Management of Hypertension in Chronic Kidney Disease

Pasquale Zamboli, MD, Luca De Nicola, MD, Roberto Minutolo, MD, Valerio Bertino, MD, Fausta Catapano, MD, and Giuseppe Conte, MD

Corresponding author
Luca De Nicola, MD
Division of Nephrology, Med School-Second University of Naples at Incurabili Hospital, via Maria Longo 50, 80138 Napoli, Italy.
E-mail: luca.denicola@unina2.it

Current Hypertension Reports 2006, **8:**497–501
Current Science Inc. ISSN 1522-6417

Optimal blood pressure control (<130/80 mm Hg) in patients with chronic kidney disease (CKD), despite being the main objective of conservative therapy, is rarely achieved in clinical practice. A major area of improvement is the correction of the extracellular volume expansion. This goal can be reached by means of dietary salt restriction (≤100 mEq/d of NaCl). If this intervention fails, hypertension can be treated by thiazide diuretics in patients with mild CKD, whereas loop diuretics at adequate doses are indicated in patients with more advanced CKD. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are more effective than other drugs in slowing progression of proteinuric diabetic and nondiabetic CKD. However, the control rates of blood pressure are usually inadequate with antihypertensive therapy including only these drugs; therefore, addition of other classes of antihypertensive drugs is often required.

Introduction

The elevation of blood pressure (BP) is the most prevalent risk factor in chronic kidney disease (CKD) [1••]. Indeed, prevalence of hypertension increases linearly from 65% to 95% as the glomerular filtration rate (GFR) declines from 85 to 15 mL/min/1.73 m² [2]. Correction of hypertension has been identified as an important intervention because uncontrolled hypertension is a recognized determinant of worsening renal function [3–6], and it also likely represents a major risk factor for the extraordinarily high mortality observed in these patients [6,7••,8,9]. Both effects have been proven in the long term [10]. Accordingly, current guidelines now strongly suggest optimal BP control, ie, to less than 130/80 mm Hg, in CKD [11].

Unfortunately, the achievement of optimal BP values remains dramatically low in clinical practice despite the prevalent use of inhibitors of the renin-angiotensin system (RAS) [1••,12]. In this article, we discuss the main areas needing improvement in BP control in CKD, such as the correction of extracellular volume (ECV) expansion by sodium restriction and diuretics, the additive effect of converting-enzyme inhibitors (CEI) and angiotensin II receptor blockers (ARBs) in proteinuric nephropathies, and the number of other prescribed antihypertensive drugs.

Sodium Restriction

In CKD, impairment of renal function causes fluid retention starting at the early stages of the disease [13]. The resulting expansion of ECV, which corresponds to about 5% of body weight in the absence of peripheral edema, restores the external salt balance at the expense of an increase in total-body sodium and persistent hypertension [14,15]. Sodium retention is of primary importance in the pathogenesis of hypertension, even if the degree of ECV expansion is insufficient to induce edema, as usually occurs in the absence of heart failure. Sodium retention, which can be evaluated by urinary fractional excretion of sodium, increases exponentially as GFR declines and precludes an optimal control of BP, especially during pharmacological treatment with vasodilator agents [1••,6,15]. In patients with CKD, moderate reduction of salt intake allows a much greater BP decrease in comparison with hypertensive patients with normal GFR undergoing major restriction of salt intake [16–18]. The different response to salt reduction is probably caused by the basal ECV. Therefore, the sensitivity of BP to sodium restriction is greatly increased in patients with advanced CKD. Specifically, Koomans et al. [18] found that a mean decrease of sodium intake of about 6 g/d led to a decrease of mean BP of about 12 mm Hg [18]. Of note, the salt sensitivity of BP is not a feature limited to the advanced stages of renal disease; it begins in the early phases of nephropathy. In particular, we found that the isolated reduction in sodium intake from 13 to 3 g/d in hypertensive patients with a GFR of about 40 mL/min restored the fractional excretion of sodium to a normal value (<1%) in association with correction of BP value [17]. Further, we and others suggested that salt restric-

tion may contribute to the improvement in renal outcome in patients treated with low- and very low-protein diets [19–21]. The need to reduce salt intake in these patients is also supported by the observation that this intervention per se enhances the antihypertensive and antiproteinuric effects of CEI, non-dihydropyridine calcium channel blockers, and ARBs [22–24]. Despite the evidence collected on the beneficial effects of salt restriction in CKD, compliance with the dietary prescription is generally poor in patients followed up in the real world of clinical practice [1••,25]. In particular, more than 80% of prevalent CKD patients regularly followed up by nephrologists in Italian renal clinics show excessive salt intake (more than 100 mEq/d) coupled with a very poor control of BP [1••].

Therefore, BP response depends on the so-called salt sensitivity, particularly in CKD [26]; however, dietary salt restriction can be considered, to a large extent, the "Cinderella" of the management of CKD patients [14], as shown by the absence of determination of urinary excretion of sodium even in the main clinical trials on BP control in CKD patients published so far. As recently reported in more in detail by our group [6], it is necessary to implement several recommendations in clinical practice to improve compliance with a low-salt diet in patients with CKD. Specifically, it is important to instruct the patient on the correct way to collect 24-hour urine specimens, to monitor 24-hour urinary sodium excretion at each visit (target: ≤100 mEq/d, equal to ≤6 g NaCl/d), to gradually reduce added salt in the diet, to cook with spices rather than salt, to choose fresh food instead of transformed or processed food, to eat low-salt bread, and to look for the amount of sodium on food labels.

Diuretic Treatment

In the presence of poor adherence to salt restriction (urinary sodium excretion >100 mEq/d), natriuretic agents become the cornerstone of treatment of hypertension secondary to CKD [5,6,15]. Hypertensive CKD patients without peripheral edema generally respond to the combination of dietary sodium restriction and diuretic therapy.

In patients with mild renal impairment (GFR >40 mL/min), thiazide diuretics are indicated [27]. It is well known, in fact, that these agents restore the antiproteinuric effect of CEI in patients not compliant to a low-salt diet and are useful in preventing the development of cardiovascular events in older persons with systolic hypertension and mild renal insufficiency [6]. Of note, thiazide diuretics diminish BP levels also by mechanisms other than reduction of volemia [6].

Loop diuretics are indicated in CKD patients with a GFR of 40 mL/min or lower. As mentioned previously, subclinical (ie, nonedematous) volume expansion contributes to the elevation in BP in most forms of chronic renal disease. Thus, loop diuretics should be titrated upwards until BP is normalized (<130/80 mm Hg) or the patient reaches the "dry weight" that, in the presence of persistent hypertension, is defined as the weight at which further fluid losses will lead either to symptoms (orthostatic hypotension, cramps, fatigue) or to decreased tissue perfusion as evidenced by an otherwise unexplained elevation of azotemia and plasma creatinine concentration. In this regard, we have shown that in patients with moderate to advanced CKD (GFR from 40 to 10 mL/min), loop diuretics efficaciously and safely reduce BP levels if the dosage is gradually titrated upwards to obtain a loss of body weight of about 500 g/d in the induction phase [28]. In this clinical trial, correction of hypertension was shown in association with a mean decrease in body weight of about 2 to 3 kg during the induction phase, without side effects, by oral administration of furosemide at doses inversely proportional to GFR level (1.0, 2.5, and 4.0 mg/kg body weight per day in patients with GFRs of 40 to 31, 30 to 20, and 19 to 10 mL/min, respectively). Recently, clinical studies showed that torasemide, 40 mg/d, or furosemide, 80 mg /day, in patients with a mean GFR of 45 mL/min induces a similar antihypertensive effect, which is strictly correlated to natriuretic response and contraction of ECV [29]. Of note, after correction of sodium retention (induction phase), which is shown by the achievement of normal BP or dry weight during up-titration of loop diuretic, the physician must down-titrate the dose of loop diuretic so that the value of dry body weight can be steadily maintained (maintenance phase). Obviously, the maintenance dose of loop diuretic is lower than that of the induction phase. It is important to remember that the efficacious dose of furosemide is characterized by a large inter-individual variability secondary to the very different bioavailability [27]. Therefore, it is useful to begin with a low dose and gradually increase the dose to obtain the progressive reduction of body weight in the range of daily and cumulative values reported previously, up to the achievement of normal BP or dry weight. Conversely, in the maintenance phase, it is necessary to adequately down-titrate the dose of loop diuretic to detect the lowest dose capable of maintaining steady body weight and target BP. An intra-individual variability in the doses of loop diuretic also may become evident; the latter phenomenon depends on variability of salt intake in the same subject [27].

To improve the modalities of diuretic treatment, it is therefore critical for the CKD patient to measure body weight and BP daily and under the same conditions. The basic recommendations to correctly prescribe loop diuretics in these patients are listed in Table 1.

Disappointingly, nephrologists are reluctant to "adequately" use loop diuretics in their hypertensive CKD patients, probably because of the fear of side effects. A recent large study found that despite poor compliance with salt restriction, diuretics were prescribed in only a minority of patients and at a dosage definitely low in relation to the GFR value [1••]; specifically, a dose of furosemide ≤25 mg/d was prescribed in one-third of patients with a GFR <15 mL/min.

Table 1. Modalities to induce and maintain correction of extracellular volume expansion by loop diuretics in nonedematous hypertensive CKD patients

Instruct the patient to measure body weight and BP daily
Up-titrate oral dose of loop diuretic to reach BP <130/80 mm Hg or "dry weight"
Adjust the initial oral dose of furosemide according to basal GFR
25 mg for GFR 60–45 mL/min
50 mg for GFR 44–30 mL/min
75 mg for GFR 29–15 mL/min
100 mg for GFR <15 mL/min
Use a dose of loop diuretic capable of inducing a daily weight loss of about 0.5 kg
After achievement of normal BP or dry weight, down-titrate the dose of loop diuretic to steadily maintain the achieved decrease in body weight
Change the maintenance dose according to the level of dietary sodium intake

BP—blood pressure; CKD—chronic kidney disease; GFR—glomerular filtration rate

Table 2. Major side effects of loop diuretics and their prevention in CKD patients during the induction phase

Excessive decrease in body weight with signs of reduced tissue perfusion
Asthenia, fatigue, cramps
Orthostatic hypotension
Increase in serum creatinine and blood urea nitrogen >30% from baseline
Hyperuricemia
Hyponatremia (due to hypovolemia-induced release of antidiuretic hormone)
Hypokalemia and metabolic alkalosis (uncommon in CKD patients)
All of these side effects are generally prevented by daily measurement of BP and body weight and by assessment of renal function and electrolytes during the up-titration phase

BP—blood pressure; CKD—chronic kidney disease.

Conversely, if patients are carefully followed, adverse effects will be less frequent and dangerous than expected. Independent of the specific agent used, a major adverse effect can be avoided if renal function and serum electrolyte levels are periodically checked in the first weeks of treatment (Table 2). The eventual fluid and electrolyte complications are the consequence of uncontrolled administration of diuretic therapy during the first weeks and will be generally reversed by appropriate replacement therapy [27].

Inhibitors of the Renin-Angiotensin System

CEIs are more effective than other antihypertensive drugs in slowing the progression of proteinuric diabetic and nondiabetic CKD. This specific renoprotective effect significantly exceeds that associated with antihypertensive drugs not active on RAS and appears to be essentially caused by the antiproteinuric action of CEIs. Experimental studies, in fact, have demonstrated a decrease in intraglomerular pressure by predominant reduction of the efferent arteriole resistance and the improvement of glomerular permselectivity during CEI administration [30,31]. In humans, the antiproteinuric effect is more prominent when patients are kept on a low-sodium diet or are treated with diuretics because relative volume depletion results in enhanced angiotensin II dependence of the glomerular microcirculation. The combination of ECV depletion and CEI in proteinuric CKD is strongly recommended because interventions that lower both BP and proteinuria lead to better renal outcome [32].

In diabetic nephropathy, CEIs are highly effective in reducing protein excretion and progression from microalbuminuria to overt proteinuria as well as in slowing the rate of decline in GFR [33,34]. This benefit also holds true in patients who are not hypertensive.

The renoprotective effectiveness of ARBs has been clearly shown in type 2 diabetic nephropathy [35,36]. A growing body of evidence suggests that ARBs are also effective in nondiabetic proteinuric nephropathies [37,38••]. Interestingly, the ARB dose associated with maximal antiproteinuric effect may be greater than that required for maximal antihypertensive effect [37].

A distinct and critical issue is the role of CEI plus ARB combination therapy. Additive antiproteinuric effect and concomitant increased efficacy in terms of slowing CKD progression has been reported in proteinuric nondiabetic CKD patients affected by IgA nephropathy in most cases [38••]. Indeed, this approach may be considered in the majority of CKD patients because the desired reduction of proteinuria to less than 500 mg/d is infrequently achieved by administration of CEI alone [39]. A low rate of prescription of this combination therapy is, however, still apparent in clinical practice [1••].

It is important to emphasize that the benefits of RAS inhibitors hold true also in patients with advanced CKD, as demonstrated in the recent study by Hou et al. [40]. The safety of CEI therapy in this study depends at least in part on the preliminary exclusion of patients suffering adverse effects of CEIs (hyperkalemia, marked increase in serum creatinine concentration, cough) and on the extensive use of diuretics that may have accounted for the absence of hyperkalemic episodes. As previously recommended for diuretics, plasma creatinine and potassium concentrations should be measured in the first weeks of therapy. Additional measures to limit hyperkalemia include reduction of the dietary intake of potassium-containing foods,

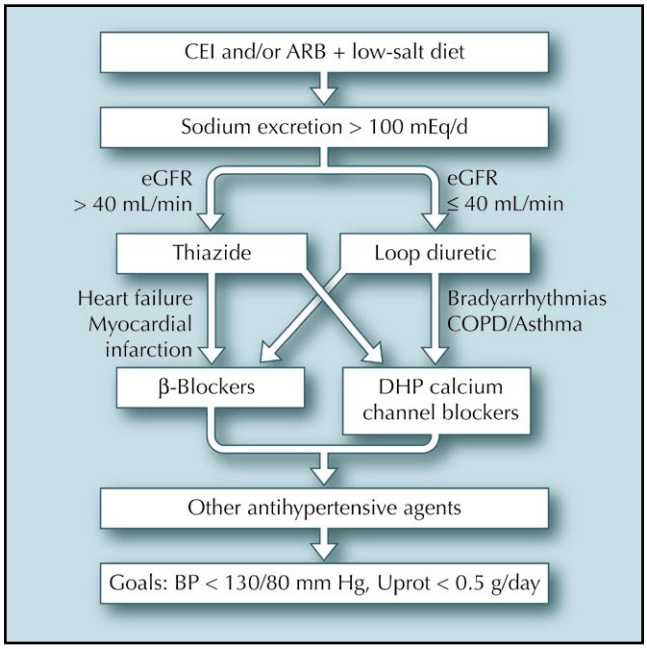

Figure 1. Suggested algorithm for treatment of hypertension in patients with chronic kidney disease. ARB—angiotensin II receptor blocker; BP—blood pressure; CEI—converting-enzyme inhibitor; COPD—chronic obstructive pulmonary disease; DHP—dihydropyridine; eGFR—estimated glomerular filtration rate; Uprot—24-hour proteinuria.

avoidance of nonsteroidal anti-inflammatory drugs, and, if necessary, prescription of potassium-binding resin. Withdrawal of CEI should be considered if hyperkalemia cannot be controlled despite the previous recommendations or the plasma creatinine concentration increases more than 30% from the basal value. Conversely, a significant decline of renal function is uncommon if the patient is not volume depleted and in the absence of renovascular disease.

At variance with proteinuric CKD, RAS inhibitors are not specifically indicated in patients with nonproteinuric renal disease; under these conditions, in fact, CEIs have not been found to be superior to standard therapy in slowing progression of the renal disease [41]. In patients with nonproteinuric nephropathy (ie, ischemic or hypertensive renal diseases), therapy should be primarily based on achievement of optimal BP control to ameliorate renal and cardiovascular prognosis.

Conclusions

Management of hypertension in CKD patients represents the main intervention for both renal and cardiovascular protection. Nevertheless, the achievement of BP goals remains dramatically low in clinical practice despite the prevalent use of RAS inhibitors.

Indeed, the management of hypertension in CKD patients appears extremely different when comparing recent observational studies, witnessing the real world of clinical practice, with the main randomized control trials carried out in the last several years. Most of the CKD patients regularly followed by nephrologists in Italian renal clinics show very poor control of BP coupled with excessive salt intake [1••]. In our recently published survey [1••], moreover, a loop diuretic was given to only a limited number of patients and, frequently, at a maintenance dose inappropriately low for the degree of renal function. Conversely, a low BP goal was achieved and maintained in the large randomized trial by Hou et al. [40], but it required use of diuretics in the 80% of patients with advanced CKD. Similarly, greater doses of furosemide (on average, 50 mg/d for GFR of 65 to 50 mL/min, 60 mg/d for GFR of 50 to 35 mL/min, and 70 mg/d for GFR of less than 35 mL/min) in combination with other agents allowed achievement of low BP levels in 60% of cases in the African American Study of Kidney Disease (AASK) [42].

In addition, in the main randomized trials, the number of antihypertensive drugs was on average greater than that reported in observational studies [1••,12]. Greater effort should be made, therefore, to increase the number of antihypertensive agents other than RAS inhibitors.

Overall, these findings identify the correction of volume expansion by salt restriction and adequate use of diuretics and the increased number of prescribed antihypertensive drugs as major areas of improvement in the conservative care of CKD from moderate to advanced stages (Fig. 1). Intensive treatment should also include maximal inhibition of RAS, by combination therapy with a CEI plus an ARB, to reach the therapeutic targets of both BP and proteinuria levels.

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