

Management of Blood Pressure in Patients With Chronic Kidney Disease Not Receiving Dialysis: Synopsis of the 2021 KDIGO Clinical Practice Guideline

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Description: The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 clinical practice guideline for the management of blood pressure (BP) in patients with chronic kidney disease (CKD) not receiving dialysis is an update of the KDIGO 2012 guideline on the same topic and reflects new evidence on the risks and benefits of BP-lowering therapy among patients with CKD. It is intended to support shared decision making by health care professionals working with patients with CKD worldwide. This article is a synopsis of the full guideline.

Methods: The KDIGO leadership commissioned 2 co-chairs to convene an international Work Group of researchers and clinicians. After a Controversies Conference in September 2017, the Work Group defined the scope of the evidence review, which was undertaken by an evidence review team between October 2017 and April 2020. Evidence reviews were done according to the Cochrane Handbook. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to guide the development of

the recommendations and rate the strength and quality of the evidence. Practice points were included to provide guidance when evidence was insufficient to make a graded recommendation. The guideline was revised after public consultation between January and March 2020.

Recommendations: The updated guideline comprises 11 recommendations and 20 practice points. This synopsis summarizes key recommendations pertinent to the diagnosis and management of high BP in adults with CKD, excluding those receiving kidney replacement therapy. In particular, the synopsis focuses on recommendations for standardized BP measurement and a target systolic BP of less than 120 mm Hg, because these recommendations differ from some other guidelines.

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Large-scale, prospective, observational studies have demonstrated a log-linear relationship between usual blood pressure (BP) (down to 115/75 mm Hg) and subsequent risk for stroke, myocardial infarction, heart failure, and other cardiovascular events (1). Interventions that lower BP result in proportional reductions in these risks (2, 3). However, the extent to which BP can safely be reduced before compromising organ perfusion has not been defined, and excessive BP reduction might be harmful, particularly in patients with stiff conduit arteries or established occlusive vascular disease. Some analyses of observational data among patients receiving anti-hypertensive medication show a J-shaped relationship, where very low achieved BP is associated with higher rates of adverse outcomes. The implications of these observational findings are controversial in their relationship to setting BP targets (4, 5) because no randomized controlled trial (RCT) to date has confirmed poorer hard outcomes with lower target BP, and the benefits of intensive reduction of systolic BP (SBP) were shown to be independent of baseline diastolic BP in SPRINT (Systolic Blood Pressure Intervention Trial). Nonetheless, a point likely exists at which BP reduction will cause net harm due to underperfusion or side effects of medications.

Observational studies also show a linear relationship between BP and subsequent risk for kidney failure (6, 7), but the causal relationship is less clear because the kidney is the central organ in BP control and most kidney diseases

cause hypertension. The evidence that BP lowering (for example, SBP <140 mm Hg, compared with a higher SBP, such as 160 mm Hg) reduces risk for kidney failure in patients with either preexisting chronic kidney disease (CKD) or “essential” hypertension is much less certain. As with the reduction of risk for cardiovascular disease, the ideal target BP remains to be defined.

In earlier RCTs testing BP targets in populations with prevalent CKD, kidney end points were relatively common (8–11) but cardiovascular events were less common, possibly because of patient selection or lack of a requirement for reporting in the trial protocols. Early trials of BP targets in the general population sought to exclude patients with advanced CKD or did not report kidney function. However, recognition of the frequency of early CKD in the population as a whole (12)—and of CKD as a major risk factor for cardiovascular disease (13, 14)—has led to recent studies including substantial numbers of patients with CKD, albeit often at an earlier stage and

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Editorial comment

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with less risk for progression to kidney failure than in previous studies done exclusively in CKD populations (15–18). In particular, SPRINT, which randomly assigned 9361 participants to intensive (SBP <120 mm Hg) or less intensive (SBP <140 mm Hg) BP control (18), included a prespecified subgroup of participants with CKD. The CKD cohort in SPRINT comprised 2646 people, with a mean estimated glomerular filtration rate (eGFR) of 47.9 mL/min/1.73 m² and mean urinary albumin-creatinine ratio of 80.6 mg/g (19). In these more recent RCTs, cardiovascular events and death were far more frequent than kidney failure.

The 2021 revision of the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for BP management in patients with CKD not receiving dialysis takes into account both the risk for progression to kidney failure and the risk for cardiovascular events. The KDIGO leadership commissioned 2 co-chairs to convene an international Work Group of researchers and clinicians. After a Controversies Conference in September 2017, the Work Group defined the scope of the guideline and clinical questions for evidence review, which was undertaken by an independent evidence review team (ERT) between October 2017 and April 2020. Evidence reviews were done according to the Cochrane Handbook. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to guide development of the recommendations and rate the strength and quality of the evidence. Practice points were included to provide guidance when evidence was insufficient to make a graded recommendation. The guideline was revised after public consultation between January and March 2020. This article provides a synopsis of the full guideline, with emphasis on areas of practice most relevant to general internists. The recommendations that may prove most controversial are to target an SBP of less than 120 mm Hg in adults with CKD and to adopt standardized techniques for the measurement of BP in the outpatient clinic if using these measurements to diagnose or treat BP. The rationale for these and other key recommendations are provided in detail subsequently.

The full guideline and its executive summary are available at <https://kdigo.org/guidelines/blood-pressure-in-ckd>. Although the full guideline also addresses BP management in children with CKD and kidney transplant recipients, this synopsis focuses on the key recommendations applicable to adults who have not received a transplant.

GUIDELINE DEVELOPMENT PROCESS, EVIDENCE GRADING, AND STAKEHOLDER AND PUBLIC REVIEW

The Work Group comprised an international group of nephrologists (both adult and pediatric), epidemiologists, and experts in hypertension, and a 12-person ERT. It defined the scope of the guideline and graded evidence according to the GRADE framework (20–23).

The PICOM (population, intervention, comparator, outcomes, and methods) questions were submitted to the ERT for formal review. The Work Group and ERT followed an iterative process of evidence review and revision of guideline statements. Where questions mapped to existing Cochrane Kidney and Transplant systematic reviews, the reviews were

updated; otherwise, new systematic reviews were done, in accordance with the Cochrane Handbook (24). From a total of 6863 citations screened, 290 RCTs, 35 systematic reviews, and 14 observational studies were included in the evidence review. Supplementary evidence tables were published with the guideline and are also available as a data supplement on the KDIGO website and on the web-based guideline publishing platform MAGICapp (<https://kdigo.org/guidelines/blood-pressure-in-ckd>). Additional details on the methodology are provided in the Methods for Guideline Development chapter of the published guideline (25), and the KDIGO Guideline Development Conflict of Interest Policy is provided in the **Supplement** (available at Annals.org).

The Work Group adhered to a consistent KDIGO structured format for recommendations informed by a systematic review, and the evidence-to-recommendation step was based on the GRADE process (21, 22). Recommendations were graded as either strong, level 1 (“we recommend”) or weak, level 2 (“we suggest”); the strength of a recommendation was based on a judgment by the Work Group on the balance of desirable and undesirable effects, the quality of the evidence, perceived patient values and preferences, and resource implications (**Appendix Table 1**, available at Annals.org). The quality of evidence was graded as high (A), moderate (B), low (C), or very low (D) (**Appendix Table 2**, available at Annals.org). The intended use of strong and weak recommendations is summarized in **Appendix Table 3** (available at Annals.org). A full discussion of the evidence base and of how the Work Group weighed all of the relevant factors is presented in the full guideline (<https://kdigo.org/guidelines/blood-pressure-in-ckd>). By definition, a greater shared decision-making process is required in clinical situations to which a weak recommendation applies.

Patients were not involved in the development of the guideline, but the Work Group and ERT sought published evidence (including the work of the SONG [Standardised Outcomes in Nephrology] Initiative: www.songinitiative.org) on how patient views and preferences might influence decision making. Formal economic evaluations of treatment options were not done. Practice points were developed for clinical situations in which guidance was considered useful despite the lack of high-certainty evidence.

Although a detailed description of all recommendations and practice points is beyond the scope of this synopsis, a full list is provided in **Table 1**.

RECOMMENDATIONS FOR BP MEASUREMENT

We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (1B).

Standardized office BP refers to measurements obtained according to recommended preparations and measurement techniques, regardless of the type of equipment used (**Figure 1**) (26). In contrast, routine office BP refers to measurements obtained without following these preparations and is often called casual office BP. Standardized BP measurement is integral to the BP target set forth by this guideline. The BP target guideline should not be applied to routine BP values because large RCTs that examined target BP, including SPRINT and

Table 1. Recommendations and Practice Points From the KDIGO 2021 Clinical Practice Guideline for the Management of BP in CKD**Chapter 1: BP measurement**

- Recommendation 1.1: We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (1B).
- Practice Point 1.1: An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes adequate preparations for BP measurement, not the type of equipment.
- Practice Point 1.2: Automated office BP, either attended or unattended, may be the preferred method of standardized office BP measurement.
- Practice Point 1.3: Oscillometric devices can be used to measure BP among patients with atrial fibrillation.
- Recommendation 1.2: We suggest that out-of-office BP measurements with ABPM or HBPM be used to complement standardized office BP readings for the management of high BP (2B).

Chapter 2: Lifestyle interventions for lowering BP in patients with CKD not receiving dialysis

- Recommendation 2.1.1: We suggest targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD (2C).
- Practice Point 2.1.1: Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.
- Practice Point 2.1.2: The DASH-type diet or use of salt substitutes that are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism or other causes of impaired potassium excretion because of the potential for hyperkalemia.
- Recommendation 2.2.1: We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).
- Practice Point 2.2.1: Consider the cardiorespiratory fitness status, physical limitations, cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.
- Practice Point 2.2.2: The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.

Chapter 3: BP management in patients with CKD, with or without diabetes, not receiving dialysis

- Recommendation 3.1.1: We suggest that adults with high BP and CKD be treated with a target SBP of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).
- Practice Point 3.1.1: It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a nonstandardized manner.
- Practice Point 3.1.2: Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.
- Recommendation 3.2.1: We recommend starting RASI therapy (ACEI or ARB) for people with high BP, CKD, and severely increased albuminuria (CKD G1–G4; albuminuria category A3) without diabetes (1B).
- Recommendation 3.2.2: We suggest starting RASI therapy (ACEI or ARB) for people with high BP, CKD, and moderately increased albuminuria (CKD G1–G4; albuminuria category A2) without diabetes (2C).

Recommendation 3.2.3: We recommend starting RASI therapy (ACEI or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (CKD G1–G4; albuminuria categories A2 and A3) with diabetes (1B).

Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASI (ACEI or ARB).

Practice Point 3.2.2: RASI (ACEI or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASI, depending on the current GFR and serum potassium.

Practice Point 3.2.4: Hyperkalemia associated with use of RASI can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASI.

Practice Point 3.2.5: Continue ACEI or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

Practice Point 3.2.6: Consider reducing the dose or discontinuing ACEI or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (eGFR <15 mL/min/1.73 m²).

Practice Point 3.2.7: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR.

Recommendation 3.3.1: We recommend avoiding any combination of ACEI, ARB, and direct renin inhibitor therapy in patients with CKD, with or without diabetes (1B).

Chapter 4: BP management in kidney transplant recipients (CKD G1T–G5T)

Practice Point 4.1: Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).

Recommendation 4.1: We recommend that a dihydropyridine calcium-channel blocker or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).

Chapter 5: BP management in children with CKD

Recommendation 5.1: We suggest that in children with CKD, 24-h mean arterial pressure by ABPM should be lowered to ≤50th percentile for age, sex, and height (2C).

Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 mo with standardized auscultatory office BP in children with CKD.

Practice Point 5.2: In children with high BP and CKD, when ABPM is not available, manual auscultatory office BP obtained in a protocol-driven standardized setting targeting achieved SBP <90th percentile for age, sex, and height of normal children is a reasonable approach.

Practice Point 5.3: Use an ACEI or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated, but they carry risk for hyperkalemia and have adverse fetal risks for pregnant women.

ABPM = ambulatory BP monitoring; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CKD = chronic kidney disease; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic BP; eGFR = estimated GFR; GFR = glomerular filtration rate; HBPM = home BP monitoring; KDIGO = Kidney Disease: Improving Global Outcomes; RASI = renin-angiotensin system inhibitor; SBP = systolic BP.

ACCORD (Action to Control Cardiovascular Risk in Diabetes), used standardized BP measurements. Further, strong evidence indicates that routine office BP and standardized office BP do not give the same values, and

the relationships between these 2 techniques are highly variable for all individuals regardless of CKD status. For example, in a study of 275 persons with CKD, standardized SBP was 12.7 mm Hg lower than routine office

Figure 1. Checklist for standardized office BP measurement.

1. Properly prepare the patient	<ol style="list-style-type: none"> 1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement 3. Ensure patient has emptied his/her bladder 4. Neither the patient nor the observer should talk during the rest period or during the measurement 5. Remove all clothing covering the location of cuff placement 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria
2. Use proper technique for BP measurements	<ol style="list-style-type: none"> 1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically 2. Support the patient's arm (e.g., resting on a desk) 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum) 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings
3. Take the proper measurements needed for diagnosis and treatment of elevated BP	<ol style="list-style-type: none"> 1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings 2. Separate repeated measurements by 1–2 min 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level 4. For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds
4. Properly document accurate BP readings	<ol style="list-style-type: none"> 1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number 2. Note the time of most recent BP medication taken before measurements
5. Average the readings	Use an average of ≥ 2 readings obtained on ≥ 2 occasions to estimate the individual's level of BP
6. Provide BP readings to patient	Provide patients with the SBP/DBP readings verbally and in writing

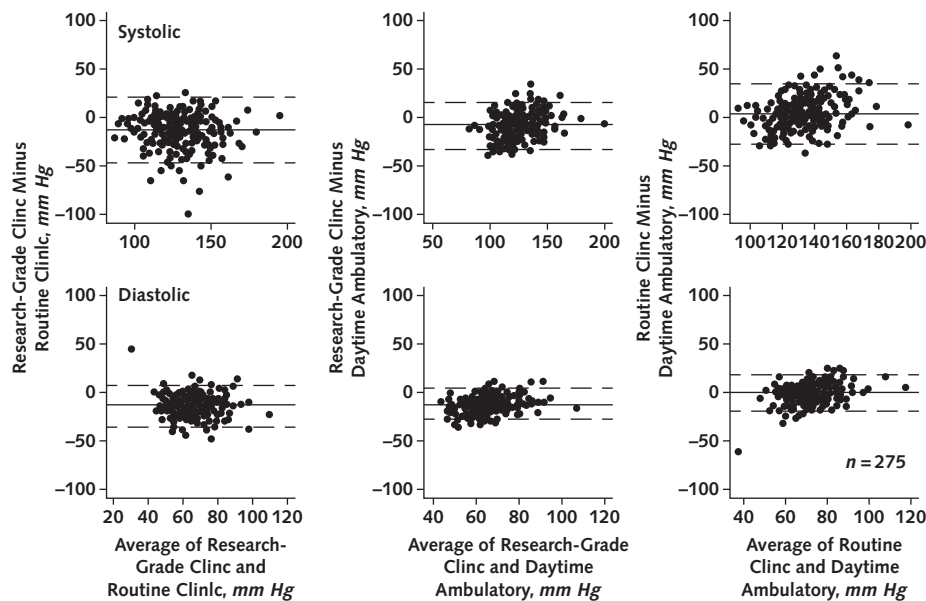
Modification for pediatrics: BP in infants should be measured while supine, and the use of the bell is recommended. BP = blood pressure; DBP = diastolic BP; SBP = systolic BP. (Reproduced from Whelton and colleagues [26], with permission.)

BP (Figure 2) (27). Similarly, a study of 3074 SPRINT participants compared 3 or more outpatient readings from the electronic health record versus standardized BP measurements taken during the trial and found that outpatient BPs were generally higher than standardized BP measurements. More important, heterogeneity in differences was high between BP recorded in the electronic health record and standardized trial measurements (28). It may seem feasible to simply subtract the mean difference from the routine BP to obtain an estimate of standardized BP; however, these data consistently show wide limits of agreement (for example, -46.1 to $+20.7$ mm Hg) (27), making such adjustments highly unreliable for the individual patient, such that both over- and undertreatment are likely if routine BPs are used to manage BP. These results highlight the importance of the standardized BP measurement technique and an inability to apply 1 common correction factor to approximate research-quality BP estimates when BP is not measured appropriately in routine clinical practice. The recommendation to measure standardized BP is consistent with other recent guidelines (for example, from the American College of Cardiology and American Heart Association [26, 29] and European Society of Cardiology and European Society of Hypertension [30]). However, whereas other guidelines have relaxed BP targets because

of concerns that the targets will be applied to routine BP measurements, this KDIGO BP guideline makes a critical distinction, recommending widespread adoption of standardized BP measurements and thereby applying SBP targets with proven efficacy in clinical trials, among participants with CKD.

The Work Group recognized that standardized BP measurements increase the burden to patients, health care providers, and health care facilities. However, this recommendation was rated as strong because obtaining standardized BPs is essential for the implementation of the BP targets developed in trials. The recommendation also places a high value on avoidance of misclassification so as to prevent over- or undertreatment of high BP—an issue that becomes increasingly important when targeting lower BPs.

Oscillometric BP devices may be preferred over manual BP devices (Table 1, Practice Point 1.1) because they minimize potential sources of inaccuracy in BP measurements that can occur with human errors associated with manual BP measurement, such as those resulting from improper deflation rate, terminal digit bias, or hearing impairment. However, RCTs have used standardized office BP measured with either oscillometric or manual devices, and studies that directly compared the 2 techniques do not suggest overt differences in

Figure 2. Bland-Altman plot showing the mean differences between various BP recordings and their limits of agreement.

The top panel shows systolic BP, and the bottom panel shows diastolic BP. Research-grade BP was, on average, 12.7/12.0 mm Hg lower (bias) than routine clinic BP and had wide limits of agreement. BP = blood pressure. (Reproduced from Agarwal [27].)

readings (31–33); therefore, manual BP devices are also acceptable when oscillometric devices are unavailable. The Work Group recognized that oscillometric BP devices may cost more and may be unavailable in some settings.

Automated office BP devices may be the preferred method for standardized office BP measurement (Table 1, Practice Point 1.2). They may increase the likelihood of adherence to proper preparation because they can be programmed to include a rest period. They can also automatically take multiple BP measurements and provide an average. Automated devices can measure BP either with or without a health care provider in the room. Although a recent meta-analysis suggested that unattended measurements result in lower average BPs than attended measurements (34), the differences were small when restricted to studies that randomized the order in which measurements were made (35–40). Of note, several large trials, including SPRINT, used automated office BP as their measurement method. The SPRINT protocol did not specify whether automated office BP should be attended or unattended, and reductions in BP and cardiovascular risk were similar regardless of whether the measurement was attended or unattended (41).

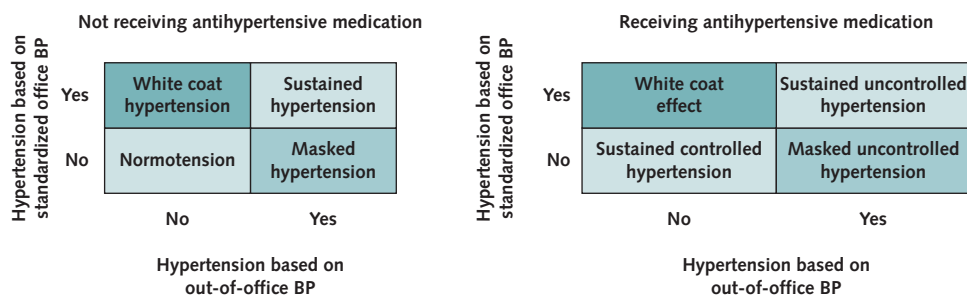
We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP (2B).

Techniques for out-of-office BP measurement include HBPM and 24-hour ABPM. In patients not receiving BP-lowering medications, the following 4 groups can be categorized on the basis of in- and out-of-office BP measurements

(Figure 3): normotension, white coat hypertension, sustained hypertension, and masked hypertension. In those receiving BP-lowering medications, 4 similar groups can be categorized: white coat effect, sustained controlled hypertension, sustained uncontrolled hypertension, and masked uncontrolled hypertension. Observational studies indicate a stronger association with cardiovascular and kidney outcomes for out-of-office than in-office BP measurements in the general population and persons with CKD (42–44). For example, masked hypertension and masked uncontrolled hypertension are associated with higher risk for cardiovascular disease and kidney outcomes than are sustained normotension and sustained controlled hypertension, respectively; these subgroups cannot be defined without ABPM measurements and have potential treatment implications (42).

The KDIGO BP guideline regarded out-of-office BP measurements as a complement to standardized office BP readings for the management of high BP. We recommend using initial ABPM, where available, to supplement standardized office BP and HBPM for ongoing management of BP. Providers working in areas where ABPM is not available may choose to use HBPM instead of an initial ABPM procedure.

The Work Group, however, acknowledged the lack of RCTs that specifically address whether and how best to treat BP profiles identified by out-of-office BP measurements (Appendix Table 4, available at Annals.org). The recommendation to obtain such measurements is therefore weak because no large RCTs have targeted out-of-office BP values in adults.

Figure 3. BP patterns informed by out-of-office BP measurements in addition to standardized office BP measurement.

BP = blood pressure.

RECOMMENDATIONS FOR BP TARGETS

We suggest that adults with high BP and CKD be treated with a target SBP of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).

This is a weak recommendation based on moderate-quality evidence.

Cardiovascular Events and Mortality

For most patients with CKD, particularly those who are older, have low levels of albuminuria, or are in the earlier stages of CKD, the risks for cardiovascular disease, including cardiovascular death, are much higher than those for kidney failure (45, 46). Two trials, ACCORD (16) and SPRINT (18, 19), have randomly assigned participants to SBP targets of less than 120 mm Hg versus less than 140 mm Hg. Both used standardized BP measurement.

ACCORD included adults with diabetes and excluded those with serum creatinine concentrations above 132.6 $\mu\text{mol/L}$ (1.5 mg/dL) and those with proteinuria higher than 1 g/24 h; therefore, it included only a small subset of patients with CKD (47). All participants in this study were concurrently randomly assigned to intensive versus standard glycemic control targets in a factorial design. The trial of glycemic control was terminated early because of higher all-cause mortality with the intensive glycemic target (16). This adverse effect of intensive glycemic control was also shown in the CKD subgroup of ACCORD (47). Intensive BP control resulted in a lower risk for stroke, a prespecified secondary end point, but no statistically significant reduction in the primary end point, a composite of fatal and non-fatal cardiovascular events (16).

SPRINT randomly assigned people without diabetes at high cardiovascular risk and showed a reduction in cardiovascular events and all-cause mortality with the lower BP target. Patients with polycystic kidney disease or proteinuria higher than 1 g/24 h were excluded; 90% of participants were receiving antihypertensive treatment at baseline (18). These benefits seemed similar in patients with CKD (19); the elderly, including those with frailty (48, 49); and those with prediabetes (50).

SPRINT showed a statistically significant reduction in the prespecified primary end point, where ACCORD did not. However, the extent of reduction in individual

outcomes in the trials was similar, and the difference in statistical significance with the primary end point may have been due to lower statistical power in ACCORD. Interpretation of ACCORD is also complicated by its factorial design and the higher mortality associated with intensive glycemic control. The reductions in cardiovascular end points and all-cause mortality due to intensive SBP control were similar in the standard glycemic target group of ACCORD and in SPRINT (51–53); in contrast, there was no statistical difference in event rates between the SBP groups in the participants assigned to intensive glycemic control. These statistical interactions lessened after discontinuation of the glycemic intervention (51). In another post hoc analysis among ACCORD participants who were receiving standard glycemic control and met the SPRINT inclusion criteria, intensive BP control provided cardiovascular benefits similar to those seen in SPRINT (54).

For these reasons, the Work Group chose not to identify different SBP targets for patients with CKD with and without diabetes. However, the evidence for benefit of targeting an SBP of less than 120 mm Hg in CKD is strongest among patients with clinical characteristics similar to those recruited to SPRINT and less strong in others (Table 2) (55). Recommendations for further research on BP targets in CKD are summarized in Appendix Table 5 (available at Annals.org).

Progression of Kidney Disease

The effects of intensive BP lowering on progression of CKD toward kidney failure are less certain. Three earlier RCTs comparing more versus less intensive BP lowering in CKD populations did not demonstrate a clear benefit of lower BP targets on the primary end point of kidney events (8, 9, 11); however, secondary analyses of these and other smaller trials have suggested that more intensive BP lowering reduces the rate of CKD progression among patients with greater baseline proteinuria (56–59). Retrospective analysis of long-term follow-up data from the MDRD (Modification of Diet in Renal Disease) study and AASK (African American Study of Kidney Disease and Hypertension) have also suggested lower risk for death among participants assigned to a lower mean arterial BP target (60, 61). In meta-analyses of trials in the general population, intensive BP lowering

Table 2. Certainty of the Evidence Supporting an SBP Target of <120 mm Hg for Patients With CKD**More certain**

Age >50 y
High risk for cardiovascular disease

Less certain

Age <50 or >80 y
Diabetes with CKD
CKD G4 or G5*
Proteinuria >1 g/d*
White coat hypertension
Pretreatment SBP of 120–129 mm Hg
Prior stroke
Very low DBP
Polycystic kidney disease
Severe hypertension—e.g., SBP ≥180 mm Hg while receiving no treatment or ≥150 mm Hg despite >4 antihypertensive agents

CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

* CKD G4–G5 indicates an estimated glomerular filtration rate <30 mL/min/1.73 m². Note that most people with CKD in the general population are older adults with CKD G1–G3 and with proteinuria <1 g/d (55) and so would fall under “more certain.”

was not associated with reduction in risk for kidney failure (3, 62). In SPRINT, the rate of eGFR decrease over time was higher in the group assigned to intensive BP lowering (19), although the absolute difference was small and occurred primarily in the first 6 months of the trial, potentially representing a hemodynamic effect; the rate of change of eGFR over time after the first 6 months was -0.47 mL/min/1.73 m² with intensive treatment and -0.32 mL/min/1.73 m² with standard treatment. Similar differences were seen in ACCORD (16). Thus, overall, intensive BP lowering seems to lead to a small but consistent reduction in eGFR shortly after initiation, compared with less intensive control. Whether intensive BP lowering is associated with improvements in kidney function, harms, or neither in the long term remains uncertain.

The KDIGO 2012 BP guideline recommended more intensive BP lowering for patients with albuminuria than those without. With the adoption of an SBP target of less than 120 mm Hg for all patients with CKD in the present revised guideline (primarily based on the evidence for cardiovascular and survival benefits), separate targets for patients with and without albuminuria were no longer considered necessary. The Work Group believed that the cardiovascular and survival benefits of intensive BP control outweighed the observed increases in risks for hyperkalemia, hypokalemia, and acute kidney injury (19).

RECOMMENDATIONS FOR CHOICE OF DRUG THERAPY

These recommendations are based on evidence that renin-angiotensin system inhibitors (RASi) (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin II receptor blockers [ARBs]) reduce both cardiovascular event rates and kidney end points among patients with CKD. The strength of evidence varies according to the presence or absence of diabetes and of proteinuria. There is a gradation of evidence

for benefit from strong in the CKD subpopulation with low eGFR and severely increased albuminuria to weak or absent in the subpopulation with normal eGFR without albuminuria. Many patients with CKD will require combination therapy to achieve the SBP target of less than 120 mm Hg; no RCTs have compared different combination therapies in CKD. Evidence-based recommendations are therefore limited to the choice of initial therapy.

We recommend starting RASi therapy (ACEI or ARB) for people with high BP, CKD, and severely increased albuminuria (CKD G1 to G4; albuminuria category A3) without diabetes (1B).

Evidence supporting use of RASi in CKD without diabetes with severely increased albuminuria comes from 4 placebo-controlled RCTs (63–67) showing clear evidence of reduction in the risks for both kidney failure and cardiovascular events (based on a meta-analysis by the guideline ERT). Meta-analyses suggest effect modification by proteinuria for kidney outcomes (68, 69).

We suggest starting RASi therapy (ACEI or ARB) for people with high BP, CKD, and moderately increased albuminuria (CKD G1 to G4; albuminuria category A2) without diabetes (2C).

This is a weak recommendation because there is no high-quality evidence from RCTs evaluating kidney outcomes in this subpopulation. The HOPE (Heart Outcomes and Prevention Evaluation) trial showed a cardiovascular benefit of ramipril over placebo, independent of BP, both in patients with moderately increased albuminuria (70) and in a prespecified analysis in the subgroup with reduced eGFR at baseline (71). Few patients developed kidney failure during the HOPE trial, with no difference between the ramipril and placebo groups (70). PEACE (Prevention of Events with ACE Inhibition) also showed a reduction in cardiovascular events in participants randomly assigned to ACEIs in the CKD subset (72). The Work Group decided that these benefits were likely to outweigh the risks for hyperkalemia and acute kidney injury for most patients.

We recommend starting RASi therapy (ACEI or ARB) for people with high BP, CKD, and moderately to severely increased albuminuria (CKD G1 to G4; albuminuria categories A2 and A3) with diabetes (1B).

Strong evidence (from IDNT [Irbesartan Diabetic Nephropathy Trial] [70] and RENAAL [Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan] [73]) indicates that RASi, compared with placebo (70, 73) or with calcium-channel blockade (70, 73), reduce risk for kidney events among patients with diabetes and severely increased albuminuria. MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes substudy of Heart Outcomes Prevention Evaluation) showed that random assignment to ramipril led to cardiovascular benefit among patients with diabetes and moderate albuminuria (74, 75). Meta-analysis by the KDIGO ERT showed that ACEIs, compared with placebo or standard of care, had no effect on all-cause mortality but caused statistically significant reductions in risks for doubling of serum creatinine and progression of albuminuria from category A2 to A3.

We recommend avoiding any combination of ACEI, ARB, and direct renin inhibitor therapy in patients with CKD with or without diabetes (1B).

Several large trials have tested the hypothesis that dual RAS blockade (a combination of 2 of ACEI, ARB, and direct renin inhibitor) would confer additional benefit, compared with monotherapy, in high-risk populations. Meta-analysis of these studies shows no evidence of benefit on cardiovascular outcomes or progression of CKD, apart from a reduction in albuminuria; adverse effects include increased risks for acute kidney injury and hyperkalemia (76).

Since the full guideline was finalized, the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial results were published, showing that the addition of finerenone to background ACEI or ARB therapy reduced the composite primary outcome of GFR decline, kidney failure, or renal death, and also reduced risk for cardiovascular events (77) but increased risk for hyperkalemia. The implications of these findings will be assessed in future updates of this guideline.

Recommendations for further research on choice of BP-lowering drug therapy are given in **Appendix Table 6** (available at Annals.org).

RECOMMENDATIONS FOR DIET AND LIFESTYLE

We suggest targeting a sodium intake of <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD (2C).

We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).

Interventional studies in the general population demonstrate a graded benefit in reduction of both BP and cardiovascular disease risk with reduced dietary sodium intake (78). Although most populations worldwide consume dietary sodium in excess of the proposed target of less than 2 g (<90 mmol) per day, even modest reductions in sodium intake that do not reach this target were associated with BP and cardiovascular disease benefits in recent studies in the general population (79). In populations with high BP and CKD, the ERT found moderate-quality evidence showing that dietary sodium reduction resulted in short-term reductions in BP (80, 81). Finally, ACEI and ARB medications are commonly used in CKD populations, and their kidney and cardiovascular benefits may be enhanced if accompanied by a low-sodium diet (82). Although data on specific targets of sodium intake in CKD populations with high BP are not firmly established, and because the KDIGO guidelines are designed to serve an international audience, the Work Group adopted the recommended target for dietary sodium intake in the general population from the World Health Organization (83). This level is consistent with sodium intake targets used in several intervention studies targeting BP in CKD populations. Finally, the recommendation is

consistent with the recently published KDIGO 2020 Guideline for Diabetes Management in CKD, providing consistency across guidelines (84).

Intervention studies and systematic reviews have firmly established the effects of regular physical activity on BP lowering, in addition to other health benefits in the general population. As with dietary sodium intake, data on effects of exercise in populations with CKD are more limited. The ERT found low-quality evidence from a single, small, randomized study in a CKD population showing that physical activity lowered SBP and diastolic BP and may limit the rate of eGFR decline over 12 months (85). Observational studies also show a dose-response relationship between greater amounts of physical activity and lower risk for death in CKD populations (86). The available data did not allow differentiation of the type, quantity, or critical elements of exercise that were most beneficial to persons with CKD. Nevertheless, the Work Group agreed that physical exercise is likely to be beneficial in CKD populations, as in the general population, and that the available data are consistent with this. However, patients with CKD have a high degree of comorbidity and frailty and will not all be able to achieve the levels of physical activity recommended for the general population. In the absence of specific information on type and intensity of exercise in CKD, the Work Group chose targets set by the World Health Organization (83) and a lifestyle guideline from the American College of Cardiology and American Heart Association for cardiovascular disease prevention (29). This recommendation is also consistent with the recently published KDIGO 2020 Guideline for Diabetes Management in CKD (84).

Finally, the Work Group discussed the effects on BP of several other lifestyle interventions, including losing weight for those who are obese or overweight, reducing alcohol consumption, and following heart-healthy diet patterns. Although these interventions may also have BP-lowering effects in patients with CKD, data were insufficient on risks and benefits in hypertensive CKD populations. Thus, the Work Group elected not to put forward specific recommendations for these interventions but made research recommendations to fill these knowledge gaps and facilitate future guidelines in this area (**Appendix Table 7**, available at Annals.org).

DISCUSSION

Since the first iteration of the KDIGO BP guideline in 2012, the results from SPRINT and the revision of BP guidelines by many task forces around the world prompted KDIGO to revise its BP guideline; the revisions were summarized here. The new KDIGO BP guideline identified 2 areas that warrant particular attention and are interdependent with one another, namely which BP to target and how to measure it. The findings from SPRINT including persons with CKD provide the main evidence by which the KDIGO BP guideline recommends targeting an SBP of less than 120 mm Hg measured by a standardized technique in the office in persons with CKD who are not receiving dialysis and have high BP.

The Work Group recognized the marked discrepancies and variability between routine office-based BP and standardized office-based BP. Because of this, and the

fact that prior trials consistently used standardized office BP measurements, the Work Group was concerned that targeting a systolic BP of less than 120 mm Hg may lead to overtreatment and associated adverse events if routine office BP was used instead of standardized BP. Thus, the KDIGO 2021 BP guideline makes detailed and strong recommendations regarding standardized BP measurement, and the target SBP of less than 120 mm Hg is specific to use of standardized BP measurements only.

The KDIGO 2021 BP guideline adopts a target SBP of less than 120 mm Hg for persons with CKD because of the benefits of intensive BP control on cardiovascular and all-cause mortality. The effects of intensive BP control on the risk for progressive CKD are much less certain.

The KDIGO 2021 BP guideline also recognizes that there are certain subpopulations in CKD where the evidence to support the SBP target of less than 120 mm Hg is less well developed, and hence the risk-benefit tradeoffs are less certain. These include persons with diabetes, advanced CKD (G4 or G5), proteinuria greater than 1 g/d, extremes of age, white coat hypertension, or very low diastolic BP. Additional RCTs are needed in these subpopulations.

The KDIGO guideline differs from other recent guidelines based on the same evidence, including those that have specific recommendations for patients with CKD (26, 30, 87, 88), in that the “default” SBP target is less than 120 mm Hg and that this target applies only to measurements taken under standardized conditions. Of note, the Hypertension Canada guidelines (89) also adopt SBP less than 120 mm Hg for adults with CKD. The SBP recommendation is conditional, implying a shared decision-making process in which clinicians and patients discuss the risks and benefits of more versus less intensive BP control. Targets should be individualized on the basis of patient preference and individual risks and benefits, particularly in groups in whom the evidence favoring more intensive control is less certain. The recommendation for standardized BP measurement is strong because overwhelming evidence indicates that “routine” office BP measurement is unreliable. Clinicians would not accept such unreliability in laboratory tests or other physiologic measurements. One of the major reasons that most other guidelines are more conservative is the concern that clinicians would apply a more intensive target to “routine” office BP measurements and thus risk overtreatment. This is understandable, but the KDIGO Work Group formed the strong view that clinical practice must change. Adoption of a more conservative SBP target and acceptance of substandard BP measurement techniques would likely result in many patients with CKD around the world being denied the clear benefits of more intensive BP control (19). These and other controversies are explored in more detail in **Appendix Table 8** (available at Annals.org).

Like all evidence-based guidelines, the KDIGO BP in CKD guideline is limited by the available evidence. In particular, evidence is lacking on how best to use ABPM or HBPM measurements in the treatment of high BP and on how patients with CKD and high BP would weigh the benefits and risks of such options as intensive versus less intensive treatment.

In summary, the Work Group recognizes that the risks for cardiovascular disease and death are greater than the risk for kidney failure in most individuals living with CKD. Recognizing

the importance of CKD as a risk factor for both high BP and cardiovascular disease, recent RCTs have systematically recruited larger subgroups with CKD to address the efficacy and safety of intensive BP lowering. With the emergence of new evidence on mortality and cardiovascular benefits of intensive BP lowering in patients with high BP and CKD, the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease in patients not receiving dialysis recommends systematically using standardized office BP measurement and targeting an SBP of less than 120 mm Hg.

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Appendix Table 1. Factors That Influence the Strength of a Recommendation

Factor	Comment
Balance of benefits and harms	The larger the difference between desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Resource use and other considerations	The higher the resource use associated with a recommendation, the less likely a strong recommendation is warranted.

Appendix Table 2. Factors That Influence the Grading for Quality of Evidence

Quality of Evidence	Meaning
High (A)	We are very confident that the true effect lies close to the estimate of the effect.
Moderate (B)	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	The true effect may be substantially different from the estimate of the effect.
Very low (D)	The estimate of the effect is very uncertain and may be far from the true effect.

Appendix Table 3. Implications of Strong Versus Weak Recommendations

Strength	Implications for Patients	Implications for Clinicians	Implications for Policy
Level 1, Strong: “We recommend”	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or performance measure.
Level 2, Weak: “We suggest”	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Appendix Table 4. Research Recommendations for BP Measurement

There are several areas in which more research is needed specifically for the CKD population:

Identify if procedures for standardized BP measurement can be simplified, such as using a shorter rest period (e.g., 1 or 2 min) or shorter interval between BP measurements (e.g., 15 or 30 s).

Compare standardized unattended vs. standardized attended automated office BP in routine clinical practice.

Determine the optimal interval for repeating ABPM and HBPM among individuals not receiving and receiving antihypertensive medications.

Determine the proportion of patients with CKD who have white coat hypertension, masked hypertension, white coat effect, and masked uncontrolled hypertension using a BP threshold of 120 mm Hg instead of 140 mm Hg and whether these phenotypes are associated with increased risk for cardiovascular disease.

Assess the cost-effectiveness of ABPM and HBPM, separately, for identifying white coat hypertension, masked hypertension, white coat effect, and masked uncontrolled hypertension.

Conduct RCTs comparing treatment based on ABPM or HBPM vs. standardized office BP measurements. Treatment based on ABPM or HBPM includes not treating patients with white coat hypertension, not intensifying treatment for white coat effect, treating masked hypertension, and intensifying treatment for masked uncontrolled hypertension.

ABPM = ambulatory BP monitoring; BP = blood pressure; CKD = chronic kidney disease; HBPM = home BP monitoring; RCT = randomized controlled trial

Appendix Table 5. Research Recommendations for BP Targets

Information is needed on how patient values and preferences influence decisions related to BP-lowering therapy. This would be an ideal topic for the SONG initiative.

Conduct adequately powered RCTs to examine the effects of intensive BP control among patients with CKD with concomitant diabetes, concomitant severely increased proteinuria (>1 g/d), or very low GFR (<30 mL/min/1.73 m²). ACCORD included only small numbers of patients with CKD, most of whom qualified for the trial as a result of albuminuria, and is, therefore, uninformative for patients with CKD G3-G5*. On the other hand, SPRINT explicitly excluded patients with diabetes.

In some Asian countries, stroke is more common than cardiac diseases as the cause of CV deaths. Whether intensive SBP control has similar, greater, or less CV-protective effect in the CKD population is unclear and may require confirmation.

Although there is strong evidence that ambulatory or home BP measurements are better predictors of adverse outcomes than office BP, all large RCTs on BP targets in adults used standardized office BP. RCTs targeting home or ambulatory BP measurements are needed.

SGLT2 inhibitors have major CV, kidney, and survival benefits among patients with CKD. In addition to reducing BP, they cause an early, acute decrease in GFR, a pattern that is also seen in intensive SBP lowering. The effects of these drugs, in combination with intensive BP-lowering therapy, on CV outcomes, all-cause mortality, and cognition, as well as acute and chronic changes in kidney function, require further examination.

ACCORD = Action to Control Cardiovascular Risk in Diabetes; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; GFR = glomerular filtration rate; RCT = randomized controlled trial; SBP = systolic BP; SGLT2 = sodium-glucose cotransporter-2; SONG = Standardised Outcomes in Nephrology; SPRINT = Systolic Blood Pressure Intervention Trial.

* GFR <60 mL/min/1.73 m².

Appendix Table 6. Research Recommendations for Choice of BP-Lowering Drug Therapy in CKD

In patients with CKD G3-G4* and albuminuria of category A1 or A2† with or without diabetes, RASi have not been adequately studied. Future studies should examine if RASi, in the presence or absence of other renoprotective agents (such as SGLT2 inhibitors and GLP-1 receptor agonists), provide kidney, cardiovascular, and survival benefits to this important subgroup.

Data are insufficient on the role of diuretics as first-line therapy for the treatment of high BP in patients with CKD. It would be helpful to clarify the role of diuretics as initial therapy in this population.

The benefits of dual therapy vs. monotherapy on major kidney outcomes in people with CKD without diabetes and heavy proteinuria (e.g., >2-3 g/d) have not been well studied. Future trials should examine this important subgroup, while curtailing the risks for hyperkalemia and acute kidney injury.

Studies should be done examining the addition of endothelin blockers or GLP-1 receptor agonists to concomitant RASi monotherapy for potential kidney benefits in the advanced CKD population and nonproteinuric CKD populations.

In the era of personalized medicine, research should be directed to identify individuals who will benefit or experience harm from these combinations in all CKD populations.

BP = blood pressure; CKD = chronic kidney disease; GLP-1 = glucagon-like peptide-1; RASi = renin-angiotensin system inhibitor; SGLT2 = sodium-glucose cotransporter-2.

* Glomerular filtration rate >15 but <60 mL/min/1.73 m².

† A1 indicates normal to mildly increased albuminuria, and A2 indicates moderately increased albuminuria.

Appendix Table 7. Research Recommendations for Diet and Lifestyle in CKD

Conduct clinical trials evaluating different dietary sodium reduction strategies for prevention of clinical end points of critical importance for CKD populations, including kidney failure, cardiovascular disease, and death.

There are inconsistencies among the studies examining the relationship between dietary sodium intake and health outcomes in persons with diabetes. Additional research is required to investigate the consistency of effects of dietary sodium changes on health benefits and harms across different causes and severities of CKD.

Whether a minimum dietary sodium level exists in CKD below which health risks are increased is unknown. Most of these data derive from studies evaluating sodium intake using spot urine sodium measurements. There is current controversy about the accuracy of assessing sodium intake using random urine specimens and the potential increased risk for adverse health outcomes at the low sodium intake range when assessed by this method. Additional research is required both in sodium intake assessment methodology in CKD and to evaluate the health effects of very low sodium intakes in CKD populations.

Recent small, single-center clinical trials evaluating long-term supplementation with oral sodium bicarbonate vs. placebo have not seen changes in BP. These findings raise the possibility that the anion associated with sodium intake may influence the BP response. Future research is required to determine if relationships of sodium intake with BP are influenced by the accompanying anion.

In the general population, potassium-containing salt substitutes have been shown to lower BP. Persons with CKD have been systematically excluded from clinical trials evaluating potassium-based salt substitutes, and some, albeit not all, observational data in CKD populations show that higher potassium intake is associated with higher risk for CKD progression and cardiovascular disease. Whether using potassium-containing salt substitutes may have health benefits or unique risks when applied to CKD populations requires future study.

Persons of African ancestry are disproportionately represented in CKD populations. Prior systematic reviews suggest that reductions in sodium intake may result in larger reductions in BP in persons of African and Asian ancestry than in White persons. Whether such racial differences can also be found in CKD populations is uncertain and should be evaluated in future studies.

Data are scarce on factors that could identify individual patients with CKD who have the greatest or least BP benefit from physical activity interventions, and also those who are at greater risk for harm. Identification of these factors and algorithms to tailor physical activity intensity and supervision to individual patients with CKD are needed.

Iodine supplements are added to salt in some countries. Future studies are required to determine whether restricting sodium intake in CKD populations may contribute to iodine deficiency in these settings.

BP = blood pressure; CKD = chronic kidney disease.

Appendix Table 8. Most Controversial Issues Raised by the KDIGO 2021 Clinical Practice Guideline for the Management of BP in CKD

Point	Counterpoint
Standardized office measurement of BP is not practical. It takes too much time in the clinic.	All trials examining BP targets and hard outcomes used standardized measurement. Because the benefits associated with proper measurement outweigh the burden of time or cost, such effort is worthwhile. Moreover, the relationship between routine nonstandardized and standardized BP measurement is unpredictable for any individual patient, and thus a correction factor cannot be applied. Would you accept a significant degree of bias or inaccuracy for measurement of serum creatinine, potassium, body weight, or age?
KDIGO recommends attended or unattended measurements, but SPRINT and ACCORD used unattended BP.	Both trials used standardized measurements, attended and unattended, with an automated device. The SPRINT protocol did not specify whether to obtain attended or unattended measurements, and similar CV risk reductions were seen regardless of attended or unattended measurement. Differences between attended and unattended BP values are notably small, so proper patient preparation and measurement is key.
The SBP target recommendation is based on a single trial. The data were extrapolated from general population to CKD, with and without diabetes.	SPRINT enrolled patients without diabetes. It is the only trial that examined CV events as the primary outcome and mortality as a secondary outcome with a prespecified CKD subgroup comparing 2 BP targets. The results are robust, and there was no effect modification from baseline CKD status for these outcomes. In the standard glycemic subgroup of the ACCORD trial (which enrolled patients with diabetes), the primary CV benefit of intensive SBP lowering was similar to that observed in SPRINT. Future research should be done in specific CKD subpopulations to confirm the broad applicability of the more intensive SBP target.
Subgroups (e.g., proteinuria >1 g/d, CKD G4* and G5†, ADPKD or other etiology) were not sufficiently addressed by SPRINT.	We agree that patients with proteinuria >1 g/d, CKD G5, and ADPKD were excluded from the SPRINT trial and that the proportion of patients with CKD G4* was small. However, there is no evidence or strong theoretical reason at this time to suggest that these subgroups would behave differently. In ADPKD, there is evidence that a target SBP <110 mm Hg is more beneficial than a higher SBP target. We agree that caution should be exercised in these subgroups and that more research specifically targeting these subgroups is needed. However, until there is evidence to the contrary, the SBP target <120 mm Hg seems to be reasonable for these subgroups.
The findings of the ACCORD trial are not consistent with the findings from SPRINT.	ACCORD did not recruit many patients with CKD because a serum creatinine level >1.49 mg/dL was an exclusion criterion. ACCORD had a factorial design, and in those randomly assigned to standard glycemic control, a target SBP <120 mm Hg was shown to be beneficial compared with <140 mm Hg. These findings are similar to those observed in SPRINT.
There is a greater risk for stroke with an SBP target <120 mm Hg vs. <140 mm Hg.	In SPRINT (including CKD) and ACCORD (primarily without CKD), stroke risk was lower or similar, but not greater, with a target SBP <120 mm Hg vs. <140 mm Hg.
It may be more realistic to have 2 targets, 1 for which there is great certainty of benefit and another that is more aspirational (e.g., SBP <140 mm Hg for all; SBP <120 mm Hg for some).	This alternative was discussed in detail by the BP Work Group but was eventually rejected on the basis that: 1) there are actually no data showing a benefit of <140 mm Hg in CKD, 2) all subgroups may actually benefit from SBP <120 mm Hg, and 3) this more complex scheme may encourage clinicians to continue adopting an SBP target <140 mm Hg for all CKD patients and deny many the potential advantages of tighter control. The relatively weak grading of the recommendation statement implies that many people would want the recommended course of action but some would not. Clinicians should understand the nature and rationale of the recommendations and engage in shared decision making with their patients.
Other institutions recommend different targets based on the identical evidence.	This is a common consequence of scientific discourse. Just as there are also other guidelines that recommend the same SBP target of <120 mm Hg, there can be differences in the interpretation of the same evidence base. Our SBP target recommendation is arrived at after a thorough systematic review of the literature, and the health gains from such intensive control are contingent on using SBP values obtained using standardized office measurement. Targets, intensive or not, are not meaningful if proper patient preparation and measure techniques are not followed.
Older adults are more likely to fall with lower SBP.	Injurious falls, syncope, postural hypotension, and serious adverse events did not differ between the lower and standard target groups of SPRINT. This was also the case in the older adult subgroup. In addition, CV, survival, and cognitive benefits were reported with a lower SBP target in SPRINT and in other studies in CKD (19, 48, 49).
In order to meet more intensive targets, frail and multimorbid patients using polypharmacy (including analgesics, sedatives, laxatives, and prostate medications) will have more adverse events.	Age and frailty were not treatment effect modifiers for the CV and mortality benefits in SPRINT. Further, serious adverse events did not differ between the standard and intensive SBP groups. One caveat to this statement is nursing home residents and those with short life expectancy, because they were not included in the SPRINT trial. The number of BP medications to achieve

Continued on following page

Appendix Table 8—Continued.

Point	Counterpoint
It is impractical and unwise to recommend targets that most health care professionals cannot follow.	<p>the SBP target during the trial also was not a determinant of these outcomes. Nevertheless, individualization of treatment is key.</p> <p>The KDIGO Work Group takes the view that patients should not be penalized for suboptimal clinical practice. Good practice takes time to be adopted, and as such recommending substandard practice of BP measurement or guidance for the sake of convenience will only perpetuate the status quo of suboptimal management and likely continue to lead to suboptimal outcomes.</p>
In some countries, patients with CKD G3 are followed mainly by primary care physicians, and these clinicians may not follow the recommendations from KDIGO.	<p>The guideline aimed to provide the best possible guidance for the treatment of patients with high BP and CKD. Because the KDIGO Work Group considers the guidelines to be appropriate, the likelihood of their immediate acceptance should not be the major criterion driving the recommended guidance. Implementation is the next step in the process where further knowledge translation will need to be performed.</p>
SPRINT and ACCORD demonstrated an increased risk for AKI and faster decline of GFR with target SBP <120 mm Hg vs. SBP <140 mm Hg.	<p>The reported AKI events were generally mild (AKI stage 1) and did not seem to lead to kidney failure during the trial in the ACCORD cohort, the SPRINT cohort, or the SPRINT-CKD cohort. The decline of eGFR in both standard and intensive SBP groups in SPRINT was slow, and the difference between the 2 groups was small. At the same time, intensive SBP lowering led to less, rather than more, albuminuria, which may portend a better long-term prognosis of the kidney. Last, a recent meta-analysis showed that intensive BP control reduces the risk for kidney failure in those with proteinuria at baseline (57). Although the long-term effects of intensive SBP lowering (<120 mm Hg) on albuminuria or GFR decline are uncertain, its effects on CV, mortality, and cognitive effects are convincing.</p>

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADPKD = autosomal dominant polycystic kidney disease; AKI = acute kidney injury; BP = blood pressure, CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated GFR; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; SBP = systolic BP; SPRINT = Systolic Blood Pressure Intervention Trial.

* GFR 15–29 mL/min/1.73 m².

† GFR <15 mL/min/1.73 m².