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# Blood pressure control in patients with chronic kidney disease

Jee Young Lee and Seung Hyeok Han

Department of Internal Medicine, Institute of Kidney Disease Research, Yonsei University College of Medicine, Seoul, Korea

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**Correspondence to**
**Seung Hyeok Han, M.D.**
Department of Internal Medicine, Institute of Kidney Disease Research, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1984
Fax: +82-2-393-6884
E-mail: hansh@yuhs.ac
https://orcid.org/0000-0001-7923-5635

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Uncontrolled blood pressure (BP) in patients with chronic kidney disease (CKD) can lead to serious adverse outcomes. To prevent the occurrence of cardiovascular events (CVEs), and end-stage kidney disease, achieving an optimal BP level is important. Recently, there has been a paradigm shift in the management of BP largely as a result of the Systolic Blood Pressure Intervention Trial (SPRINT), which showed a reduction in CVEs by lowering systolic BP to 120 mmHg. A lower systolic blood pressure (SBP) target has been accepted by the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines. However, whether intensive control of SBP targeting < 120 mmHg is also effective in patients with CKD is controversial. Notably, this lower target SBP is associated with a higher risk of adverse kidney outcomes. Unfortunately, there have been no randomized controlled trials on this issue involving only patients with CKD, particularly those with advanced CKD. In this review, we discuss the optimal control of BP in patients with CKD in terms of reduction in death and CVEs as well as attenuation of CKD progression based on the evidence-based literature.

**Keywords:** Chronic renal insufficiency; Renal insufficiency, chronic; Blood pressure

## INTRODUCTION

Chronic kidney disease (CKD) and hypertension are closely connected and affect each other. Hypertensive kidney disease is the second most common cause of kidney failure with replacement therapy (KFRT), and deterioration of kidney function is accelerated by excessive high blood pressure (BP) [1-4]. Uncontrolled hypertension can cause adverse cardiovascular and cerebrovascular outcomes such as acute coronary syndrome, hemorrhagic and ischemic stroke, heart failure, and even death [5-10]. Therefore, in clinical practice, physicians typically prioritize BP control to preserve kidney function and reduce the rate of cardiovascular events (CVEs) and mortality in patients with CKD.

Therefore, the question for consideration is, "What is the optimal target BP that will achieve these goals in patients with CKD?" Unfortunately, this issue has not yet been resolved. In addition to reducing the rate of adverse CVEs and mortality in patients with and without CKD, other important goals of BP control are to prevent the development of CKD for non-CKD patients and to attenuate the deterioration of kidney function in patients with CKD. Epidemiologic studies have shown that, in patients without CKD, even a pre-hypertension level of systolic blood pressure (SBP; 130 to 140 mmHg) is associated with a higher risk of CKD development compared with an SBP of < 120 mmHg [11-14]. In addition, a me-

**Table 1. Guideline comparisons of goal BP and first-line treatment for CKD patients with hypertension**

| Guideline | BP target in CKD patients without proteinuria, mmHg | BP target in CKD patients with proteinuria, mmHg | Recommended first-line treatment |
|---|---|---|---|
| ISHIB [35] | < 130/< 80 | < 130/< 80 | Diuretic or CCB |
| NICE [19] | < 140/< 90 | < 130/< 80 | ACEi or ARB |
| JNC8 [18] | < 140/< 90 | < 140/< 90 | ACEi or ARB |
| ACC/AHA [32] | < 130/< 80 | < 130/< 80 | ACEi |
| ESC/ESH [34] | SBP 130–139 | SBP 130–139 | ACEi or ARB |
| ISH [33] | < 130/< 80 | < 130/< 80 | ACEi or ARB |
| Hypertension Canada [22] | SBP < 120 | SBP < 120 | ACEi or ARB |
| KDIGO [25] | SBP < 120 | SBP < 120 | ACEi or ARB |

BP, blood pressure; CKD, chronic kidney disease; ISHIB, International Society on Hypertension in Blacks; CCB, calcium channel blocker; NICE, National Institute for Health and Clinical Excellence; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; JNC8, Eighth Joint National Committee; ACC/AHA, American College of Cardiology/American Heart Association; ESC/ESH, European Society of Cardiology and the European Society of Hypertension; SBP, systolic blood pressure; ISH, International Society of Hypertension; KDIGO, Kidney Disease: Improving Global Outcomes.

ta-analysis of observational data showed a higher risk of CVEs in individuals with an SBP of 120 to 129 mmHg compared to those with an SBP of < 120 mmHg [15]. Notably, guidelines from various countries do not agree on BP control in patients with CKD [16-22]. Over the last two decades, < 140/90 mmHg has typically been the target BP in patients without albuminuria and < 130/80 mmHg in those with albuminuria [17,23]. This conventional concept has been challenged by the results of the Systolic Blood Pressure Intervention Trial (SPRINT) study, which demonstrated the benefit of intensive control of SBP < 120 mmHg compared with the conventional target of < 140 mmHg [24]. The SPRINT study results are included in the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines, which suggest a target SBP of < 120 mmHg in patients with CKD [25]. However, not all studies favor this lower target, given the negative results of intensive BP control [26-28]. In fact, some guidelines still recommend the conventional BP target for patients with CKD [29-31]. BP targets in patients with CKD are listed in Table 1 [18,19,22,25,32-35].

In this article, we discuss the following three goals of optimal BP control in patients with CKD: (1) to prevent CVEs and all-cause death, (2) to prevent the development of incident CKD, and (3) to delay the progression of CKD. Finally, we briefly describe conventional and potential drug therapies for improving outcomes in pa-

tients with CKD.

## BP MEASUREMENT

The KDIGO 2021 BP guidelines recommend use of standardized rather than routine office BP measurement [25], as suggested by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines [32]. Standardized office BP measurement refers to BP measurement following the recommended preparation procedure. A summary of standardized office BP measurement is provided in Table 2 [32]. In contrast, routine office BP measurement is performed without considering the recommended BP measurement procedure. Notably, BP readings using office BP measurement are typically higher than those using standardized BP measurement [36]. BP measurement procedures vary among clinical trials, a critical point that should be considered when interpreting study results. However, for the sake of convenience, routine office BP measurement is commonly used in the real world. Given the possible risk of overtreatment and hypotension events associated with office BP measurement, use of standardized BP measurement should be encouraged in clinical practice.

**Table 2. Summary of standardized office BP measurement**

| | |
|---|---|
| Preparing the patient | Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measuring BP. Make sure the patient emptied their bladder before BP measurement. The patient should be seated in a chair with back support and feet placed on the floor, then relax for more than 5 minutes. The patient or the observer should not talk during the resting and measurement period. All clothing covering the cuff placing location should be removed. |
| Choosing the BP measurement for diagnosis and treatment of elevated BP | Measure BP from both arms on the first visit, and choose the arm with the higher BP for the following measurements. |
| BP measuring technique | Use validated BP measuring device, which should be regularly calibrated. Patient should have arm-support, with the cuff positioned on upper arm of patient. Use proper sized cuff, with the bladder 80% of the arm circumference. |
| Documentation of BP measurement | ≥ 2 BP measurements with 1–2 minutes interval should be taken, and document the average of these BP measurements. Record both SBP, DBP, and the time of most recent BP medication intake prior to BP measurement. |

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

## BP CONTROL FOR PREVENTION OF CARDIO-VASCULAR DISEASE AND DEATH IN CKD

Given the lack of randomized controlled trials (RCTs) in patients with only CKD, this issue has been evaluated by analyses of secondary outcomes. As mentioned above, the SPRINT study demonstrated that intensive control of SBP to < 120 mmHg resulted in better cardiovascular outcomes compared to control to < 140 mmHg [24]. This finding has been adopted by the ACC/AHA 2017 guidelines [16] and the KDIGO 2021 guidelines [25]. Notably, the SPRINT study excluded patients with diabetes and a history of stroke. Most participants with CKD had CKD G3a; their mean estimated glomerular filtration rate (eGFR) was 48 mL/min/1.73 m². Therefore, it is unclear whether intensive control using a lower BP target is beneficial in other risk groups, such as patients with diabetes or CKD G3b, G4, or G5. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial involving patients with type 2 diabetes, intensive control of SBP < 120 mmHg did not reduce the rate of a composite outcome of fatal and nonfatal major CVEs or death as compared with a standard target (< 140 mmHg), although intensive control decreased the rate of nonfatal stroke events [26]. Nevertheless, 2,646 participants with an eGFR of < 60 mL/min/1.73 m² in the SPRINT study provided adequate statistical power to examine the effect of intensive BP control on cardiovascular outcomes in patients with early CKD. In this separate analysis of

participants with CKD, the intensive SBP intervention group had a 19% lower risk of composite cardiovascular outcomes and a 28% lower risk of all-cause death compared to the standard BP control group [37]. In addition, in a meta-analysis of 123 trials including 613,815 participants with BP lowering intervention, each 10 mmHg reduction in SBP significantly decreased the risk of major CVEs and all-cause mortality [38]. Notably, a greater reduction in SBP resulted in a larger decrease in the relative risk of CVEs. That study also showed a significant risk reduction with a decrease in SBP in patients with CKD. However, a pooled analysis of four multicenter RCTs including 4,983 CKD patients with control of SBP to < 130 mmHg did not improve all-cause mortality and cardiovascular outcomes compared to standard control of SBP to < 140 mmHg [39]. In that study, the average BP achieved was 125.0 mmHg in the intensive group and 136.9 mmHg in the standard group. After excluding patients with an eGFR of ≥ 60 mL/min/1.73 m² and intensive glucose control, the all-cause mortality rate was reduced in the intensive BP control group. Finally, in another meta-analysis of patients with CKD G3–G5, more intensive control (SBP 132 mmHg) resulted in a 14.0% lower risk of all-cause mortality compared with less intensive control (SBP 140 mmHg) [40]. Therefore, the evidence supports intensive BP control to reduce adverse CVE and all-cause mortality rates, even in patients with CKD. A summary of these RCTs is presented in Table 3 [24,26,27,37,41,42]. In contrast to RCTs, analyses of

**Table 3. Summary of the major clinical trials with BP intervention for cardiovascular outcomes and mortality**

| Trial | Number | | BP target (achieved), mmHg | | Diabetes | CKD | Main outcomes | Key findings (risk reduction vs. standard group) |
|---|---|---|---|---|---|---|---|---|
| | Active | Standard | Active | Standard | | | | |
| HOT [42] | | | DBP (achieved), mmHg ≤ 80 (81.1) (n = 6,262) ≤ 85 (83.2) (n = 6,264) ≤ 90 (85.2) (n = 6,264) | | 1,503 (8) | 1,367 (7)[a] | Composite nonfatal MI, nonfatal stroke, or CVD death | NR (↓51 vs. ≤ 90 mmHg among diabetic patients) |
| UKPDS [41] | 758 | 390 | < 150/85 (144/82) | < 160/90 (154/87) | 1,148 (100) | 198 (17)[b] | All-cause mortality | NR |
| | | | | | | | MI | NR |
| | | | | | | | Stroke | ↓44% |
| | | | | | | | PVD | NR |
| | | | | | | | Microvascular disease[c] | ↓37% |
| ACCORD [26] | 2,362 | 2,371 | SBP < 120 (119.3) | SBP < 140 (133.5) | 4,733 (100) | 403 (9) | Composite nonfatal MI, nonfatal stroke, or death from CVD | NR |
| SPRINT [24] | 4,678 | 4,683 | SBP < 120 (121.4) | SBP < 140 (136.2) | None | 2,646 (28) | Composite MI, ACS, stroke, HF, or CVD death | ↓25% |
| HOPE-3 [27] | 6,356 | 6,349 | SBP < 130 (128) | SBP < 140 (134) | 731 (8) | 348 (3) | Composite cardiovascular death, nonfatal MI, or nonfatal stroke | NR |
| SPRINT post hoc analysis in CKD [37] | 1,330 | 1,316 | SBP < 120 (123.3) | SBP < 140 (136.9) | None | 2,646 (100) | Composite MI, ACS, stroke, HF, or CVD death | NR |
| | | | | | | | Composite MI, ACS, stroke, HF, CVD death, or all-cause death | NR |
| | | | | | | | All-cause death | ↓28% |

Values are presented as number (%).

BP, blood pressure; CVD, cardiovascular disease; HOT, Hypertension Optimal Treatment; DBP, diastolic blood pressure; MI, myocardial infarction; NR, no reduction in relative risk; UKPDS, UK Prospective Diabetes Study Group; PVD, peripheral vascular disease; ACCORD, Action to Control Cardiovascular Risk in Diabetes; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; ACS, acute coronary syndrome; HF, heart failure; HOPE-3, Heart Outcomes Prevention Evaluation-3.

[a]Definition of CKD: serum creatinine > 115 μmol/L.
[b]Definition of CKD: albuminuria ≥ 50 mg/L.
[c]Retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or nonfatal renal failure.

observational cohort studies have shown a U-shaped association between SBP and the risk of death in patients with CKD, suggesting a potential hazard for excessively low BP [43-46]. A low BP itself may reflect an unhealthy condition and underlying disease burden.

## BP CONTROL FOR THE PREVENTION OF CKD

No RCT has examined the effect of intensive BP control on the development of incident CKD. Studies on this issue are mostly *post hoc* analyses of RCTs comparing the effect of intensive versus standard BP control in patients with high cardiovascular risk. Among these, the ACCORD trial showed that intensive control of SBP < 120 mmHg increased the risk of incident CKD [26]. In line with this study, a similar SBP intervention in the SPRINT study resulted in a higher frequency of adverse kidney outcomes among patients without diabetes [24]. Therefore, intensive BP control is not beneficial for preserving kidney function. However, intensive BP control is effective in reducing albuminuria. Despite the increased risk of CKD, the ACCORD trial showed a significant reduction in macroalbuminuria by intensive BP control. In a similarly designed RCT involving patients with type 2 diabetes, active BP control significantly reduced the risk of microalbuminuria and macroalbuminuria [47,48]. A reduction in albuminuria by intensive BP control was also found in a meta-analysis of 19 RCTs including both diabetic and non-diabetic patients [49]. For the prevention of CKD, these studies indicate that intensive BP control carries both a risk and a benefit: a decline in eGFR and reduction in albuminuria. To mitigate concerns on the increase in the risk of adverse kidney outcomes by intensive BP control, the SPRINT and ACCORD investigators showed that various kidney injury markers were not elevated in the intensive BP control group, suggesting that the increased serum creatinine level was associated with hemodynamic alterations [50,51]. Despite the debate on its validity as a surrogate marker of renal function, albuminuria is widely accepted as an appropriate target or surrogate marker for kidney disease progression [52]. The United States Food and Drug Administration recently agreed to use early change in albuminuria as a surrogate marker for kidney disease progression in phase 3 trials dealing with diseases involving moderate to severe albuminuria, and intervention trials in which decreasing albuminuria is presumed to be the primary mechanism of action [53]. The key findings of major RCTs are shown in Table 4.

In contrast to previous RCTs involving patients with an increased risk of CVD and a baseline SBP of ≥ 130 mmHg, observational studies provide comprehensive information on individuals at low risk of CKD and few comorbidities, even those without pre-existing hypertension. Interestingly, there was a graded relationship between SBP and the risk of incident CKD, and the risk was lower for an SBP of < 120 mmHg [11-13,54,55]. We observed similar findings in two large representative Korean adult cohorts using meticulous analytical approaches [56,57]. These findings raised the question of whether reducing SBP to < 120 mmHg in individuals with hypertension and at high risk of CVD is equivalent to an intrinsically normal BP in healthy adults. In summary, intensive BP control for the prevention of incident CKD has not yet been justified. If kidney injury associated with intensive BP control is minimal and reversible, a lower BP target can be implemented in clinical practice with a permissive decline in eGFR given the proven benefit on prevention of adverse CVEs.

## BP CONTROL FOR DELAYING THE PROGRESSION OF CKD

CKD progression is generally faster in patients with than in those without diabetes. In non-diabetic patients with CKD, three clinical trials have evaluated the effect of intensive BP control on CKD progression: the Modification of Diet in Renal Disease (MDRD) study; the AASK trial; and the Blood Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) trial [28,58,59]. The African-American Study of Kidney Disease and Hypertension (AASK) and REIN-2 trials excluded patients with diabetes. Only 5% of participants in the MDRD study were patients with diabetes. The target BPs in the intensive control arm were < 125/75 mmHg (mean arterial pressure < 92 mmHg) for the MDRD study and < 130/80 mmHg for the AASK and the REIN-2 trials. The MDRD study, published in 1994, showed that the beneficial effect of a lower BP target was particularly evident in patients with

**Table 4. Summary of the major clinical trials with BP intervention for adverse kidney outcome**

| Trial | Number | | BP target (achieved), mmHg | | Main outcomes | Key findings |
|---|---|---|---|---|---|---|
| | Active | Standard | Active | Standard | | |
| MDRD [59] | 432 | 408 | MAP < 92, SBP/DBP < 125/75 (93.3, 126/77) | MAP < 107, SBP < 140 (98.4, 134/81) | GFR decline | ↓29%[a] |
| | | | | | KFRT or death | NR |
| ABCD [65] | 237 | 243 | SBP/DBP < 130/80 (128/75) | SBP/DBP < 140/90 (137/81) | CCl | NR |
| | | | | | Albuminuria | |
| | | | | | Normoalbuminuria to microalbuminuria | → |
| | | | | | Microalbuminuria to overt albuminuria | → |
| REENAL post hoc [66] | Post hoc analysis categorized SBP into < 130 (n = 169), 130–139 (n = 209), 140–159 (n = 610), 160–179 (n = 373), and ≥ 180 mmHg (n = 152) | | | | Composite 2XSCr, KFRT, or death | HR (95% CI) vs. SBP < 130 mmHg: 1.08 (0.83–1.40), 1.49 (1.18–1.90), 2.74 (2.12–3.54), and 3.51 (2.50–4.93) |
| REIN-2 [28] | 167 | 168 | SBP/DBP < 130/80 (130/80) | SBP/DBP < 135/90 (134/82) | KFRT | NR |
| IDNT post hoc [67] | Post hoc analysis categorized SBP into < 145 (n = 391), 145–158 (n = 411), 159–170 (n = 383), and > 170 mmHg (n = 405) | | | | Composite 2XSCr or KFRT | RR vs. SBP > 170 mmHg: 0.55, 0.92, 0.66, and 0.70 |
| ADVANCE [47] | 5,569 | 5,571 | SBP 145–135[b] | SBP 145–140[b] | Composite macroalbuminuria, 2XSCr, KFRT, renal-cause death, or microalbuminuria | ↓21% |
| | | | | | Composite macroalbuminuria, 2XSCr, KFRT, renal-cause death | ↓18%[c] |
| | | | | | Microalbuminuria | ↓21% |
| ACCORD [26] | 2,362 | 2,371 | SBP < 120 (119.3) | SBP < 140 (133.5) | Serum creatinine elevation[d] | NR |
| | | | | | Decreased eGFR < 30 mL/min/1.73 m² | NR |
| AASK [58] | 540 | 554 | SBP/DBP < 130/80 (130/78) | SBP/DBP < 140/90 (141/86) | Composite 2XSCr, KFRT, or death | ↓27%[e] |
| SPRINT [24] | 4,678 | 4,683 | SBP < 120 (123.3) | SBP < 140 (136.2) | Participants with baseline CKD | NR |
| | | | | | Composite ≥ 50% reduction eGFR to < 60 mL/min/1.73 m², long-term dialysis, or KT | |

**Table 4. Continued**

| Trial | Number | | BP target (achieved), mmHg | | Main outcomes | Key findings |
|---|---|---|---|---|---|---|
| | Active | Standard | Active | Standard | | |
| | | | | | Participants without baseline CKD | ≥ 30% eGFR reduction to <60 mL/min/1.73 m² NR |

BP, blood pressure; MDRD, Modification of Diet in Renal Disease; MAP, mean arterial pressure; SBP, systolic blood pressure; GFR, glomerular filtration rate; KFRT, kidney failure with replacement therapy; NR, no reduction in relative risk; ABCD, Appropriate Blood Control in Diabetes; CCl, creatinine clearance; REENAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; 2XSCr, doubling of serum creatinine; HR, hazard ratio; REIN-2, Blood Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease; IDNT, Irbesartan Diabetic Nephropathy Trial; RR, relative risk; ADVANCE, Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ACCORD, Action to Control Cardiovascular Risk in Diabetes; eGFR, estimated glomerular filtration rate; AASK, African-American Study of Kidney Disease and Hypertension; SPRINT, Systolic Blood Pressure Intervention Trial; CKD, chronic kidney disease; KT, kidney transplantation.

a In subgroup patients with GFR 22–55 mL/min/1.73 m².
b Change in SBP from baseline to follow-up; There was no pre-specified BP target in ADVANCE trial.
c Relative reduction: p value 0.055.
d Men > 1.5 mg/dL, women > 1.3 mg/dL.
e In patients with baseline urinary protein-to-creatinine ratio > 0.22.

daily urinary protein excretion > 1.0 g [59]. Long-term follow-up of the MDRD study with observation extended to 10 years also showed that CKD outcomes and the all-cause mortality rate were decreased by intensive BP control [60]. However, the AASK and REIN-2 trials failed to delay the progression of CKD or the development of KFRT in patients with intensive BP control. Notably, in the AASK trial, a subgroup of patients with CKD and a protein-to-creatinine ratio of ≥ 0.22 g/g in the intensive BP control group had a significant reduction in the risk of KFRT or death. These findings suggest that intensive BP control is more effective in non-diabetic patients with CKD and significant proteinuria. A systemic review and meta-analysis supports the ability of intensive control of BP < 130/80 mmHg to attenuate CKD progression in non-diabetic patients with CKD and significant proteinuria [61,62].

The clinical benefits of intensive BP control are unclear in patients with type 2 diabetes. The BP goals in most early studies were > 140 mmHg, which was considered suboptimal [41,42,63,64]. The Appropriate Blood Control in Diabetes (ABCD) study evaluated the effect of a lower BP target of < 130/80 mmHg on the preservation of kidney function in patients with type 2 diabetes compared with a standard control of < 140/90 mmHg but failed to demonstrate a benefit of intensive BP control [65]. However, two *post hoc* analyses of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) showed that a lower BP level was associated with improved kidney outcomes [66,67]. In contrast to the less-intensive BP targets in the studies above, the intervention in the ACCORD trial lowered SBP to < 120 mmHg [26]. However, as discussed above, a lower target BP increased the frequency of adverse kidney events such as an elevated serum creatinine level or a decline in eGFR of < 30 mL/min/1.73 m². It should be noted that the ACCORD study excluded patients with a serum creatinine level of > 1.5 mg/dL; therefore, the participants were unlikely to be representative of patients with CKD and diabetes. We have summarized the results of major RCTs on this topic in Table 4 [24,26,28,47,58,59,65-67].

**Table 5. Summary of major intervention trials with RAS blockers and new potential drugs for kidney outcomes**

| Trial | Number | Main inclusion criteria | Intervention | Control | Main outcome | Key findings | BP by intervention, mmHg | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Baseline | Follow-up |
| **RAS blockers** | | | | | | | | |
| Lewis et al. [68] | 409 | Diabetic nephropathy | Catopril | Placebo | 2XSCr | ↓48% risk | SBP 135 | SBP 128–134 |
| IDNT [70] | 1,715 | Type 2 diabetic nephropathy | Irbesartan<br>Irbesartan | Placebo<br>Amlodipine | Composite 2XSCr, KFRT, or all-cause death | ↓20% risk<br>↓23% risk | 160/87<br>159/87 | 140/77<br>141/77 |
| RENAAL [71] | 1,513 | Type 2 diabetic nephropathy | Losartan | Placebo | Composite 2XSCr, KFRT or death | ↓16% risk | 152/82 | 140/74 |
| BENEDICT [72] | 904 | DM without microalbuminuria | Trandolapril + verapamil<br>Trandolapril | Placebo<br>Placebo | % Microalbuminuria | 5.7% vs. 10%<br>6.0% vs. 11.9 % | 151/88<br>151/88 | 139/80<br>139/81 |
| **Mineralocorticoid receptor antagonists** | | | | | | | | |
| Bianchi et al. [87] | 165 | CKD treated with RASi | Spironolactone + RASi | RASi | Proteinuria reduction eGFR decline (mL/min/1.73 m²) | ↓54.2%<br>−6.2 vs. −9.0 | 133/79 | 127/76 |
| FIDELIO-CKD [92] | 5,734 | CKD, T2DM | Finerenone + RASi | RASi | Kidney failure[a], eGFR decrease ≥ 40%, or renal death | ↓18% risk | SBP 138 | 120/75 |
| **Endothelin receptor antagonists** | | | | | | | | |
| DUET [85] | 109 | FSGS, eGFR > 30 mL/min/1.73 m², UPCR ≥ 1.0 g/g | Sparsentan | Irbesartan | Proteinuria reduction FSGS PR | ↓26%<br>↓19% risk | 132/84 | 120/75 |
| SONAR [84] | 2,648 | CKD, T2DM, albuminuria | Atrasentan | Placebo | 2XSCr or KFRT | ↓35% risk | 136/75 | 139/- |
| **SGLT2 inhibitors** | | | | | | | | |
| EMPA-REG post hoc [78] | 7,020 | T2DM, eGFR ≥ 30 mL/min/1.73 m² | Empagliflozin | Placebo | Macroalbuminuria, 2XCr, RRT, or renal death<br>2XCr with eGFR ≤ 45 mL/min/1.73 m² | ↓39% risk<br>↓44% risk | Patients with eGFR < 60 mL/min/1.73 m²: 136/75<br>Patients with eGFR ≥ 60 mL/min/1.73 m²:135/77 | - |

**Table 5.** Continued

| Trial | Number | Main inclusion criteria | Intervention | Control | Main outcome | Key findings | BP by intervention, mmHg | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Baseline | Follow-up |
| CANVAS [77] | 10,142 | T2DM, high CVD risk[b] | Canagliflozin | Placebo | Composite CVD death, nonfatal MI, nonfatal stroke / 40% eGFR reduction, RRT, or renal death | ↓14% risk / ↓40% risk | 136/78 | 131/73 |
| DECLARE–TIMI 58 [93] | 17,160 | T2DM with CVD[c] or multiple CVD risk factors[d] | Dapagliflozin | Placebo | 40% eGFR reduction, KFRT, or renal/CVD death / 40% eGFR reduction, KFRT, or renal death | ↓24% risk / ↓47% risk | Patients with eGFR <60 mL/min/1.73m²: 134/75 Patients with 60 ≤eGFR<90 mL/min/1.73 m²: 135/78 Patients with eGFR ≥90 mL/min/1.73 m²: 135/79 | - |
| CREDENCE [74] | 4,401 | T2DM with albuminuric CKD | Canagliflozin | Placebo | Composite KFRT, 2XSCr, or renal/CVD death | ↓30% risk | 140/78 | 136/76 |
| DAPA-CKD [80] | 4,300 | G2–4 CKD, albuminuria | Dapagliflozin | Placebo | Composite eGFR decline ≥50%, KFRT, renal/CVD death | ↓39% risk | 137/77 | - |

RAS, renin-angiotensin system; BP, blood pressure; 2XSCr, doubling of serum creatinine; SBP, systolic blood pressure; IDNT, Irbesartan Diabetic Nephropathy Trial; KFRT, kidney failure with replacement therapy; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; DM, diabetes mellitus; CKD, chronic kidney disease; RASi, renin-angiotensin system inhibitor; eGFR, estimated glomerular filtration rate; FIDELIO-CKD, Finerenone in Reducing Kidney Failure and Disease Progression in Chronic Kidney Disease; T2DM, type 2 diabetes mellitus; DUET, Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with Focal Segmental Glomerulosclerosis (FSGS); FSGS, focal segmental glomerulosclerosis; UPCR, urine protein-to-creatinine ratio; PR, partial remission; SONAR, Study of Diabetic Nephropathy with Atrasentan; SGLT2, sodium-glucose co-transporter 2; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; RRT, renal replacement therapy; CANVAS, Canagliflozin Cardiovascular Assessment Study; CVD, cardiovascular disease; MI, myocardial infarction; DECLARE–TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease.

[a]KFRT or an eGFR less than 15 mL/min/1.73 m².

[b]Age ≥ 30 years with symptomatic atherosclerotic CVD history or age ≥ 50 years with ≥ 2 risk factors for CVD: diabetes duration ≥ 10 years, SBP ≥ 140 mmHg while antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein cholesterol level <1 mmol/L (38.7 mg/dL).

[c]Age ≥ 40 years and either ischemic heart disease, cerebrovascular disease, or peripheral arterial disease.

[d]Age ≥ 55 years (men) or ≥ 60 years (women) plus at least one of dyslipidemia, hypertension, or current tobacco use.

## DRUG TREATMENT

Besides achieving the optimal BP, choosing medications with renoprotective effects is important. A detailed description of this issue is beyond the scope of this review. Here, we briefly describe conventional drugs and introduce several with potential for prevention of CKD progression.

Renin-angiotensin system blockers (RASBs), such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), are a cornerstone therapy in patients with CKD. In a groundbreaking study by Lewis et al. [68], captopril was first used to protect against a decline in kidney function in patients with insulin-dependent type 1 diabetes and CKD studies with RASBs have consistently demonstrated the renoprotective effects of these drugs, including a reduction in proteinuria and attenuation of eGFR decline. These beneficial effects were evident in patients with and without diabetes. In the AASK trial, patients randomly assigned to ramipril showed a slower decline in eGFR compared to those on other treatments [69]. In patients with type 2 diabetes and CKD, the RENAAL and IDNT studies confirmed the superior protective effects of ARBs against the progression of CKD [70,71]. RASBs have been tested in patients with early CKD, even those without microalbuminuria. In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), ACEi prevented the onset of microalbuminuria in patients with type 2 diabetes and normal urinary albumin excretion [72]. All guidelines recommend the use of RASBs as first-line therapy based on high-quality evidence [18,19,22,25,32-34].

RASBs cannot stop the progression of CKD and no other drugs are used widely in clinical practice. Recently, many studies with new anti-diabetic drugs, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA), have consecutively demonstrated outstanding renoprotective effects [73,74]. The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the KDIGO accepted the results of these studies and recommend SGLT2i and GLP1RA as first-line therapies for patients with diabetic kidney disease [75,76]. Interestingly, these drugs have also been reported to reduce adverse CVEs and death [77-79]. Moreover, in the Dapagliflozin and Prevention of Adverse Outcomes

in Chronic Kidney Disease (DAPA-CKD) trial, dapagliflozin reduced the risk of the composite outcome of kidney failure or death from renal or cardiovascular causes even in non-diabetic patients with CKD [80]. In addition, these drugs can reduce BP by 5 mmHg [79,81,82].

Atrasentan is a highly selective endothelin receptor A receptor ($ET_AR$) antagonist, the short-term use of which reportedly reduces albuminuria in patients with diabetic nephropathy [83]. The Study of Diabetic Nephropathy with Atrasentan (SONAR) tested the long-term effect of atrasentan in 2,648 patients with type 2 diabetes and overt albuminuria [84]. Atrasentan resulted in a significant reduction in the composite adverse kidney outcome of doubling serum creatinine or KFRT. A recent phase 2 study of sparsentan, a dual $ET_AR$ antagonist and ARB, also showed a significant reduction in proteinuria in patients with primary focal segmental glomerulosclerosis [85]. $ET_AR$ antagonists are reported to decrease BP [85,86]. The effects of $ET_AR$ antagonists are under investigation in other primary glomerular diseases (NCT03762850, NCT03493685, NCT04573478).

Finally, mineralocorticoid receptor antagonists (MRAs) have renoprotective and cardioprotective effects [87-89]. It also reduces BP in individuals with resistant hypertension [90,91]. Spironolactone, a first-generation nonselective MRA, was initially reported to provide renoprotective effects by reducing proteinuria and preserving eGFR in non-diabetic patients with CKD [87]. Recently, finerenone, a new-generation selective MRA, has emerged as a potential therapy. In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study, finerenone reduced the risk of CKD progression and the development of CVEs in patients with CKD and type 2 diabetes [92]. These drugs are promising and expected to improve kidney survival and major clinical outcomes in combination with RASBs. Table 5 lists clinical trials of drug treatments [68,70-72,74,77,78,80,84,85,87,92,93].

## CONCLUSIONS

In patients with CKD, the scope of 'optimal BP control' should encompass improved cardiovascular outcomes, reduced mortality, and delayed CKD progression. However, despite much research, the optimal BP reduction

**Table 6. Key BP control recommendations and suggestions by the KDIGO 2021 guideline**

| | |
|---|---|
| BP management in patients with non-dialysis CKD, with, or without diabetes. | |
| Recommendation 1 | We recommend adults with high BP and CKD be treated with a target SBP < 120 mmHg, when tolerated, using standardized office BP measurement (2B). |
| Recommendation 2 | We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (1B). |
| Recommendation 3 | We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (2C). |
| Recommendation 4 | We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2, and A3) with diabetes (1B). |
| Recommendation 5 | We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes (1B). |

1B, strong recommendation based on moderate quality evidence; 2C, weak recommendation based on low quality evidence; A1, ACR < 30 mg/g (< 3 mg/mmol); A2, ACR 30–300 mg/g (3–30 mg/mmol); A3, ACR > 300 mg/g (> 30 mg/mmol).
BP, blood pressure; KDIGO, Kidney Disease: Improving Global Outcomes; CKD, chronic kidney disease; SBP, systolic blood pressure; RASi, renin-angiotensin system inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

to achieve these goals has not been determined. Table 6 presents a summary of BP control based on the KDIGO 2021 guidelines. These recommendations and suggestions are helpful in clinical practice, and the guidelines support intensive BP control targeting an SBP of < 120 mmHg because the cardiovascular benefits of SBP intervention outweigh the risk of kidney injury associated with the lower BP target. However, many uncertainties remain to be resolved in future trials. We anticipate that a greater number of well-designed RCTs will assess the effects of intensive BP control by various interventions in diverse groups of patients with CKD with and without diabetes, a high cardiovascular risk, or proteinuria, and with early versus late CKD.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Oh KH, Kang M, Kang E, et al. The KNOW-CKD Study: what we have learned about chronic kidney diseases. Kidney Res Clin Pract 2020;39:121-135.
2. Son HE, Ryu JY, Go S, et al. Association of ambulatory blood pressure monitoring with renal outcome in patients with chronic kidney disease. Kidney Res Clin Pract 2020;39:70-80.
3. Ezzatzadegan Jahromi S, Haghighi G, Roozbeh J, Ebrahimi V. Comparisons between different blood pressure measurement techniques in patients with chronic kidney disease. Kidney Res Clin Pract 2019;38:212-219.
4. Kim K, Lee SH, Lee SW, Lee JP, Chin HJ; Korean GlomeruloNEphritis sTudy (KoGNET) Group. Current findings of kidney biopsy including nephropathy associated with hypertension and diabetes mellitus in Korea. Korean J Intern Med 2020;35:1173-1187.
5. Kim H, Yoo TH, Choi KH, et al. Baseline cardiovascular characteristics of adult patients with chronic kidney disease from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci 2017;32:231-239.
6. Jha V, Modi GK. Getting to know the enemy better-the global burden of chronic kidney disease. Kidney Int 2018;94:462-464.
7. Kim KM, Oh HJ, Choi HY, Lee H, Ryu DR. Impact of chronic kidney disease on mortality: a nationwide cohort study. Kidney Res Clin Pract 2019;38:382-390.
8. Baek SH, Cha RH, Kang SW, et al. Circulating renalase predicts all-cause mortality and renal outcomes in patients with advanced chronic kidney disease. Korean J Intern Med 2019;34:858-866.
9. Lee C, Yun HR, Joo YS, et al. Framingham risk score and risk of incident chronic kidney disease: a community-based prospective cohort study. Kidney Res Clin Pract

2019;38:49-59.

10. Park S. Management plans for populations with normal-to-hypertensive blood pressures: risks and benefits of antihypertensive drug treatment in populations previously defined as having high-normal blood pressure. Korean J Intern Med 2019;34:44-49.

11. Obermayr RP, Temml C, Knechtelsdorfer M, et al. Predictors of new-onset decline in kidney function in a general middle-european population. Nephrol Dial Transplant 2008;23:1265-1273.

12. Reynolds K, Gu D, Muntner P, et al. A population-based, prospective study of blood pressure and risk for end-stage renal disease in China. J Am Soc Nephrol 2007;18:1928-1935.

13. Xue H, Wang J, Hou J, et al. Prehypertension and chronic kidney disease in chinese population: four-year follow-up study. PLoS One 2015;10:e0144438.

14. Garofalo C, Borrelli S, Pacilio M, et al. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. Am J Kidney Dis 2016;67:89-97.

15. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-1913.

16. Colantonio LD, Booth JN 3rd, Bress AP, et al. 2017 ACC/AHA blood pressure treatment guideline recommendations and cardiovascular risk. J Am Coll Cardiol 2018;72:1187-1197.

17. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-2219.

18. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-520.

19. Jaques H; National Institute for Health and Clinical Excellence (NICE). NICE guideline on hypertension. Eur Heart J 2013;34:406-408.

20. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 2014;32:3-15.

21. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease: summary of recommendation statements. Kidney Int Suppl 2013;3:5-14.

22. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol 2020;36:596-624.

23. Becker GJ, Wheeler DC, De Zeeuw D, et al. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:337-414.

24. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-2116.

25. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int 2021;99:S1-S87.

26. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-1585.

27. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-2020.

28. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet 2005;365:939-946.

29. Cuspidi C, Tadic M, Grassi G, Mancia G. Treatment of hypertension: the ESH/ESC guidelines recommendations. Pharmacol Res 2018;128:315-321.

30. Pilmore H, Dogra G, Roberts M, et al. Cardiovascular disease in patients with chronic kidney disease. Nephrology (Carlton) 2014;19:3-10.

31. Prichard S. Clinical practice guidelines of the Canadian Society of Nephrology for the treatment of patients with chronic renal failure: a re-examination. Contrib Nephrol 2003;140:163-169.

32. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA

guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13-e115.

33. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens 2020;38:982-1004.

34. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018;36:1953-2041.

35. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. Hypertension 2010;56:780-800.

36. Ahmad FS, Chan C, Rosenman MB, et al. Validity of cardiovascular data from electronic sources: the multi-ethnic study of atherosclerosis and HealthLNK. Circulation 2017;136:1207-1216.

37. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol 2017;28:2812-2823.

38. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-967.

39. Aggarwal R, Petrie B, Bala W, Chiu N. Mortality outcomes with intensive blood pressure targets in chronic kidney disease patients. Hypertension 2019;73:1275-1282.

40. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. JAMA Intern Med 2017;177:1498-1505.

41. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-713.

42. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755-1762.

43. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. J Am Soc Nephrol 2005;16:2170-2179.

44. Kovesdy CP, Lu JL, Molnar MZ, et al. Observational modeling of strict vs conventional blood pressure control in patients with chronic kidney disease. JAMA Intern Med 2014;174:1442-1449.

45. Sim JJ, Shi J, Kovesdy CP, Kalantar-Zadeh K, Jacobsen SJ. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. J Am Coll Cardiol 2014;64:588-597.

46. Navaneethan SD, Schold JD, Jolly SE, et al. Blood pressure parameters are associated with all-cause and cause-specific mortality in chronic kidney disease. Kidney Int 2017;92:1272-1281.

47. Patel A; ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829-840.

48. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883-892.

49. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435-443.

50. Nadkarni GN, Chauhan K, Rao V, et al. Effect of intensive blood pressure lowering on kidney tubule injury: findings from the ACCORD Trial Study participants. Am J Kidney Dis 2019;73:31-38.

51. Rocco MV, Sink KM, Lovato LC, et al. Effects of intensive blood pressure treatment on acute kidney injury events in the Systolic Blood Pressure Intervention Trial (SPRINT). Am J Kidney Dis 2018;71:352-361.

52. Heerspink HJL, Greene T, Tighiouart H, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol 2019;7:128-139.

53. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early

stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis 2020;75:84-104.

54. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 2005;165:923-928.

55. Schaeffner ES, Kurth T, Bowman TS, Gelber RP, Gaziano JM. Blood pressure measures and risk of chronic kidney disease in men. Nephrol Dial Transplant 2008;23:1246-1251.

56. Chang TI, Lim H, Park CH, et al. Associations of systolic blood pressure with incident CKD G3-G5: a cohort study of South Korean adults. Am J Kidney Dis 2020;76:224-232.

57. Joo YS, Lee C, Kim HW, et al. Association of longitudinal trajectories of systolic BP with risk of incident CKD: results from the Korean Genome and Epidemiology Study. J Am Soc Nephrol 2020;31:2133-2144.

58. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918-929.

59. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994;330:877-884.

60. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 2005;142:342-351.

61. Tsai WC, Wu HY, Peng YS, et al. Association of intensive blood pressure control and kidney disease progression in nondiabetic patients with chronic kidney disease: a systematic review and meta-analysis. JAMA Intern Med 2017;177:792-799.

62. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 2013;185:949-957.

63. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996;276:1886-1892.

64. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999;340:677-684.

65. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-1097.

66. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 2003;163:1555-1565.

67. Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005;16:3027-3037.

68. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-1462.

69. Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001;285:2719-2728.

70. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-860.

71. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-869.

72. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941-1951.

73. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019;394:131-138.

74. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-2306.

75. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of

hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-2701.

76. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98:S1-S115.

77. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-657.

78. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-334.

79. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-357.

80. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-1446.

81. Wang B, Zhong J, Lin H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. Diabetes Obes Metab 2013;15:737-749.

82. Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes. Diabetes Care 2015;38:429-430.

83. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. J Am Soc Nephrol 2011;22:763-772.

84. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet 2019;393:1937-1947.

85. Trachtman H, Nelson P, Adler S, et al. DUET: a phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. J Am Soc Nephrol 2018;29:2745-2754.

86. Raichlin E, Prasad A, Mathew V, et al. Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. Hypertension 2008;52:522-528.

87. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 2006;70:2116-2123.

88. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-717.

89. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-1321.

90. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059-2068.

91. Krieger EM, Drager LF, Giorgi DMA, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT Randomized Study (Resistant Hypertension Optimal Treatment). Hypertension 2018;71:681-690.

92. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219-2229.

93. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7:606-617.