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Hypertension Management in Patients with Chronic Kidney Disease in the Post-SPRINT Era

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The management of high blood pressure (BP) is crucial for improving outcomes in patients with chronic kidney disease (CKD). The updated Kidney Disease: Improving Global Outcomes 2021 BP guideline proposes treating adults with CKD to a target systolic BP (SBP) of <120 mmHg based on the standardized office BP measurement. This suggestion is largely based on the finding of SPRINT (Systolic Blood Pressure Intervention Trial) that targeting an SBP of <120 mmHg versus <140 mmHg is beneficial for cardiovascular and mortality outcomes, regardless of the patient's kidney disease status. However, extended follow-up studies of CKD trials showed that intensive versus usual BP control was associated with a lower risk of kidney failure in patients with, but not in those without, proteinuria. Similarly, a recent population-based study in Korea demonstrated that the optimal on-treatment BP for composite cardiorenal and mortality outcomes was left-shifted in adults with CKD, particularly in those with albuminuria, relative to that in patients without CKD. Moreover, in meta-analyses of randomized trials, more intensive versus standard BP control was associated with a lower risk of all-cause mortality in patients with CKD and albuminuria but not in those without CKD. Meanwhile, a 2020 Cochrane review reported that lower BP targets (≤135/85 mmHg), compared with standard targets (≤140/90 mmHg), resulted in a small reduction in cardiovascular events, an increase in other serious adverse events, and no reduction in total serious adverse events. Lowering SBP to <120 mmHg can potentially increase the risk of treatment-related adverse events beyond the cardioprotective benefits, and standardized BP measurement increases the burden on patients and resources. Thus, targeting a BP of <130/80 mmHg with appropriate office BP measurement can be an option in patients with CKD. The presence of albuminuria would need to be additionally considered to determine individualized BP targets.

Key Words: Antihypertensive agents, Blood pressure, Chronic kidney disease, Practice guideline

Chronic kidney disease (CKD) is a common health problem worldwide and is associated with a high risk of adverse renal and cardiovascular events. Hypertension is common in patients with CKD, and the management of blood pressure (BP) is known to be crucial for slowing the progression of kidney disease and for reducing the rates of cardiovascular events. In early 2021, the Kidney Disease: Improving Global Outcomes (KDIGO) released an updated BP guideline that suggests a target systolic BP (SBP) of <120 mmHg based on the standardized office measurement in adults with CKD[1]. However, this suggestion is largely based on the results of a single trial, SPRINT (Systolic Blood Pressure Intervention Trial), and standardized BP measurements require efforts from patients and health-care providers. The limitations of the evidence and gaps between guidelines and practice will be reviewed here.

Table 1. Extended follow-up studies for intensive versus usual BP control in CKD

Clinical Trial (Follow-up)	Target MAP, mmHg	Baseline Kidney Function	Progression to ESKD, HR (95% CI)	All-cause Death, HR (95% CI)
CKD with Severe Proteinuria				
MDRD-a subset[3] (median 10.7 y)	<92 vs. <107	Urine protein ≥1 g/d and GFR 13-55	0.55 (0.41-0.72)	NA
AASK subset[6] (median 14.4 y)	≤92 vs. 102-107	Urine protein ≥1 g/d and GFR 20-65	0.59 (0.41-0.85)	NA
CKD without Severe Proteinuria				
MDRD-a subset[3] (median 10.7 y)	<92 vs. <107	Urine protein <1 g/d and GFR 13-55	0.81 (0.64-1.02)	NA
AASK subset[6] (median 14.4 y)	≤92 vs. 102-107	Urine protein <1 g/d and GFR 20-65	1.05 (0.83-1.32)	NA
CKD, Total Participants				
MDRD-b[5] (median 19.3 y)	<92 vs. <107	GFR 13-55, urine protein ≥0.3 g/d in 51.8%	0.86 (0.73-1.00)	0.82 (0.68-0.98)
AASK[6] (median 14.4 y)	≤92 vs. 102-107	GFR 20-65, PCR ≥0.22 in 32.6%	0.92 (0.75-1.12)	0.92 (0.77-1.10)

*Data are for all participants with or without severe proteinuria.
BP, blood pressure; CI, confidence interval; ESKD, end-stage kidney disease; GFR, glomerular filtration rate (mL/min/1.73 m^2); HR, hazardratio; MAP, mean arterial pressure; NA, not available; PCR, urineprotein-to-creatinineratio (g/g); s-Cr, serum creatinine.

The KDIGO 2021 BP Guideline

The KDIGO BP guideline recommends starting renin-angiotensin system inhibitors (RASi) (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin II receptor blockers [ARB]) in persons with high BP, CKD, and severely increased albuminuria (estimated glomerular filtration rate [eGFR] categories G1-G4, urine albumin-to-creatinine ratio [ACR] category A3) without diabetes and in persons with high BP, CKD, and moderately to severely increased albuminuria (G1-G4, A2-A3) with diabetes. The guideline suggests starting ACEi or ARB in persons with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without diabetes. Furthermore, the guideline recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor therapy in persons with CKD, with or without diabetes.

The key points of the 2021 guideline are the recommendation of a standardized office BP measurement instead of a routine office BP measurement for the management of high BP in adults and the suggestion of treating adults with high BP and CKD to a target SBP of <120 mmHg, when tolerated, based on the standardized office BP measurement. The guideline suggests using out-of-office BP measurements with ambulatory BP monitoring or home BP monitoring as complementary readings to standardized office BP readings.

In comparison, the original KDIGO BP guideline recommends maintaining an office BP of <130/80 mmHg in patients with CKD and albuminuria and <140/90 mmHg in patients with CKD without albuminuria[2]. This recommendation was based on the results of extended follow-up studies of randomized trials in patients with CKD (Table 1)[3-6]. Conversely, the recommendation of a target SBP of <120 mmHg with the standardized measurement is largely based on the findings of SPRINT in CKD subsets, in which BP was determined as an average of 3 readings obtained after a rest period of 5 min, with the patients sitting with their back supported and without talking[7]. Standardized BP measurements increase the burden on patients, health-care providers, and facilities. Although ambulatory or home BP monitoring can be used to complement standardized office BP measurements, no completed large clinical trials have recommended an out-of-office BP target.

Table 2. Renin-angiotensin system inhibitors in CKD

Clinical Trial (Index Disease)	Treatment vs. Control Group	Baseline Kidney Function	CKD Progression, Risk Reduction %	All-cause Death, Rate %
Benazepril[8] (nondiabetic CKD)	Benazepril vs. placebo	eGFR 30-60, mean urine protein 1.8 g/d	53% for s-Cr doubling or ESKD	2.7% vs. 0.4%
Benazepril[12] (nondiabetic CKD)	Benazepril vs. placebo	s-Cr 3.1-5.0 mg/dL and urine protein ≥0.3 g/d	48% for s-Cr doubling or ESKD	0.9% vs. 0.0%
REIN[9] (nondiabetic CKD)	Ramipril vs. placebo	Urine protein 1.0-3.0 g/d and CrCl 20-70	56% for ESKD	1.0% vs. 0.0%
REIN[10] (nondiabetic CKD)	Ramipril vs. placebo	Urine protein ≥3.0 g/d and CrCl 20-70	49% for s-Cr doubling or ESKD	2.6% vs. 1.1%
AASK[16] (hypertensive CKD)	Ramipril vs. amlodipine	GFR 20-65, PCR >0.22 in 32.6%	38% for GFR decline or ESKD	1.5% vs. 1.7%
Captopril[13] (DKD, T1D)	Captopril vs. placebo	Urine protein ≥0.5 g/d and s-Cr ≤2.5 mg/dL	50% for ESKD or death	3.9% vs. 6.9%
RENAAL[14] (DKD, T2D)	Losartan vs. placebo	ACR ≥0.3 and s-Cr 1.0-3.0 mg/dL	21% for s-Cr doubling or ESKD	21.0% vs. 20.3%
IDNT[15] (DKD, T2D)	Irbesartan vs. amlodipine or placebo	Urine protein ≥0.9 g/d and s-Cr 1.0-3.0 mg/dL	21% for s-Cr doubling, ESKD, or death	15.0% vs. 15.5%

ACEi, angiotensin-converting enzyme inhibitor; ACR, urine albumin-to-creatinine ratio (g/g); ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CrCl, creatinine clearance (mL/min/1.73 m^2); DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESKD, end-stage kidney disease; GFR, glomerular filtration rate (mL/min/1.73 m^2); PCR, urine protein-to-creatinine ratio (g/g); s-Cr, serum creatinine; T1D, type 1 diabetes; T2D, type 2 diabetes.

Renin-Angiotensin-Aldosterone System Inhibitors

Randomized controlled trials have shown the clinical benefits of RASi in patients with CKD and proteinuria (Table 2). The renoprotective effect of ACEi was demonstrated in trials for nondiabetic kidney disease with overt proteinuria[8-10], and the benefit persisted even in patients with advanced CKD (eGFR <30 mL/min/1.73 m^2)[11,12]. The beneficial effect of ACEi was also shown in a trial for type 1 diabetes with proteinuria (urine protein ≥500 mg/day)[13]. The renoprotective effect of ARB was demonstrated in trials for type 2 diabetes with severely increased albuminuria (urine ACR ≥300 mg/g)[14,15].

However, combination therapy with ACEi and ARB increased the risks of adverse events, such as acute kidney injury and severe hyperkalemia, without providing clinical benefits in patients at a high risk of vascular events and in those with type 2 diabetes and severely increased albuminuria (Table 3)[17,18]. Similarly, treatment with aliskiren, a direct renin inhibitor, in combination with either an ACEi or ARB resulted in more adverse events with no additional benefits in trials for type 2 diabetes with CKD or cardiovascular disease and for heart failure with an ejection fraction of ≤35%[19,20]. In contrast, finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, in combination with an ACEi or ARB showed benefits in terms of slowing the progression of kidney disease and reducing the rates of cardiovascular events in trials for type 2 diabetes with CKD[21,22].

New Classes of Drugs

Besides RASi, other new classes of drugs have shown a noticeable renoprotective benefit in randomized controlled trials (Table 4). Sacubitril-valsartan, an angiotensin receptor–neprilysin inhibitor (ARNi), reduced the risk of kidney disease progression and hyperkalemia compared with either an ACEi or ARB in patients with heart failure[23,24]. ARNi can also be considered in patients with CKD at a risk of hyperkalemia, although direct evidence in CKD would be needed to confirm the benefit.

Table 3. Combination therapy with renin-angiotensin-aldosterone system inhibitors

Clinical Trial (Index Disease)	Treatment vs. Control Group	Participants	Kidney Disease Progression, HR (95% CI)	All-cause Death, HR (95% CI)	Hyperkalemia,* Rate %
ONTARGET[17] (high risk patients)	Ramipril-telmisartan vs. ramipril	Vascular disease or high risk of diabetes	1.24 (1.01-1.51) for s-Cr doubling or all dialysis	1.07 (0.98-1.16)	5.6% vs. 3.3% for s-K^+ >5.5 mmol/L
VA NEPHRON-D[18] (DKD, T2D)	Losartan-lisinopril vs. losartan-placebo	ACR ≥0.3 and eGFR 30-90	0.78 (0.58-1.05) for eGFR decline or ESKD	1.04 (0.73-1.49)	9.9% vs. 4.4%
ALTITUDE[19] (DKD, T2D)	Aliskiren vs. placebo†	High risk of cardiovascular and renal events	1.03 (0.87-1.23) for s-Cr doubling or ESKD	1.06 (0.92-1.23)	11.2% vs. 7.2%
ATMOSPHERE[20] (heart failure)	Aliskiren-enalapril vs. enalapril	Chronic heart failure with ejection fraction ≤35%	1.50 (0.82-2.74) for s-Cr doubling, ESKD, or renal death	0.91 (0.82-1.02)	5.0% vs. 3.6%
FIDELIO-DKD[21] (DKD, T2D)	Finerenone vs. placebo†	"ACR 0.03-0.3, eGFR 25-60, and retinopathy" or "ACR 0.3-–5 and eGFR 25-75"	0.82 (0.73-0.93) for eGFR decline, ESKD, or renal death	0.90 (0.75-1.07)	4.5% vs. 1.4%
FIGARO-DKD[22] (DKD, T2D)	Finerenone vs. placebo†	"ACR 0.03-0.3 and eGFR 25-90" or "ACR 0.3-5 and eGFR 25-75"	0.87 (0.76-1.01) for eGFR decline, ESKD, or renal death	0.89 (0.77-1.04)	2.3% vs. 1.2%

*Data are rates for s-K^+ >6.0 mmol/L unless otherwise stated.
†All patients were treated with either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker.
ACR, urine albumin-to-creatinine ratio (g/g); CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HR, hazard ratio; s-Cr, serum creatinine; s-K^+, serum potassium; T2D, type 2 diabetes.

Table 4. Angiotensin receptor-neprilysin inhibitors in heart failure and sodium-glucose transporter-2 inhibitors in CKD

Clinical Trial (Index Disease)	Treatment vs. Control Group	Participants	Kidney Disease Progression, HR (95% CI)	All-cause Death, HR (95% CI)	Other Outcomes, Rate %*
PARAGON-HF[23] (heart failure)	Sacubitril-valsartan vs. valsartan	Symptoms of heart failure and ejection fraction ≥45%	0.50 (0.33-0.77) for eGFR decline, ESKD, or renal death	0.97 (0.84-1.13)	3.1% vs. 4.3% for s-K^+ >6.0 mmol/L
PARADIGM-HF[24] (heart failure)	Sacubitril-valsartan vs. enalapril	Symptoms of heart failure and ejection fraction ≤40%	0.86 (0.65-1.13) for eGFR decline or ESKD	0.84 (0.76-0.93)	4.3% vs. 5.6% for s-K^+ >6.0 mmol/L
CREDENCE[29] (DKD, T2D)	Canagliflozin vs. placebo	ACR 0.3-5 and eGFR 30-90	0.66 (0.53-0.81) for s-Cr doubling, ESKD, or renal death	0.83 (0.68-1.02)	33.5% vs. 36.7% for total serious adverse events
DAPA-CKD[31] (CKD with albuminuria)	Dapagliflozin vs. placebo	ACR 0.2-5 and eGFR 25-75, T2D in 67.5%	0.56 (0.45-0.68) for eGFR decline, ESKD, or renal death	0.69 (0.53-0.88)	29.5% vs. 33.9% for total serious adverse events
SCORED[35] (CKD with decreasede GFR, T2D)	Sotagliflozin vs. placebo	eGFR 25-60	0.71 (0.46-1.08) for eGFR decline or ESKD	0.99 (0.83-1.18)	23.4% vs. 25.2% for total serious adverse events

*Differences were statistically significant ($p<0.05$) for the presented other outcomes.
ACR, urine albumin-to-creatinine ratio (g/g); CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESKD, end-stage kidney disease; HR, hazard ratio; s-Cr, serum creatinine; s-K^+, serum potassium; T2D, type 2 diabetes.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), which reduce both BP and blood glucose levels[25-27], have shown a consistent benefit in reducing renal and cardiovascular events in clinical trials[25-30]. Particularly, dapagliflozin, an SGLT2i, has been shown to reduce all-cause mortality as well as the renal and cardiovascular risk in patients with CKD and severe albuminuria, irrespective of the presence of diabetes[31]. In meta-analyses, the relative risk reduction with SGLT2i was similar among patients with different baseline conditions[32,33]. Accordingly, the absolute benefits may be greater in patients at a higher risk of developing renal and cardiovascular events. In a 2021 meta-analysis, the absolute risk reduction in cardiovascular events was greater in patients with a lower eGFR and more severe albuminuria,

and the absolute renoprotective benefit was greater in patients with more severe albuminuria[34]. In addition, SGLT2i consistently reduced the rate of total serious adverse events in patients with CKD (Table 4)[29,31,35]. These indicate that the benefits of SGLT2i treatment outweigh the harms in patients with CKD. Furthermore, the net benefit of SGLT2i is greater in patients with CKD, particularly in those with severe albuminuria, than in those without CKD.

Target BP in CKD

Several randomized trials that compared intensive BP control with conventional control in CKD failed to show a benefit in slowing the progression of kidney disease during the trial period[36-38]. However, in extended follow-up studies of the trials, intensive BP control targeting a mean arterial pressure of ≤92 mmHg (e.g., BP ≤125/75 mmHg), compared with usual control targeting a mean arterial pressure of ≤107 mmHg (e.g., BP ≤140/90 mmHg), was associated with a reduced risk of end-stage kidney disease among patients with CKD and severe proteinuria (Table 1)[3-6].

Meanwhile, in SPRINT, in nondiabetic patients at a high risk of cardiovascular events, targeting an SBP of <120 mm Hg, compared with <140 mmHg, resulted in lower rates of cardiovascular events and all-cause mortality[7]. Of the 9,361 SPRINT participants, 2,646 (28%) had an eGFR of <60 mL/min/1.73 m^2 and 1,723 (19%) had a urine ACR of ≥30 mg/g. In subgroup analyses, intensive BP lowering was associated with similar risk reductions in cardiovascular events and all-cause mortality among patients with and without an eGFR of <60 mL/min/1.73 m^2 [7,39]. Likewise, the risk reductions in the outcomes of interest with intensive therapy did not clearly differ between patients with and without a urine ACR of ≥30 mg/g[40].

Comparison between SPRINT and Other Studies

In contrast to SPRINT, the Action to Control Cardiovascular Risk in Diabetes trial showed that targeting an SBP of <120 versus <140 mmHg did not reduce all-cause or cardiovascular mortality among patients with type 2 diabetes and a mean eGFR of 92 mL/min/1.73 m^2 [41]. Similarly, in the Heart Outcomes Prevention Evaluation-3 trial, treatment with candesartan and hydrochlorothiazide did not reduce the risk of composite cardiovascular events among patients with a baseline SBP of ≤143.5 mmHg who did not have cardiovascular disease or advanced CKD[42]. Meanwhile, in SPRINT, the relative risk reduction in cardiovascular events with intensive therapy tended to be greater among patients with a baseline SBP of ≤132 mmHg than among patients with a baseline SBP of 132 to <145 mmHg and those with an SBP of ≥145 mmHg[7]. This is contradictory to the observations that the benefit in terms of BP reduction was greater among patients with higher baseline BP[43] and the relative risk reduction was proportional to the magnitude of BP lowering[44,45]. Assuming that the optimal on-treatment SBP is ≤120 mm Hg, lowering SBP from a level of 132 to 144 mmHg to a level of ≤120 mmHg, compared with lowering SBP from a level of ≤132 mmHg, is expected to result in greater risk reduction. Given these discrepancies between SPRINT and other studies, the results of SPRINT should be interpreted with caution.

In addition, randomized trials include participants who are not necessarily representative of a real-world population[46,47]. Moreover, subgroup analyses are observational in nature and can be influenced by confounders. SPRINT included older adults with a high cardiovascular risk and excluded patients with diabetes or proteinuria (urine protein >1.0 g/day). In addition, there were imbalanced confounders between subgroups with and without CKD (e.g., older adults with CKD). In contrast to the subgroup analyses of SPRINT, a population-based cohort study in Korea matched CKD and non-CKD populations using propensity scores to address potential confounding by imbalanced covariates between the populations. The cohort study revealed that intensively lowered SBP (115 to <125 mmHg), compared with conventionally controlled SBP (135 to <145 mmHg), was associated with a reduced risk of a composite of end-stage kidney disease, cardiovascular events, and all-cause mortality in patients with CKD, particularly in those with albuminuria, but not in their propensity score-matched counterparts without CKD[48]. Considering this finding together with the extended follow-up results of CKD trials (renoprotective effects of intensive BP control were observed in patients with, but not in those without, proteinuria), albuminuria may be an effect modifier of optimal BP, in contrast to the subgroup analysis findings of SPRINT.

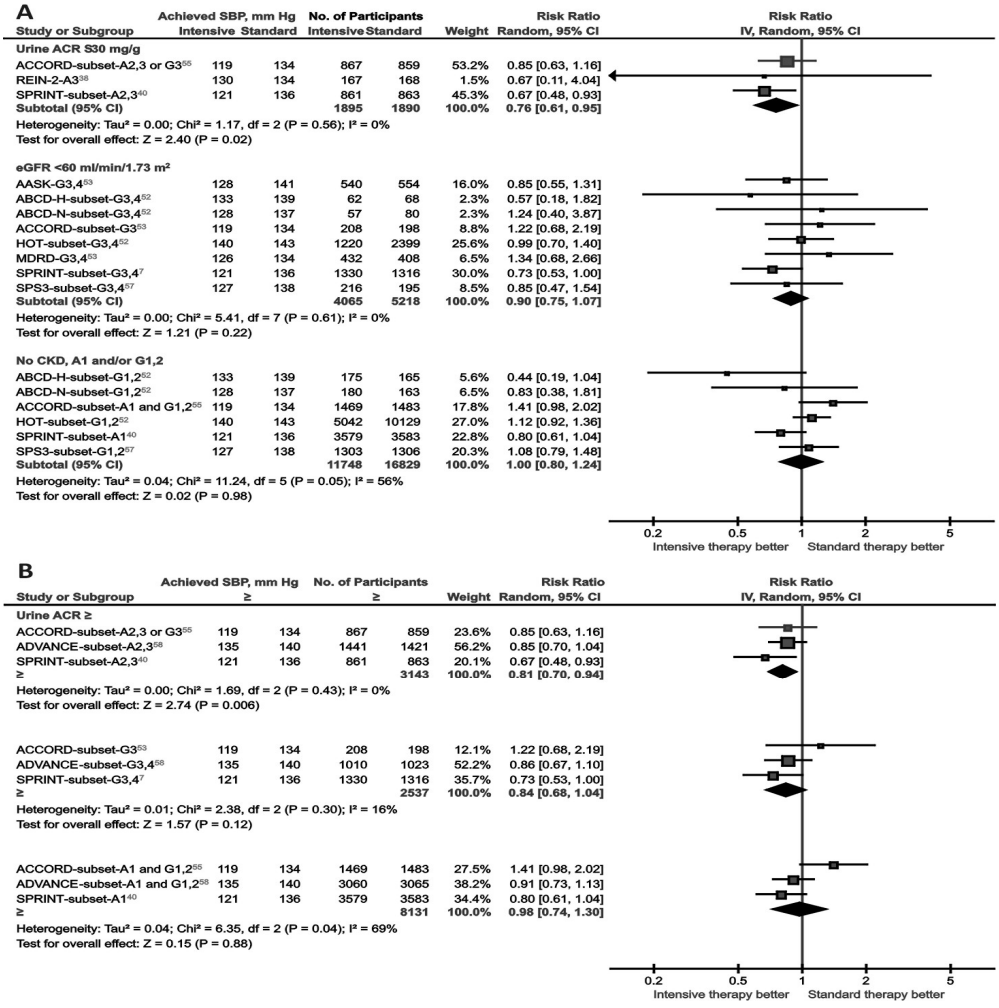

Fig. 1. Comparison of all-cause mortality between the lower BP target and standard BP target groups, according to kidney disease status.

A meta-analysis was conducted using the random-effects model. The primary analysis included trials that compared lower BP targets with standard targets (SBP ≤140 mmHg, diastolic BP ≤90 mmHg, or mean arterial pressure ≤107 mmHg) **A**, and secondary analyses were restricted to trials facilitating within-trial comparisons but extended to a trial with a placebo control achieving an SBP of 140 mmHg **B**. The subset "ACCORD-subset- A2,3 and G3" had a urine ACR of ≥0.03 in most participants and an eGFR of 30 to <60 mL/min/1.73 m² in 23.2% of participants. A1, urine ACR <30 mg/g; A2, urine ACR 30 to 300 mg/g; A3, urine ACR >300 mg/g; ACR, albumin-to-creatinine ratio; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; G1, eGFR ≥90 mL/min/1.73 m^2; G2, eGFR 60 to <90 mL/min/1.73 m^2; G3, eGFR 30 to <60 mL/min/1.73 m^2; G4, eGFR 15 to <30 mL/min/1.73 m^2; SBP, systolic blood pressure.

All-cause Mortality

All-cause mortality can reflect the net benefit of BP reduction. A meta-analysis of clinical trials showed that treatment to a target SBP of <150 mmHg reduced all-cause mortality (risk ratio [RR] 0.90, 95% confidence interval [CI] 0.83 to 0.98) in adults aged ≥60 years with a baseline SBP of ≥160 mmHg[49]. Similarly, a 2019 Cochrane review that compared active treatment with no treatment or placebo reported that antihypertensive drug therapy reduced the rates of both all-cause mortality (RR 0.91, 95% CI 0.85 to 0.97) and cardiovascular events (RR 0.72, 95% CI 0.68 to 0.77) in adults aged ≥60 years with a baseline BP of

>140/90 mmHg[50]. However, in a 2020 Cochrane review that compared lower BP targets (≤135/85 mmHg) with standard targets (≤140/90 mmHg), all-cause mortality did not differ between the lower and standard target groups (RR 0.95, 95% CI 0.86 to 1.05) in the general population of adults with hypertension[51].

In CKD populations, a recent meta-analysis showed that more intensive BP control, compared with less intensive control, was associated with a reduced risk of all-cause mortality (RR 0.86, 95% CI 0.76 to 0.97) in patients with an eGFR of <60 mL/min/1.73 m^2 [52]. However, the analysis included trials with a control group receiving placebo or no treatment or those targeting a BP higher than standard targets. To compare lower BP targets with standard targets, I conducted a meta-analysis including trials with available data on baseline kidney function that compared lower BP targets with a control targeting an SBP of ≤140 mmHg, a diastolic BP of ≤90 mmHg, or a mean arterial pressure of ≤107 mmHg. I meta-analyzed a total of 9 randomized studies comprising 3 trials in patients with nondiabetic CKD[36-38,53], 3 trials in patients with type 2 diabetes[52,54,55], a trial in adults with diastolic hypertension[52,56], a trial in patients without diabetes with a high cardiovascular risk[7,40], and a trial in patients with lacunar stroke[57], which met the inclusion criteria and had a sample size of ≥50 in each target group. I found that more intensive BP control was associated with a lower risk of all-cause mortality in patients with albuminuria (RR 0.76, 95% CI 0.61 to 0.95) but not in those without CKD (Fig. 1A). In patients with an eGFR of ≤60 mL/min/1.73 m^2, intensive versus standard BP control was associated with a reduced risk of all-cause mortality (RR 0.83, 95% CI 0.75 to 0.91) when the extended follow-up data of 2 CKD trials[5,6] were included, but not when only trial-phase data were analyzed (Fig. 1A). Even when the analysis was restricted to trials facilitating within-trial comparisons but extended to a trial with a placebo control achieving an SBP of 140 mmHg[58], the results were similar to those of the primary analysis (Fig. 1B). Moreover, in a population-based study in Korea, the optimal on-treatment BP with the best survival outcome was left-shifted in patients with CKD and albuminuria relative to that in patients without CKD[48]. These findings support the assertion that treatment targets lower than standard targets are needed for the management of BP in patients with CKD.

Adverse Effects

Antihypertensive treatment increases the rate of adverse events and symptoms, including hypotension, dizziness, electrolyte disturbance, arrhythmia, erectile dysfunction, headache, edema, and cough[49]. To achieve lower BP targets, increased numbers and higher doses of antihypertensive drugs are needed. The use of more drugs and higher drug doses can increase the treatment-related adverse effects and the burden on patients. Studies have shown that more intensive BP control increased withdrawals because of adverse events[49,59,60]. This could lead to higher rates of permanent treatment discontinuation. Treatment to lower BP targets also increased the rate of syncope and other adverse events[49]. In SPRINT, targeting an SBP of <120 mm Hg versus <140 mmHg increased the rate of hospitalization or emergency department visits for hypotension, syncope, electrolyte disturbance, and acute kidney injury[7].

In the 2020 Cochrane review that compared lower BP targets (≤135/85 mmHg) with standard targets (≤140/90 mmHg), although the cardiovascular event rates were reduced (RR 0.84, 95% CI 0.73 to 0.96 for myocardial infarction; RR 0.88, 95% CI 0.77 to 1.01 for stroke; and RR 0.75, 95% CI 0.60 to 0.92 for heart failure) in the lower (vs. higher) target group, the rate of other serious adverse events was increased in the lower target group (RR 1.44, 95% CI 1.32 to 1.59) and the rate of total serious adverse events did not differ between the target groups (RR 1.04, 95% CI 0.99 to 1.08)[51]. The authors concluded that the benefit of lower BP targets, compared with standard targets, did not outweigh the harms in the general population of persons with high BP.

CONCLUSIONS

Drugs such as SGLT2i, finerenone, and ARNi, in addition to RASi, have shown a benefit in preventing CKD progression in randomized controlled trials. In particular, SGLT2i consistently improved the renal and cardiac outcomes and reduced the rate of total serious adverse events in patients with CKD, and dapagliflozin, an SGLT2i, even reduced all-cause

mortality in patients with severe albuminuria. With respect to the target BP, the KDIGO 2021 BP guideline suggests treating adults with CKD to a target SBP of <120 mmHg based on standardized office BP measurement. This SBP target is largely based on the finding of SPRINT that targeting an SBP of <120 mmHg versus <140 mmHg has both a survival benefit and cardioprotective effects, irrespective of the patient's baseline kidney function. However, previous studies have indicated that albuminuria is an effect modifier of BP targets for renal and mortality outcomes and suggested that a decreased eGFR may be an effect modifier of BP for mortality. Meanwhile, a Cochrane review reported that targeting a BP lower than the standard target (≤140/90 mmHg) does not further reduce the rate of total serious adverse events despite having a small additional benefit in reducing cardiovascular events. Lowering SBP to <120 mmHg may increase the risk of other serious adverse events beyond the benefit in cardiovascular risk reduction, and a standardized BP measurement increases the burden on patients and resources. Thus, targeting a BP of <130/80 mmHg using an appropriate office BP measurement can be considered an option in patients with CKD. The presence and degree of albuminuria would need to be additionally considered to determine individualized BP targets. Clinical trials evaluating home or ambulatory BP as a treatment target are warranted, and more studies are needed to confirm the role of albuminuria as an effect modifier of BP for overall outcomes.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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