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Systemic hypertension and nondiabetic chronic kidney disease: the best evidence-based therapeutic approach today

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Abstract. – Despite the high prevalence and significant morbidity and mortality associated with high chronic kidney disease (CKD) in patients with hypertension, it remains vastly under-diagnosed and under-treated. Consequently, many patients develop kidney failure requiring dialysis or kidney transplant. Moreover, patients with CKD represent the group at highest risk from cardiovascular complications, even greater than patients with diabetes mellitus. Therefore, management of hypertension in such patients needs to be more aggressive compared to those with normal kidney function. This review provides guidelines for treatment of hypertension in patients with nondiabetic CKD based on updated evidence from clinical trials data. Following these recommendations is likely to minimize the risk of development of kidney failure and cardiovascular disease.

Key words:
Hypertension, Chronic kidney disease, Albuminuria, Proteinuria, ACE-inhibitors.

Introduction

Chronic Kidney Disease (CKD) is a worldwide public health problem. CKD prevalence was 11% among U.S. adults surveyed in 1988 to 1994[1]. A sharp increase in the incidence of advanced CKD is seen in Europe, the United States, and Australia over the past decade[2-4]. Emerging evidence from developing countries also indicates a high burden of CKD, which is only expected to rise rapidly as both the age of the population and the prevalence of hypertension and diabetes are projected to increase dramatically[5].

Most patients with CKD have hypertension[6]. Elevated blood pressure (BP) is an established risk factor for the development and progression of kidney failure[7,8]. Control of BP to evidence-based targets with appropriate antihypertensive agents has the potential of preventing some of the serious consequences of CKD[9,10]. This review will focus on the evidence for management of hypertension in patients with nondiabetic CKD.

Definition of CKD

CKD is defined as kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR).

The presence of significant reduction in GFR (<60 mL/min/1.73 m^2) for 3 months, with or without kidney damage or the presence of albuminuria (>30 mg/d) increases the risk of progressive CKD[11]. Generally, a serum creatinine of >1.5 mg/dl in men or >1.3 mg/dl in women approximates a GFR of <60 mL/min per 1.73 m^2. However, more precise prediction formulas have been developed to estimate GFR from serum creatinine concentration, age, sex, and body size, and are convenient for use in clinical practice[12,13].

Non-Diabetic Kidney Disease

The term "nondiabetic kidney disease" is not a diagnosis. It includes a variety of diseases that are often grouped together in epidemiologic studies and clinical trials, but differ widely in terms of patient's history, clinical

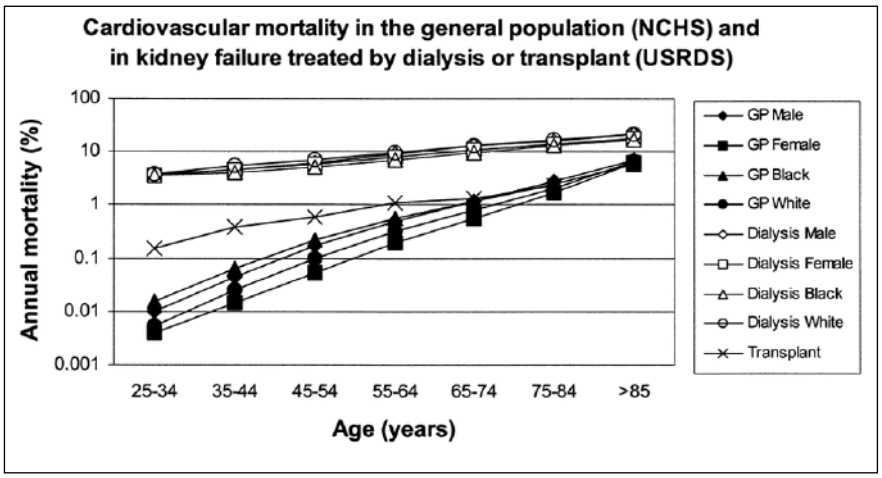

Figure 1. Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in general population (GP; National Center for Health Statistics [NCHS] multiple cause of mortality data files International Classification of Diseases, 9th Revision [ICD 9] codes 402, 404, 410 to 414, and 425 to 429, 1993) compared with kidney failure treated by dialysis or kidney transplant (United States Renal Data System [USRDS] special data request Health Care Financing Administration form 2746 Nos. 23, 26 to 29, and 31, 1994 to 1996). Data are stratified by age, race, and sex. CVD mortality is underestimated in kidney transplant recipients owing to incomplete ascertainment of cause of death. Reproduced and modified with permission from Foley et al. Clinical epidemiology of cardiovascular disease in chronic renal disease[68].

presentation, risk of progression, and response to treatment. These diseases include glomerular diseases, vascular diseases, tubulointerstitial diseases, and cystic kidney diseases, which accounted for about 18%, 20%, 7%, and 5% of all cases of kidney failure in the United States in 1999, respectively[14].

Complications of CKD

Kidney Failure. Patients with CKD may develop progressive kidney damage leading to kidney failure, which is defined as a GFR <15 ml/min/1.73 m^2, and is accompanied in most cases by signs and symptoms of uremia, or a need to start kidney replacement therapy (dialysis or transplantation)[11].

Cardiovascular Disease in CKD. Cardiovascular disease (CVD) is frequently associated with CKD[15]. CVD risk factors in patients with CKD are those altered by the "uremic" state (for example, hypertension, dyslipidemia, homocysteine) and those that are characteristic of the "uremic" state (for example, inflammation, malnutrition, anemia, oxidative stress, hyperparathyroidism, and increased calcium-phosphorus concentration product)[16]. Evidence suggests that individuals with CKD are more likely to die of CVD than to develop kidney failure[17,18]. In 1998, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD[19]. This report showed that there was a high prevalence of CVD in CKD and that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population[20] (Figure 1). The task force recommended that patients with CKD be considered in the "highest risk group" for subsequent CVD events and that treatment recommendations based on CVD risk stratification should take into account this high risk status of patients with CKD.

Both kidney failure and CVD in CKD are potentially preventable, which are the main goals of treatment of patients with CKD[18].

Pathophysiological Role of BP in CKD

Experimental studies have suggested that systemic hypertension can be transmitted to glomeruli and that glomerular hypertension

is harmful to the kidney[21]. The hypertrophic hyperplastic processes that follow any loss of nephrons and the increased protein ultrafiltration are important factors in progressive kidney damage[22]. Hypertension itself accelerates decline in kidney function, which is likely to be due to the associated increased glomerular capillary hypertension. The markedly lower BP threshold for kidney damage necessitates that BP be lowered into the normotensive range to prevent progressive kidney damage[23].

Atherosclerosis and arteriosclerosis are the two main subtypes of arterial vascular disease in patients with CKD[24,25]. Patients with CKD also have a high prevalence of cardiomyopathy[26]. The complications of arteriosclerosis result in pressure overload and lead to concentric left ventricular hypertrophy (increased wall-to-lumen ratio), which is compounded in the presence of systemic hypertension, fluid overload, and arteriovenous fistulae. These structural abnormalities may lead to diastolic and systolic dysfunction and may be detectable by echocardiography. Clinical presentations of cardiomyopathy include heart failure and ischemic heart disease, even in the absence of arterial vascular disease. Strict control of BP is important for minimizing this risk of CVD.

Importance of Detection of Albuminuria in Patients with Hypertension

Albuminuria is important in CKD for a number of reasons. In particular, monitoring albuminuria over time has been recommended to assess progression or remission of kidney damage. In most causes of CKD, an increase in the level of albuminuria over time is associated with a higher risk of progression of kidney disease.

The normal rate of albumin excretion is less than 20 mg/day. Persistent values between 30 and 300 mg/day are called microalbuminuria. Values above 300 mg/day are considered to represent clinical proteinuria (macroalbuminuria) as urine for dipstick gives a positive test for protein at such levels[27,28]. Urine albumin can be excreted transiently in certain conditions including fever, exercise, heart failure and poor glycemic control. Hence urine albumin should be remeasured for diagnosis of persistent albuminuria, which indicates pathology in the kidney.

Protein in the urine, especially when elevated, represents mainly albuminuria and signifies glomerular involvement. However, there are other types of proteins in the urine including low molecular weight proteins, which are typically indicative of tubular damage. The prognostic and therapeutic significance of this type of proteinuria is not known. Further, measurement of protein in the urine is rather insensitive, and does not give positive results until albumin is raised significantly (>300 mg/d). Therefore, specific measurement of urine albumin is preferred over that of total urine protein

Persistent albuminuria is an early, sensitive, and important prognostic factor for faster progression of kidney disease and an increased risk of CVD[29,30]. Further, as discussed below, presence of albuminuria also dictates several therapeutic targets and choices of antihypertensive agents.

Measurement of urine albumin. Measurement of the excretion of albumin in a timed urine sample is the gold standard for the quantitative assessment of proteinuria. However, 24 hour collection of urine is cumbersome for routine clinical practice. The most frequently used screening method for albuminuria is the urinary dipstick in an untimed "spot" urine specimen. Because it is the concentration of urine albumin that is measured with dipstick, false-negative results may occur with very dilute urine. Nevertheless, urine dipstick for albumin or even protein could be valuable in certain settings where cost and difficult access to central laboratory facility are of major concerns. An alternative method for the detection and monitoring of albuminuria is measurement of the ratio of albumin or protein to creatinine in a spot urine specimen. This method corrects for variations in urinary albumin levels that are due to hydration, is more convenient than timed urine collections, and provides a reasonably accurate estimate of the rate of excretion of albumin[31-33]. The ratio provides a standardized estimate of daily excretion of albumin in grams/body surface area of 1.73 m^2.

Lowering of BP in Non-Diabetic CKD – Choice of Treatment

Angiotensin-Converting-Enzyme (ACE) Inhibitors

Efficacy in Slowing Progression of CKD. Much experimental and clinical evidence has been published that suggests the renin-angiotensin-aldosterone system (RAAS) has an important role in progression of non-diabetic disease[34-36]. Apart from its beneficial antihypertensive effect, RAAS blockade normalizes glomerular capillary pressure as a result of attenuation of the angiotensin II vasoconstrictive effect on glomerular efferent arterioles and inhibition of cellular proliferation. In addition, RAAS inhibition is speculated to restore endothelial activity, inhibit platelet reactivity, and act as an antioxidant. These properties potentially contribute to a decrease in albuminuria, slowing progression of CKD, and prevention of CVD[37].

A number of clinical trials have compared the efficacy of ACE-inhibitors with other classes of antihypertensive agents in slowing the progression of nondiabetic CKD. The ACE Inhibition in Progressive Renal Disease (AIPRD) Study Group conducted a pooled analysis of data from 11 randomized trials, including two large studies – the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study[36] and the Ramipril Efficacy in Nephropathy (REIN) Study[38,39]. Its results demonstrated that compared to other antihypertensive agents, ACE-inhibitors were superior in decreasing urinary albumin excretion, and slowing the progression of kidney disease. Further, these effects of ACE-inhibitors appeared to be mediated by factors beyond their effects on BP[39]. Moreover, the beneficial effect of ACE-inhibitors was greater in patients with higher rates of urine albumin excretion but appeared to extend to patients without albuminuria. The findings of African American Study of Kidney Disease and Hypertension (AASK) also corroborated that ACE-inhibitors were more efficacious than other antihypertensive agents in slowing progression of CKD in hypertensive nephrosclerosis, which is typically not associated with albuminuria[40].

These findings provide strong evidence for use of ACE-inhibitors as antihypertensive agents of first choice for slowing progression of CKD, especially in patients with clinical albuminuria.

Efficacy in Preventing CVD. Results of data on the benefit of ACE-inhibitors over other antihypertensive agents on prevention of CVD have been conflicting. The Heart Outcomes Prevention Evaluation (HOPE) study showed that ACE-inhibitors were more beneficial on cardiovascular outcomes in patients at high risk for CVD. However, a substudy of HOPE showed that ambulatory BP levels were lower in patients receiving ACE-inhibitors[41]. Thus, it is somewhat unclear whether the observed benefit of ACE-inhibitors in this study was due to a greater reduction in BP or due to ACE-inhibition per se.

The Second Australian National BP (ANBP), a trial on 6805 hypertensive elderly subjects aged 60 to 85 years, showed a clear benefit of ACE-inhibitors over diuretics on cardiovascular outcomes[42]. The Prevention of Renal and Vascular Endstage Disease (PREVEND) study also showed a trend towards superiority of ACE-inhibitors on cardiovascular morbidity and mortality in 864 albuminuric patients, and this benefit was greater in patients with higher levels of albuminuria.

However, results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that risk of CVD was not improved in hypertensive patients receiving ACE-inhibitors or calcium channel blockers or beta blockers compared to those on thiazide-type diuretic (chlorthalidone)[43-45]. Moreover, the recently reported Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study also failed to show benefit of ACE-inhibitors in predominantly nondiabetic patients at low risk of CVD[46].

While these data cannot support recommendation for use of ACE-inhibitors in all patients with hypertension, their use as first line antihypertensive agents in patients with albuminuria may be justifiable for efficacy in BP control as well as potential benefit on CVD outcomes.

Angiotensin Receptor Blockers (ARBs)

Efficacy in Slowing Progression of CKD. ARBs are generally considered the appropriate alternative medication for patients who have an indication for ACE-inhibitor therapy but are intolerant to the latter. However, un-

like ACE-inhibitors, there is little evidence to support the use of ARBs in nondiabetic CKD. Therefore, the benefits of ARBs must often be extrapolated from studies of ACE-inhibitors[14], or from studies of ARBs in patients with diabetic CKD[47,48].

Efficacy in Preventing CVD. Results of data on benefit of ARBs versus other antihypertensive agents on prevention of CVD have been conflicting. Findings of the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study showed that losartan prevented more cardiovascular morbidity and death than atenolol for a similar reduction in BP in patients with hypertension and left ventricular hypertrophy[47]. However, subsequently reported Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial reported no significant difference in benefit between valsartan versus amlodipine in patients with hypertension, BP albeit levels were lower in patients receiving amlodipine[49]. Thus, the evidence for incremental benefit of ARBs over good BP control in prevention of CVD has not been established.

Combination of ACE-inhibitors and ARBs

Efficacy in Slowing Progression of CKD. Findings from recent studies suggest that monotherapy with ACE-inhibitors may be insufficient for complete inhibition of the RAAS, which would prevent progression of non-diabetic CKD. A small crossover study on 33 patients comparing ACE-inhibitors and ARBs as monotherapy reported that 18% of patients responded to ACE-inhibitors but not to ARBs, and 15% of patients responded to ARBs but not to ACE-inhibitors[50]. This finding may highlight the different mechanisms of action between the two classes of medications, and thus the potential for combination therapy[51].

Results of the COOPERATE study in which 263 patients with albuminuric nondiabetic kidney disease were randomly assigned ARB (losartan, 100 mg daily), ACE-inhibitor (trandolapril, 3 mg daily), or a combination of both drugs at equivalent doses, showed that the combination treatment safely retards progression of non-diabetic CKD compared with monotherapy[52]. Thus, patients with albuminuric nephropathies may benefit from combination therapy with an ACE-inhibitor and an ARB. However, this needs more study.

Efficacy in Preventing CVD. The effect of ARBs on cardiovascular outcomes was assessed in a large meta-analysis that evaluated 12,469 patients from 17 randomized, double-blind, placebo-controlled trials[53]. There was no significant reduction in mortality among patients treated with an ARB or an ARB plus an ACE-inhibitor. Patients treated with the combination, however, had a lower risk of hospitalization for heart failure compared with patients treated with an ACE-inhibitor alone. Thus, at present, strong evidence in favor of combination treatment for prevention of CVD is lacking.

Other Antihypertensive Agents

While blockers of renin-angiotensin system have been shown to be particularly beneficial in the presence of albuminuria, the choice of antihypertensive agent is generally felt to be less important than the achievement of optimal BP control, and patients often ultimately require 3 or more agents[54]. Thus, in addition to ACE-inhibitors and ARBs, thiazide diuretics, beta blockers, and calcium channel blockers are effective antihypertensive agents and should be used without reservations in patients with CKD. Alpha blockers are the only class of antihypertensive agents which are not recommended for use in monotherapy[40,45]. However, they are useful as add-on therapy.

Lowering of BP in Non-Diabetic CKD – Target BP

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP recommends a target BP of less than 130/80 mm Hg in patients who have CKD[55]. However, this simplistic approach may be less than optimal in patients with albuminuria. Results of clinical trials suggest that the even lower levels of BP achieved during antihypertensive therapy may provide greater benefit in patients with high levels of urine albumin excretion[56]. The same for prevention of CVD in patients with CKD has not been well studied.

Slowing Progression of CKD. In the Modification of Diet in Renal Disease (MDRD) Study 840 patients with predominantly nondiabetic CKD were randomly as-

signed to a usual blood pressure goal (target mean arterial pressure, ≤107 mm Hg) for patients or a strict blood pressure goal (target mean arterial pressure, ≤92 mm Hg). The strict blood pressure goal had a greater beneficial effect in persons with higher baseline proteinuria (>1 g/d). However, in patients with low levels of proteinuria (<0.5 to 1 g/d) enrolled in the MDRD as well as AASK no significant beneficial effect of strict blood-pressure versus usual control was observed[10,40,57].

More recently, findings of the AIPRD Study metaanalysis on 1860 patients during 22,610 patient visits showed that the benefit conferred by the level of BP achieved by antihypertensive therapy is determined by the level of achieved urine albumin excretion (Figure 2)[56]. This study showed that the lowest risk for kidney disease progression appeared to be at levels of achieved systolic BP of 110-129 mm Hg. However, the relationship of the level of achieved systolic BP with the risk of kidney disease progression varied with the level of urine albumin excretion achieved during antihypertensive therapy. At levels of urine albumin excretion greater than 1.0 g/d, there was a steep rise in risk of kidney disease progression at levels of achieved systolic BP greater than 120-130 mm Hg. However, at levels of urine albumin less than 1.0 g/d; there was little relationship between risk of kidney disease progression and levels of systolic BP from 110-159 mm Hg. At both levels of urine albumin, achieved systolic BP <110 mm Hg was associated with a higher risk of kidney disease progression. The findings were similar in patients receiving antihypertensive regimens with or without ACE-inhibitors.

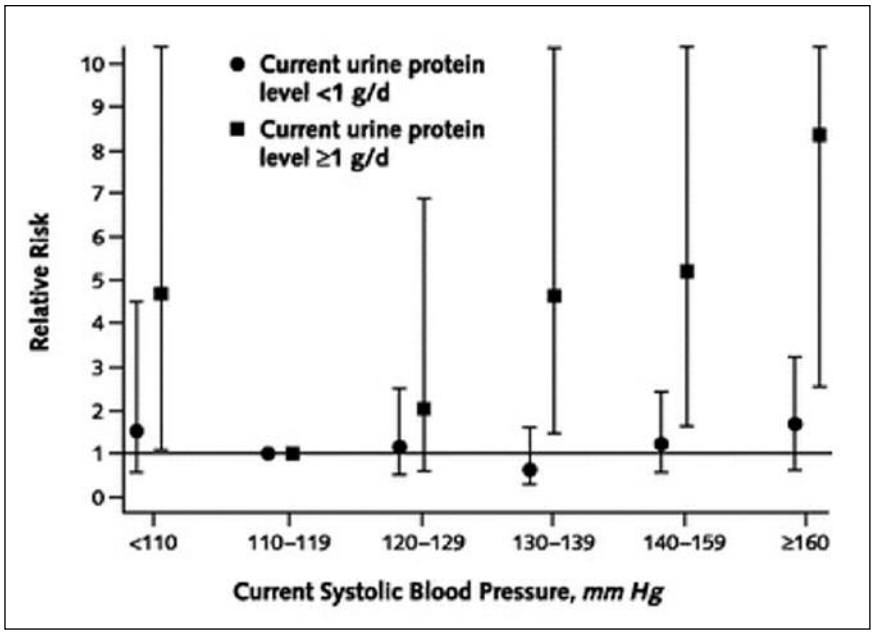

Figure 2. Relative risk for kidney disease progression based on current level of systolic BP and current urine protein excretion. The relative risk for patients with a current urine protein excretion of 1.0 g/d or greater represents 9336 patients (223 events), and the relative risk for patients with a current urine protein excretion less than 1.0 g/d represents 13 274 visits (88 events). The reference group for each is defined at a systolic BP of 110 to 119 mm Hg. Confidence intervals are truncated, as shown. Results are from a single multivariable model including two levels for urine protein excretion, six levels for systolic BP, and the interaction of current systolic BP and current urine protein excretion. Covariates include assignment to angiotensin-converting enzyme inhibitor versus control group, sex, age, baseline systolic BP, baseline diastolic BP, baseline urine protein excretion, baseline serum creatinine concentration (<2.0 or ≥2.0 mg/dL [<177 or ≥177 μmol/L]), interaction of baseline serum creatinine and baseline urine protein excretion, interaction of baseline serum creatinine and current urine protein excretion, and study terms. Reproduced with Permission From: Jafar T: Ann Intern Med, Volume 139(4); August 19, 2003, pp 244-252.

Thus, these data support the recommendation of lowering systolic BP to about 110-129 mm Hg in patients with urine albumin excretion of 1 g/d or greater. Reduction of systolic BP to levels less than 110 mm Hg should be avoided.

Prevention of CVD. The optimal level of BP for prevention of CVD in patients with nondiabetic CKD, and its relation to levels of albuminuria have not been well studied. To date, only a few studies have been primarily designed to study the same in patients with essential hypertension. In the Hypertension Optimal Treatment (HOT) study in 18,790 hypertensive individuals, the lowest incidence of major cardiovascular events occurred at a mean achieved diastolic BP of 82.6 mm Hg, and the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg[54]. However, advanced CKD was an exclusion criterion in this study. Moreover, systolic rather than diastolic BP may be a better predictor of CVD outcomes in patients with CKD[56]. Thus, future studies are needed to assess that impact of various target levels of systolic BP in patients with non CKD.

Lowering of BP in Non-Diabetic CKD – Titrating therapy to Level of Urine Albumin

The role of albuminuria in prognosis of CKD and CVD, and modification of this risk by the reduction of albuminuria in CKD has only come to light recently.

Slowing Progression of CKD. Results of the MDRD, REIN and AIPRI studies suggested that progression of CKD was significantly faster in patients with higher levels of albuminuria at baseline than those with lower levels[36,38,57]. Findings of the AIPRD Study confirmed that albuminuria is independently associated with more rapid progression of CKD[39]. In addition, reduction in albuminuria during antihypertensive therapy was associated with an incremental benefit over that conferred by reduction in the level of BP. Furthermore, therapy with ACE-inhibitors led to a greater reduction in albuminuria as compared to other antihypertensive agents[30,39]. Subsequent analysis of the same dataset also revealed that urine albumin excretion of less than 1-2 g/d achieved during follow-up was associated with the lowest risk for progression of nondiabetic CKD. However, further benefit was not observed at even lower values[56]. It is possible that this lack additional benefit was because of the small number of events in patients with low levels of albuminuria in these trials.

Prevention of CVD. A graded risk for subsequent cardiovascular morbidity and mortality in hypertensive patients has been observed in patients with hypertension and left ventricular hypertrophy[47]. More recently, even very low levels of albuminuria have been shown to be independent determinant of coronary artery disease and death[58]. There is evidence that this risk may be modifiable. Data from Reduction in Endpoints in type 2 diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL), a double-blind, randomized trial in 1513 type 2 diabetic patients with nephropathy showed that patients with high baseline albuminuria ($\geq$3 g/d) had a 1.92-fold (95% CI, 1.54 to 2.38) increase in risk for cardiovascular end points compared with patients with low albuminuria (<1.5 g/d). Reducing albuminuria in the first 6 months appears to afford cardiovascular protection in these patients[59]. Based on this, the investigators recommend that the lowest achievable level of albuminuria should be viewed as a goal for future renoprotective treatments[59]. Data from the LIFE study suggest the same may apply to patients without diabetes as well[60]. However, target levels of urine albumin excretion were not assessed in these studies[61].

It must be emphasized that the current evidence of benefit of lowering urine albumin excretion on progression of CKD as well as prevention of CVD, although compelling, is based on post hoc analyses. Prospective randomized studies are needed with pre-specified targets of urine albumin excretion to conclusively demonstrate a beneficial effect of lowering of urine albumin excretion on CKD and CVD outcomes. Nonetheless, based on evidence presented above, it appears prudent to aim to reduce urine albumin excretion levels to at least less than 1 g/d.

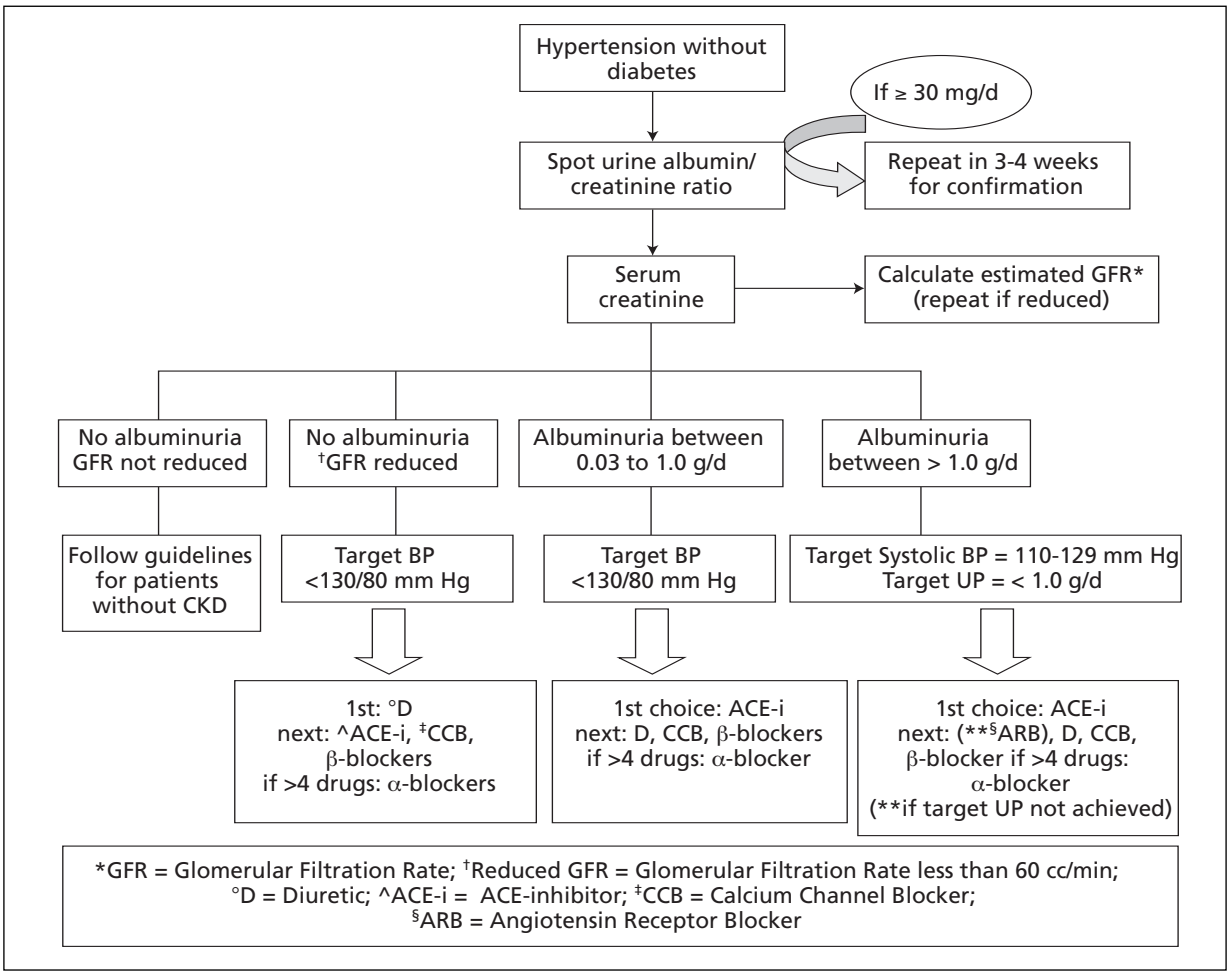

Figure 3. Treatment Algorithm for Patient with Hypertension and Chronic Kidney Disease (CKD).

Conclusions and Recommendations

Evaluation of patients with hypertension must include assessment of other CVD risk factors for risk stratification, and end organ damage[55]. An essential component of this evaluation is screening for CKD, even in patients without diabetes. In such patients, physicians should measure a spot urinary albumin-creatinine ratio, and estimate GFR from serum creatinine using the GFR prediction equation (Table I)[13]. In those patients where the initial assessments are abnormal, measurements should be repeated for confirmation in 3-4 weeks. This information is of prognostic value, as well as for making therapeutic decisions.

In nondiabetic patients with reduced GFR (<60 cc/min/1.73 m^2) without albuminuria, the target BP should be <130/80 mm Hg. Diuretics should be the preferred antihypertensive agent of choice. A second or third antihypertensive agent may be required to control BP. Other antihypertensive agents may also be used, as needed.

In nondiabetic patients with or without reduced GFR and (micro- or macro-) albuminuria of less than 1 g/d, the target BP should be <130/80 mm Hg. ACE-inhibitors should be the preferred antihypertensive agent of choice. In case of ACE-inhibitor induced cough, ARBs would be good substitute. A second or third antihypertensive agent may be required to control BP. Diuretics would be an effective and affordable second choice. Other antihypertensive agents may also be used, as needed.

In nondiabetic patients with or without reduced GFR and albuminuria of over 1 g/d, a target systolic BP of around 120 mm Hg

Table I. Equations to Predict GFR Based on Serum Creatinine.

Cockcroft Gault GFR equation = (140-age in yeas) × (weight in kgs)/serum creatinine × 72 × (0.85 if female)[12].
Abbreviated MDRD GFR equation = 186 × (serum creatinine)–1.154 × (age)–0.203 × (0.742 if female)[13].

MDRD indicates Modification of Diet in Renal Disease; and serum creatinine is measured in mg/dl.

should be aimed. However, reduction below 110 mm Hg should be avoided. In addition, reduction in urine albumin excretion levels to less than 1 to 2 g/d (that is, a spot urinary albumin-creatinine ratio ≤1) is recommended. Levels of systolic and not diastolic BP should be targeted. ACE-inhibitors should be used as antihypertensive agents of first choice. A second or third antihypertensive agent may be required to control BP. Diuretics would be an effective and affordable second choice. Other antihypertensive agents may also be used, as needed. Some patients have only a partial reduction in albuminuria when they are treated with an ACE-inhibitor, combining an angiotensin-receptor blocker with an ACE-inhibitor, even when systolic BP is controlled to less than 130 mm Hg.

BP, serum creatinine, and serum potassium should be measured within one to two weeks after the initiation of therapy with ACE-inhibitors or ARBs. A mild reduction in the glomerular filtration rate (usually less than 10 ml per minute per 1.73 m^2) and an increase in the serum potassium level should be expected (usually less than 0.5 mmol per liter). The development of hypotension, acute kidney failure, or severe hyperkalemia (defined by a serum potassium level of more than 5.5 mmol per liter) after treatment with an ACE-inhibitor/ARBs is initiated should prompt discontinuation of the drug.

It is important to emphasize that in most patients, achieving maximal kidney and cardiovascular protection requires a multidrug regimen, usually including several antihypertensive agents. Further, antihypertensive therapy should be coordinated with other therapies for CKD as part of a multi-intervention strategy. Lifestyle modifications recommended for CVD risk reduction should be recommended as part of the treatment regimen. Dietary sodium intake of less than 2.4 g/d (less than 100 mmol/d), achieving and maintaining ideal body weight, regular exercise, DASH-eating plan, and moderate alcohol consumption should be recommended in most adults with CKD and hypertension. Dyslipidemia should be treated with diet and a statin, and smoking cessation should be recommended[62-64]. These interventions may slow the progression of kidney disease as well as reduce the risk of CVD. Finally, timely referral to a nephrologist is especially important for improved outcomes in patients who do progress to kidney failure[65-67]. It is recommended that in patients with reduced GFR or clinical albuminuria, a nephrologist should be consulted at least once with respect to detailed evaluation of CKD and planning the strategy to be followed.

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