

## Controversies in cardiovascular medicine

# Renal function and target organ damage in hypertension

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Received 27 November 2010; revised 20 December 2010; accepted 6 January 2011; online publish-ahead-of-print 28 March 2011

Chronic kidney disease (CKD) is frequently observed in patients with arterial hypertension. The same factors that promote the appearance and progression of atherosclerosis can also promote the development of CKD. Two parameters are usually measured to estimate alterations in renal function, the presence of albuminuria, and the estimation of glomerular filtration rate (GFR). Microalbuminuria and a decreased estimated GFR ( $<60$  mL/min/1.73 m<sup>2</sup>) are both accompanied by a significant increase in cardiovascular (CV) risk. Chronic kidney disease can develop all over the cardiorenal continuum and its presence in hypertensive patients with already developed CV disease contributes to a further increase in the development of events and death. Renal protection will in turn obtain CV protection and the treatment to be used is similar to that employed to prevent or to treat established CV disease.

**Keywords** Hypertension • Chronic kidney disease • Cardiovascular disease • Albuminuria • Target organ damage

## Introduction

In the past decade, a heightened awareness has developed of chronic kidney disease (CKD) with formal stages defined, (Table 1).<sup>1</sup> One of the main reasons contributing to the awareness of the term CKD is the recognition that those with Stage 3 or higher, i.e. estimated glomerular filtration rate (eGFR  $<60$  mL/min), have a significantly higher occurrence of cardiovascular (CV) events including stroke.

The relationship between advanced CKD and increased CV events was initially observed in an analysis of the Hypertension Detection and Follow-up Program, where an elevated serum creatinine predicted an increased mortality.<sup>2</sup> Similar data were published by Samuelsson<sup>3</sup> that supported the predictive value of proteinuria and CV morbidity in hypertensive patients. More recently, the very large analysis by Go *et al.*<sup>4</sup> of over a million patients clearly documents the importance of advanced CKD and its contribution to CV risk.

## Early detection of chronic kidney disease

It is clear that there is a need for more sensitive and accurate techniques to screen patients for the presence of CKD. The two most relevant measures used to evaluate the existence of CKD are an

eGFR, usually evaluated through a formula and the presence of urine albumin.<sup>1,5</sup> The original equation to estimate GFR was published in 1999<sup>6</sup> and since then has been constantly refined to improve its use in the general population. The most recent iteration incorporates data from a broader group of patients with earlier stages of CKD including many more African Americans.<sup>7</sup> This updated formula is known as the CKD-EPI equation and corrects for much of the overestimation of CKD especially among those with eGFRs between 60 and 89 mL/min/1.73 m<sup>2</sup>.<sup>8</sup> The formula has also been adapted for other ethnicities in particular of Asian origin.<sup>9,10</sup> Formulae to assess eGFR rely on the accuracy of serum creatinine measurement that must avoid circulating chromogens that contribute to falsely increased serum creatinine values of as high as 20%.<sup>11</sup> An inadequate methodology to measure serum creatinine can lead to an inadequate estimation of the prevalence of CKD.<sup>12</sup> An example of overestimation of CKD was observed during recruitment of the ALTITUDE study.<sup>13</sup> This trial will assess CV outcomes in patients with type 2 diabetes using as a composite primary endpoint the mixture of cardiorenal endpoints. Unpublished data from this trial demonstrate that in all the countries participating, more than 30% of cases selected as having Stage 3 CKD according to an eGFR of  $<60$  mL/min/1.73 m<sup>2</sup> of body surface area at baseline were false-positive cases not confirmed by the core laboratory of the trial where an

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adequate methodology to estimate serum creatinine was used. Standardization of the methodology to estimate serum creatinine is absolutely required following criteria established by entities like the Cleveland Clinic Research Laboratories.<sup>14</sup> Table 1<sup>1</sup> represents the five different stages in which eGFR is divided according to the level of renal dysfunction. Stage 3 and higher represent the stage where CV risk is most pronounced, and within that stage, the risk is particularly elevated in those patients with Stage 3b, i.e. eGFR < 45 mL/min/1.73 m<sup>2</sup>.<sup>4</sup> This fact does not impede the recognition that in less advanced degrees of CKD, an elevated CV mortality has been described either in the general population<sup>15</sup> or, particularly, in patients with cardiac malfunction.<sup>16</sup>

The various classifications of abnormal levels of urinary albumin excretion based on different collection techniques are summarized in Table 2.<sup>17</sup> Albuminuria can be determined in 24 h (mg/24 h) or overnight ( $\mu$ g/min) urine collections but the presence of albuminuria is most frequently assessed by obtaining three early-morning spot urine at different times over a month or two. Albuminuria is then expressed as milligrams of albumin excreted per gram of creatinine. Microalbuminuria is a marker of high CV risk and can be detected in any of the five stages of CKD, whereas eGFR determines whether kidney dysfunction itself is contributing to CV risk.<sup>18–21</sup> The presence of microalbuminuria is also accompanied by an elevated risk of developing a progressive fall in GFR.<sup>22</sup>

**Table 1** Five stages of CKD (reproduced with permission from ref.<sup>5</sup>)

Stage	Description	GFR
At increased risk	Risk factors for kidney disease (diabetes, high blood pressure, familial history, older age, ethnic group)	>90
Stage 1	Kidney damage (albuminuria) and normal renal function	>90
Stage 2	Kidney damage and mild decrease in GFR	60–89
Stage 3	Moderate decrease in GFR	30–59
Stage 4	Severe decrease in GFR	15–29
Stage 5	Kidney failure (dialysis needed soon)	<15

Values of GFR represent eGFR measured with the MDRD formula.<sup>6</sup>

Data of a recent meta-analysis,<sup>23</sup> including 105 872 participants with urine albumin-to-creatinine (ACR) ratio measurements and 1 128 310 with urine protein dipstick measurement in whom eGFR was calculated (Figure 1), confirmed that eGFR < 60 mL/min/1.73 m<sup>2</sup> and ACR > 1.1 mg/mmol (>10 mg/g) are independent predictors of mortality risk in the general population. Both measures were multiplicatively associated with the risk of mortality without evidence of interaction.

## Epidemiology of chronic kidney disease: effects of ageing

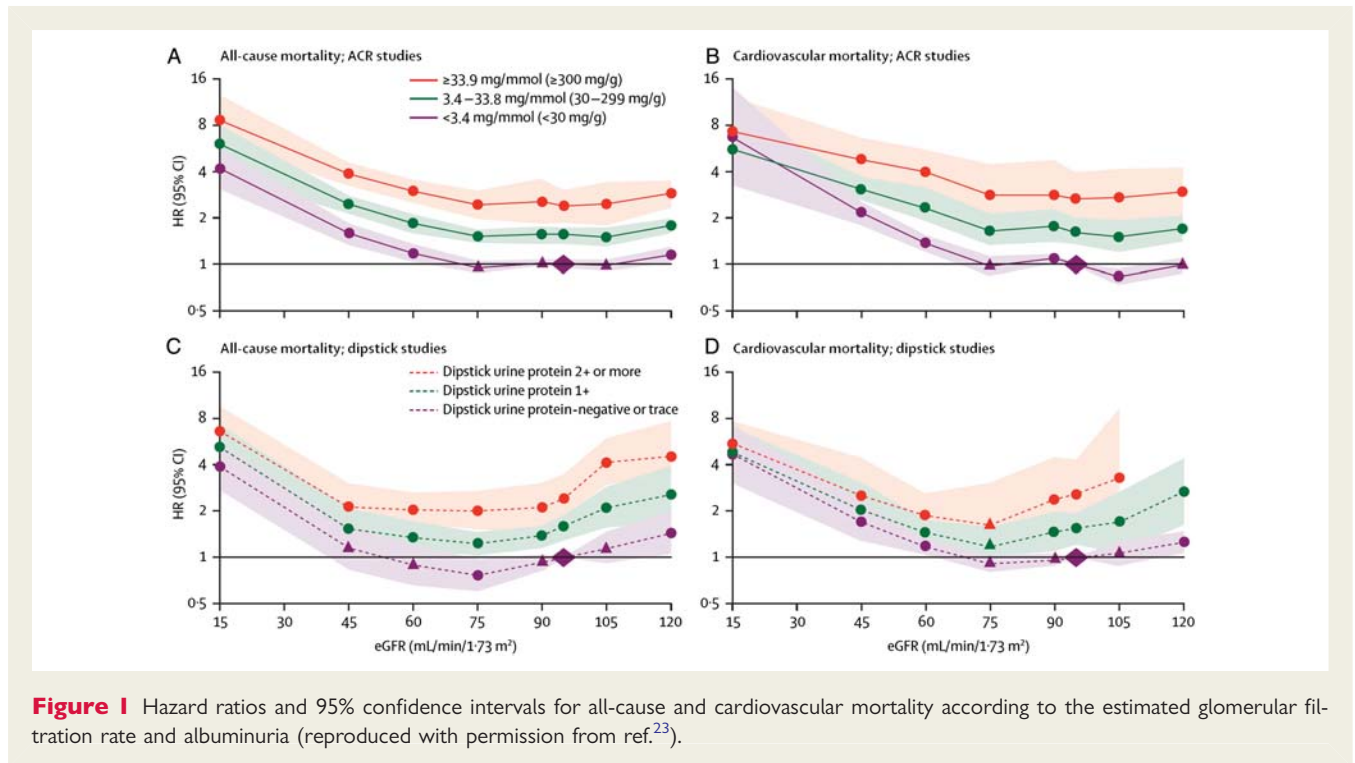
On the basis of most current definitions using the eGFR < 60 mL/min/1.73 m<sup>2</sup>, CKD is common and its prevalence is raising.<sup>24</sup> A number of explanations for the high prevalence of CKD have been put forward, including the increasing incidence of hypertension, obesity, diabetes, and ageing of the population. The current definition and classification of CKD and methods of detection may also in part explain the high rates. The current classification allows the labelling of Stages 1 and 2 based on the sole presence of persistent microalbuminuria. This definition and classification has resulted in estimates of CKD prevalence in excess of 10% of the population with 6–7% having only microalbuminuria.<sup>24,25</sup> Estimates of CKD prevalence based only on a low eGFR tend to be around 3–5% of the population but the inadequacy of the formulas used to estimate renal function can overestimate, as previously commented, this prevalence and consequently many subjects are labelled as suffering from CKD (mostly in Stage 3a, 45–59 mL/min/1.73 m<sup>2</sup>) based on an inaccurate eGFR estimation.

Elderly people can present only a slight diminution of renal function and a preserved renal functional reserve until the age of 80 years,<sup>26</sup> but most of the perceived prevalence of CKD is accounted for by individuals older than 60 years<sup>8,27</sup> in whom formulas used to estimate GFR are inaccurate, but declined renal function with age is more prevalent.

Recently, El Nahas<sup>28</sup> attempted to reconcile the high prevalence of CKD with ageing and the criticisms made to the methodology of classification of CKD in elderly people. He concludes that the high prevalence of CKD in the elderly population is likely to reflect the underlying high prevalence of overt and subclinical atherosclerosis

**Table 2** Classification of abnormal urinary albumin excretion (reproduced with permission from ref.<sup>17</sup>)

	24 h UA (mg/24 h)	Overnight UA ( $\mu$ g/min)	Spot urine UA (mg/L)	Albumin/creatinine ratio		
				Gender	mg/mmol	mg/g
Normal	<15	<10	<10	M	<1.25	<10
				F	<1.75	<15
High normal	15 to <30	10 to <20	10 to <20	M	1.25 to <2.5	10 to <20
				F	1.75 to <3.5	15 to <30
Microalbuminuria	30 to <300	20 to <200	20 to <200	M	2.5 to <25	20 to <200
				F	3.5 to <35	30 to <300
Macroalbuminuria	>3	>200	>200	M	>25	>200
				F	>35	>300



and CV disease. Chronic kidney disease would then be a reflection of diffuse and age-related cardio-kidney damage that justifies the attention with the reduction of lifelong CV risks and careful evaluation and treatment.

The histological abnormalities of CKD associated with hypertension are global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis, which together can be described as nephrosclerosis, which is rarely accompanied by macroalbuminuria.<sup>29</sup> Interestingly, in healthy adults (kidney donors), an association between age and nephrosclerosis occurs that is not explained by differences in CKD risk factors, urinary albumin excretion, or the level of GFR.<sup>30</sup> In other words, the fall in GFR with ageing does not correlate with nephrosclerosis, neither with risk factors for the development of renal dysfunction. In turn, nephrosclerosis correlates with hypertension, in particular nocturnal blood pressure, and urinary albumin excretion.<sup>30</sup>

Like serum creatinine, cystatin C is an endogenous substance that can serve as a marker of renal function. This low-molecular-weight molecule is a cysteine protease inhibitor produced at a near-constant rate by most nucleated cells and freely filtered and cleared by the glomerulus. An improved accuracy for cystatin compared with serum creatinine has been considered,<sup>31</sup> but it has been noted that factors other than renal function may affect its serum concentration.<sup>32</sup>

## Increased cardiovascular risk and chronic kidney disease

It is recognized that death is more likely than attaining end-stage renal disease (ESRD) at all CKD stages.<sup>33</sup> Since the prevalence of patients over age 60 is the highest among those with CKD, even

**Table 3** Risk factors for chronic kidney disease (modified from ref.<sup>32</sup>)

Predisposing	Initiating	Perpetuating
	Primary renal diseases	
	Urological disorders	
	Nephrotoxins	Nephrotoxins
Older age		
Gender		
Ethnicity		
Family history of CKD		
Metabolic syndrome		
Hyperfiltration states		
Low nephron numbers		Low nephron number
Diabetes mellitus		
BP > 125/75 mmHg		SBP > 130 mmHg
Obesity		High protein intake
Anaemia		Anaemia
Albuminuria		Proteinuria
Dyslipidaemia		Dyslipidaemia
CV disease		CV disease
		Hyperuricaemia
		Smoking
		Hypoproteinaemia

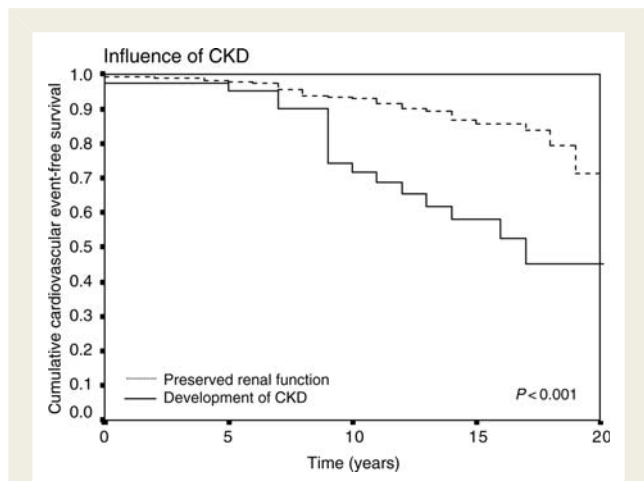
The table represents the factors that predispose, initiate, or perpetuate CKD. There is a high coincidence between factors predisposing and perpetuating CKD and those perpetuating CV disease.

with the newer formulae, it is worth examined competing risk of death vs. dialysis. A recent study addresses the issue of competing risks for progression to ESRD vs. death. They examined the age-

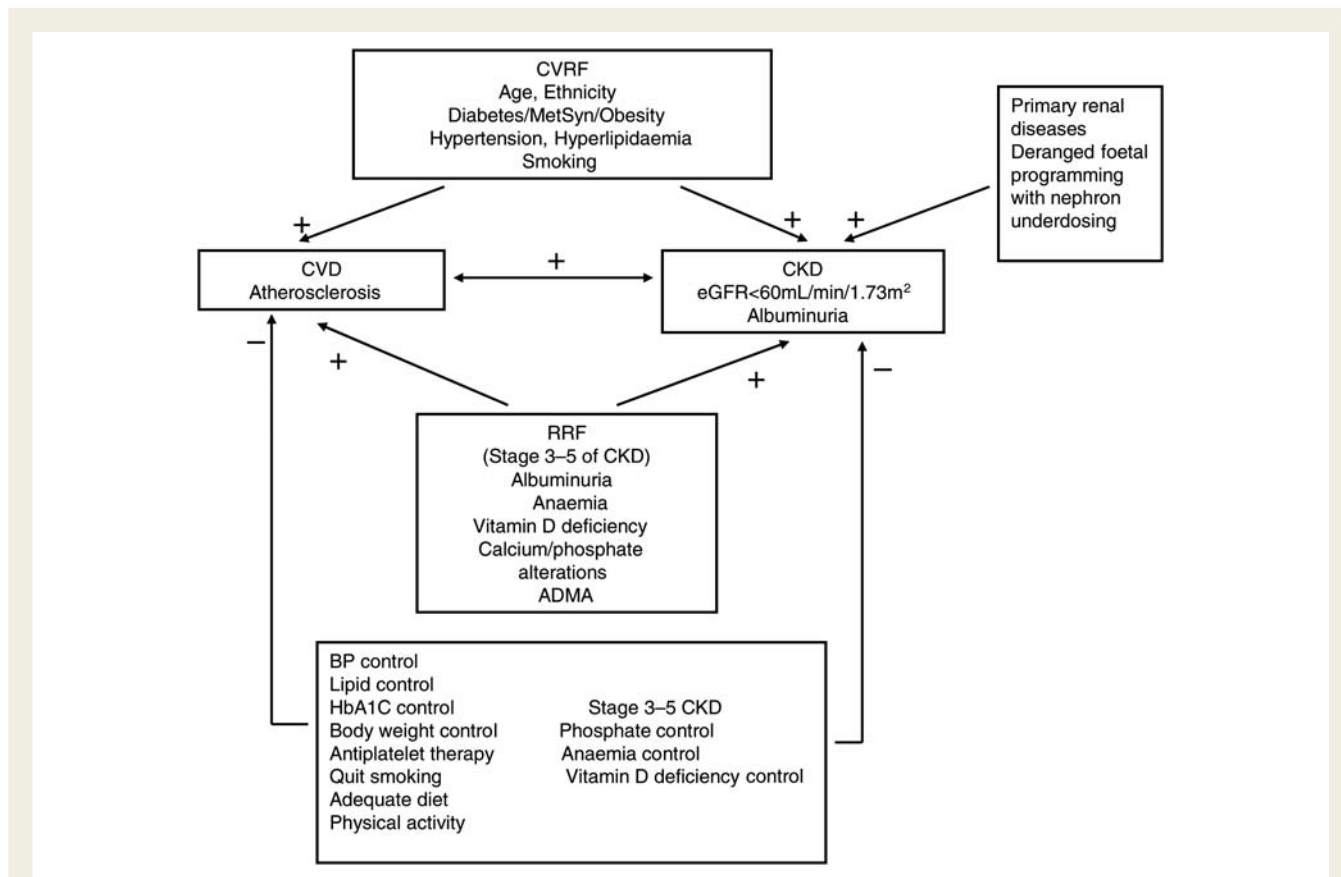
specific incidence of death, ESRD, and change in eGFR among more than 200 000 US veterans in Stages 3–5 CKD. They noted that at comparable levels of eGFR, older patients had higher rates of death and lower rates of ESRD than younger patients.<sup>34</sup> Thus, age has to be considered together with the stage of CKD when assessing whether the risk of death or ESRD is greater. In patients receiving dialysis, CV events remain as the most common cause of death. However, unlike earlier stages of CKD, there are relevant differences in response to therapies as exemplified by the absence of CV risk reduction in response to lipid-lowering therapy<sup>35</sup> and a high incidence of sudden cardiac death.<sup>36</sup>

Established CV risk factors (age, body mass index, diabetes, smoking, hypertension, HDL cholesterol, and the level of eGFR) are associated with the development of new-onset kidney disease.<sup>37</sup> The same CV risk factors that justify the development of CV disease and atherosclerosis promote the development of kidney disease. Patients with levels of eGFR < 90 mL/min/1.73 m<sup>2</sup> and established CV risk factors should be monitored for progression to kidney disease.<sup>37</sup>

Table 3<sup>38</sup> lists the most common factors contributing to the development of CKD progression. They are divided into those initiating CKD, those predisposing to, and those perpetuating renal dysfunction. Predisposing and perpetuating factors are



**Figure 2** Cardiovascular prognosis between patients developing chronic kidney disease and those with preserved renal function (reproduced with permission from ref.<sup>44</sup>).



**Figure 3** Pathophysiological mechanisms involved in the cross-talk between cardiovascular system and the kidney. CVRF, cardiovascular risk factors; MetSyn, metabolic syndrome; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RRF, renal risk factors; ADMA, asymmetric dimethyl-L-arginine.

similar to those predisposing and perpetuating CV disease and atherosclerosis.

## Chronic kidney disease in patients with overt cardiovascular disease

Primary hypertension participates actively in the development of cardiac (coronary artery disease, heart failure, and atrial fibrillation), cerebral (stroke and transient ischaemic attack), and peripheral arterial disease. The presence of CKD, usually considered as a form of target organ damage, can be detected throughout the CV continuum. The higher the level of global CV risk, the higher the level of accompanying CKD with up to 35% of people with hypertension and high or very high added risk having an eGFR values below 60 mL/min/1.73 m<sup>2</sup>.<sup>39</sup>

The coexistence of CKD and CV disease is accompanied by a significantly worse prognosis in situations such as stable coronary artery disease,<sup>40</sup> heart failure,<sup>41</sup> coronary intervention,<sup>42</sup> and peripheral arterial disease.<sup>43</sup> Conversely, the progressive development of CKD defined by a progressive decay in eGFR is accompanied by an increase in the number of CV events and death. *Figure 2*<sup>44</sup> represents the different cumulative CV free survival in patients developing and not developing CKD determined by a fall in eGFR to values below 60 mL/min/1.73 m<sup>2</sup>. In fact, it has recently been published that a faster rate of decline in renal function associates with a higher mortality.<sup>45</sup>

In summary, CKD is frequently observed in arterial hypertension and is accompanied by a significant enhance in CV risk that reinforces the need for a simultaneous protection of both the renal and the CV system. *Figure 3* summarizes the pathophysiological mechanisms underlying the cross-talk between CV and renal systems. Simultaneous damage on both systems depends on the presence of a similar origin facilitated by similar risk factors. The existence of a deranged foetal programming with nephron underdosing has been considered to facilitate the cross-talk.<sup>46</sup> Once the kidney is damaged and renal function decreases, new risk factors are added that favour the simultaneous progression of atherosclerosis and renal function. Finally, the treatment to slow down the progression of atherosclerosis and renal failure is common for both processes with the exception of specific therapies for primary renal diseases. This treatment is, in principle, useful for patients with CV and renal disease at any age, albeit in elderly patients more evidences on the value of some of the different components of the treatment are warranted.<sup>47</sup>

**Conflict of interest:** none declared.

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