Therapeutic Approaches to Hypertension in Kidney Disease

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Abstract

Chronic kidney disease (CKD) and hypertension commonly coexist. In patients with CKD the goals of antihypertensive therapy are to lower blood pressure, reduce the risk of cardiovascular disease (CVD), and slow the progression of kidney disease.

For patients with CKD and/or diabetes all major international guidelines have recommended a blood pressure goal <140/80 mmHg. In CKD patients with albuminuria, a blood pressure target of less than 130/80 mmHg may be appropriate. However, The Systolic Blood Pressure Intervention Trial (SPRINT) supported the further reduction of the systolic blood pressure to 120 mm Hg. It should be mentioned that a blood pressure level above 140/90 mm Hg in CKD patients requires after lifestyle modifications(<130/80 mmHg), multiple antihypertensive medications. The purpose of this paper is to discuss the existed therapeutic approaches for the management of hypertension in patients with renal disease for reducing the risk of CVD and slowing the progression of kidney damage.

Agents that block the renin-angiotensin-aldosterone system (RAAS) should be the drugs of first choice. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) consistently reduce proteinuria and slow the decline in kidney function. A calcium channel blocker (CCB) should be considered as an add-on therapy to the RAAS blocker. Additionally, non-dihydropyridine CCBs beyond their blood pressure-lowering effects can also reduce proteinuria.

Diuretics represent the cornerstone in the management of CKD patients. However, thiazide and thiazide-like diuretics become less effective when GFR falls below 30 mL/min/1.73 m^2 compared to a loop diuretic. In patients with CKD and proteinuria, aldosterone receptor antagonists, spironolactone or eplerenone in low doses can also be used. Beta-blockers should be used preferably in patients with a recent myocardial infarction or coronary artery disease. Central alpha-adrenergic agonists, alpha-adrenergic blockers as well as vasodilators should be considered when blood pressure levels are still above the target.

Keywords: Chronic kidney disease; Hypertension; Antihypertensive therapy; ACE-inhibitors; ARBs; Proteinuria

Introduction

Over the past three decades chronic kidney disease (CKD) has been recognized as a worldwide epidemic. Indeed, individuals with kidney failure treated by dialysis and transplantation continue to increase. The annual incidence of CKD in people older than 65 years in the USA is more than 1200 per million [1].

It is suggested that by the year 2030, the CKD patients with end-stage renal disease (ESRD) requiring treatment will be more than 2.2 million individuals [2].

In approximately 80-85 percent of patients with CKD hypertension coexists. For example, in the Third National Health and Nutrition Examination Survey (NHANES III), among the 3% of the population that had elevated serum creatinine levels, 70% also had hypertension [3]. This is also exemplified by data from the Multiple Risk Factor Intervention Trial (MRFIT) where the level of blood pressure predicted the development of ESRD in more than 330,000 middle-aged men over a 16 year period [4].

Hypertension substantially increases the risk of microvascular and macrovascular complications in patients with or without diabetes. In diabetic patients hyperglycemia-induced metabolic and hemodynamic pathways which have been recognized to be mediators of kidney disease [5] of course, CKD is characterized by increased levels of oxidative stress and inflammation resulting in further damage of renal tissue [6]. On the top of this, uncontrolled systemic hypertension induces a kidney injury that causes loss of single nephron units and results in hypertension in the remaining glomeruli. Glomerular hypertension can lead to injury to the glomerular basement membrane causing a leak of plasma proteins into the urine [5,7].

The goals of antihypertensive therapy in patients with CKD are to lower blood pressure, reduce the risk of CVD and slow the progression of kidney disease. During the past few years, a blood pressure goal <140/80 mm Hg for patients with CKD and/or diabetes have been recommended by all major international guidelines including those from the Eighth Report of the Joint National Committee (JNC-8), the European Society of Hypertension-European Society of Cardiology committee, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Working Group on CKD and Diabetes and the American Diabetes Association (ADA) [8-11].

Some evidence exist that CKD patients with 1 g or more of albuminuria require a blood pressure target of less than 130/80 mmHg [8]. The resent ADA recommendations suggest that in diabetic individuals at high risk of cardiovascular disease a lower systolic and diastolic blood pressure target (<130/80 mmHg), may be appropriate, if it can be achieved without undue treatment encumbrance [11].

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) supported the reduction of the systolic blood pressure to 120 mm Hg. The

trial was designed to test the benefits of a systolic blood pressure target below 120 mmHg compared with <140 mm Hg in non-diabetic patients older than 55 years of age, including a substantial subgroup with CKD. The study showed that the reduction of the systolic blood pressure to 120 mmHg reduced the combined rate of having a heart attack, acute coronary syndrome, heart failure or stroke by nearly one third, and reduced deaths from any cause by nearly a one-quarter compared to reducing blood pressure to less than 140 mm Hg [12]. SPRINT study did not systematically include CKD patients. Since only approximately 30% of SPRINT patients in the 120 mmHg arm had CKD the generalizability of the study results to CKD patients is limited. Of course the study reaffirms the need for a more strict blood pressure control in patients with kidney dysfunction [13].

Achievement of a blood pressure target <140/90 mmHg in CKD patients is difficult and requires lifestyle modifications, and multiple antihypertensive medications. Indeed, the percent of people with CKD achieving blood pressure control still remains below 50% [14].

A wide variety of dietary factors affect blood pressure control. Lifestyle modifications including dietary changes, weight loss and exercise are of crucial importance for the effective control of blood pressure. A recent systemic study revealed that a healthy diet comprising of many fruits and vegetables, fish, legumes, whole grains, and fibers and also the reduction of red meat and refined sugar intake was associated with lower mortality in individuals with CKD. Furthermore, sodium restriction may be appropriate due to the impaired salt excretion in these patients [15].

Physicians and patients usually overestimated BP control rates and this may contribute to therapeutic inertia and poor BP control in CKD patients [16]. Clinical inertia is a major factor that contributes to inadequate chronic disease care in patients with DM, HT, and CKD [17]. Inappropriate inertia should be addressed carefully. Poor adherence to drug therapies should be also taken into account. Thus, an effort focusing on antihypertensive treatment initiation and adherence is likely to provide major benefits. Thus, improving adherence to control blood pressure in CKD patients may prevent renal disease progression [18]. Finally, patients participating in a cardiac rehabilitation program may also improve blood pressure levels and reduce their overall reliance on medications [19].

The proper blood pressure medications should be carefully titrated to reduce proteinuria. It is well known that the presence of proteinuria is associated with faster progression to renal failure and with increased risk of CVD. It is suggested that reductions in proteinuria are well correlated with preservation of renal function and with reduction in cardiovascular mortality [20].

The Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

Chronic kidney disease is an independent risk factor for CVD, the most common cause of death among patients with CKD.

Agents that block the renin angiotensin-aldosterone system (RAAS) should be the drugs of choice in CKD patients. The role of RAAS in the pathogenesis of cardiovascular and renal disease is well documented. RAAS plays a crucial role in circulatory homeostasis and endothelial function. The effects of angiotensin II include vasoconstriction, enhanced susceptibility to thrombosis, superoxide production, vascular smooth muscle growth, myocyte hypertrophy, fibrosis, remodeling of tissues, and stimulation of other hormonal mediators that drive cardiovascular and renal pathology. Sympathetic over activity stimulates the RAAS, which, in turn, promotes retention of sodium and leads to increases in intravascular volume and peripheral vascular resistance [21,22].

ACE inhibitors and ARBs consistently reduce proteinuria and also slow the decline in kidney function [23]. The evidence for preferential use of ACE inhibitors/ARBs is strongest for CKD patients with hypertension, as well as in those with micro- or macro-albuminuria whether they are diabetic or not [24]. The risk of ESRD in hypertensive patients with diabetic nephropathy is more likely related to the albuminuria reduction than to lowering blood pressure [25]. In CKD patients without proteinuria there is no evidence that the use of ACE inhibitors/ARBs is more effective compared with other antihypertensive agents. There is no strong evidence that would suggest a preference for ACE Inhibitors versus ARBs. For these agents an equivalent efficacy was found and no differences in renal and cardiovascular outcomes have been observed between them [8]. In addition no differences exist between ARBs and ACE inhibitors in their ability to provide protection to target organs in high-risk patients [8].

These agents are contraindicated for use in pregnancy because they are extremely teratogenic. In addition ACE inhibitors/ARBs should not be used in patients with a history of angioedema. Of course, ARBs are better tolerated and do not exhibit the side effects of cough seen with ACE inhibitors. Moderate to high doses are often required to achieve blood pressure goals as well as to lower proteinuria. The side-effect profile of these agents is not affected by their dose [8].

An increase in serum creatinine often occurs after the administration of these agents. The RAAS blockers are generally avoided by most physicians in patients with an eGFR less than 50 ml/min/1.73 m^2. On the other hand, substantial evidence from outcome trials has demonstrated the greatest benefit of ACE inhibitors and ARBs on slowing CKD progression in these patients [1,24,26,27]. However, in the everyday clinical practice these agents are being given with a very low frequency to such patients and often are avoided because of the increases in creatinine or the fear of hyperkalemia. It is suggested that a rise in serum creatinine in these patients within a few weeks of starting ACE inhibitors or ARBs is associated with better CKD outcomes especially in those with advanced nephropathy and correlates with the preservation of kidney function over a mean follow-up period of 3 or more years [28]. However, if serum creatinine increases by >30% or continues to rise after 3 months of therapy, other causes should be carefully considered, such as bilateral renal artery stenosis, volume depletion, unsuspected left ventricular dysfunction and/or the use of non-steroidal anti-inflammatory agents. Thus, RAAS-blocking therapy should be withdrawn only when the rise of serum creatinine exceeds baseline values more than 30% within the first 3 to 4 months of therapy or when hyperkalemia occurs [28].

All recent guidelines do not support the combination of ACE inhibitors with ARBs. Dual blockade of the RAAS, with the use of ACE inhibitors and ARBs, has been discarded due to an increased concern regarding the adverse events, such as symptomatic hypotension, renal dysfunction, and hyperkalemia in high risk patients with CKD [10,11].

In patients with proteinuric CKD, aldosterone receptor antagonists, such as spironolactone or eplerenone in low doses may be also indicated. Indeed, a combination of ACE-inhibitor or an ARB, with an aldosterone receptor antagonist may be more beneficial in patients with proteinuric nephropathy because this combination results in a further reduction of urine protein excretion. However, in this case serum potassium levels should be closely monitored [29]. Potassium levels rise in a dose-dependent fashion after aldosterone antagonist's administration, thus a dose adjustment or a concomitant use of a loop diuretic therapy should be considered. Novel agents for potassium lowering in patients with CKD represent the first new pharmacologic therapy for hyperkalemia. These two ion exchange resins named Patiromer and Sodium Zirconium Cyclosilicate are the two novel agents with promising results in treating hyperkalemia in patients with nephropathy. Both agents did not exhibit serious adverse effects [30].

Diuretics

In patients with kidney function deterioration, volume overload is often present. Thus, diuretics have been a linchpin in the management of CKD patients. Thiazide and thiazide-like diuretics, chlorthalidone and indapamide become less effective when GFR falls below 30 mL/min/1.73 m^2 compared to a loop diuretic. In fact, in severe renal insufficiency loop diuretics exhibit a higher intrinsic efficacy compared with thiazides. If serum potassium is >5.2 mmol/L potassium-sparing diuretics, such as spironolactone or eplerenone as well as triamterene and amiloride, should be avoided. On the other hand, in hypokalemic patients with CKD, supposing that dietary causes have been excluded, an ACE inhibitor or an ARB, or a low-dose of an aldosterone antagonist, may also provide some additional benefit in terms of correction of hypokalemia as well as proteinuria reduction [29].

Calcium Channel Blockers (CCBs)

In patients with nephropathy CCBs are very effective antihypertensive drugs. Additionally, non-dihydropyridine CCBs, verapamil and diltiazem also exhibit positive effects on proteinuria reduction beyond their blood pressure–lowering effects among CKD patients with proteinuria. Inversely, dihydropyridine CCBs, nifedipine, felodipine or amlodipine may reduce proteinuria only when used in combination with a RAAS blocker [1,23]. It should be mentioned that manidipine, compared to amlodipine showed a larger reduction in the urinary albumin excretion rate despite similar blood pressure reductions [30]. Indeed, it has been shown that manidipine reduces, whereas amlodipine increases intraglomerular pressure resulting in their disparate effects on albuminuria [31,32].

Compared to an ACE inhibitor/ARB, dihydropyridine CCBs are less efficient agents in kidney disease retardation. Thus, in renal disease patients with proteinuria CCBs should be used preferably in combination with an ACE inhibitor or an ARB. Recent guidelines clearly state that if blood pressure is >20/10 mm Hg above the goal two or more antihypertensive agents such as a combination of an ACE inhibitor or an ARB with a CCB should be initially used [10,11].

A calcium antagonist should be considered as an add-on therapy to the RAS blocker regimen according to the results of the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (Accomplish) trial. In the aforementioned study a greater risk reduction of adverse cardiovascular outcome was noticed when the RAAS blocker benazepril was paired with the calcium antagonist amlodipine compared to the combination of benazepril with a diuretic. In the subgroup analysis, patients with CKD randomized to RAAS blocker plus the calcium antagonist showed a slower progression of kidney disease compared to patients randomized to RAAS blocker plus the diuretic [33].

Agents Blocking the Sympathetic Nervous System

Beta-blockers

Beta-blockers have been shown to reduce cardiovascular mortality in high-risk patients, whereas their renoprotective effects have not been well established [34]. Beta-blockers should not be used as first line therapy in the treatment of hypertension, particularly in patients over 60 years of age unless the patient exhibits a recent myocardial infarction or established coronary artery disease. Furthermore, β-blockers are not indicated in patients with bradycardia or with second- or third-degree heart block. It should be mentioned that β-blockers should not be combined with nondihydropyridine CCBs. In CKD patients with type 2 diabetes and proteinuria, after 4.5 years of follow- atenolol administration was associated with a rise in creatine compared with verapamil administration

[35]. It is worth mentioning that β-blockers with vasodilating properties compared to the traditional beta-blockers exhibit a better metabolic profile including lipid metabolism and insulin sensitivity [36].

Central alpha-adrenergic agonists

Inhibitors of the sympathetic nervous system include peripheral alpha and central alpha-2 receptor antagonists. These agents mitigate the increased sympathetic activity in CKD patients. Their side effects are dose-dependent and their tolerability is poor. Clonidine is the most commonly used [37]. Moxonidine is also an effective adjunctive therapy in combination with other antihypertensive agents. This drug can improve the metabolic profile in patients with hypertension and diabetes mellitus or impaired glucose tolerance [38]. Methyldopa is now used primarily in pregnancy [39]. A combination of an alpha-adrenergic agonist with a beta blocker can cause bradycardia and is not recommended [40].

Alpha-adrenergic blockers

Alpha-blockers have not been shown to reduce cardiovascular events in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [41]. Furthermore these agents also failed to slow renal disease progression or improve proteinuria in diabetic patients. However, alpha blockers could be used as add on therapy in patients with benign prostatic hyperplasia [42].

Vasodilators

Vasodilators, minoxidil or hydralazine are considered fourth-line agents and are used when the other agents have failed. Because their administration is associated with reflex tachycardia it is suggested that a combination with a beta-adrenergic blocker is always required. After initiating vasodilator therapy patients should always be closely monitor their weight. Treatment of hypertension with vasodilator therapy has not been shown to improve kidney outcomes [43].

Conclusions

Chronic kidney disease (CKD) is a global health burden. Hypertension commonly coexists in approximately 80-85% of patients with CKD. In this paper we discuss the existing therapeutic approaches for the management of hypertension in patients with CKD.

The blood pressure goal in CKD patients is difficult to be achieved and requires multiple antihypertensive medications while lifestyle modifications are crucial for effective blood pressure control. In CKD patients therapeutic inertia and a poor adherence to drug therapies should be addressed carefully. From the antihypertensive medications ACE inhibitors and ARBs consistently reduce proteinuria and slow the decline in kidney function. A CCB should be considered as an add-on therapy to the RAAS blocker. Diuretics (thiazides and thiazides-like drugs) become less effective when GFR falls below 30-40 mL/min/1.73 m^2 and a loop diuretic should be considered. Aldosterone receptor antagonists in low doses may also be indicated. Beta-blockers should be used preferably in patients with a recent myocardial infarction or established coronary artery disease. All the other agents, including central alpha-adrenergic agonists, alpha-adrenergic blockers and vasodilators should be also considered when the aforementioned drugs are not indicated or have failed.

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