

Chronic Kidney Disease as a Situation of High Added Risk in Hypertensive Patients

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Recent guidelines for the management of hypertension have recognized the relevance of renal function on cardiovascular prognosis of hypertensive patients. In fact, growing evidences have confirmed that as soon as renal function exhibits minor derangements, cardiovascular risk starts a continuous rise until the development of end-stage renal disease. Both estimated glomerular filtration rate and urinary albumin excretion are associated with an increased incidence of cardiovascular events and death among hypertensive patients and in general population. Consequently, hypertensive patients presenting with chronic kidney disease are considered by guidelines as high-risk patients, and strict blood pressure control should be considered as a part of an integrative therapeutic approach, including correction of anemia, treatment of dyslipidemia, cessation of tobacco use, and antiplatelet therapy. This paper briefly reviews the most recent evidences about pharmacologic therapies in high-risk patients, focusing on benefits related to improvement of cardiovascular risk factors in hypertensive patients with chronic kidney disease.

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Recently, the Seventh Report of the Joint National Committee (JNC-7) has recognized microalbuminuria and an estimated GFR (eGFR) value <60 ml/min per 1.73 m² as two major cardiovascular risk factors (CVRF) (1). In the same line, the Guidelines of the European Society of Hypertension–European Society of Cardiology (ESH-ESC) (2) define the existence of a high added risk in hypertensive patients by the presence of a given level of BP accompanied or not by the presence of associated CVRF, target organ damage (TOD), diabetes, or associated clinical conditions (ACC). These guidelines consider slight increase in serum creatinine (1.3 to 1.5 mg/dl in men, 1.2 to 1.4 mg/dl in women) and microalbuminuria as TOD, and higher values of serum creatinine or the presence of proteinuria as ACC (2). The presence of very elevated BP levels is required in the absence of other CVRF to consider that a patient has a high added CV risk, whereas only high-normal BP levels or even lower values are required for the same recognition when the patient presents with three or more associated CVRF, TOD, diabetes, or ACC. According to this, hypertensive patients with a high-added level of CV risk can be found in any of the three stages of the CV and renal continuum (Figure 1). Since the publication of the guidelines, growing evidence has been added to confirm that as soon as renal function exhibits minor derangements, CV risk starts a continuous rise until the development of ESRD (3,4).

Chronic Kidney Disease in the General Population and in High-Risk Subgroups

The presence of chronic kidney disease (CKD) relies on the determination of serum creatinine, creatinine clearance, and/or urinary albumin excretion (UAE). The Framingham Heart Study showed a relevant prevalence of mild renal insufficiency in the general population, on the basis of serum creatinine values (8.7% in men and 8.0% in women) (5). 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 Survey (6,7). Among patients who were referred to our hypertension unit, 7.6% have a decreased renal function according to serum creatinine levels, and one of every four patients has a decreased creatinine clearance (8).

Recently, community-based longitudinal studies have demonstrated that CKD is an independent risk factor for the composite study outcome, including myocardial infarction, fatal coronary heart disease, stroke, and death (9). These results were confirmed recently in a Japanese population (10) and in a population with preexisting CV disease (11). In essential hypertensive patients with normal renal function (defined as eGFR >90 ml/min per 1.73 m²), those who developed CKD during 13 yr of follow-up presented a rate of CV events 2.5 times higher than those with preserved renal function (12).

Microalbuminuria is associated with an increased incidence of CV events and death, as well as with all-cause mortality. Initial evidence came from observations involving high-risk patients (13–15). The data from the HOPE study (16) came to confirm the predictive value of microalbuminuria that attained a predictive capacity similar to that of previous coronary artery disease and was equal for patients with and without accompanying diabetes. The relevance of UAE as a CVRF in hypertensive patients without diabetes (13,17–19) and in the general

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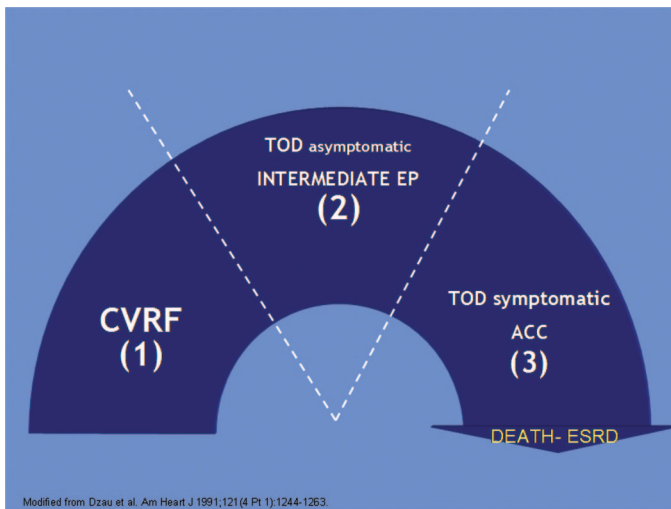


Figure 1. Progression of cardiovascular and renal disease. CVRF, cardiovascular risk factors; TOD, target organ damage; ACC, associated clinical conditions.

population (20,21) also has been demonstrated. Some of these studies (16,21) have described that the relationship between urinary albumin and CV risk is a continuum that starts below the cutoff point of 30 mg/d albumin (or 30 mg/g creatinine) that normally allows the classification of a given patient as having microalbuminuria. This fact has led to questioning whether the actual threshold to define a normal value of this parameter is adequate (22).

Definitely, both UAE and reduced GFR are associated with an increased CV risk. Nevertheless, the percentage of patients who present both disturbances is not well established. We have analyzed the prevalence of microalbuminuria and proteinuria according GFR values in a cohort of 1047 essential hypertensive patients who attended our hospital-located hypertension unit. As can be seen in Table 1, the prevalences of microalbuminuria and proteinuria increase significantly at eGFR values <60 ml/min per 1.73 m². Both microalbuminuria and proteinuria were significantly associated with lower values of eGFR, diabetes (42.4%), male gender (36.4%), age above 60 yr (33.2%), and the presence of TOD or ACC (39.6%). These findings contribute to explain the exponential increase in CV risk that was observed with progressive decay in renal function (23). Moreover, CKD could appear together with other TOD as left ventricular hypertrophy

Table 1. Prevalences of microalbuminuria and proteinuria according to estimated GFR values^a

Estimated GFR (ml/min per 1.73 m ²)	n (%)	Microalbuminuria (%)	Proteinuria (%)
>90	680 (65)	31.9	3.5
60 to 90	240 (23)	30.2	5.0
<60	127 (12)	37.6	10.2
Total	1047	31.3	4.7

^aGFR, glomerular filtration rate.

(LVH). In fact, the fall in GFR in hypertensive patients is particularly accelerated when the elevated BP is accompanied by the concentric pattern of LVH (24). Concentric LVH is a strong marker of the severity of hypertension (25), and it could be an indicator that CV and renal damages are closely related.

Pharmacologic Therapy in High-Risk Hypertensive Patients

Results from big trials in hypertensive patients show that controlling BP is the most important issue (26). However, there is general agreement in considering that patients with a high-added CV risk require antihypertensive therapy to lead BP to the expected goal of control, which is <130/80 mmHg in most cases. This BP goal must be attained in patients with ACC or any degree of renal damage and also in patients with diabetes (2). The presence of other forms of TOD and/or three or more associated CVRF require that BP levels be maintained at levels <140/90 mmHg.

All of the recently published trials in arterial hypertension have been reviewed in the Trialists Meta-analysis (27). Data contained in this meta-analysis refer most importantly to the comparison of active therapy and placebo and of lower and higher BP goal and to the comparison between different antihypertensive drug classes. All of these comparative data have been constructed by the comparison of the time elapsed until the development of one event or death in the required number of patients according to the initial sample size calculation. Practically, it can be considered that the great majority of the events and death considered in this meta-analysis took place in patients with high-added CV risk, for whom the greatest likelihood for CV morbidity and mortality was present. The main conclusion of this meta-analysis is that it is attainment of BP control and not the type of therapy used that matters when antihypertensive therapy is concerned. It is true that the class of the angiotensin receptor blocker showed positive differences when compared with other therapies, in particular diuretics and β blockers. However, data from the VALUE trial (28) were not included. This fact is relevant also for the analysis of the calcium channel blockers as will be the inclusion of the INVEST, MOSES, ACTION, and CAMELOT trials (29–32). Considering these new trials, recent analysis suggests that antihypertensive drug treatment improves outcome mainly through lowering of systolic BP (33).

Treatment of Patients with CKD

In addition to antihypertensive therapies, recent evidence seems to indicate that a statin must be included in the treatment of a relevant percentage of high-risk hypertensive patients, at least in patients with diabetes in any of the three stages and in all of those in stage 3 (34,35). Once BP control is attained, antiplatelet therapy with aspirin must be contemplated at least in patients at stage 3 (36). These added therapies could contribute to bias the effect of a given antihypertensive therapy (whether monotherapy or a combination). Statins have proved to be of great value in patients with an elevated global CV risk accompanied or not by elevated LDL cholesterol levels (37). Moreover, the overall clinical benefits that are observed with statin therapy seem to be greater than what might be expected

from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels. In fact, much evidence has shown the pleiotropic effects of statins in improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and vascular inflammation (38). Recent data from the Brisighella Heart Study demonstrated that the use of lipid-lowering measures could significantly improve BP control in patients with both hypercholesterolemia and hypertension, enhancing the reduction in BP in patients who are treated with statins (39).

Patients who present with CKD experience higher mortality and adverse CV event rates, which remains significant after adjustment for conventional CVRF (40). Moreover, CKD is common in patients with heart failure and coronary artery disease, and these patients have more advanced atherosclerosis (41,42). Nevertheless, there is a lack of appropriate risk factor modification and intervention, despite established awareness of their high CV risk and the evidence of better outcomes if they receive adequate therapy (40,41,43). In fact, pravastatin reduces CV event rates in people who have or are at risk for coronary disease and concomitant moderate CKD, many of whom have serum creatinine levels within the normal range (43). Indeed, there is controversial evidence about the effects of lipid-lowering therapy on rate of kidney loss in people with coronary heart disease. The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study showed that in untreated dyslipidemic patients with coronary heart disease and normal renal function at baseline, creatinine clearance declines over a period of 3 yr, but statin treatment prevents this decline and significantly improves renal function (44). By contrast, a recent study that included 18,569 patients who had or were at risk for coronary disease, 3402 of whom had moderate CKD, showed that pravastatin modestly reduced the rate of kidney function loss (45). Similarly, there is recent evidence about the efficacy and the safety of low-dose aspirin in patients with CKD (46), although this therapy is underused when CKD is associated with acute myocardial infarction (47,48).

In CKD, there is good evidence about the benefits related to BP control, correction of anemia, treatment of dyslipidemia, cessation of tobacco use, and antiplatelet therapy (49). The relevance of CKD in high-risk patients requires an integrative therapeutic approach to protect fully and simultaneously renal and CV systems (50,51).

Conclusion

CKD is a situation of high added CV risk in hypertensive patients. Strict BP control must be obtained in most cases by combination therapy that must include an ACE or an angiotensin receptor blocker. This must be accompanied by statin and aspirin (the later once BP control has been attained).

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