CHAPTER 53

Current Standards of Management of Hypertension in Chronic Kidney Disease

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There is a bidirectional relationship between hypertension and kidney disease, with one exacerbating the effect of the other. Kidney disease is an important end-organ effect of hypertension, and hypertension is a frequent finding and the most common comorbidity in both acute and chronic kidney diseases. Elevated blood pressure is an important modifiable risk factor for cardiovascular disease and progression of kidney disease.

The frequency and pathogenesis of hypertension varies with the type of kidney disease (eg, glomerular versus vascular) and with the duration of disease (acute versus chronic).

This chapter will briefly discuss the aspects of pathophysiology of hypertension in kidney diseases that have an effect on management, and the current guidelines for management of hypertension amongst patients with kidney diseases.

PATHOPHYSIOLOGY

Acute kidney disease

Acute glomerular diseases are characterized by sodium retention leading to volume expansion. Volume expansion suppresses the renin-angiotensin-aldosterone system and promotes release of atrial natriuretic peptide. The sodium retention is due to increased reabsorption in the collecting tubules secondary to resistance to the action of atrial natriuretic peptide and hyperactive $Na\text{-}K^{+}$-ATPase pump in the cortical collecting tubule.

In contrast, acute vascular disease produces renal ischemia, either in the whole kidney or in segments that leads to activation of the renin-angiotensin system which causes renin-mediated hypertension.

Chronic kidney disease

Hypertension is found in about 80-85% of patients with chronic kidney disease (CKD). The prevalence increases as the glomerular filtration rate falls progressively. In the Modification of Diet in Renal Disease (MDRD) study, about 65% patients exhibited raised blood pressure at a glomerular filtration rate (GFR) of 85 mL/min per 1.73 m2. This figure went up to 95% as the GFR fell to 15 mL/min per 1.73 m2. The prevalence is also affected by other patient related factors – such as ethnicity, body weight etc. While sodium retention is of primary importance in the genesis of hypertension in CKD, other factors like enhanced activity of the renin-angiotensin system, sympathetic overactivity, secondary hyperparathyroidism (by raising the intracellular calcium concentration), impaired vasodilatation secondary to reduced endothelial nitric oxide synthesis and iatrogenic factors like therapy with erythropoiesis-stimulating agents also contribute. Other features of hypertension in CKD are increase in central pulse pressure and isolated systolic hypertension secondary to increased vascular wall stiffening and absence of normal nocturnal decline in blood pressure.

In patients with CKD, hypertension not only hastens progression of kidney disease, it also increases likelihood of developing adverse cardiovascular outcomes such as myocardial infarction, stroke and heart failure. Moreover, a fair degree of interaction is noted between hypertension and proteinuria, so that the same level of blood pressure is associated with greater risk of adverse outcomes in patients with proteinuria compared to those without this abnormality. As a result, hypertension treatment goals are usually aligned with some urine protein reduction targets (typically <1 g/day), and lower targets have been suggested in those with significant persistent proteinuria.

MANAGEMENT OF HYPERTENSION IN KIDNEY DISEASE

The only firm statement that can be made regarding blood pressure management in CKD is that blood pressure lowering is desirable. Kidney Disease: Improving Global Outcomes (KDIGO) Workgroup performed a rigorous review of evidence, and developed guidelines for management of hypertension in CKD in 2012 (Table 1). However, there are no strong recommendations supported by high quality evidence regarding the level of blood pressure reduction, the goal blood pressure or choice of therapy in different situations. Several professional societies have produced commentaries on the KDIGO guidelines to provide practical recommendations on its application. It has been emphasized that guidelines should not be used as a cookbook, and application of recommendations should be tailored to the needs of an individual patient. Recommendations might vary depending on ethnicity or gender. For example, calcium channel blockers might be more effective compared to other drugs in black patients.

Blood pressure measurement

A few words are necessary on describing the techniques of BP measurement on CKD. Most of the data on BP control comes from studies where BP has been measured in physicians' offices. To minimize the possibility of confounding due to white coat hypertension, blood pressure should be measured more than once during the same visit, with an interval of at least 1– 2 min. BP should

Table 1: Summary of KDIGO recommendation statements

Chapter	Number	Intervention (threshold)		Target	Grading
(2) Lifestyle and pharmacological treatments					
General strategies	2.1	Individualize of targets and agents according to age, CVD, comorbidities, risk of CKD progression, retinopathy (DM) and tolerance of treatment			Not graded
	2.2	Inquire about postural dizziness Check for postural hypotension regularly			Not graded
Lifestyle Modification	2.3.1	Achieve/maintain healthy weight		BMI 20-25 kg/m^2	ID
	2.3.2	Lower salt intake		<90 mmol/day (<2 g/day) of sodium	1C
	2.3.3	Exercise Programme		≥30', 5x/week	ID
	2.3.4	Limit alcohol intake		≤2 drinks/day (male); ≤1 drink/day (female)	2D
(3/4) CKD patients without/with diabetes (DM-/DM+)					
	DM-/DM+	Ualb (Uprot)[a]	BP threshold[b]	BP target[c]	DM-/DM+
	3.1/4.1	<30(<150)	>140/90	≤ 140/90	1B/1B
		Agent: no recommendation			
	3.2; 3.3/4.2	≥30(≥150)	>130/80	≤ 130/80	2D;2C/2D
	3.4; 3.5/4.3; 4.4	Agent: ACE-I or ARB			2D;1B/2D;1B
(5) Kidney transplants					
	5.1	Any	>130/80	≤ 130/80	2D
	5.2	Agent: time after transplantation, use of calcineurin inhibitors, albuminuria, comorbidities			Not graded
(6) Children					
	6.1/6.2	Any	>90th percentile[d]	≤50th percentile[d]	1C/2D
	6.3	Agent: ACE-I or ARB			2D
(7) Elderly					
	7.1	• Tailor, age, co-morbidities, other therapies • Gradual escalation • Close attention to adverse events: electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects			Not graded

[a]Ulb, albuminuria; Uprot, proteinuria; in g/24 h or g/g urinary creatinine.
[b]BP, blood pressure (mmHg); should be consistently above the systolic or diastolic threshold.
[C]BP, blood pressure (mmHg); should be consistently at or below the systolic and diastolic goal.
[d]Thresholds and targets for mean arterial pressure, percentiles for height, age and sex.

be measured in both arms when the patient is seen for the first time, and when possible, measurements should be made on more than one occasion. The utility of home and ambulatory blood pressure monitoring are less clearly established. However, for those who measure BP at home, as a rule of thumb, target values should be 5– 10 mmHg lower.

The use of oscillometric devices is increasing. However, they may produce erroneous readings in patients with advanced arteriosclerosis and arterial stiffness, common in patients with advanced kidney disease.

Goal blood pressure

Hypertension in CKD is a chronic condition, and the arterial system adapts to a higher pressure by remodeling. Therefore, rapid lowering of blood pressure should be avoided; the longer hypertension exists, the longer it should take to obtain the desired target. Another point of note is to look for consistency in blood pressure measurements and not to make changes based on a single measurement alone unless the value is clearly abnormal. Finally, the aim of treatment should be to achieve a blood pressure that is below a target in resting conditions most of the time.

Patients with CKD exhibit vascular stiffness related to changes in the blood vessel wall and/or vascular calcification. This leads to a situation where the measured systolic blood pressure stays relatively high whereas the diastolic blood pressure can fall to dangerously low levels. It is therefore important to be on the lookout for warning signs such as postural dizziness. Regular inquiry about symptoms of postural hypotension should be made. Altering antihypertensive therapy to reduce asymptomatic postural hypotension or to achieve a target standing BP has not been recommended since there is no evidence to show benefit from such approach.

A major issue which has seen fair amount of controversy in the last two decades is the goal blood pressure in patients with CKD. The most recent evidence has been provided from the Systolic Blood Pressure Intervention Trial (SPRINT). A total of 9361 nondiabetic individuals over 50 years of age with high cardiovascular risk were randomized to a systolic blood pressure target < 140 mm Hg (standard arm) or < 120 mm Hg (intensive arm). The study had targeted to include over 40% patients with CKD, but the final population had only about 28% with CKD. Individuals with eGFR <20 ml/min/1.73 m^2, proteinuria ≥1 g/d or equivalent, or polycystic kidney disease were excluded.

Individuals assigned to the intensive arm experienced a significant reduction in the primary composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular death, as well as several secondary outcomes (hazard ratio 0.75, 95% confidence interval [CI] 0.64–0.89). There was also a 27% reduction in all-cause mortality in the intensive arm.

For subjects with baseline CKD, there was no significant between-group difference in the composite renal outcome of ESRD or a 50% decline in eGFR. However, participants without CKD at baseline randomized to intensive therapy had a greater likelihood of ≥30% decline in eGFR to < 60 ml/min/1.73 m^2 (hazard ratio 3.49, 95% CI 2.44–5.10). In addition, subjects assigned to intensive arm 70% increased risk of developing acute kidney injury (AKI).

The study was stopped before reaching full recruitment target in view of the clear benefit in terms of cardiovascular events and all-cause mortality. The number of antihypertensive agents was 1.8 in the standard treatment and 2.8 in the intensive treatment arm. It should be noted that over 50% of the participants in the intensive therapy arm of had systolic blood pressure > 120 mm Hg after 1 year, highlighting the challenges of achieving and maintaining a lower target blood pressure.

General strategies and lifestyle modification

Most of the evidence around the effect of lifestyle changes such as physical exercise and salt restriction comes from general population studies. Several observational studies have demonstrated a salutary effect of physical activity on various end points such as mortality and quality of life, but none have specifically investigated the effect on BP control in the CKD population.

Sodium restriction is central to management of hypertension. In addition to a direct salutary effect, this enhances the antihypertensive effect of many drugs, especially angiotensin inhibitors. In a controlled trial, in patients with proteinuric CKD, a low-sodium diet decreased blood pressure to a greater degree than addition of valsartan. It is less clear that salt restriction alone would have a similar effect in patients with CKD as seen in the general population since the primary defect in these subjects is in reduced capability of kidneys to handle a given salt load. The recommended salt intake varies from 4-5 gm/day (corresponsing to 1.5-2 g of sodium).

Given the primacy of salt and water overload in genesis of hypertension in dialysis patients, the major therapeutic goal in hypertensive dialysis patients is gradual fluid removal to attain dry weight. Daily nocturnal dialysis is superior to standard 3/week dialysis for this purpose.

Maintenance of ideal body weight is a common-sense advice based on data from general population. Obesity has been associated with CKD progression. However, there is no data to show that reducing body weight improves kidney disease progression in obese patients. Rather, body weight is positively associated with outcomes amongst patients on dialysis. Finally, weight-loss diets are often high in potassium and protein which may be harmful in CKD.

Also, in the absence of data from CKD population, recommendation on smoking cessation and limitation of ethanol intake have been derived from general population as common sense recommendations.

Choice of antihypertensive agents

*Angiotensin converting e*nzyme-inhibitors (ACE-I) and angiotensin receptor blockers (ARB): Most guidelines support the primacy of place given to this class of antihypertensive agents in patients with kidney disease, based on evidence from multiple large randomized clinical trials. The effect is particularly evident in patients with proteinuric CKD. Doubts have, however, been raised whether the apparent superiority of these agents is not simply a reflection of better BP control. Although there is a theoretical rationale for combining these two classes of amgiotensin blocking agents, agents, risk of harm in the form of hyperkalemia has led to recommendation against combining these agents. Caution should be also exercised in patients with advanced CKD even on a single agent. In particular, suggestion has been made that these agents should be discontinued in patients with CKD stages 4–5. Current guidelines do not support discontinuation of these agents, but emphasize the need for close monitoring and careful selection. Availability of new potassium lowering agents, such as patiromer and sodium zirconium cyclosilicate might make these concerns moot.

These agents should also be avoided early after kidney transplantation as they may alter renal hemodynamics leading to elevation in serum creatinine that will need to be differentiated from other causes of graft dysfunction, and produce some lowering of hemoglobin.

Table 3: Randomized Controlled Hypertension Treatment Trials for Patients With CKD

Trial	Study Population	BP Targets	Kidney Disease Outcomes	Comments
MDRD[14]	Pts 18-70 y with Scr 1.2-7.0 mg/dL (women), 1.4-7.0 mg/dL (men), or CL_{cr} < 70 ml_/min/1.73 m^2 and MAP ≤ 125 mm Hg; excluded DM requiring insulin or proteinuria > 10 g/24 h	Low BP goal MAP< 92 mm Hg for age < 60 y, <98mm Hg for age > 61 y; usual BP goal MAP< 107 mm Hg for age < 60 y, <113mm Hg for age > 61 y	Low BP goal group had significantly reduced proteinuria and faster GFR decline during the first 4 mo and a slower subsequent decline in GFR	There was greater use of ACE inhibitors in the low-BP group; not powered to detect differences in CV event rates
REIN-2[15]	Pts 18-70 y with nondiabetic proteinuric kidney disease (>1 g/24 h) not receiving ACE-inhibitor therapy; CL_{cr} < 45 mL/min/1.73 m^2 if 1-3 g proteinuria, or <70 mL/min/1.73 m^2 if ≥ 3 g	Intensified control < 130/ 80 mm Hg; conventional control < 90 mm Hg diastolic	No additional benefit on rate of progression to ESRD from further BP reduction by adding felodipine to ACE-inhibitor therapy	Not powered to detect differences in CV event rates
AASK[16,17]	African Americans 18-70 y with hypertension, GFR 20-65 mL/min/1.73 m^2, and no other identified cause of CKD; excluded DM, proteinuria (protein-creatinine ratio > 2.5 g), malignant hypertension, CHF	Lower MAP goal ≤ 92 mm Hg; usual MAP goal 102-107 mm Hg	Mean GFR slope from baseline through 4 y did not differ significantly between lower-BP and usual-BP group; lower BP goal did not significantly reduce rate of clinical composite outcome; follow-up trial; no significant between-group difference in risk for primary outcome, with potential benefit in patients with protein-creatinine ratio > 0.22	Not powered to detect differences in CV event rates
HALT-PKD[18]	Pts 15-49 y with ADPKD and eGFR > 60 mL/min/ 1.73 m^2	Low BP target 95/60 to 110/75 mm Hg; standard BP target 120/ 70 to 130/80 mm Hg	Annual percentage increase in total kidney volume was significantly lower in the low-BP than standard-BP group without significant differences between the lisinopril-telmisartan group and lisinopril-placebo group	Not powered to detect differences in CV event rates
ACCORD BP[2]	Type 2 DM and either ≥40 y with CV disease or ≥55 y with atherosclerosis, albuminuria, LVH, or 2 additional CV disease risk factors, plus SBP 130-180 mm Hg taking 0-3 agents and <1.0g/d proteinuria	Intensive therapy target SBP 120 mm Hg; standard therapy target 140 mm Hg	Only primary outcome benefit was reduced strokes with intensive therapy; kidney end points of eGFR and macroalbuminuria were reduced in the intensive treatment group with no difference in ESRD rates	Excluded patients with Scr > 1.5 mg/ dL or proteinuria >1g/d

Table 3: Randomized Controlled Hypertension Treatment Trials for Patients With CKD

Trial	Study Population	BP Targets	Kidney Disease Outcomes	Comments
SPRINT[1]	Pts ≥50 y, SBP 130-180 mm Hg taking 0-4 agents with increased CV risk (prior CV event but not stroke), CKD with eGFR 20-<60 mL/min/ 1.73 m^2, age ≥ 75 y, or 10-y risk for CV events ≥ 15%	Intensive therapy target SBP 120 mm Hg; standard therapy target 140 mm Hg	Primary CV outcomes were reduced with intensive treatment for pts with pre-existing CKD as with the full study population; no difference in rates of 50% reduction of eGFR or ESRD rates; more pts without incident CKD had >30% decline in eGFR with intensive treatment	Excluded pts with stage > 4 CKD or proteinuria > 1 g/d; trial terminated early

Abbreviations; AASK, African American Study of Kidney Disease and Hypertension; ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACE, angiotensin-converting enzyme inhibitor, ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; CHF, congestive heart failure; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; CV, cardiovascular, DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; GFR, glomerular filtration rate; HALT-PKD, Halt Progression of Polycystic Kidney Disease; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; pt, patient; REIN-2, Ramipril Efficacy In Nephropathy-2; SBP, systolic blood pressure; Scr, serum creatinine; SPRINT, Systolic Blood Pressure Intervention Trial.

Diuretics: The use of diuretic therapy as primary antihypertensive agent for subjects with edema due to salt and water overload, and an add-on therapy to other agents is well-established. Most data is available for thiazide- like diuretics, such as hydrochlorothiazide, chlorthalidone and indapamide. The latter may be preferred in CKD because of its better metabolic side-effect profile and potassium-depleting effect. Thiazides become less effective as the glomerular filtration rate falls. Loop diuretics need to be used as initial therapy in these patients, with some preference for torsemide, which has a longer duration of action than furosemide. Higher doses are typically required in patients with CKD who are usually volume expanded even in the absence of edema. If edema persists despite loop diuretic therapy, a thiazide can be added. The diuretic efficacy of thiazides is enhanced in those already on a loop diuretic. Diuretics also enhance the BP lowering effect of ACE-I and ARBs.

Diuretic therapy should be increased until either the BP goal is achieved; or the patient develops symptoms related to volume loss (cramps, fatigue, orthostatic hypotension or unexplained elevation in the serum creatinine).

Calcium channel blockers: Dihydropyridine calcium-channel blockers abolish renal autoregulation and can increase proteinuria when used as a single agent and hence should be used only as a second-line therapy after angiotensin-blocking drugs. Non-dihydropyridine agents, however do not have this disadvantage.

The use of diltiazem in kidney transplant recipients demands caution because of its effect on cytochrome P-450 system that metabolizes immunosuppressive agents, leading to need to dose reduction.

Beta-blockers: Beta-blockers have fallen out of favour as first-line antihypertensive agents because of their short duration of action, heart rate lowering effect, and lack of effect on central blood pressure. They may however provide beneficial effect on patients with CKD at risk of sudden cardiac death by lowering sympathetic overactivity. Finally, newer class of beta blockers such as carvedilol, nebivolol and celiprolol do not share the aforementioned negative properties.

Finally, subjects with CKD are likely to require more drugs for BP control, and suffer from resistant hypertension. They are also on multiple drugs, raising the possibility of side effects and drug interactions. It is important to look into these points as they will impact adherence to treatment.

Nocturnal therapy: Normally, the blood pressure is approximately 15 percent lower during night. Failure of the blood pressure to fall by at least 10 percent during sleep is called “nondipping”, a common phenomenon amongst CKD subjects and associated with adverse cardiovascular outcomes. Studies have shown that shifting of at least one antihypertensive medication from the morning to the evening can restore the normal nocturnal blood pressure dip.

Renal denervation: Renal denervation (RDN) involves introduction of catheter into the renal arteries, and application of radiofrequency energy against the blood vessel wall to damage the nerve fibers (in particular the sympathetic fibres) surrounding the artery. Although the first sham-controlled study did not show a benefit of this approach, recent years have seen a revival with doubts on the technical approach used in the earlier study. Special case has been made for its use in subjects with CKD from a pathophysiological perspective, and selecting CKD patients for RDN have been described. This strategy, however, must be considered experimental at this stage.

While there is a general agreement on the KDIGO treatment recommendations and blood pressure targets in most CKD subpopulations (with or without diabetes, proteinuric and non proteinurics, dialysis or nondialysis, and special populations – children, elderly and kidney transplant recipients), some differences have been expressed by other societies, in particular the Canadian Society of Nephrology suggestion of keeping the BP target <130/80 for all non-dialysis diabetic subjects irrespective of the degree of proteinuria.

CONCLUSIONS

Although there are several clinical trials on management of hypertension in CKD (Table 3), most of them have shortcomings that limit the extraction of high quality evidence that could lead to strong statements. The lack of 1A guideline for such a common clinical problem is disappointing, and imposes a burden of further research on the nephrology community. Also, the presence of guidelines should not detract from the need to exercise clinical judgement in making therapeutic decisions. The key to success of any therapeutic approach for a chronic condition lies in making decisions that have real-world validity, communicating the rationale to the patient and revisiting periodically to ensure long-term compliance.

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