

The Kidney, Hypertension, and Remaining Challenges

Nitin Khosla, MD^a, Rigas Kalaitzidis, MD^b, George L. Bakris, MD^{b,*}

KEYWORDS

- Kidney • Hypertension • Failure • Morbidity
- African-American

Chronic kidney disease (CKD) is a major worldwide public-health problem.¹ Eight million people in the United States had an estimated glomerular filtration rate (eGFR) less than 60 mL per minute per 1.73 m².² The estimated prevalence of CKD is about 14.8% of the general population.³ Patients with CKD have significant morbidity, increased risk of cardiovascular disease,⁴ progression to end-stage renal disease (ESRD), and death.⁵ Furthermore, patients with CKD are 5 to 10 times more likely to die than to advance to ESRD;^{3,6} among such patients, the rate of sudden death is three times higher.

A survey of the National Health and Nutrition Examination Survey database indicates that the prevalence of CKD has increased from 10.0% between 1994 and 1998 to 13.1% from 1999 to 2004.² In 2006, the estimated cost to treat hypertension and its comorbid conditions in the United States exceeded 55 billion dollars.⁷ Similarly, the estimated cost for Medicare patients with CKD exceeded 49 billion dollars, nearly five times greater than costs in 1993. Overall Medicare expenditures, in contrast, have grown only 91% in the same period.⁸

One of the most difficult problems in managing patients with CKD is the achievement of blood pressure (BP) targets recommended by guidelines. The degree and duration of either systolic or diastolic BP elevation strongly influences cardiovascular (CV) outcomes in all patients. In the general population, risk of a CV event doubles for every increment of 20/10 mm Hg increase in BP over 115/75 mm Hg.⁹ Not only is this risk amplified in patients with CKD, but hypertension accelerates the progression of CKD as well, especially when levels of proteinuria are greater than 300 mg/day.^{10–14}

^a Department of Medicine, Section of Nephrology and Hypertension, University of California at San Diego, San Diego, CA, USA

^b Department of Medicine, Hypertensive Diseases Unit, Section of Endocrinology, Diabetes, and Metabolism, University of Chicago-Pritzker School of Medicine, 5841 South Maryland Avenue MC 1027, Chicago, IL 60637, USA

* Corresponding author.

E-mail address: gbakris@gmail.com (G.L. Bakris).

Post hoc analyses of randomized clinical trials in patients with greater than 300 mg/day of proteinuria have found that lower BP levels yield slower declines in kidney function. These observations have led to the development of lower BP targets (ie, to <130/80 mm Hg) in those with CKD in an attempt to decrease the incidence of adverse CV and renal outcomes.^{10,15}

This article focuses exclusively on management of hypertension in CKD and addresses the following issues: How good are the data to support a lower target BP in CKD? Are the data supporting a lower BP stronger in those with diabetes with CKD? Should reduction in proteinuria be a key element in choosing antihypertensive medications to prevent progression of CKD?

Before addressing these questions, however, some background information is pertinent. First, it has long been felt that management of hypertension in patients with advanced CKD (ie, eGFR <60 mL/min) will not be successful without using strategies that lower both BP and the spectrum of albuminuria. Microalbuminuria (MA) is defined as a protein excretion of greater than 30 mg to 299 mg per day or 20 µg to 200 µg per minute present on two different occasions.¹⁶ MA is a marker of endothelial dysfunction and is an independent risk marker for CV events.^{17–20} It is not, however, a marker of kidney disease,²¹ but if measured with a simple spot urine, can provide as much if not more information as other inflammatory markers, such as highly sensitive C-reactive protein.¹⁶ A guide to the evaluation of MA is presented in **Fig. 1**.²² The best evidence demonstrating the association between MA reduction and reduction in CV events comes from a post hoc analysis of the Losartan Intervention for Endpoint trial, where an early reduction in MA was associated with a greater reduction in CV events that persisted over the 5-year follow-up.²³

MA or proteinuria, defined as a protein excretion greater than 300 mg/day or greater than 200 µg/min,²² is associated with a much higher CV risk and does indicate presence of CKD; there is a direct relationship between the degree of proteinuria and progression to ESRD.²⁴ Post hoc analyses of three appropriately powered CKD outcome trials demonstrate that reduction in MA (proteinuria) in those with advanced CKD delays CKD progression, an effect that could not be explained by BP lowering

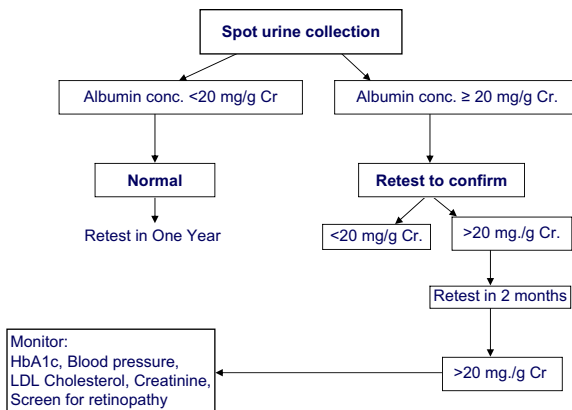


Fig. 1. Evaluation and Work-up of MA proposed by the National Kidney Foundation. (Data from Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003;42(5):1057.)

alone.²⁵ These studies demonstrate a reduction in proteinuria of more than 30% resulted in a 39% to 72% risk reduction for dialysis at 3 to 5 years (**Table 1**).²⁵⁻²⁷

Given this information, there have been numerous attempts to have the Food and Drug Administration approve changes in albuminuria as a surrogate marker for CKD progression. This effort has failed because there is no randomized prospective trial that demonstrates a change in albuminuria alters CKD progression independent of BP reduction. Hence, albuminuria does not qualify as a surrogate marker.^{28,29}

Finally, studies involving hypertension in CKD must be evaluated in the following context: (a) BP actually achieved (independent of what target BP was) and time to achieve goal; (b) level of renal function at time of enrollment; and (c) amount of protein excretion present (MA versus proteinuria). The alpha blockade arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) illustrates the first point. Though this arm was terminated early because of a higher incidence of stroke and the combined outcome of stroke, angina treated outside the hospital, heart failure, and peripheral arterial disease, the alpha blocker arm had a consistently higher BP than the diuretic arm and this difference was greatest after the first year.³⁰ This likely contributed to the differences in outcome observed. Baseline kidney function and level of protein excretion are also key determinants of outcomes in CKD trials. The earlier a BP intervention occurs, the more likely it will stop kidney disease progression. Similarly, a late intervention will only slow progression already underway. In The Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the average GFR was more than 80 mL/min at the start of the trial, whereas in most other diabetes trials, baseline GFR is generally less than 50 mL/min.³¹ Early and aggressive BP lowering (ie, <130/80 mmHg) in the ABCD trial was associated with GFR decline being slowed to rates seen in people with normal kidney function. Conversely, in other trials of more advanced CKD, GFR loss occurred at a rate of 2 mL to 7 mL per minute per year (see **Fig. 1**).^{15,32} Thus, results of trials in patients with advanced CKD should not be extrapolated to patients with early CKD, as rates of decline in kidney function are not similar.

BP GOAL OF LESS THAN 130/80 MM HG: DOES THE EVIDENCE SUPPORT THIS BP IN CKD?

All published guidelines define goal BP as less than 130/80 mm Hg for those with diabetes or CKD (**Table 2**).^{10,15} Data to support the goal of less than 130/80 mm Hg, among those with diabetic nephropathy, come from post hoc analyses of three different trials of patients with advanced (eGFR <60 mL/min) proteinuric (>300 mg/day) kidney disease. All these trials have a range of BPs at study end between 120 and 152/68 and 86 mm Hg; the mean is much higher than 130/80 mm Hg. Post hoc analyses of these diabetic nephropathy trials have also pointed to a J-shaped relationship, suggesting that a BP below 120/85 mm Hg may actually increase cardiovascular risk in these patients.³³ Thus, even in diabetic nephropathy where the data are somewhat more robust, the argument for a BP less than 130/80 mm Hg is weak.

Nondiabetic CKD trials are less robust with regard to BP goal, as only two such trials exist, the Modification of Diet in Renal Disease Study (MDRD) and the African American Study of Kidney Disease (AASK). These trials, like those in patients with diabetic nephropathy, were executed in patients with an eGFR less than 60 mL/min and with albuminuria.

The MDRD provides data that is instructive about advanced nephropathy progression. This is the first trial to randomize to two levels of BP and follow nephropathy progression, a mean arterial pressure (MAP) of less than 92 mm Hg versus one between 102 mm Hg and 107 mm Hg. When the trial ended, mean follow-up of 2.7 years, there was no advantage on CKD slowing in the lower BP group. However, after 8 additional years of follow-up, those with baseline proteinuria of more than 1 gm/day

Table 1
Outcomes studies with primary CKD progression endpoint

Study	Treatment Groups	Follow up (Mean in Years)	Achieved BP (mm Hg)	Change in Proteinuria	Relevant Outcomes
Captopril trial	Captopril or placebo	3 (median)	MAP 96 MAP 100	−30%	Captopril delays the progression of diabetic nephropathy
AASK ^a	Metoprolol, ramipril, or amlodipine and conventional or intensive blood pressure targets	4	128/78 for lowergroup 141/85 for usual group	−14% for metoprolol−20% for ramipril+58% for amlodipine at 6 months	Ramipril slowed the progression of renal disease when compared with the other groups
RENAAL ^a	Losartan or placebo	3.4	140/74 142/74	−35%	Losartan delayed the need for dialysis by 2 years when compared with placebo
IDNT ^a	Irbesartan or amlodipine or placebo	2.6	140/77 141/77 144/80	−33% −6% −10%	Irbesartan reduced proteinuria to a greater extent and lead to slower progression of renal disease when compared with the other groups

Abbreviations: AASK, African American Study of Kidney Disease; IDNT, Irbesartan in Diabetic Nephropathy Trail; RENAAL, Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan.

^a Indicates studies where post hoc analysis show significant risk reduction for CKD progression when proteinuria reduced by greater than 30% at 6 months.

Table 2
Summary of guidelines and position papers for goal BP in people with kidney disease or diabetes from various consensus committees around the world

Group	Goal BP (mm Hg)	Initial Therapy
Am. Society of HTN (2008)	<130/80	ACE inhibitor/ARB ^{a,b}
Canadian HTN Society (2007)	≤ 130/80	ACE inhibitor/ARB
Am. Diabetes Assoc. (2005)	<130/80	ACE inhibitor/ARB ^a
Japanese HTN Society (2006)	≤ 130/80	ARB ^{a,b}
National Kidney Foundation (2004)	<130/80	ACE inhibitor/ARB ^a
British HTN Society (2004)	≤ 130/80	ACE inhibitor/ARB
JNC 7 (2003)	<130/80	ACE inhibitor/ARB ^a
ISH/ESC (2003)	<130/80	ACE inhibitor/ARB
Australia-New Zealand (2002)	<130/85	ACE inhibitor
WHO/ISH (1999)	<130/85	ACE inhibitor

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ESC, European Society of Cardiology; HTN, hypertension; ISH, International Society of Hypertension; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; WHO, World Health Organization.

^a Indicates potential use of initial combination therapy with a thiazide diuretic, if BP is substantially higher than goal.

^b Calcium antagonists could also be combined.

randomized to the lower target BP of 92 mm Hg, had a slower decline in kidney function, and a lower incidence of renal failure compared with those randomized to a MAP of 107 mm Hg.³⁴ This difference was apparent within a year after the study ended.

The AASK study adds support to the notion that patients with significant proteinuria benefit from a lower BP target. The primary analysis of AASK demonstrated that patients randomized to a lower BP target of a MAP less than 92 mm Hg derived no additional benefit on CKD slowing over the high BP group. However, a subgroup analysis showed that the lower BP target did preserve kidney function in the small subset of patients with proteinuria less than 1 gm/day, with a trend toward a slower decline in GFR in the cohort of patients with proteinuria greater than 300 mg/day.³⁵

Many cite the Ramipril Efficacy in Nephropathy trial (REIN-2) as evidence to contradict lower BP targets in patients with proteinuria.³⁶ However, this study was grossly underpowered to detect a difference in decline in GFR between the two BP groups, as the median follow-up was only 1.6 years and there was only a 4.8-mm Hg difference in systolic BP difference between treatment groups. All of these trials are limited because the data presented to support the lower BP goal are derived from post hoc analyses.

Perhaps the most supportive evidence to re-evaluate the goal BP in CKD patients comes from the latest 10-year follow-up of the AASK trial. To date, no trial has had an average BP difference of 13/8 mm Hg for a duration of 5 years, and then everyone followed for an additional 5 years with systolic BP levels averaging less than 135 mm Hg in the entire cohort.³⁷ Even with this level of control, about 65% of the cohort still had progression of CKD, albeit markedly slowed. A potential reason for this was the discovery of masked and nocturnal hypertension that was missed by routine BP measurement.³⁸ Taken together, these data support the following: (a) routine BP measurement are not adequate for determining risk of CKD progression in patients with pre-existing CKD; (b) the goal of less than 130/80 mm Hg in CKD cannot be supported by appropriately powered trials in CKD but comes from meta-analyses of these

smaller trials and post hoc analyses of larger databases;^{15,39} (c) a goal of less than 130/80 mm Hg does have support in the subgroup of patients with MA or proteinuria and CKD. In the long-term follow-up of MDRD and the small subgroup of people ($n = 52$) in AASK with proteinuria greater than 300 mg/day, there was a slower CKD progression in those randomized to the lower BP goal, which averaged between 127 and 132/77 and 80 mm Hg. This benefit, however, took 5 years to become apparent on average.

Taken together, these data suggest that in patients with baseline GFR values less than 50 mL/min, those with BPs that approach 130/80 mm Hg have slower rates of decline in kidney function among those with advanced proteinuric CKD (**Fig. 2**).

SHOULD PROTEINURIA REDUCTION BE CONSIDERED IN DEVELOPING A BP-LOWERING STRATEGY?

Proteinuria or MA (>300 mg/day) is not an approved surrogate marker for CKD progression by the Food and Drug Administration. The reasons for this were previously mentioned, but proteinuria is felt to be a result of and not a cause of the underlying disease process. Nevertheless, the data are clear that development of proteinuria despite adequate BP control is a clue that CKD is present and progressing. Proteinuria greater than 2.5 g per day is an uncommon consequence of hypertension alone and should prompt consideration of a renal biopsy to determine the etiology of renal disease.

Post hoc analyses of all studies to date, demonstrate that maximal slowing of nephropathy occurs only when proteinuria is reduced in concert with BP.⁴⁰ Proteinuria reduction of at least 30% below baseline measurement when treatment started; generally this should occur at 6 months (see **Table 1**). Note, however, that this is not true for patients with CKD and MA, and there is no randomized trial with proteinuria reduction as a primary endpoint linked to nephropathy progression.^{16,40} Nevertheless, the totality of the data argues for a strategy that lowers both proteinuria and BP to maximally reduce nephropathy progression.^{40,41}

THERAPEUTIC APPROACHES TO HYPERTENSION IN KIDNEY DISEASE

Given the new trial information on CKD progression and information about proteinuria, there have been some proposed changes in management of BP in CKD and they are summarized in this section. The lifestyle approaches to treating BP in those with early CKD have not changed since being published in the 2004 National Kidney Foundation

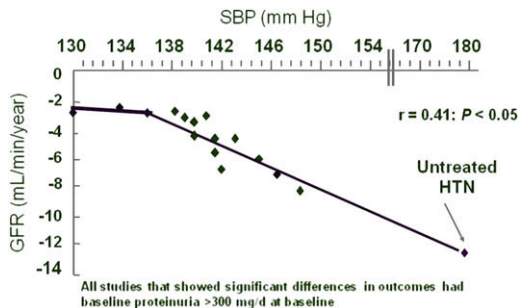


Fig. 2. The relationship between achieved level of BP and rate of decline in renal function in renal outcome trials over the past decade.

(NKF) guidelines.^{10,15} The available data, however, suggest that lifestyle modifications alone are inadequate for management of hypertension in patients with CKD.

There are a few aspects of lifestyle management, however, that need emphasis. First, is sodium restriction. High-sodium intake is particularly injurious in African Americans because they excrete a lower sodium load than their White counterparts.⁴² This difference of renal-sodium handling is borne out by the results of the dietary approaches to stop hypertension (DASH) diet, where hypertensive Black females had a 6 mm Hg greater reduction in BP compared with hypertensive White females on this low-sodium, high-potassium diet.⁴³ Care should be given when prescribing the DASH diet to anyone with Stage 4 or higher nephropathy because of risk of hyperkalemia.

Those with CKD are sodium avid, a phenomenon that is amplified in those with diabetes or metabolic syndrome, because the high levels of insulin seen in these conditions affect the tubular reabsorption of sodium.^{44–47} Hence, those who are obese or have diabetes are relatively volume expanded.⁴⁸ Ingesting large sodium loads also restriction attenuates the antiproteinuric effects of the renin angiotensin aldosterone system blockers (RAAS).^{49–51} Therefore, limitation of daily sodium intake to 2 g/day to 4 g/day is a logical initial therapeutic approach with use of a thiazide diuretic in those who do not fully adhere to this recommendation.

Pharmacologic Treatment

The guidelines of both the JNC 7 and the NKF state that management of hypertension in CKD should focus on reducing BP, with the NKF also emphasizing reducing protein excretion. First line agents to achieve these goals are RAAS blockers, ACE inhibitors, or ARBs,^{10,15} generally used in concert with either diuretics or calcium antagonists. The American Society of Hypertension has recently updated the existing guidelines summarizing the approach in a position paper. The algorithm summarized in the paper is shown in **Fig. 3**.^{10,15,52}

SPECIFIC ANTIHYPERTENSIVE DRUG CLASSES

RAAS Blockers

The RAAS blockers have not been used appropriately by most physicians in the patients who would garner the greatest benefit: that is, those with an eGFR less than 50 mL/min with proteinuria. These are the profiles of people in the outcome studies, yet data from practice databases indicate that these agents are being given with a very low frequency to such patients.

ACE Inhibitors

The mechanism of renal protection from RAAS blockers relates to many factors, including hemodynamic and antifibrotic effects, as well as effects on renal reserve. The nephron responds to a variety of factors, such as increased protein intake, with an elevation in GFR. This is referred to as “renal reserve” because it reflects the ability of the kidney to increase its clearance rate in the presence of higher urea genesis.⁵³ The increase in GFR is a result of signaling from the macula densa to the afferent glomerular arterioles, resulting in a vasodilator response to various amino acids. ACE inhibitors blunt the rise in GFR that follows a protein load by blocking this afferent arterial dilation.⁵⁴ Thus, agents that block the RAAS protect the kidney in a manner similar to the way β -blockers provide cardioprotection.

The first trial to demonstrate a benefit of ACE inhibitors was the Captopril Nephropathy Trial in Type-1 diabetics. This trial demonstrated an almost 75% risk reduction in

If Blood Pressure >130/80 mm Hg in Diabetes ($eGFR \geq 50 \text{ ml/min}^A$)

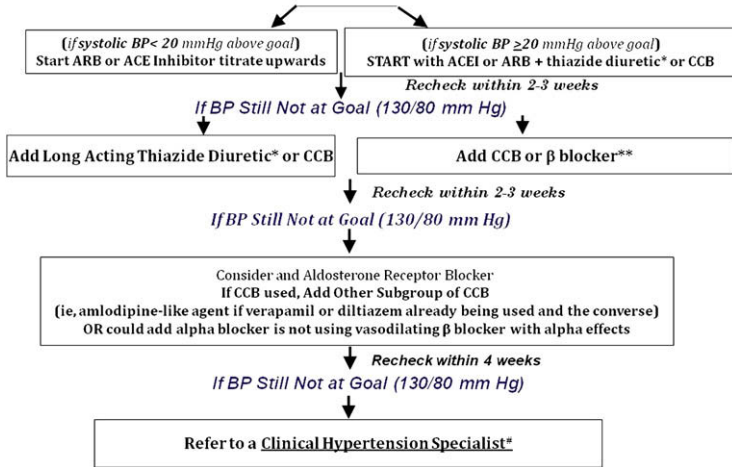


Fig. 3. An approach to lower arterial pressure to goal in patients with diabetes or albuminuria. It represents an update of previous guidelines published in 2003/2004 by the JNC 7 and NKF. #, Everyone with diabetes and CKD should be instructed on lifestyle modifications as per the JNC 7. Everyone should also be started on pharmacologic therapy, if blood pressure is greater than 130/80 mm Hg. Note: If BP is less than 20/10 mm Hg above goal (130/80 mm Hg), then ACE inhibitors or ARBs, titrated to maximal doses, alone may be used. *Nondihydropyridine calcium channel blockers (CCBs) (verapamil and diltiazem reduce both CV mortality, proteinuria, and diabetic nephropathy progression independent of ACE inhibitors or ARBs). β -blockers may be substituted for CCBs if the patient has angina, heart failure or arrhythmia, or a high heart rate (ie, >84 beats per minute at rest), necessitating their use. β -blockers with proven efficacy to reduce CV events and the lowest side-effect profile are preferred; of those available, carvedilol and nebivolol meets these criteria. Note that use of a β -blocker with a nondihydropyridine CCB should be avoided in the elderly and those with conduction abnormalities. Otherwise, such combinations are safe and particularly effective for lowering blood pressure. Also note that other agents, such as minoxidil, hydralazine, and clonidine or methyldopa can be used as adjunctive agents to help achieve goal BP. Clonidine should not be used with β -blockers or high-dose verapamil for numerous reasons, not the least of which is a high likelihood of severe bradycardia.

doubling of serum creatinine and in the combined outcome death, dialysis, and kidney transplantation in those treated with captopril when compared with placebo in those whose serum creatinine values were greater than 2 mg/dL. In those with serum creatinine values of less than 1 mg/dL, there was no significant benefit to ACE inhibition when similar BPs were achieved.⁵⁵ The REIN trial also demonstrated a 62% reduction in renal disease progression in those with serum creatinine values greater than 2 mg/dL and greater than 3 g/day proteinuria, compared with a 22% reduction in those with MA alone.⁵⁶ Similar findings have been noted in meta-analyses of nondiabetic renal disease.³⁹

Early clinical trial data suggested that ACE inhibitors may provide additional protection against nephropathy progression, independent of BP, but this has not been borne out in larger clinical trials.^{39,57} In a post hoc analysis of the ALLHAT trial, there was no evidence favoring the concept that ACE inhibitors have unique effects, independent of BP control, on preservation of renal function.⁵⁷ This difference in renal outcomes among these trials relates to several issues. In earlier studies, all patients had

advanced CKD: that is, GFR less than 50 mL/min with more than 500-mg/day proteinuria. The ALLHAT trial was not powered for CKD outcomes and had no proteinuria data, with very few people in advanced Stage 3 and 4 nephropathy. Moreover, early in the ALLHAT, as much 6 mm of mercury difference in systolic BP existed between the ACE-inhibitor group and comparator groups. Consequently, the observed lack of selective benefit of ACE inhibitor treatment is difficult to interpret.

In clinical practice, increases in serum creatinine are commonly seen within a few weeks of starting ACE inhibitors or ARBs, especially in those with advanced nephropathy. A rise in serum creatinine limited to 30% to 35% within the first 4 months of starting RAAS-blocking therapy, however, correlates with preservation of kidney function over a mean follow-up period of 3 or more years (Fig. 4).^{15,58} This correlation between a limited early rise in serum creatinine and long-term preservation of kidney function was restricted to patients under the age of 66 years, with baseline serum creatinine values less than or equal to 3.5 mg/dL. If acute increases in serum creatinine of greater than 40% occur in fewer than 4 months of RAAS-blocker therapy, the physician should evaluate the patient for (a) volume depletion (the most common etiology), (b) worsened heart failure, or (c) bilateral renal-artery stenosis.⁵⁸ Elevations in serum potassium only become clinically relevant at levels markedly exceeding 6 mEq/L or 5 mEq/L in the presence of digitalis preparations. Data from the recent heart failure trial demonstrated a CV risk reduction in people with CKD with serum potassium levels up to 5.7 mEq/L.⁵⁹ Hyperkalemia can be addressed by advising avoidance of high-potassium foods, such as fruits and vegetables, appropriately dosing diuretics, and stopping agents known to increase potassium, such as nonsteroidal anti-inflammatory agents.

ARBs

The RENAAL trial and the IDNT demonstrated that in advanced nephropathy, using an ARB to reduce BP led to a decrease in rate of nephropathy progression greater than that seen with other agents (ie, amlodipine or β -blockers/diuretics).^{60,61} The primary composite endpoint for both studies was time to doubling of baseline serum creatinine, onset of ESRD, or death. In the RENAAL study of 1,513 patients, followed for an average of 3.4 years, and the IDNT of 1,715 patients, followed for an average of

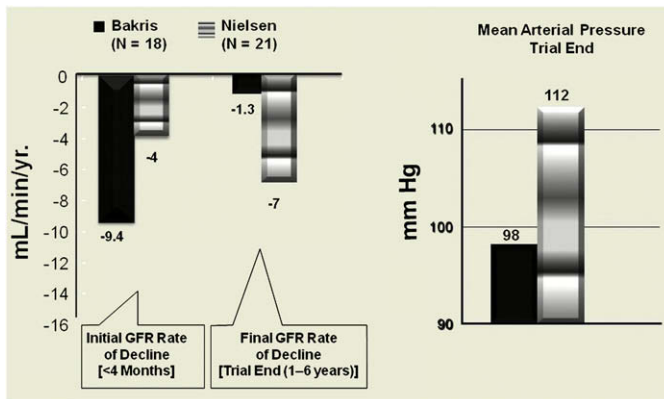


Fig. 4. Initial and long-term change in GFR in patients with Type-2 diabetes initially started on the ACE inhibitor, lisinopril. Note, GFR was measured using ^{99}Tc -diethylenetriamine pentaacetate. Patient baseline characteristics were similar in both studies.⁵⁸ Note as well, with better BP reduction, the GFR dropped more, initially in the study, but the overall rate of decline at 5 years was less in the group with better BP control, in spite of a greater initial fall.

2.7 years, there was a 16% and 37% risk reduction by losartan and irbesartan, respectively, for the primary endpoint. In RENAAL, there was a 28% reduction in time ESRD. It was estimated that losartan could delay the need for dialysis or transplantation for 2 years.⁶⁰ Taken together, these trials reinforce the importance of selecting agents that both help achieve BP goal and reduce proteinuria (see **Table 1**).

Data directly comparing renal outcomes of ARBs and ACE inhibitors is limited to one trial that was underpowered and not in a cohort that would yield a meaningful outcome on CKD progression; hence, no difference was noted between the two classes.⁶² The COOPERATE trial also compared these classes, but there were major data inconsistencies and hence, the trial is not discussed.⁶³

In general, ARBs are generally better tolerated than ACE inhibitors, in that they are associated with a lower incidence of cough (presumably because they do not affect bradykinin), angioedema, taste disturbances, and hyperkalemia.⁶⁴

Direct Renin Inhibitors

Aliskiren is the first and only approved direct renin inhibitor. The mechanism of action of this drug is unique in that it blocks the RAAS by binding to a pocket in renin itself, preventing it from cleaving angiotensinogen to angiotensin I. Aliskiren has a half-life of 24 hours and a side-effect profile similar to that of ARBs.⁶⁵ The role for aliskiren in the management of hypertension has yet to be fully determined, but it effectively reduces BP when used alone or in combination with other classes of medications, such as diuretics, ARBs, and CCBs.⁶⁶

Limited data are available describing the use of aliskiren in CKD patients. The Aliskiren in the Evaluation of Proteinuria in Diabetes study compared the effect of aliskiren combined with losartan and losartan combined with placebo on albumin excretion in 599 patients with diabetes. Both groups had similar BPs and the aliskiren group had a 20% reduction in urinary albumin-to-creatinine ratios when compared with the placebo group at 6 months.⁶⁷ While these results are promising, we must await the results of the ALTITUDE trial to see if the effects are similar on diabetic nephropathy progression to that of ACE inhibitors and ARBs.

Aldosterone Antagonists

Current recommendations are to use aldosterone antagonists for treating hypertension in patients with advanced heart failure and postmyocardial infarction.¹⁰ However, the role of these medications continues to expand. A post hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm demonstrated that adding spironolactone as fourth-line therapy led to a dramatic 21.9/10.5 mm Hg reduction in BP.⁶⁸ Others have looked at using aldosterone antagonists as a way to reduce proteinuria. A recent systematic review demonstrated that use of aldosterone antagonist given either alone or in concert with other RAAS agents provided significant reduction in proteinuria as well as BP.⁶⁹ It should be noted that patients involved in these studies had reasonable kidney function with estimated GFRs between 57 mL and 67 mL per minute. It is unclear whether aldosterone antagonists can be used in patients with more advanced nephropathy, especially given the risk of hyperkalemia.

DIURETICS

Thiazide diuretics have gained a renewed importance in treating hypertension since the publication of the ALLHAT.⁷⁰ Renal outcomes were analyzed post hoc and there was no difference in development of ESRD between the treatment groups.⁵⁷

Although JNC 7 makes no specific recommendation about the particular thiazide diuretic used, strong consideration should be given to using chlorthalidone over hydrochlorothiazide. No trial has ever been designed to directly compare the two medications; however, almost all the major outcome trials supporting diuretics used chlorthalidone.^{70,71} Though the two drugs are thought to have similar efficacy, chlorthalidone is likely more potent because of its longer half-life (44 hours for chlorthalidone versus 12 hours for hydrochlorothiazide).^{72,73} This difference in duration of action translated into an additional 7-mm Hg reduction in systolic BP when substituted for hydrochlorothiazide.⁷²

A potential side effect seen with thiazide diuretics is an increase in blood-glucose levels. The mechanism of this increase is believed to be mediated through hypokalemia, leading to glucose intolerance.⁷⁴ However, the increase in glucose at currently used doses is quite small and the risk of new onset diabetes is decreased further when combined with an ACE inhibitor or ARB.⁷⁵ Furthermore, no study to date has been able to link thiazide-induced hyperglycemia to worse CV or renal outcomes.

In general, thiazide diuretics are effective in patients that have an estimated GFR greater than 50 mL/min. Loop diuretics should be given to patients with lower levels of renal function. Typically, they should be dosed twice daily unless using the longer-acting torsemide. Diuretic resistance is a commonly encountered problem and relates to either under dosing, severe hypoalbuminemia, or heart failure. Classically, the approach to these patients involves increasing the dose of diuretic to the appropriate level and combining a loop diuretic with a diuretic that acts at the distal tubule. While this approach is reasonable, consideration should be given to using a potassium-sparing diuretic, such as amiloride, with a loop diuretic. The rationale behind this is that the chronic exposure to loop diuretics leads to hypertrophy of the epithelial sodium channel in the cortical collecting duct, the target of amiloride.⁷⁶

CALCIUM CHANNEL BLOCKERS

When used in patients without proteinuric renal disease, both dihydropyridine CCBs (amlodipine, nifedipine) and nondihydropyridine CCBs (verapamil or diltiazem) are effective in lowering BP and both classes have been shown to lower CV events in high-risk populations.⁷⁷ These agents appear to have particular efficacy for CV risk reduction when paired with an ACE inhibitor. In the recently published Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), patients that were high risk for a CV event that were treated with a background of ACE inhibition had a 19% CV event relative-risk reduction when treated with amlodipine, compared with those treated with hydrochlorothiazide.⁷⁸ Similarly, verapamil has been shown to be effective in reducing CV outcomes in patients with hypertension and coronary artery disease.⁷⁹

Both preclinical and clinical data demonstrate different renal effects of dihydropyridine CCBs and nondihydropyridine CCBs in patients who have proteinuria, as dihydropyridine CCBs do not reduce albuminuria to the same extent as do nondihydropyridine CCBs.^{80,81} The mechanism of this difference relates to differences in glomerular permeability that occur in patients with advanced nephropathy.^{82,83} This difference in antiproteinuric effect has translated into worse renal outcomes in advanced nephropathy, with proteinuria treated with dihydropyridine CCBs when compared with those treated with blockers of the RAAS.⁸³

CCBs should not be used to decrease protein excretion in those with MA. In the Bergamo Nephrologic Diabetes Complications Trial, which compared nondihydropyridine CCBs with ACE inhibitors, alone or in combination, in patients with hypertension,

Type-2 diabetes mellitus, and normal urinary albumin excretion, no significant effect on reduction of MA was seen by verapamil alone. MA development, the primary endpoint, occurred with similar frequency in the verapamil and placebo group.⁸⁴ These results were foreseeable, as neither class of CCBs have anti-inflammatory effects on the vasculature and, as such, are unlikely to have any impact on endothelial damage, the antecedent of MA.^{16,85}

In summary, both classes of CCBs should be used aggressively for BP reduction in patients without proteinuric renal disease. In those with advanced proteinuric nephropathy, nondihydropyridine CCBs are preferred, per guidelines, but dihydropyridine CCBs should be used only in combination with an ACE inhibitor or ARB to maximally reduce BP and slow nephropathy progression.¹⁵

β-ADRENERGIC BLOCKERS

Despite being quite effective at lowering BP, clinicians have been reluctant to use β-blockers because of a significant, adverse metabolic profile. Furthermore, recent data have called into question use of β-blockers for treating hypertension, although the data are focused on atenolol rather than the class.⁸⁶ Moreover, recent studies demonstrate that excessive reduction in heart rate may be a problem with this class, although more than 80% of the studies quoted were with atenolol.⁸⁷ All advanced nephropathy patients have an increase in sympathetic activity and a high CV event rate. Data clearly indicate a benefit of β-blockers in such patients, yet they are not used, a trend that should change to reduce CV risk.⁸⁷

The emergence of newer β-blockers may expand the role for these agents, especially in diabetes or those with MA. The combined α- and β-blocker, carvedilol, and the β-1 vasodilating agent, nebivolol, have neutral glycemic and lipid parameters. Carvedilol, reduces CV morbidity and mortality and the risk of MA development in those with hypertension and diabetes.^{88,89} The mechanism of decreasing MA development likely relates to the antioxidant properties of carvedilol. Thus, vasodilating β-blockers can be used in patients with compelling indications, and are excellent add-on agents to reduce risk and achieve BP targets.

α-ADRENERGIC BLOCKERS

The use of α-adrenergic antagonists, although effective in reducing BP, has not been shown to slow CKD progression or consistently reduce albuminuria in either animal models or patients with Type-2 diabetes.⁹⁰ This class of agents also fails to reduce CV events in patients with heart failure, as evidenced by the results of the long-acting α-blocker arm of ALLHAT, which was stopped early because of increased events.³⁰

CHALLENGES FOR THE FUTURE

Many physicians fail to use more than one or two medications and then at low doses, hence they fail to achieve BP goal. The average number of agents needed to approach the current guideline goal of less than 130/80 mm Hg for those with CKD in clinical trials is 3.3 agents at maximally tolerated doses (**Fig. 5**). Thus, we must overcome physician inertia and use more fixed-dose combinations if as guidelines state, BP is greater than 20/10 mm Hg above the goal. Data from ACCOMPLISH make a compelling argument for this tenant, and also the use of combinations other than those with a diuretic, as there was an additional 20% CV risk reduction over the diuretic/ACE inhibitor combination.

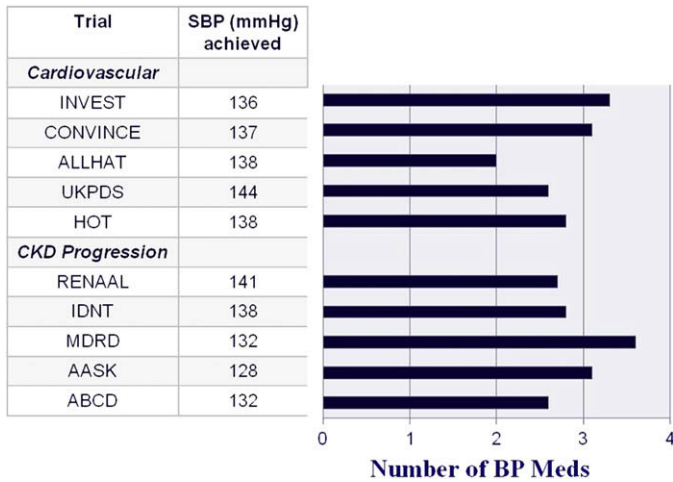


Fig. 5. Number of antihypertensive medications required to achieve BP goals in major clinical trials over the past decade.

There has been concern about the potential risks of aggressive BP lowering, particularly in elderly patients with Type-2 diabetes. Reducing diastolic BP to less than 80 mm Hg has been thought to increase CV risk in this group, but no convincing evidence of this possibility was found in prospective clinical trials.^{91,92} Retrospective analyses suggested that there might be a J-shaped relationship between diastolic BP and the rate of CV disease mortality in patients with established symptomatic coronary artery disease or unstable angina. However, a post hoc analyses of two separate renal outcome trials has failed to demonstrate a J curve for BP until levels get to less than 115/55 mm Hg.⁹³ Thus, the putative J curve should not serve as a deterrent to lowering BP to recommended goals in the absence of any clear evidence of coronary disease or unstable angina.

BP goal should be achieved within 3 to 4 months in most patients, but longer periods may be required in those with previous strokes or autonomic dysfunction. BP should be monitored with patients in both the sitting and the upright position to exclude the possibility of orthostatic hypotension, because autonomic denervation is frequent among patients with Type-2 diabetes who have nephropathy and polyneuropathy.

One of the main reasons for the failure to achieve BP goal is inadequate drug dosing, which is related to emotion-based rather than evidence-based medicine. Physicians recall that there are dose-dependent side-effects of drugs. Although this is true for older antihypertensive agents, it is not true for ACE inhibitors or ARBs. Thus, to optimize CV and renal risk reduction, physicians should set BP, lipid, and glucose goals with their patients and state them on paper, keep a copy in the chart, and give one to the patient. To maximize reduction in CV and renal mortality, the patient and the physician should be aware of treatment goals and discuss progress toward them at each visit.

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