Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

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The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease for patients not receiving dialysis represents an update to the KDIGO 2012 guideline on this topic. Development of this guideline update followed a rigorous process of evidence review and appraisal. Guideline recommendations are based on systematic reviews of relevant studies and appraisal of the quality of the evidence. The strength of recommendations is based on the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. The scope includes topics covered in the original guideline, such as optimal blood pressure targets, lifestyle interventions, antihypertensive medications, and specific management in kidney transplant recipients and children. Some aspects of general and cardiovascular health, such as lipid and smoking management, are excluded. This guideline also introduces a chapter dedicated to proper blood pressure measurement since all large randomized trials targeting blood pressure with pivotal outcomes used standardized preparation and measurement protocols adhered to by patients and clinicians. Based on previous and new evidence, in particular the Systolic Blood Pressure Intervention Trial (SPRINT) results, we propose a systolic blood pressure target of less than 120 mm Hg using standardized office reading for most people with chronic kidney disease (CKD) not receiving dialysis, the exception being children and kidney transplant recipients. The goal of this guideline is to provide clinicians and patients a useful resource with actionable recommendations supplemented with practice points. The burden of the recommendations on patients and resources, public policy implications, and limitations of the evidence are taken into consideration. Lastly, knowledge gaps and recommendations for future research are provided.

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The original KDIGO Management of Blood Pressure (BP) in Chronic Kidney Disease (CKD) guideline in the CKD population not receiving dialysis was published in 2012. Since then, completion of the Systolic Blood Pressure Intervention Trial (SPRINT) sponsored by the National Institutes of Health along with several related meta-analyses and the revision of BP guidelines by many guideline task forces around the world prompted the re-examination of the KDIGO guideline on BP. A Work Group (WG) was formed in 2018 and supported by the Evidence Review Team from the Cochrane Kidney and Transplant Group. Further, new online publishing software, MAGICapp, was introduced with the aim to create a "living guideline" that can be updated conveniently.

As for many previous guidelines sponsored by KDIGO, a Controversies Conference was held to help better identify the emerging evidence, ongoing controversies, and unsettled questions. The conclusions from that conference helped frame the Scope of Work for this guideline update. It was decided that, since the definition, management, and nuances of high BP in the maintenance dialysis population are significantly different from those in the CKD population not receiving dialysis, the WG should confine its purview to the latter population, in keeping with the 2012 guideline.

Relevant Cochrane systematic reviews were updated with literature searches conducted through September 2019 and updated in April 2020. The primary data and meta-analyses used to generate this guideline are available on the KDIGO website and MAGICapp platform (https://kdigo.org/guidelines/blood-pressure-in-ckd/). Evidence from the systematic reviews was summarized into tables using the standard Cochrane and the GRADE methods (Appendix Tables 1–3). Although no economic analyses were conducted to inform the guideline, resource use and costs were implicitly considered in the formulation of recommendations.

To supplement graded recommendations, the KDIGO guideline includes "practice points" that are consensus statements representing the WG's expert judgment on a specific aspect of care. This format was used when no formal systematic evidence review was undertaken or there was insufficient evidence to provide a graded recommendation; yet, these practice points may at times be supported by the best available evidence. An explicit public review process was undertaken to obtain feedback from external stakeholders, and comments and suggestions from the external review are incorporated as appropriate.

The WG identified 2 major areas that warrant particular attention in this guideline update because of new evidence and interests emerged since the publication of the original guideline. These 2 areas are (i) BP measurement (Chapter 1) and (ii) BP targets in CKD patients (Chapter 3). These 2 issues are closely related as the systolic BP (SBP) target of <120 mm Hg recommended in Chapter 3 is contingent upon proper adherence to standardized preparation and measurement protocols by patients and clinicians.

The term "high BP" is used to denote BP above the target for the respective subpopulations (adult patients with CKD, pediatric patients with CKD, and kidney transplant recipients). This target varies depending on the particular subpopulation. After deliberation, the guideline WG decided not to redefine "hypertension." The major rationale for this decision is that the term may have epidemiologic, psychosocial, financial, and other implications, and it does not necessarily facilitate the management of BP in the CKD population.

Many insightful comments from the public review helped shape the final recommendations. The main issues pertain to the perceived impracticality of performing standardized office BP measurements, and achieving the new SBP target of <120 mm Hg. These 2 topics are tightly connected but are addressed in Chapter 1 and Chapter 3, respectively.

Chapter 1: Blood pressure measurement

This chapter is a new addition to the original KDIGO BP guideline and includes recommendations on how to measure BP in adults with CKD. The rationale for adding this chapter is the increasing recognition of the high variability of BP values in the routine office setting and the availability of results of large randomized trials consistently utilizing standardized, not routine, BP measurements. The key recommendation is the employment of standardized office BP measurement for the management of high BP in adults (Figure 1).

Standardized office BP refers to measurements obtained using recommended preparations and measurement techniques, regardless of the type of equipment used. These standardized procedures are presented in Figure 2[1], which is adapted from the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guidelines. In contrast, routine office BP refers to measurements obtained without using these preparations and is often called casual office BP. Standardized BP measurement is crucial and is an integral part of the foundation for the BP target described in Chapter 3. The BP target cannot be applied if routine BP values are obtained, because large randomized trials that examined target BP, such as SPRINT, employed standardized BP. Further, there is strong evidence that the relationship between routine office BP and standardized office BP is highly variable, for individuals with and without CKD. Thus, it is not possible to apply a correction factor to translate a given routine BP value to a standardized BP value.

It is recognized that standardized BP measurements increase the burden to patients, health care providers, and health care facilities. However, this recommendation is rated as strong because the WG considers it to be essential and it outweighs any potential burden to its implementation. The

Chapter 1: Blood pressure 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*).
• Recommendation 1.2	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*).
Chapter 2: Lifestyle interventions for lowering blood pressure 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*).
• 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*).
Chapter 3: Blood pressure 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 systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (*2B*).
• Recommendation 3.2.1	We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (*1B*).
• Recommendation 3.2.2	We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (*2C*).
• Recommendation 3.2.3	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 3.3.1	We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes (*1B*).
Chapter 4: Blood pressure 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 (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (*1C*).
Chapter 5: Blood pressure management in children with CKD	
• Recommendation 5.1	We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to ≤50th percentile for age, sex, and height (*2C*).

Figure 1 | Key guidance from KDIGO 2021 Clinical Practice Guideline for BP Management in CKD. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; RASi, renin-angiotensin system inhibitor.

recommendation should be widely adopted in clinical practice since accurate measurements will ensure that proper guidance is being applied to the management of BP, as it is to the management of other risk factors.

The WG further provides practice points that favor the use of an automated oscillometric BP device over a manual device for standardized office BP measurement. However, the emphasis of standardization is on the appropriate preparations and the measurement technique, and not on the type of equipment.

Out-of-office BP measurement is a timely topic and includes home BP and 24-hour ambulatory BP monitoring (ABPM). Observational studies show a stronger association of out-of-office BP measurements than office BP measurements with cardiovascular and kidney outcomes in both the general population and CKD population. Home BP monitoring is more readily available than 24-hour

ABPM and may be particularly important for BP management when a clinic visit is impractical, for example, during the coronavirus disease 2019 (COVID-19) pandemic. Out-of-office BP measurements are therefore recommended as a complement to standardized office BP readings for the management of high BP. This is a weak recommendation as there are no completed large randomized outcome trials that target out-of-office BP values in adults. Hence, one important future research recommendation focuses on randomized outcomes trials targeting out-of-office BP.

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

This chapter focuses exclusively on the effects of lifestyle interventions on high BP and does not address its effects on

1 Properly prepare the patient	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	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	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	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

Figure 2 | Checklist for standardized office BP measurement. Reprinted from the *Journal of the American College of Cardiology*, Volume 71, 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, Pages e127–e248, © 2018 with permission from the American College of Cardiology Foundation and the American Heart Association, Inc.[1] BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

broader health issues, which are beyond the scope of this guideline.

Dietary salt restriction. Available data from both the general population and the CKD population demonstrate that reductions in dietary salt intake induce short-term reductions in BP and suggest that this benefit reduces the need for antihypertensive medications. Therefore, consistent with guidelines for the general population, the WG suggests that CKD patients with high BP consume <2 g (or <90 mmol) per day of sodium (Figure 1). The recommendation is rated 2C, because direct evidence in the CKD population is weak. There is also moderate strength of evidence that lowering of dietary salt intake reduces cardiovascular disease in the general population. The systematic review conducted for this guideline, however, found no randomized trial data evaluating the effects of dietary salt reduction on cardiovascular disease, kidney failure, or mortality in the CKD population.

Even in trials, few participants actually adhere to a diet with <2 g per day of sodium in the long term. Recent meta-analyses of randomized trials in non-CKD populations, however, demonstrate a graded benefit in both BP and cardiovascular disease risk reduction with reductions in sodium intake. Therefore, sodium reductions that involve levels less stringent than <2 g per day may still be beneficial.

There are cautions associated with this recommendation. One relates to patients with CKD and salt-wasting nephropathy, for whom reduction in salt intake may be inappropriate. The second caution relates to the Dietary Approaches to Stop Hypertension (DASH) diet, and salt substitutes that are often used in reduced-salt diets. DASH diets employed to lower BP are rich in potassium, and salt substitutes usually contain potassium as the primary cation. These approaches may predispose some patients with CKD to hyperkalemia. Compliance to dietary salt reduction is often a barrier to

implementation, owing to taste preference and the fact that processed foods are often less expensive than fresh food alternatives, but generally higher in salt content.

The WG agrees that decreasing dietary sodium intake is likely to be appropriate in children with CKD also, with the <2 g (<90 mmol) daily target adjusted for body weight.

Physical activity. Intervention studies in the general population have firmly established the beneficial effects of regular physical activity on BP-lowering, physical fitness and strength, weight loss, and lower risks of dysglycemia and diabetes. In the CKD population, the evidence is much more limited. Nonetheless, our systematic review in the CKD population found low-quality evidence suggesting that physical activity decreases BP and body weight, and improves quality of life. Observational data also show a dose–response relationship between greater levels of physical activity and lower risk of mortality in CKD patients. In view of these findings, the WG suggests that patients with high BP and CKD 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 (Figure 1). This recommendation also aligns with the recent KDIGO 2020 Guideline for Diabetes Management in CKD (https://kdigo.org/guidelines/diabetes-ckd/).

The WG recognizes a higher prevalence of comorbidity and frailty in the CKD population that might limit the level of physical activity by CKD patients and increase the risk of adverse events. Because of this uncertainty and the limited evidence specifically in the CKD population, this recommendation is rated 2C. As a practice point, the degree of physical activity should be individualized according to the patient's cognitive and physical conditions, which may change over time. Further, health benefits may be realized even if physical activity falls below the proposed targets.

Other lifestyle interventions. Several other lifestyle interventions, including weight loss and reduction of alcohol consumption, have been demonstrated in randomized trials to lower BP in the general population. However, insufficient data on the risks or benefits of these interventions on BP specifically in CKD populations preclude specific recommendations.

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

Target blood pressure. We suggest that adults with high BP and CKD be treated to a target systolic blood pressure (SBP) of <120 mm Hg, as determined by standardized office measurement, if tolerated (Figure 1). This recommendation does not apply to patients with a kidney transplant or to those receiving dialysis. This SBP target is lower than the BP of <130/80 mm Hg recommended in the KDIGO 2012 BP guideline and is based largely on its cardioprotective, survival, and potential cognitive benefits as shown in the SPRINT trial. The overall evidence suggests that there is no renoprotective effect at this SBP level. The recommendation is weak by GRADE standards (2B) because it is based on a single, albeit high-quality, randomized trial with a predefined CKD

subgroup showing cardiovascular and survival benefits in the study cohort randomized to a SBP goal of <120 mm Hg versus <140 mm Hg.[2] Importantly, this recommendation assumes that standardized office BP measurement is taken as described in Chapter 1. Despite the recommended SBP target, the WG emphasizes that individualization, including consideration of the patient's characteristics, tolerability, and preferences, is crucial in BP management, as in other areas of medical management.

A meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, including trials of antihypertensive drugs versus placebo and trials of different BP targets, found that the proportional reduction in cardiovascular events with more intensive BP treatment was independent of CKD.[3] The meta-analysis of Ettehad et al. also reported a risk reduction for cardiovascular events with intensive BP-lowering in those with CKD, although the size of the risk reduction was less than that in those without CKD.[4] The totality of the evidence supports a SBP target of <120 mm Hg over <140 mm Hg in recent large outcome trials that included a prespecified CKD subgroup, because of the cardiovascular and survival, but not renoprotective, benefits of the lower target.

In most CKD patients with high BP, including the frail and elderly, the cardiovascular benefits of a target SBP <120 mm Hg versus <140 mm Hg appear to outweigh the risks of harm, such as acute kidney injury and electrolyte abnormalities,[5,6] and the risk of cognitive impairment may actually be lower with a target SBP <120 mm Hg.[6] However, the evidence supporting the SBP target of <120 mm Hg is less certain in some subpopulations, including those with diabetes, advanced CKD (G4 and G5), significant proteinuria (>1 g/d), baseline SBP 120–129 mm Hg, the young (age <50 years) or very old (age >90 years), and those with "white-coat" or severe hypertension. As such, randomized trials targeting these subpopulations are necessary. People with underlying coronary artery disease and a low baseline diastolic blood pressure (DBP) may in theory have an increased risk of myocardial infarction with intensive BP-lowering, since coronary perfusion depends on DBP. In SPRINT, however, patients in the lowest DBP quintile at baseline had similar cardiovascular and survival benefits from intensive SBP reduction as those with higher baseline DBP.

Finally, we address target BP in diabetes with CKD. Although SPRINT explicitly excluded patients with diabetes, one subgroup with impaired glucose metabolism (fasting serum glucose ≥100 mg/dl [5.55 mmol/l]), however, exhibited cardiovascular benefits similar to those for patients with normal fasting glucose metabolism.[7] On the other hand, Action to Control Cardiovascular Risk in Diabetes (ACCORD) studied exclusively people with diabetes and randomized them to the same SBP targets as in SPRINT (<120 mm Hg vs. <140 mm Hg), but excluded those with a serum creatinine level >1.5 mg/dl (133 μmol/l). ACCORD demonstrated no overall cardiovascular benefit, although there was a substantial reduction in stroke events in the low-

SBP arm. The analyses of ACCORD suggest a cardiovascular benefit of the lower BP target in those randomized to standard glucose control but no benefit in those randomized to intensive glucose control, though the data remain hypothesis-generating.[8] Based on these and other data, the WG feels that cardiovascular benefits of intensive BP-lowering cannot be excluded in patients with concomitant diabetes and CKD and that a large randomized trial addressing this issue is warranted.

Uncertainty about benefits and risks of intense BP-lowering in the various scenarios above does not necessarily imply that intensive SBP-lowering is not warranted, but does suggest that the uncertainty and the potential adverse effects should be taken into consideration when deciding on the BP target for individual patients. If the patient cannot tolerate SBP <120 mm Hg despite a slow, gradual decrease in SBP over months, an individualized approach should be followed, as in many other aspects of medical practice.

There is a common perception that BP-lowering is reno-protective. This concept is likely true if SBP is lowered from >160 mm Hg to <140 mm Hg. There were 3 medium-sized trials that enrolled exclusively CKD patients and compared a higher versus a lower target BP level with kidney outcomes as primary outcomes: the Modification of Diet in Renal Disease (MDRD) trial,[9] the African American Study of Kidney Disease and Hypertension (AASK),[10] and the Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) trial,[11] with few non-kidney events observed during the trial. A further caveat of MDRD and AASK is that both trials targeted mean arterial BP (MAP), rather than SBP or DBP. The lower target was a MAP of <92 mm Hg (equivalent to 125/75 mm Hg, 160/58 mm Hg, or many other combinations) and varied by age in MDRD.[12] Whether lowering SBP from <140 mm Hg to <120 mm Hg is renoprotective is far from certain. Indeed, the long-term rate of decline of estimated glomerular filtration rate (eGFR) in SPRINT was greater in the intensive SBP arm (<120 mm Hg) than in the standard SBP arm (<140 mm Hg) in patients with CKD, although albuminuria during treatment was lower in the intensive SBP arm.[5] Similar findings in eGFR differences were observed in the non-CKD subgroup in SPRINT,[13] in ACCORD,[14] and in the Secondary Prevention of Small Subcortical Strokes Trial (SPS3) trial.[15] Hence, the recommendation of target SBP <120 mm Hg is based not on renoprotective effects but on cardioprotective and survival benefits. This is a clear distinction from the recommendation in the original KDIGO BP guideline.

The 2017 ACC/AHA BP guideline offers a target of <130/<80 mm Hg for patients with CKD, which is more aggressive than that recommended by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH; SBP target 130–139 mm Hg), and different from that recommended by the National Institute of Health and Care Excellence (NICE; SBP target 120–139 mm Hg).[1,16–18] KDIGO recommends SBP <120 mm Hg, as measured using standardized office BP, because the WG takes the view that patients should not be penalized for suboptimal clinical practice and that standardized BP must be used to guide therapy. Hypertension Canada also recommends a SBP target of <120 mm Hg, consistent with the present guideline.[19]

Antihypertensive drugs. There is limited evidence on the use of specific antihypertensive agents to treat high BP in CKD. Many people with CKD and BP who are at least 20 mm Hg above the target will need combinations of 2 or more antihypertensive drugs. Starting combination therapy in such people is, therefore, suggested. There are, however, no randomized trials comparing different drug combinations in CKD, as there are no randomized trials on antihypertensive classes other than renin-angiotensin system inhibitors (RASi), β-blockers, and calcium-channel blockers (CCBs) compared to placebo or to each other. Any antihypertensive treatment algorithm in CKD, therefore, beyond monotherapy, is based on expert opinion, pathophysiologic or pharmacodynamic considerations, or extrapolation from findings in the general population or from surrogate outcomes. Figure 3 displays the algorithm for BP therapy used in SPRINT.[2]

A recent network meta-analysis by Xie *et al.*, including 119 randomized trials conducted in 64,768 patients with CKD with or without diabetes and albuminuria, examined the benefits of treating with RASi compared to other active therapies or placebo for kidney and cardiovascular outcomes.[20] Both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) reduced the risk of kidney failure and major cardiovascular events. However, ACEi, but not ARB, reduced the odds of all-cause death compared to active control.

In those with CKD without diabetes and severely increased albuminuria, 3 moderate quality trials (REIN Stratum-1, GISEN [REIN Stratum-2], Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency [AIPRI], and Hou *et al.*) suggest CV benefits of RASi versus placebo in addition to kidney benefits (Figure 4[21–24]). The results of AASK support the kidney benefit of RASi in CKD based on the analysis of the slope of glomerular filtration rate (GFR) over time.[10]

In those with concomitant diabetes and CKD with severely increased albuminuria, 2 studies demonstrated kidney benefits from RASi independent of BP control. These are the 3-arm Irbesartan Diabetic Nephropathy Trial (IDNT), in which ARB was compared with placebo and with CCB,[25] and the 2-arm Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL), in which ARB was compared to placebo.[26] In a meta-analysis performed by the guideline Evidence Review Team, ACEi did not reduce the risk of all-cause mortality in patients with diabetes with or without albuminuria compared to placebo or standard of care. The risk of doubling of serum creatinine was, however, reduced. The effect of ARBs was similar to those of ACEi (Guideline Supplementary Tables S21 and S22).

A summary of the strength of recommendations for the use of RASi in the presence or absence of diabetes and various albuminuric states is presented in Figures 1 and 5.
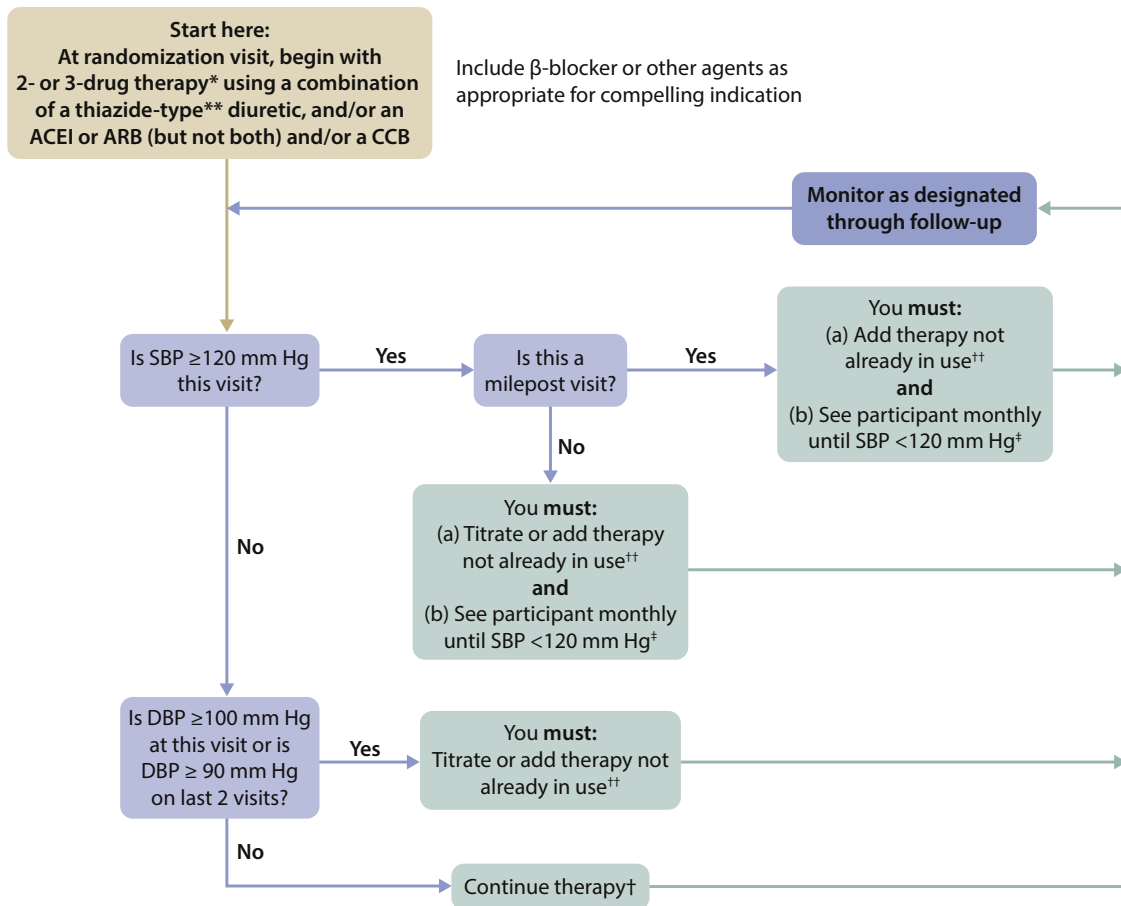
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Figure 3 | Treatment algorithm for intensive SBP arm (target SBP <120 mm Hg) in SPRINT trial protocol. From *The New England Journal of Medicine*, the SPRINT Research Group, A Randomized Trial of Intensive Versus Standard Blood-Pressure Control, Volume 373, Pages 2103–2116, Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial. *May begin with a single agent for participants aged ≥75 years with SBP <140 mm Hg on 0–1 medications at study entry. A second medication should be added at the 1-month visit if participant is asymptomatic and SBP ≥130 mm Hg. **May use loop diuretic for participants with advanced CKD. †Unless side effects warrant change in therapy. ††Consider adding a fifth antihypertensive medication. ‡Or until clinical decision is made that therapy should not be increased further.

Diuretics are often used in CKD patients with high BP because many of them have fluid overload, but the literature on the effects of diuretics on major clinical outcomes in this population is limited. The mineralocorticoid receptor antagonist finerenone was examined for kidney and cardiovascular outcomes in CKD with diabetes in a randomized trial. In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study, finerenone showed kidney and cardiovascular protection with modest effects on SBP (2–3 mm Hg lower) but a higher incidence of hyperkalemia.[27] At the writing of this guideline, finerenone has not been approved for clinical use. The trial was published after the evidence review cutoff for the guideline but will be assessed in future updates.

An important future research topic calls for randomized trials examining various BP targets in advanced CKD, CKD with diabetes, and severely increased albuminuric CKD, with cardiovascular, cognitive, and survival outcomes.

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

BP targets. There are no completed randomized trials in kidney transplant recipients that examined different BP targets for clinically important outcomes such as graft survival, cardiovascular events, or mortality, to provide practice guidance. Therefore, in the present guideline document a definitive recommendation on a BP target in this population is not provided. Instead, a practice point is put forward that suggests a target of <130/<80 mm Hg. This practice point is identical to the recommendation in the KDIGO 2012 BP guideline and is also consistent with the target of <130/80 mm Hg recommended in the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. It is important to emphasize that, as noted in Chapters 1 and 3, the targets for transplant recipients are contingent upon BP being measured in a standardized fashion in the office.

The major rationale for the discrepancy between these BP targets in the transplant recipients and the SBP target of <120
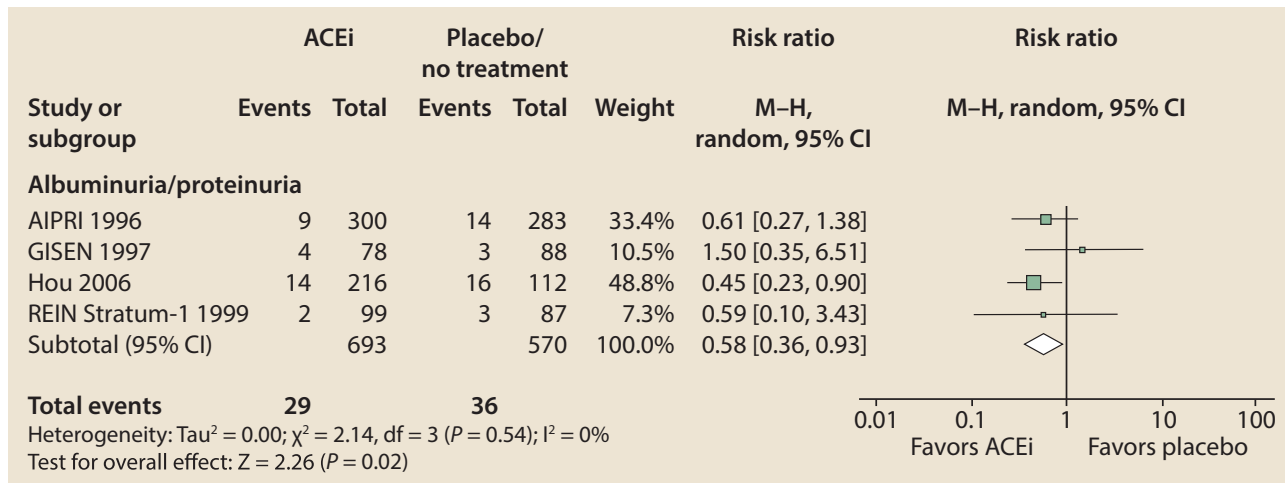
Figure 4 | Cardiovascular events in patients with CKD G3–G4, A3 without diabetes. This meta-analysis was conducted by the Cochrane Kidney and Transplant Evidence Review Team as part of the guideline evidence review. GISEN reported data from the REIN Stratum-2 group (baseline proteinuria ≥3 g/24 h), in contrast to REIN Stratum-1 (baseline proteinuria 1–3 g/24 h). A3, severely increased albuminuria; ACEi, angiotensin-converting enzyme inhibitor; AIPRI, Angiotensin-Converting Enzyme Inhibitors and Kidney Protection; CI, confidence interval; CKD, chronic kidney disease; events, number of events; M–H, Mantel-Haenszel; REIN, Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease; total, number of participants.

mm Hg in Chapter 3 for the general CKD population are two-fold. Foremost is the exclusion of transplant recipients in large randomized trials on BP targets, such as SPRINT, that demonstrated cardiovascular and survival benefits. Second is the concern about the higher, albeit modest, incidence of acute kidney injury and rate of loss in eGFR in the arm randomized to SBP <120 mm Hg, compared to the higher SBP arm in SPRINT. It is conceivable that the potential loss of autoregulation of arteriolar blood flow, and hence GFR, in the solitary denervated transplant kidney may aggravate this adverse effect of lower BP on the kidney, although this hypothesis has not been substantiated by clinical data. The WG notes that kidney allograft survival was unequivocally the dominant priority for patients, caregivers and health professionals in the Standardised Outcomes in Nephrology—Kidney Transplantation (SONG-Tx) project.[28] Hence, there is significant hesitance to lower the SBP target to <120 mm Hg in the absence of further evidence to support its benefits.

Albuminuria category	Diabetes	No diabetes
A1	PP (not graded)	PP (not graded)
A2	1B	2C
A3	1B	1B

Figure 5 | Strength of recommendation for use of RASi in people with high BP and CKD according to diabetes and albuminuric status. 1B, strong recommendation based on moderate quality evidence; 2C, weak recommendation based on low quality evidence; ACR, albumin-creatinine ratio; 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; CKD, chronic kidney disease; PP, practice point; RASi, renin-angiotensin system inhibitors.

Choice of antihypertensive agents. Compared to BP targets, there are more randomized trials on antihypertensive agents in adult kidney transplant recipients. Based on results of these trials, the WG recommends that a dihydropyridine CCB or an ARB be used as the first-line antihypertensive agent in this population (Figure 1). This recommendation relies heavily on the importance of preventing graft loss to kidney transplant recipients and clinicians. The evidence review, which included both hypertensive and normotensive patients, has found that, in randomized trials compared to placebo, the use of dihydropyridine CCBs or ARBs caused a reduction in graft loss. There are no survival or cardiovascular benefits of these 2 classes of drugs. Nonetheless, this recommendation is rated 1C on the basis of their renoprotective effects. The beneficial effects of ACEi appear to be less well established. Randomized trial evidence shows that this class of drug reduces BP and proteinuria in kidney transplant recipients, but it has no effects on all-cause mortality or graft loss. Separate analysis of the randomized trial data on the 2 classes of CCBs showed that the beneficial effects on graft survival were seen in the dihydropyridines but not the non-dihydropyridines.

There are other considerations in the selection of antihypertensive agents in the kidney transplant recipients. For example, in kidney transplant recipients with proteinuria, ARBs should be considered first, given the known antiproteinuric effects of these medications. In contrast, in the early post-transplant period, ARBs should be avoided until kidney transplant function has stabilized, as their acute negative effect on GFR can be confused with other causes of graft dysfunction such as rejection. Women trying to conceive or who are pregnant should be treated with a CCB, which is generally safe during pregnancy and lactation, whereas ARBs are contraindicated under these conditions.

Perhaps the most important recommendation for future research for BP management in kidney transplant recipients is

Appendix Table 1 | Classification for quality of evidence

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

adequately powered randomized trials evaluating the cardio-vascular, kidney, and survival effects of targeting SBP <120 mm Hg versus higher targets.

Chapter 5: Blood pressure management in children with CKD

BP target. Compared to the adult CKD population, the pediatric CKD population is small. Sizable randomized trials are also more limited. A single moderately sized randomized trial on BP targets, the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients (ESCAPE) trial, forms the basis of the following recommendation.[29] In this trial, intensified BP control targeting a 24-hour ambulatory MAP at <50th percentile of normal children was compared to standard BP control targeting a MAP within the 50th–99th percentile. The results showed a probable benefit in slowing kidney disease progression and no greater risk of adverse events, such as hypotension or an acute decrease in GFR. This study in children was not powered for and did not demonstrate differences in mortality. Primarily based on the results of this trial, the WG recommends that in children with CKD, 24-hour MAP measured using ABPM should be lowered to one that is at ≤50th percentile of normal children with corresponding age, sex, and height (Figure 1). This recommendation is rated 2C. It is unclear if the renoprotective benefits of BP-lowering extend to subpopulations characterized by different causes of CKD, levels of albuminuria, races, and ethnicities. A key difference between the current and prior KDIGO recommendations on BP management in children with CKD is that the prior KDIGO guideline made a recommendation for the initiation of antihypertensive medication when the office SBP

Appendix Table 3 | Hierarchy of outcomes considered in evidence review in the present guideline

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Cardiovascular mortality • Kidney failure (formerly known as ESKD) • Cardiovascular events (MI, stroke, HF) • Dementia or cognitive impairment
Important outcomes	• Doubling serum creatinine • AKI • Falls • Fatigue • Body weight • Blood pressure
Outcomes of limited importance	• eGFR/creatinine clearance • Proteinuria

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MI, myocardial infarction.
The critical and important outcomes were voted by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes median was rated between 7 and 9 and important outcomes were rated 4–6 on the 9-point scale.

or DBP is consistently above the 90th percentile for gender, age, and height, whereas in the current guideline, all children with CKD and 24-hour ABPM MAP consistently above the 50th percentile should be treated.

BP measurement. In contrast to the adult CKD population that was included in SPRINT, there are no randomized trials in the pediatric CKD population targeting standardized office BP with meaningful clinical outcomes. ABPM is, however, burdensome and resource-intensive. Therefore, a practice point has been added that ABPM should be performed annually, supplemented by standardized auscultatory office BP every 3–6 months in children with CKD. Proper preparations and techniques are essential for office BP measurement in children, similar to those described in Chapter 1 for adults, with the exception that auscultatory BP is preferred over automated oscillometric BP, since normative BP data in children were derived using the former technique.

ABPM may not be available at all in most clinics. There are also young children who will not tolerate ABPM. In those circumstances, manual office-based auscultatory or oscillometric BP measurement obtained in a standardized manner, targeting achieved SBP at <90th percentile for age, sex, and height of normal children, is a reasonable approach.

Appendix Table 2 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade	Patients	Clinicians	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 a 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.

Choice of antihypertensive agents. It is further suggested as a practice point that an ACEi or ARB be used as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well-tolerated, although the literature in children is not as vast as that in adult CKD patients.

An important recommendation for future research is an adequately powered randomized trial targeting home BP or standardized office BP in children with CKD.

Conclusions

Our current guideline, updated from the 2012 version, strongly emphasizes the use of standardized measurement of BP and recommends a SBP target of <120 mm Hg in most subpopulations of people with CKD, contingent upon this technique. More large randomized trials on BP targets, powered for cardiovascular, kidney, cognitive, and/or mortality outcomes, in CKD are needed, especially for subpopulations that have not been adequately represented in previous trials.

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