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REVIEW ARTICLE

Review Series - Recent Advances in the Management of Secondary Hypertension

Recent advances in the management of secondary hypertension: chronic kidney disease

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Abstract

Hypertension in chronic kidney disease (CKD) is the most commonly observed comorbidity and is a risk factor for end-stage renal disease (ESRD) as well as cardiovascular disease (CVD) and mortality. Therefore, suitable blood pressure (BP) control in CKD patients is very important in preventing both CVD and ESRD. We herein describe the recommendations of target BP and the pharmacological drug options from the evidence-based clinical practice guidelines for CKD in 2018 by the Japanese Society of Nephrology (JSN CKD 2018) and recent advances in the management of hypertension in CKD, including sodium-glucose cotransporter (SGLT) 2 inhibitors, mineralocorticoid receptor blockers, and renal denervation. In particular, SGLT2 inhibitors are a new class of "antihypertensive drugs" that have a homeostatic mechanism that regulates body fluid volume in addition to diuretic action, which may be closely associated with their cardiorenal protective properties.

Keywords Chronic kidney disease (CKD) · Fluid volume · Mineralocorticoid receptor (MR) blocker · Sodium-glucose cotransporter 2 (SGLT2) inhibitor · Renal denervation

Introduction

Hypertension is an important risk factor for cardiovascular disease (CVD) and mortality. Recently, the number of chronic kidney disease (CKD) patients has been globally increasing, and hypertension is the most common comorbidity in these patients [1]. In addition, hypertension in CKD patients is a risk factor for end-stage renal disease (ESRD) as well as cardiovascular events and mortality [1, 2]. Therefore, favorable blood pressure (BP) control in CKD patients is an essential treatment strategy for preventing ESRD and CVD [3].

In this review, we describe the recommendations for target BP and the pharmacological drug options from the evidence-based clinical practice guidelines for CKD established in 2018 by the Japanese Society of Nephrology (JSN CKD 2018) [4], and we discuss the recent advances in the management of hypertension in CKD, including sodium-glucose cotransporter (SGLT) 2 inhibitors, mineralocorticoid receptor (MR) blockers, and renal denervation.

Target blood pressure

The recent guideline JSN CKD 2018 [4] recommends a target BP of <140/90 mmHg in nondiabetic CKD patients without proteinuria and of <130/80 mmHg in other CKD patients (Table 1). On the other hand, it recommends a BP target of <150/90 mmHg in elderly patients over 75 years of age, regardless of the presence or absence of diabetes mellitus. If there are no adverse events such as orthostatic hypotension, a target BP of <140/90 mmHg is recommended (Table 1). However, lowering the systolic BP to <110 mmHg is not recommended in any CKD patients because there is no beneficial effect from such a level (Table 1).

Next, we introduce the major clinical studies that were the basis for setting the BP target in the JSN CKD 2018 [4]. In the ACCORD study [5], stroke and albuminuria were significantly reduced in type 2 diabetes patients who underwent intensive therapy (target systolic BP <120 mmHg) compared with the standard therapy (target systolic BP <140 mmHg), but the reduction in renal function (estimated glomerular

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Table 1 Target blood pressure for CKD patients

		<75 years	≥75 years
Diabetes (−)	Proteinuria (−)	<140/90	<150/90
	Proteinuria (+)[a]	<130/80	<150/90
Diabetes (+)		<130/80	<150/90

A target BP <140/90 mmHg is recommended for elderly patients over 75 years of age, if antihypertensive agents do not induce any adverse events such as hypotension and acute kidney injury. A systolic BP suppression below 110 mmHg is not recommended for adults with hypertension and CKD, regardless of CKD stage

[a]Proteinuria (+): urinary protein/Cr ratio of ≥0.15 g/gCr (CKD Practice guideline 2018 by the Japanese Society of Nephrology) [4]

filtration [eGFR]) was significantly greater in the intensive therapy group. A meta-analysis of 13 randomized clinical trials (RCTs) of type 2 diabetic patients revealed that a systolic BP <130 mmHg reduced the risk for stroke but increased serious adverse events such as hypotension and hyperkalemia [6]. In the SPRINT study [7], the intensive-treatment group (target systolic BP <120 mmHg) demonstrated a significant reduction in cardiovascular events and death compared with the standard-treatment group (target systolic BP <140 mmHg) in nondiabetic patients. However, serious adverse events, including hypotension and acute kidney injury or failure, were higher in the intensive-treatment group than in the standard-treatment group [7]. In a large-scale cohort study from Japan [8], a systolic BP ≥134 mmHg in proteinuria-positive cases and a systolic BP ≥141 mmHg in proteinuria-negative cases were indicative of a significantly high risk for progressing to CKD stage 3 or higher. The post hoc analysis of the ORIENT trial [9] showed that a systolic BP ≥131 mmHg increased renal events compared with a systolic BP <130 mmHg.

Selection of antihypertensive drugs

Multiple meta-analyses and RCTs show that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduce the risk of progression to ESRD and renal death, regardless of either the diabetic status or CKD stage [10, 11]. On the other hand, there is no consensus on whether ACEIs and ARBs have a superior cardiovascular protective effect compared with other antihypertensive drugs in patients with CKD [10, 12]. Based on such evidence, ACEIs and ARBs are recommended as first-line drugs for diabetic and nondiabetic patients with proteinuria, while ACEIs, ARBs, calcium channel blockers (CCBs), and thiazide diuretics are recommended for nondiabetic CKD stage 1–3 patients without proteinuria (Table 2).

There is no RCT that includes only elderly CKD patients over 75 years of age. A large cohort study of younger patients with CKD stage 5 (mean age: 64.7 years) reported that the administration of ACEIs or ARBs improved renal prognosis in comparison with other antihypertensive drugs [13]. Nevertheless, the JSN CKD 2018 recommends CCBs in CKD patients over 75 years because elderly people with severe atherosclerosis are vulnerable to dehydration and ischemia, and ACEIs and ARBs may cause a rapid onset of renal dysfunction. These inconsistencies show the difficulty of applying the results of large-scale trials in real clinical settings and the importance of balancing the risks and benefits of medications.

Controversy regarding hypertension management in CKD

To date, there remains much debate about the best target BP and antihypertensive drug selection. The main reason for this controversy depends on the goal of what is the highest priority outcome. The major outcomes of antihypertensive therapy in CKD are “cardiovascular events” and “renal prognosis”. The target BP and the selection of antihypertensive drugs are then determined based on these outcomes. Unfortunately, however, the risk of cardiovascular and renal events is not always compatible at the same target BP or for the same drug selection. For example, in the SPRINT study [7], the intensive-treatment group (target systolic BP <120 mmHg) demonstrated a significant reduction in cardiovascular events and deaths compared with the standard-treatment group (target systolic BP <140 mmHg). However, the risk of acute renal injury was conversely higher in the intensive-treatment group [14, 15]. Thus, achieving compatibility of cardiorenal protection at the same target BP is difficult.

The impact of each antihypertensive drug on cardiorenal outcomes is different in CKD patients. ACEIs and ARBs reduce the risk of progression to ESRD and renal death [10, 11], but no superior benefit of ACEIs and ARBs was observed in cardiovascular protective effects compared with other antihypertensive drugs [10, 12].

Recent advances

SGLT2 inhibitor

SGLT2 inhibitors are a new class of antidiabetic drugs that increase urinary glucose levels and sodium (Na^+) excretion, thereby decreasing BP as well as blood glucose levels [16–18]. In particular, a higher body mass index (BMI) and baseline BP are predictors of a good BP response to SGLT2

Table 2 Recommended antihypertensive agents according to the CKD stages and age category

CKD stage	<75 years		75 years ≤
	Diabetes and non-diabetes with proteinuria[a]	Non-diabetes without proteinuria	
Stages 1–3 [eGFR ≥30 ml/min/1.73 m^2]	(1) ACEIs or ARBs (2) CCBs (high risk of CVD) or thiazide diuretics (fluid retention)	ACEIs, ARBs, CCBs, or thiazide diuretics (fluid retention)	Same as less than 75 years
Stages 4, 5 [eGFR <30 ml/min/1.73 m^2]	(1) ACEIs or ARBs (2) CCBs (high risk of CVD) or loop diuretics (fluid retention)	ACEIs, ARBs, CCBs, or loop diuretics (fluid retention)	CCBs

In CKD stages 4, 5, low dose ACEIs or ARBs are recommended as an initial therapy. If ACEIs or ARBs induce either a worsening of the renal function or hyperkalemia, then CCBs should be used

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor antagonists, *CCBs* calcium channel blockers, *CVD* cardiovascular disease

[a]Proteinuria: urinary protein/Cr ratio of ≥0.15 g/gCr (Clinical Practice Guidelines for Chronic Kidney Disease 2018) [4]

inhibitors [18]. In the SACRA study, reductions in the daytime and 24-h systolic BP at 12 weeks with empagliflozin were significantly greater than with a placebo (–9.5 and –7.7 mmHg, respectively; $p \leq 0.002$) in obese diabetes patients with uncontrolled hypertension (mean age 70 years, mean BMI 26 kg/m^2, mean HbA1c 6.6%) [19].

Recent clinical trials have shown that SGLT2 inhibitors exhibit cardiorenal protective properties in patients with type 2 diabetes and heart failure [20–25]. A meta-analysis of type 2 diabetes patients showed that SGLT2 inhibitors reduced the risk of cardiovascular death or hospitalization for heart failure by 23% (hazard ratio 0.77 [95% confidence interval 0.71–0.84], $p < 0.0001$) and reduced the risk of progression of renal disease by 45% (0.55 [0.48–0.64], $p < 0.0001$), regardless of baseline atherosclerotic risk category or history of heart failure [26]. Furthermore, the CREDENCE trial, which includes type 2 diabetes and albuminuric patients with an eGFR of 30 to <90 ml/min/1.73 m^2, shows that the SGLT2 inhibitor canagliflozin suppresses the composite renal endpoints (doubling of serum creatinine, ESRD, or death from renal or cardiovascular causes) regardless of baseline eGFR [24]. Therefore, the reductions in hospitalization for heart failure and progression of renal disease by SGLT2 inhibitors do not depend on baseline atherosclerotic risk category or renal function [24, 26].

The amelioration of extracellular volume expansion, including the reduction in the plasma volume, is one of the most promising BP-lowering mechanisms by SGLT2 inhibitors [17, 18, 27–30], which may lead to beneficial cardiorenal outcomes [16, 31–33]. Human and animal studies have shown that SGLT2 inhibitors induce natriuresis and glucose-induced osmotic diuresis by inhibiting the transporter SGLT2 in the early proximal tubule [30, 34–36]. We previously reported that the SGLT2 inhibitor dapagliflozin predominantly ameliorates extracellular volume expansion with a mild and transient increase in urinary Na^+ levels and fluid excretion in diabetic kidney disease patients [37, 38]. On the other hand, SGLT2 inhibitors have a protective effect against hypovolemia. In euvolemic animal models, the SGLT2 inhibitor ipragliflozin did not decrease the body fluid volume (extracellular water [ECW], intracellular water, and total body water) despite causing an increase in both urinary fluid levels and Na^+ excretion [39, 40]. The detailed mechanisms for this interesting finding are (1) the compensatory increase in fluid and food intake and (2) the suppression of excessive urine volume by vasopressin-induced solute-free water reabsorption in the collecting duct [39, 40]. These homeostatic mechanisms of SGLT2 inhibitors on the body fluid status were confirmed in our recent clinical study, in which dapagliflozin decreased the extracellular volume in patients with fluid retention, but it did not show any such decrease in the extracellular volume in those without fluid retention [41]. Similarly, several studies of type 2 diabetes patients without fluid retention showed that SGLT2 inhibitors transiently decreased the ECW or body fluid balance within 1 week, and then it returned to the initial value after that time [42, 43]. In contrast to SGLT2 inhibitors, the body fluid responses to the loop diuretic furosemide and vasopressin V2 receptor antagonist tolvaptan did not clearly vary depending on the pretreatment extracellular volume status (Fig. 1) [41]. The compatibility of the amelioration of extracellular fluid retention and the prevention of extracellular hypovolemia by SGLT2 inhibitors may contribute to cardiorenal protection in terms of the reduction in heart failure and BP, a lowering of acute kidney injury risk and the prevention of the persistent activation of the renin–angiotensin aldosterone (RAS) system [25, 36, 42, 44–46]. Thus, SGLT2 inhibitors are a new class of "antihypertensive drugs" that have a homeostatic mechanism that regulates body fluid volume in addition to diuretic action, which may play an important role in long-term cardiorenal protection.

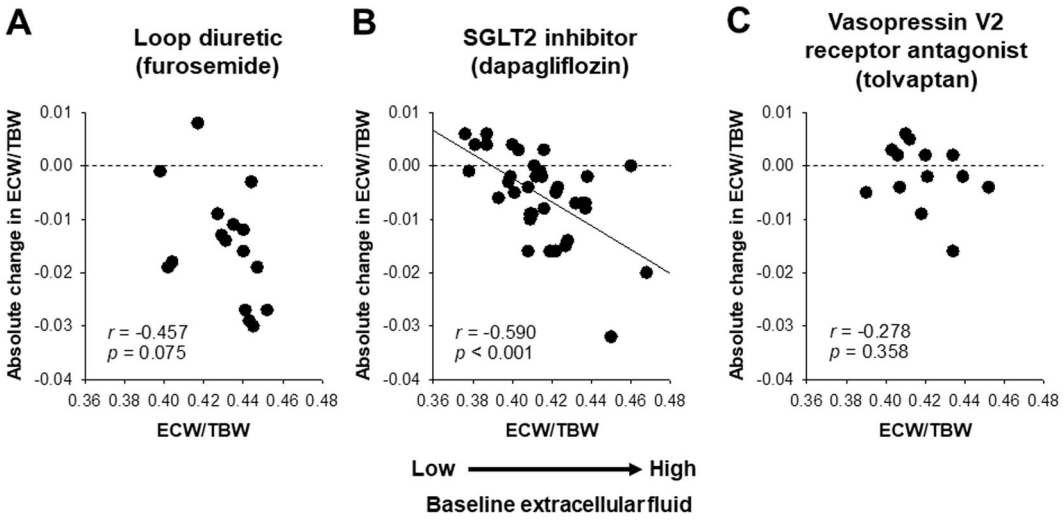

Fig. 1 The correlation between baseline extracellular fluid status (the ratio of extracellular water to total body water [ECW/TBW]) and the absolute change in ECW/TBW in response to loop diuretic furosemide (**a**), SGLT2 inhibitor dapagliflozin (**b**), and vasopressin V2 receptor antagonist tolvaptan (**c**) for 1 week. In the furosemide (**a**) and tolvaptan (**c**) groups, the ECW/TBW level was not significantly correlated, while in the dapagliflozin group (**b**), it was negatively and significantly correlated (modified from ref. 41)

MR blocker

The MR is a nuclear receptor that is abundantly present in the distal tubules and collecting ducts, and it serves as a regulator of the fluid volume and plasma Na^+, K^+, and Cl^- flux mechanisms in the segment [47, 48]. MR regulates BP and therefore is involved in the pathogenesis of heart failure and CKD progression [49–52]. MR is activated mainly by aldosterone, but Ras-related C3 botulinum toxin substrate 1 (Rac1) also contributes to the activation of MRs [53]. Interestingly, in the context of salt-sensitive hypertension, high salt loading suppresses plasma aldosterone but activates MR signaling via Rac1, which causes BP elevation and kidney disease progression [47, 54].

The EVALUATE study, a randomized, placebo-controlled trial, showed that the MR blocker eplerenone significantly reduced albuminuria and BP in nondiabetic CKD patients who were already on ACEIs or ARBs [52]. In the post hoc analyses of the study, the renoprotective effects of eplerenone were prominent in those with high urinary sodium excretion, indicating the strong association between salt intake and MR signaling. Esaxerenone, a novel highly potent and selective nonsteroidal MR blocker that has been used for hypertension in Japan [55], has a stronger inhibitory effect on MR than spironolactone or eplerenone [56]. In a randomized, double-blind, placebo-controlled, phase 2 trial that enrolled 365 hypertensive or normotensive patients with type 2 diabetes mellitus and microalbuminuria, the addition of esaxerenone for 12 weeks to ongoing use of RAS inhibitors significantly reduced the urinary albumin-to-creatinine ratio [57]. Furthermore, the double-blind randomized phase 3 study comparing esaxerenone and eplerenone in patients with essential hypertension demonstrated that the proportions of patients achieving target sitting BP (<140/90 mmHg) were 31.5%, 41.2%, and 27.5% with esaxerenone 2.5 and 5 mg/day and eplerenone 50 mg/day, respectively [58]. The incidences of adverse events were similar across all treatment groups [58]. These results indicate that esaxerenone is an effective and well-tolerated MR blocker in patients with essential hypertension.

Renal denervation

Catheter-based renal denervation, which reduces sympathetic efferent and afferent sensory nerve activity, is an alternative treatment option for patients with uncontrolled hypertension [59]. The inhibition of the RAS system by sympathetic efferent nerve ablation causes a reduction in BP through an increase in renal blood flow and a reduction in salt sensitivity [59]. The SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial, a recent randomized, sham-controlled trial to assess the efficacy of catheter-based renal denervation, has shown that the treatment difference between renal denervation and the sham procedure for 24-h systolic BP was –3.9 mmHg, and for office systolic BP, the difference was –6.5 mmHg from baseline to 3 months after the procedure [60]. The SYMPLICITY HTN-Japan, the first randomized controlled trial in Asia, also shows that renal denervation maintained the systolic BP reduction for up to 36 months (office systolic BP reduction -32.8 ± 20.1 mmHg) [61].

Several studies in CKD patients showed the long-term sustained BP-lowering effect of renal denervation. Ott et al. reported that renal denervation in patients with CKD stages 3 and 4 reduces office BP by $20 \pm 20/8 \pm 14$ mmHg and average 24-h ambulatory BP by $9 \pm 14/4 \pm 7$ mmHg after 1 year [62]. A recent report from Kiuchi et al. showed the mean change in systolic ambulatory BP monitoring compared with baseline to be -21.3 ± 14.1 mmHg at 24 months in patients with CKD stages 2–4 [63]. Furthermore, the Global SYMPLICITY Registry, a prospective, open-label registry in hypertensive patients undergoing renal denervation, showed the renal function decline in patients with CKD (eGFR <60 ml/min/1.73 m^2) to be mild for 3 years (-3.7 ml/min/1.73 m^2) [64]. In these reports, no apparent long-term safety concerns were observed following the renal denervation procedure [62–64]. From such evidence, renal denervation may therefore be suitable for individuals with resistant hypertension or noncompliant patients, including those with CKD [65].

Conclusion

The clinical guideline JSN CKD 2018 recommends new target BP and the pharmacological drug options for hypertension in CKD patients. The important change from the previous version is that CCBs are recommended in CKD stages 4 and 5 patients over 75 years of age because elderly people with severe atherosclerosis are vulnerable to dehydration and ischemia. Among the recent advances in this field, SGLT2 inhibitors are a promising "antihypertensive drug" for preventing both CVD and ESRD. In particular, they have a homeostatic mechanism to regulate the body fluid volume in addition to a diuretic action, and therefore, they may be a novel mechanism for achieving cardiorenal protection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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