2 diabetes and established cardiovascular or renal disease (including moderately or

#### Box 2 | Stages of CKD<sup>44</sup>

- Stage 1: albuminuria and normal renal function (eGFR >90 ml/min/1.73 m<sup>2</sup>)
- Stage 2: mild decrease in eGFR (60–89 ml/min/1.73 m<sup>2</sup>)
- Stage 3: moderate decrease in eGFR (30–59 ml/min/1.73 m<sup>2</sup>)
- Stage 4: severe decrease in eGFR (15–29 ml/min/1.73 m<sup>2</sup>)
- Stage 5: kidney failure (eGFR <15 ml/min/1.73 m<sup>2</sup>)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

severely increased albuminuria) included common cardiovascular and renal outcomes in the primary composite end point. Patients receiving standard therapy with either an angiotensin-converting-enzyme (ACE) inhibitor or an ARB were randomly assigned to the addition of the direct renin inhibitor aliskiren or placebo. This study was stopped prematurely owing to futility to show a positive effect of aliskiren on cardiovascular or renal end points, possibly because disease was too advanced to regress with therapy. Future studies should, therefore, include patients in earlier stages of cardiorenal disease associated with type 2 diabetes. Data from the ALTITUDE trial,<sup>28</sup> ONTARGET,<sup>15,26</sup> and the VA NEPHRON-D trial<sup>29</sup> on combined angiotensin inhibition have led to the recognition that dual blockade of the RAS cannot be recommended, as reflected by guidelines published in 2013 and 2014.<sup>19,30,31</sup>

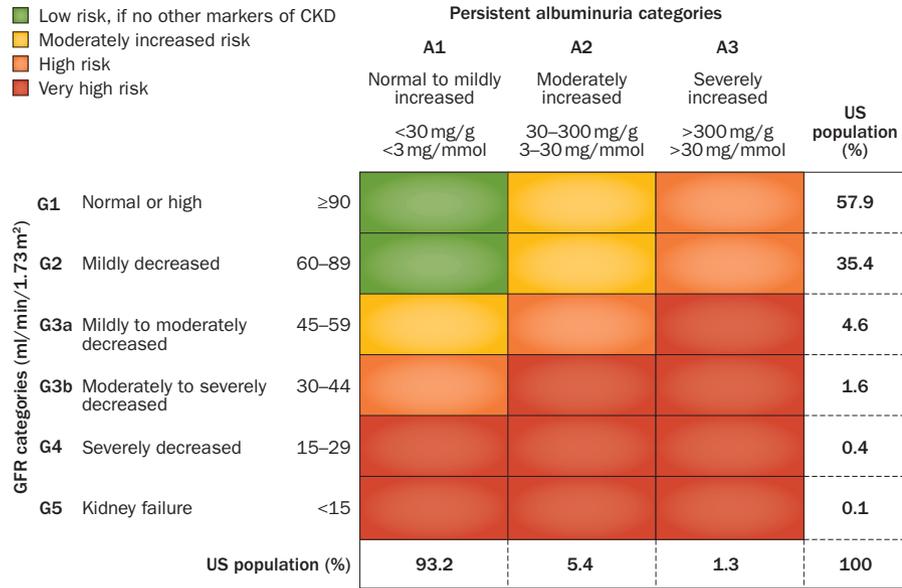
#### Prognostic role of albuminuria

A considerable body of evidence supports the role of albuminuria in the prediction of cardiovascular events and death.<sup>1,2</sup> Conversely, a decrease in the amount of albumin excreted in urine has been shown to be a sign of decreased renal risk, particularly in patients with severely increased albuminuria and type 2 diabetes.<sup>10,11</sup> A decrease in albuminuria has also been proposed to protect the cardiovascular system, as shown by data from the RENAAL study.<sup>32</sup> However, in the ACCOMPLISH<sup>24</sup> and ALTITUDE<sup>28</sup> studies, the significant decrease in albuminuria within the moderately increased albuminuria range (30–300 mg/g of creatinine) was not accompanied by a significant improvement in cardiovascular outcome. Moreover, in the ACCOMPLISH trial,<sup>24</sup> improved cardiorenal outcome was preceded by a lower drop in albuminuria among patients receiving combined therapy with an ACE inhibitor and a calcium-channel blocker compared

#### Box 1 | CKD risk factors that promote CVD<sup>1,2</sup>

- Persistently elevated BP (>140/90 mmHg with three or more antihypertensive drugs)
- Endothelial dysfunction (ADMA)
- Calcium and phosphate abnormalities
- Sodium and water overload
- Chronic inflammation
- Soft tissue calcification
- Erythropoietin resistance
- Presence of uraemic toxins
- Parathyroid hormone imbalance
- Overactivity of the sympathetic nervous system

Abbreviations: ADMA, asymmetric dimethylarginine; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease.



**Figure 2** | Risk of developing CKD by categories of GFR and albuminuria. The percentage of the US population in each risk category is shown. Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate. Permission obtained from Kidney Disease: Improving Global Outcomes (KDIGO) © KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* [online], [http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/CKD/KDIGO\\_2012\\_CKD\\_GL.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf) (2013).<sup>45</sup>

with patients who received an ACE inhibitor and a diuretic. The issue of changes in albuminuria and improvement in cardiovascular outcome might depend on the magnitude of the decrease in albuminuria from baseline values. In this context, data from the ONTARGET study<sup>33</sup> have shown that only a decrease in albuminuria of >50% from the baseline value is associated with prevention of cardiovascular events.

**Preventive strategies**

Risk factors for both cardiovascular and renal disease, such as obesity, diabetes, lipid alterations, and high BP, are often the result

of an unhealthy lifestyle. A healthy diet has been shown to reduce the risk of cardiovascular events<sup>34</sup> and to slow the progression of CKD.<sup>35</sup> However, data from the Look AHEAD study<sup>36</sup> show that the amount of body weight lost through dietary intervention had no effect on the incidence of cardiovascular events or death. Further studies seem to be required to address this issue.

The combination of RAS blockade with ACE inhibitor or ARB monotherapy at maximal doses, plus other antihypertensive drugs to control BP constitute the main therapy for patients at increased cardiovascular risk related to elevated BP.<sup>37</sup> On the other hand,

for patients with CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Guideline Development Work Group recommends treatment with a statin alone or a statin plus ezetimibe for adults aged ≥50 years with an eGFR <60 ml/min/1.73 m<sup>2</sup> not receiving dialysis or undergoing kidney transplantation.<sup>7</sup> In most guidelines, the target for BP control is <140/90 mmHg,<sup>19,30,31</sup> with the exception of the 2012 KDIGO guidelines,<sup>5</sup> in which BP values <130/80 mmHg are recommended for patients with CKD. These lower values remain a matter of debate, because no evidence exists for a positive effect of BP <130/80 mmHg on cardiovascular outcome.<sup>38</sup>

When eGFR is <45 ml/min/1.73 m<sup>2</sup>, and in particular <30 ml/min/1.73 m<sup>2</sup>, the administration of an ACE inhibitor or an ARB can lead to the development of hyperkalaemia, which can necessitate a reduction in the dose of the drug or even its withdrawal. Mineralocorticoid-receptor blockers, frequently used to correct severely increased albuminuria, are also prohibited when eGFR is <45 ml/min/1.73 m<sup>2</sup>, owing to a high prevalence of hyperkalaemia particularly in patients with diabetes.<sup>39</sup> As a consequence, the advantages of RAS blockade are often limited to the advanced stages (3–5) of CKD that confer the highest cardiorenal risk. A meta-analysis of randomized controlled trials of patients with arterial hypertension confirmed that BP lowering is an effective prevention strategy, reducing the incidence of cardiovascular events by about one-sixth per 5 mmHg of reduction in systolic BP.<sup>38</sup> In the HOT study,<sup>40</sup> the use of aspirin in patients with CKD and hypertension was shown to reduce mortality and the rate of major cardiovascular events. However, among patients with moderately reduced eGFR

**Table 1** | Clinical trials demonstrating parallel cardiovascular and renal protection

Trial	Population	Treatment	Mean BP (systolic/diastolic; mmHg)	Mean BP difference (systolic/diastolic; mmHg)	Reduction in cardiovascular outcomes	Reduction in renal outcomes
ASCOT-BPLA <sup>20</sup>	Hypertension with at least three other cardiovascular risk factors	Atenolol-based regimen vs amlodipine-based regimen	Atenolol: 137.7/79.2 Amlodipine: 136.1/77.4	2.7/1.9	Total coronary events: -13% Cardiovascular events: -16% Cardiovascular mortality: -24% Fatal CHD: -13% Fatal and nonfatal stroke: -23%	Development of renal impairment: -15%
ADVANCE <sup>21,22</sup>	Type 2 diabetes mellitus	Standard therapy plus placebo vs standard therapy plus perindopril and indapamide	Placebo: 145.0/81.0 Perindopril and indapamide: 139.4/78.8	5.6/2.2	Macrovascular and microvascular events: -9% Risk of cardiovascular death: -18%	Risk of renal events: -21%
ACCOMPLISH <sup>23,24</sup>	Hypertension	Benazepril plus hydrochlorothiazide vs benazepril plus amlodipine	Hydrochlorothiazide: 132.5/74.4 Amlodipine: 131.6/73.3	0.9/1.1	Cardiovascular risk: -20%	Risk of renal events: -48%

Abbreviations: BP, blood pressure; CHD, coronary heart disease.

(30–59 ml/min/1.73 m<sup>2</sup>), little evidence exists to support the choice of a particular class of antihypertensive drug.<sup>41</sup>

The misclassification of BP at the clinic is very common in patients with hypertension and CKD. In a study of 5,693 patients with CKD, 36.8% exhibited white-coat hypertension (that is, increased in-office BP with normal ambulatory or home BP) whereas 32.1% had masked hypertension.<sup>42</sup> These data point to the requirement for improved knowledge of actual BP values in patients with CKD. Over-treatment of white-coat hypertension or under-treatment of sustained masked hypertension could contribute to an increase in cardiorenal risk in these patients. Therefore, ambulatory BP monitoring, home BP monitoring, or both should be considered in these patients to exclude the presence of white-coat and masked hypertension.<sup>42</sup> We believe that the best methods to prevent both CVD and CKD are: adequate changes in lifestyle and increased physical activity; a realistic estimation of BP (using a combination of automated office BP, ambulatory BP monitoring, and home BP monitoring) and consequent pharmacological intervention; correction of classic cardiovascular risk factors (for example, diabetes, metabolic syndrome, hypertension, hyperlipidaemia, and smoking); and correction of renal risk factors that develop with CKD (for example, alterations in calcium and phosphate levels, anaemia, and increase in sympathetic nervous system activity).

## Conclusions

The main 'take home' messages from this article are presented in Box 3. Cardiovascular and renal diseases frequently coexist. Risk factors for these diseases are similar, and new risk factors can precipitate simultaneous cardiorenal damage owing to the progression of CKD. In the future, clinical trials need to be designed to demonstrate that cardioprotective treatment regimens can simultaneously translate into renal protection, provided that a sufficient percentage of patients enrolled in the study are at risk of developing progressive CKD. However, we do not yet fully understand why a high proportion of patients with CKD progress to ESRD, or die from cardiovascular disease, whereas the condition of other patients remains stable. Identification of individualized determinants of CKD or CVD progression will enable personalization of medical therapy, and lead to innovative nephroprotective and cardioprotective pharmacological treatment in these high-risk patients.<sup>43</sup>

### Box 3 | Take-home messages

- Some of the same risk factors are involved in the development of CVD and CKD
- Cardiovascular and renal protection includes the control of classic cardiovascular and renal risk factors, the latter of which generally manifest during stages 3–4 of CKD
- The same therapies can simultaneously protect the cardiovascular and renal systems
- However, the development of new drugs devoted preferentially to cardiovascular or renal protection should not be precluded

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease.

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#### Author contributions

L.M.R. researched data for the article. Both authors contributed equally to the discussion of the content, wrote the article, and reviewed/edited the manuscript before submission.