

Influence of Chronic Kidney Disease Development and Renin-angiotensin System Inhibition on Cardiovascular Prognosis

J. Segura*, C. Campo and L.M. Ruilope

Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain

Abstract: Recently published guidelines recognize the relevance of the development of chronic kidney disease in the stratification of risk of the hypertensive patient. Adequate assessment of renal function, including estimation of glomerular filtration rate, is mandatory in order to ensure an adequate evaluation of global cardiovascular risk in the hypertensive patient. The presence of subtle elevations of serum creatinine concentrations is a potent predictor of a poor cardiovascular prognosis. Clustering of associated risk factors seems to justify the elevated cardiovascular risk observed in patients with essential hypertension and mild renal function derangement.

Chronic kidney disease is associated with a significant increase in cardiovascular risk attributable to the simultaneous existence of other risk factors related to the metabolic syndrome. The inhibition of the effects of angiotensin II is necessary to ensure the best degree of renal protection. It has demonstrated to improve the long-term renal outcome of patients with nephrosclerosis and to reduce the appearance of cardiovascular complications in high risk patients. The high prevalence of chronic kidney disease in the general and in the hypertensive populations forces the recognition of its relevance and the need for an integrative therapeutic approach to protect simultaneously renal and cardiovascular systems.

Key Words: Arterial hypertension, chronic kidney disease, antihypertensive therapy, angiotensin-converting enzyme inhibitors, cardiovascular risk.

INTRODUCTION

The relation between elevated blood pressure (BP) and end-stage renal disease (ESRD) is well established [1]. In fact, high levels of treated blood pressure are positively and significantly related to early decline in kidney function among hypertensive men [2], and hypertensive nephrosclerosis is recognised as a major cause of ESRD [3,4]. The prevalence of chronic kidney disease (CKD) in essential hypertension has been considered to be low (<2%) based on serum creatinine concentration as the index to estimate renal function [5,6]. However, other evidences indicate that renal prognosis is not so benign in hypertensive patients [4,7-9], and that CKD is more prevalent than previously expected in treated essential hypertension [10-12].

ASSESSMENT OF RENAL FUNCTION DURING LONG-TERM FOLLOW-UP IN HYPERTENSIVE PATIENTS

Evaluation of renal function in long-term treated hypertensive patients has two main difficulties: first, the slow rate of progression to ESRD of nephrosclerosis, requiring very long follow-ups to investigate the evolution of renal function [4]; second, the low discriminatory capacity of serum creatinine levels as an indicator of the renal filtration capacity and its changes with time [13,14]. The need to estimate the level of glomerular filtration rate (GFR) has

been recently emphasized by the K/DOQI Clinical Guidelines of the National Kidney Foundation [14], and a classification of the different stages of CKD depending on the level of estimated GFR is widely accepted (Table 1). In clinical practice, measurement of creatinine clearance with 24-hour urine collection is considered as an adequate estimate of GFR. This parameter can also be estimated from serum creatinine levels by using prediction equations (Cockcroft-Gault or Modification of Renal Disease [MDRD] equations) that take into account age, sex, race, and body weight [15,16], although it has been described that MDRD equation consistently underestimate GFR, whereas the Cockcroft-Gault equation overestimate measured GFR in people with normal renal function [17].

EVIDENCES OF RENAL FUNCTION IMPAIRMENT IN LONG-TERM TREATED HYPERTENSIVE PATIENTS

The Framingham Heart Study showed a relevant prevalence of mild renal insufficiency in the general population, based on serum creatinine values (8.7% in males and 8.0% in females) [11]. The prevalence of a mild decrease in renal function in the community could be even higher according to the values of estimated creatinine clearance seen in the Third National Health and Nutrition Examination (NHANES III) Survey [7,18]. The Heart Outcomes Prevention Evaluation (HOPE) study showed a prevalence of CKD of 10.4% according to serum creatinine values >1.4 mg/dl [19]. Recently, we have described that 7.6% of patients referred to our hypertension unit have a decreased renal function according to serum creatinine

*Address correspondence to this author at the Hypertension Unit, Hospital 12 de Octubre, Av. Córdoba s/n, 28041 Madrid, Spain; Tel: 34 91 3908198; Fax: 34 91 3908035; E-mail: juliansegura@mi.madridtel.es

Table 1. Stages of Chronic Kidney Disease (From Ref. 14).

Stage	Description	GFR* (ml/min/1.73m ²)
1	Kidney damage with normal or increased GFR	90
2	Kidney damage with mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	<15 or dialysis

*As estimated from serum creatinine measurements and calculation of estimated GFR from the abbreviated MDRD formula for adults with CKD.

levels, and one of every four patients has a decreased creatinine clearance [12].

Perneger *et al.* published an integrated analysis of data from several population studies showing a crude annual incidence of hypercreatininemia in hypertensive patients of 4.61 per 1000 subjects [9]. Adjusting for gender and race, annual rates of hypercreatininemia were 4.06, 1.84, 8.41 and 4.96 per 1000 subjects in white men, white women, African-American men and African-American women, respectively [9]. On average, these results suggest that one in 13 hypertensive patients' progresses to hypercreatininemia every year [9]. Nevertheless, this study assessed renal function according to serum creatinine level, a poor indicator of GFR [13,14]. Ronstand *et al.* showed a deterioration of renal function in a 15% of treated hypertensive patients also according serum creatinine levels [10]. Recently, we have described a similar percentage (14.6%), but according to a more sensitive parameter, the creatinine clearance [20]. Furthermore, in our study the mean follow-up was long enough (13.2±4.8 years) to ensure an enough big number of renal events: development of CKD, estimated as a creatinine clearance below 60 ml/min/1.73m², in hypertensive patients with baseline normal renal function is a non infrequent finding along follow-up: 14.6 per 100 patients included developed CKD during more than 13 years of mean follow-up [20]. This finding means an annual rate of 1.11 per 100 patients, and it represents more than two times the incidence of hypercreatininemia described by Perneger *et al.* in white men [9]. Cox regression analysis showed that baseline serum creatinine level is the strongest predictor of CKD development. Every increase of 0.1 mg/dl in serum creatinine level increases by six-times the risk of CKD. Furthermore, in patients with normal renal function (creatinine clearance >90 ml/min/1.73m²), the presence of mild increases of serum creatinine levels could have a high predictive capacity. This finding was true even through in normal range of serum creatinine levels (Fig. 1). Other independent predictors were the age and systolic blood pressure at the beginning of follow-up and serum total cholesterol level [20].

RENAL FUNCTION DERANGEMENT AND CARDIOVASCULAR RISK

In recent years a large body of information has come to confirm that as soon as renal function exhibits even minor derangements, cardiovascular risk starts a continuous rise till

the development of end-stage renal disease (ESRD)[21,22], independently of renal etiology [23].

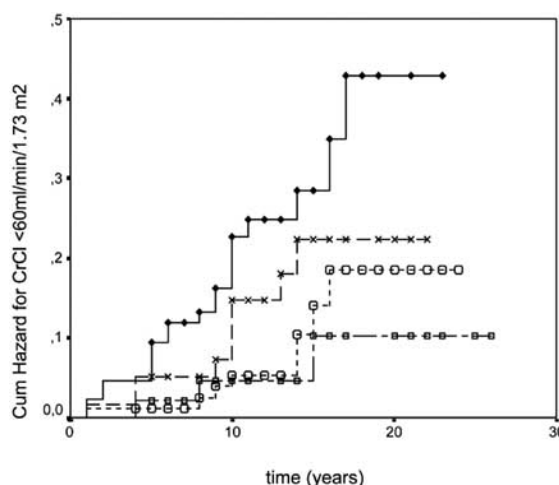


Fig. (1). Risk of chronic kidney disease development according baseline serum creatinine distribution (1st quartile [- -]: SCr<1 mg/dl for male, <0.7 mg/dl for female. 2nd quartile [-o-]: SCr 1.0-1.1 mg/dl for male, 0.7-0.9 mg/dl for female. 3rd quartile [-x-]: SCr 1.1-1.2 mg/dl for male, 0.9-1.0 mg/dl for female. 4th quartile [-●-]: SCr>1.2 mg/dl for male, >1.0 mg/dl for female).

The Hypertension Detection and Follow-up Program trial [24] showed for the first time that the presence of elevated serum creatinine values (> 1.7 mg/dl) at baseline was a very potent predictor for five- and eight-year all-cause mortality. Data from the Hypertension Optimal Treatment (HOT) [25] showed that serum creatinine levels above 1.5 mg/dl were accompanied by an adjusted relative risk of major CV events of 2.05 and for CV mortality of 3.24. The predictive capacity of serum creatinine have been confirmed by the data of the Intervention as a Goal in Hypertension Treatment (INSIGHT) [26], Systolic Hypertension in Europe (SYST-EUR) [27], Systolic Hypertension in China (SYST-CHINA) [28] and Systolic Hypertension in the Elderly Program (SHEP) [29] studies. In fact, the capacity of serum creatinine was comparable to that of other well established major CV risk factors like diabetes or a previous myocardial infarction in the HOT study [30]. Recent data from the ARIC (Atherosclerosis Risk on Communities) study has shown that

the level of GFR is an independent risk factor for atherosclerotic CV disease [31]. The HOORN study showed that mild to moderate loss of renal function is strongly associated with an increased risk of CV mortality [32].

Recently published Guidelines [33,34] have come to recognise the relevance of the finding of CKD which relies on the finding of slight elevations in serum creatinine, a diminished value of creatinine clearance (CrCl) and/or the presence of albuminuria. The Seventh Report of the Joint National Committee (JNC-7)[33] included microalbuminuria and a diminished estimated level of glomerular filtration rate (GFR) (< 60 ml/min) in the group of major cardiovascular (CV) risk factors. The European Society of Hypertension/European Society of Cardiology Guidelines [34] go even further and list slight elevations in serum creatinine and microalbuminuria among evidence of target organ damage, thus stratifying all hypertensive patients with minor renal derangements in the high-risk stratum. Unfortunately, no prospective therapeutic trials aimed at reducing the cardiovascular burden in people with CKD are available [23]. We have recently described that hypertensive patients who developed CKD presented a rate of cardiovascular events 2.5 times higher than those with preserved renal function [20]. Forty-one out of 281 (17.4%) patients presented a cardiovascular event (16 acute myocardial infarction, 9 angina, 8 congestive heart failure, 16 stroke) during follow-up: 17 (40.6%) patients who developed CKD and 32 (13.3%) patients with preserved renal function ($p < 0.001$) (Fig. 2A). Among patients receiving an ACE inhibitor ($n=128$), 16 (12.5%) presented a cardiovascular event, in comparison with 33 (21.6%) out of 153 patients receiving other antihypertensive drugs (log rank test $p < 0.05$) (Fig. 2B). After adjustment in a Cox multivariate analysis, age, development of CKD during follow-up and male gender were independent predictors of the appearance of cardiovascular events [20].

CHRONIC KIDNEY DISEASE AND OTHER CARDIOVASCULAR RISK FACTORS

The presence of CKD not only is accompanied by more primary CV events and death, but is also the most important factor in predicting adverse outcomes after virtually all cardiac events including acute coronary syndromes [35], as well as heart failure [36], coronary angiography patients [37], major surgery [38] or patients admitted in intensive care units [39].

Detection of a slightly diminished value of CrCl at baseline is accompanied by higher initial levels of BP, a predominantly male gender, higher initial levels of uric acid and triglycerides and lower levels of high-density lipoprotein cholesterol [40]. Mild degrees of renal failure have been shown to be associated to a series of risk factors or markers that are summarized in Table 2. It has also been shown to accelerate coronary artery calcification, above and beyond conventional risk factors [56]. A similar clustering of risk factors has been reported in microalbuminuric subjects, in particular those linked to insulin resistance [57]. Available data point to the association in hypertensives between CKD and the components of the metabolic syndrome. Very recent data from our Unit have shown that among young hypertensive patients with metabolic syndrome, the presence of minor abnormalities of renal function is mostly related to the presence of metabolic alterations of glucose, together with BP levels [58].

PREVENTION AND TREATMENT OF CHRONIC KIDNEY DISEASE

The prevalence of CKD in the US adult population is 11% (19.2 million) according to NHANES III data [7]. Persistent albuminuria with a preserved estimated GFR (> 60 ml/min, stages 1 and 2, see Table 1) was present in 11.2 million people while the remaining presented different

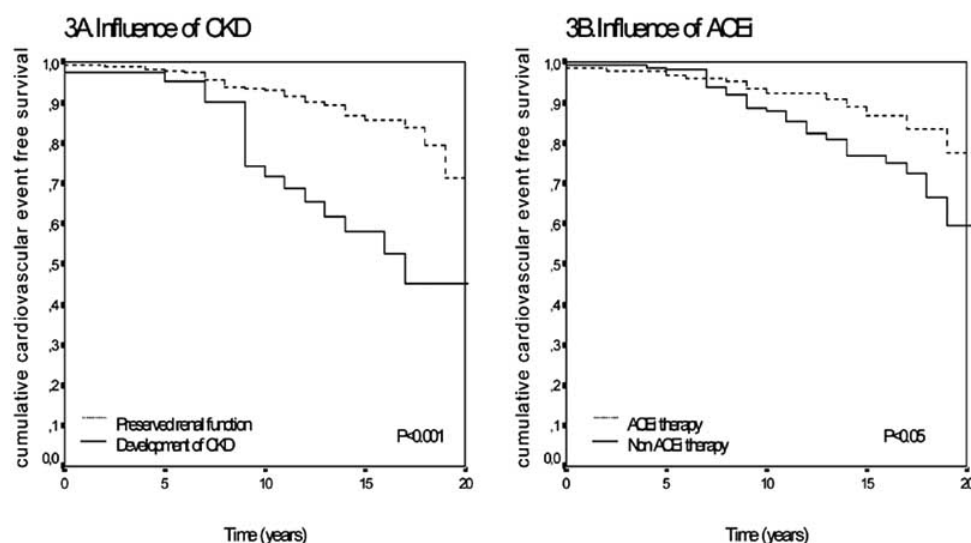


Fig. (2). A. Cardiovascular prognosis between patients developing chronic kidney disease (CKD) and those with preserved renal function. B. Cardiovascular prognosis between patients receiving angiotensin-converting enzyme inhibitors and those receiving other antihypertensive therapies.

Table 2. Cardiovascular Risk Factors or Markers Associated to a Mild Decrease in Estimated GFR.

-	Disturbed lipoprotein(a) concentrations [41]
-	Insulin resistance and impaired glucose tolerance [42-44]
-	Increased oxidative stress [45,46]
-	Increment in pulse wave velocity [47]
-	Increased serum uric acid levels [48]
-	Sympathetic overactivity [49]
-	Accumulation of ADMA* [50,51]
-	Inflammatory and procoagulant biomarkers (CRP**, fibrinogen, interleukin 6, factor VIIc, factor VIIIc, plasmin-antiplasmin complex, and D-dimer) - [52,53]
-	Obesity and body fat distribution [54,55]
-	Non-dipping pattern of ambulatory blood pressure [33]

*ADMA: Asymmetric dimethylarginine

**CRP: C-reactive protein

degree of chronic renal failure with or without albuminuria. These data justify the need for an adequate prevention and treatment of CKD. Furthermore, any activity in this sense must contemplate the simultaneous protection of the renal and the CV systems both in diabetic and in non-diabetic patients. Recently it has been proposed that screening of microalbuminuria in the general population could be a tool to detect subjects at risk for progressive renal failure based on the fact that glomerular hyperfiltration and microalbuminuria are early signs of a later development of progressive renal failure in diabetic and in non-diabetic [59]. The cost of albumin determination in the population probably makes this possibility unfeasible. However, estimation of GFR followed by albumin/creatinine ratio in those presenting hyperfiltration could be further more cost-effective for prevention of CKD.

A sustained elevation in BP can cause CKD and lower goal BP has to be achieved in patients with CKD [33,34]. However, data available indicate that very strict (<130/80) BP control does not ensure a better outcome of GFR when compared to BP control values in the high normal range albeit this control could offer a better CV protection [60-62]. An interesting paper by Fesler *et al.* [63] has demonstrated that the fall in GFR in hypertensive patients is particularly accelerated when the elevation in BP is accompanied by the concentric pattern of LVH. Concentric LVH is a strong marker of the severity of hypertension [64] and it could be an indicator that cardiovascular and renal damages are closely related.

Table 3 summarizes the therapeutic attitudes that must be considered in presence of CKD. They contemplate the simultaneous performance of cardiovascular and renal protection. Life-style changes, with particular relevance of diminishing salt intake, avoiding obesity, and refraining from smoking are very important. Strict blood pressure control (probable below 125/75 mmHg) is required, and the administration of a combination of drugs needed [33,34]. The inhibition of the effects of angiotensin II, through a

diminished synthesis of angiotensin II by means of an ACE inhibitor, or through the blockade of the AT1 receptor by means of an angiotensin II receptor blocker, is necessary to ensure the best degree of renal protection, as a consequence of the capacity of these two classes of drugs to facilitate systemic BP control and to reduce urinary albumin excretion [65]. The blockade of angiotensin II effects has demonstrated to improve the long-term renal outcome of patients with nephrosclerosis [60,66], and to reduce the appearance of cardiovascular complications in essential hypertensive patients [20], or patients with coronary artery disease [67]. Recently, the dual blockade of renin-angiotensin system combining an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker have demonstrated its efficacy in lowering blood pressure and proteinuria in CKD accompanied by proteinuria [68].

Table 3. Therapeutic Attitudes in Patients with Chronic Kidney Disease and Hypertension.

LIFE-STYLE CHANGES (Reduction of salt intake and body weight, aerobic exercise and avoid smoking)
STRICT BLOOD PRESSURE CONTROL (<125/75 mmHg). Combination therapy required in most cases Blockade of angiotensin II effects is required
CONTROL OF ASSOCIATED RISK FACTORS Lipids: Statins, fibrates Insulin resistance: Insulin sensitizers (metformin, glitazones?) Platelet aggregation: Aspirins, others?

According to the National Kidney Foundation task force recommendation, patients with CKD should be considered in the highest-risk group for CV events. The JNC-7 includes CKD as a "compelling" indication, justifying lower target

blood pressure and treatment with specific antihypertensive agents [33]. Similarly, the recently published "NKF-K/DOQI Clinical Practice Guidelines on Managing Dyslipidemia in Chronic Kidney Disease" recommend that all patients with CKD be included in the highest-risk group, justifying a lower target low-density lipoprotein cholesterol level [69]. The American Heart Association suggests that the routine evaluation of patients with CV disease or those at high CV risk should include measurement of spot urine albumin-to-creatinine ratio or total protein-to-creatinine ratio and estimation of GFR by serum creatinine and prediction equations [21].

In summary, CKD is associated with a significant increase in CV risk attributable to the simultaneous existence of other CV risk factors related to the metabolic syndrome. The high prevalence of CKD in the general and in the hypertensive populations forces the recognition of its relevance and the need for an integrative therapeutic approach to fully protect simultaneously renal and CV systems.

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