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A NEW APPROACH TO THE CONSIDERATION OF HYPERTENSION IN CHRONIC KIDNEY DISEASE THROUGH THE PRISM OF THE LAST KDIGO GUIDE 2021

Biserka Tirmenštajn Janković (1), Dušan Bastać (2)

(1)DEPARTMENT OF NEPHROLOGY AND HEMODIALYSIS, HEALTH CENTER "ZAJEČAR", ZAJEČAR; (2) OFFICE FOR INTERNAL MEDICINE „DR BASTAĆ“, ZAJEČAR;

Summary: Hypertension associated with chronic kidney disease (CKD) is related with a high risk of cardiovascular disease (CVD), which is the most common cause of morbidity and mortality in patients with CKD. Control of hypertension is important primarily because it reduces the risk of CVD and all-cause mortality in patients with CKD. The new KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the management of blood pressure in CKD were published in 2021 and represented an updated version of the original guideline from 2012. This guideline covers all topics contained in the original instructions, such as optimal blood pressure targets, lifestyle interventions, choice of antihypertensive drugs, and specific management in kidney transplant recipients and children. Some aspects of general and cardiovascular health, such as lipid control and smoking, are excluded. In addition, this guideline introduces a chapter dedicated to proper blood pressure measurement as all large randomized trials from which the evidence and recommendations of this guide emerged used standardized preparation and measurement protocols adhered to by patients and clinicians. The key recommendation of the KDIGO guideline refers to target systolic blood pressure under120 mmHg in most adults with CKD, provided that the standardized office blood pressure measurement is used. Despite recommendations for lowering target blood pressure, general lack of evidence, especially in patients with diabetes and advanced CKD, still suggests the need to individualize targets according to the characteristics, tolerances, and preferences of each patient. Larger randomized controlled trials are needed to examine the effects of blood pressure targets on major adverse events and mortality in patients with CKD, especially in subpopulations that were not adequately represented in previous studies.

Key words: chronic kidney disease, hypertension, KDIGO, blood pressure measurement, blood pressure targets, lifestyle, physical activity, antihypertensive agents.

INTRODUCTION

High blood pressure (BP) is the leading correctible risk factor for chronic diseases in the world [1]. High BP is not only an important risk factor for chronic kidney disease (CKD) [2], but also an important comorbidity that occurs with a prevalence of 86% in the population of patients with CKD not receiving dialysis [3]. The combination of CKD and hypertension leads to a high risk of cardiovascular disease (CVD), which is the most common cause of morbidity and mortality in patients with CKD [4]. Several clinical studies and meta-analyses have shown that aggressive treatment of hypertension in patients with and without CKD reduces the risk of CVD, as well as all-cause mortality, although the protective effects of BP reduction on renal function remain controversial [5,6]. For these reasons, several different guides/guidelines for the treatment of hypertension in CKD have been published so far, the last few of which are listed in Table 1.

Table 1. Comparison of several recent hypertension guidelines

	KDIGO[10]	ACC/AHA[15]	ECC/ESH[16]	ISH[63]
Year	2021	2017	2018	2020
Specific population	CKD	NA	NA	NA
Dietary sodium intake	<2 g/day	<1.5 g/day	<2 g/day	Reduce salt intake
Physical activity	Moderate-intensity physical acivity for ≥150 min/wk, or to a level compatible with CV and physical tolerance	Aerobic or resistance exercise 90-150 min/wk; isometric resistance exercise 3 times/wk for 8-10 wk	Moderate-intensity aerobic exercise for ≥30 min 5-7 d/wk; resistance exercises 2-3 d/wk	Moderate-intensity aerobic exercise for 30 min 5-7 d/wk; or high-intensity interval training; resistance/strength exercises 2-3 d/wk
Standardize BP measurement	Yes	Yes	Yes	Yes
Out-of-office BP	Yes	Yes	Yes	Yes
SBP treatment target	<120 mmHg	<130 mmHg	<65 y: <140 mmHg (toward 130); ≥65 y: 130-139 mmHg (could be <130 if tolerated; never <120)	<140/90 mmHg (<65 y: <130/80 but >120/70; ≥65 y: <140/80 in „elderly“)
BP target (CKD)	<120 mmHg	<130/80 mmHg	130-139 mmHg	<130/80 mmHg (<140/80 in elderly)
BP target (DM)	SBP <120 mmHg	<130/80 mmHg	<140 mmHg (toward 130; could be <130 if tolerated; never <120)	<130/80 mmHg (<140/80 in elderly)
BP target (Tx)	SBP <130 mmHg DBP <80 mmHg	<130/80 mmHg	ND	ND
BP target (peds)	Lower MAP by ABPM to ≥50th percentile for age, sex and height	NA	ND	ND
First-line Rx (nonproteinuric CKD)	RASI (ACEI or ARB)	ND	ND	RASI
First-line Rx (proteinuric CKD)	RASI (ACEI or ARB)	ACEI (ARB if ACEI not tolerated)	Combination of RASI with a CCB or a diuretic	RASI
First-line Rx (diabetic CKD)	RASI (ACEI or ARB)	ACEI or ARB in the presence of albuminuria	Combination of RASI with a CCB or a diuretic	RASI

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; MAP, mean arterial pressure; NA, not applicable; ND, not discussed; peds, pediatric; RASI, renin-angiotensin system inhibitors; Rx, prescription; SBP, systolic blood pressure; Tx, transplant;

The original KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for the management of blood pressure in the population of CKD patients not receiving dialysis was published in 2012. [7]. Since then, several articles have been published reporting on the primary results and important secondary analyses of large, randomized trials of hypertension treatment in various populations, including patients with CKD. Intensive lowering of systolic blood pressure (SBP) to a target of 120 mmHg in SPRINT (Systolic Blood Pressure Intervention Trial) reduced the risk for CVD and all-cause mortality to a similar extent in patients with and without CKD [5].Secondary combined analyzes of SPRINT and ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure) trials showed a similar reduction in the primary composite outcome of CVD and all-cause mortality for the SPRINT study and the standard glycemic control arm of the ACCORD-BP trial [8]. In the VA NEPHRON-D study (Veterans Affairs Nephropathy in Diabetes), combination therapy with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increased the risk of acute kidney injury (AKI) and hyperkalaemia, and showed no benefit for renal or cardiovascular outcomes. [9]. In 2017, KDIGO undertook a multi-year process of updating its original guideline, and the results of these and many other studies are included in the updated guideline published in 2021. [10].

The 2021 revision of the KDIGO guideline also applies only to the population of patients with CKD not receiving dialysis and it covers topics contained in the original guideline, such as optimal blood pressure targets, lifestyle

interventions, choice of antihypertensive drugs and specific management in kidney transplant recipients and children (Table 2). Some aspects of general and cardiovascular health, such as lipid control and smoking, are excluded. A Work Group of researchers and clinicians working on the revision of the original guideline identified 2 major areas that warrant particular attention due to the emergence of new evidence: BP measurement and BP target in patients with CKD. These 2 problems are closely related, because the target SBP <120 mmHg depends on the proper adherence to standardized preparation and measurement protocols by patients and clinicians. On the other hand, the main objections are also aimed to these 2 focuses: the observed impracticality of standardized BP measurement in clinical practice and the difficulty in achieving new SBP targets [10].

Table 2. Key recommendations from KDIGO 2021 Clinical Practice Guideline for BP Management in CKD.

Blood pressure measurement
✓ A standardized office BP measurement in preference to routine office BP measurement for the management of the high BP in adults is recommended.
✓ It is suggested 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.
Lifestyle interventions for lowering BP in patients with CKD not receiving dialysis
✓ Targeting a sodium intake <2g of sodium per day (or < 90 mmol sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD is suggested.
✓ It is suggested that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance.
Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis
✓ It is suggested that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement.
✓ 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 is recommended.
✓ Starting RASI (ACEI or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without diabetes is suggested.
✓ Starting RASI (ACEI or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1-G4, A2 and A3) with diabetes is recommended.
✓ Avoiding any combination of ACEI, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes is recommended.
Blood pressure management in kidney transplant recipients
✓ Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement.
✓ It is recommended that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as a first-line antihypertensive agent in adult kidney transplant recipients.

BLOOD PRESSURE MEASUREMENT

Sphygmomanometry is the first practical method that Riva Rocci introduced in 1896 for estimation of SBP [11]. Diastolic blood pressure (DBP) readings became feasible in 1905, when Korotkov described his auscultatory method of measurement [20]. It was soon noticed that BP varies dramatically from one reading to another, so attention was focused on standardizing BP measurement methods to avoid errors in estimation. However, despite all the issued guidelines, recommendations and specific approaches to improve the accuracy of measuring BP, a recent meta-analysis documented that the average SBP in routine clinical practice is almost 15 mmHg higher than in research studies [13].

Chapter 1 is a new addition to the original KDIGO BP guideline that highlights the importance of accurate BP measurement in adults. Standardized office BP refers to measurements obtained in accordance with recommended preparations and measurement techniques, regardless of the type of equipment used, as opposed to routine office BP measurements performed without these preparations Standardized BP measurement is an integral part of BP target and the BP target guideline cannot rely on routine BP measurements, because large randomized trials

that examined target BP, including SPRINT and ACCORD, have consistently used standardized BP measurements [10]. Furthermore, strong evidence shows that routine office BP and standardized office BP measurements do not give the same values, and the relationships between these 2 techniques are highly variable, so it is not possible to use some correction factor to convert routine values to standardized BP values [14]. The KDIGO recommendations for measuring standardized BP are in line with other recent guidelines [15-18], but what makes a critical distinction is the insistence on widespread adoption of standardized BP measurement in patients with CKD, because it allows the use of lower target SBP with proven efficacy in clinical trials.

Key elements for successful BP measurement in the office include proper patient preparation, use of a validated measuring device, correct techniques, and average BP values from at least 2 measurements (Table 3). Patients should be instructed to empty their bladder and avoid smoking, caffeine, and physical activity for at least 30 minutes before measuring their BP. They should be seated comfortably with their back supported and feet on the ground > 5 minutes before the readings. The patient and the observer should refrain from talking during the rest period and during BP measurement. The patient's arm should be supported, and all clothing covering the location of cuff placement should be removed. Cuff size should correspond to the circumference of the patient's arm, and the cuff should be placed at heart level (the midpoint of the sternum). The guidelines recommend using an average 2 or more readings obtained on 2 or more occasions to estimate the individual's level of BP. Patients should be informed of their BP values [10,15-18].

Table 3. Checklist for standardized measurement of blood pressure in the office

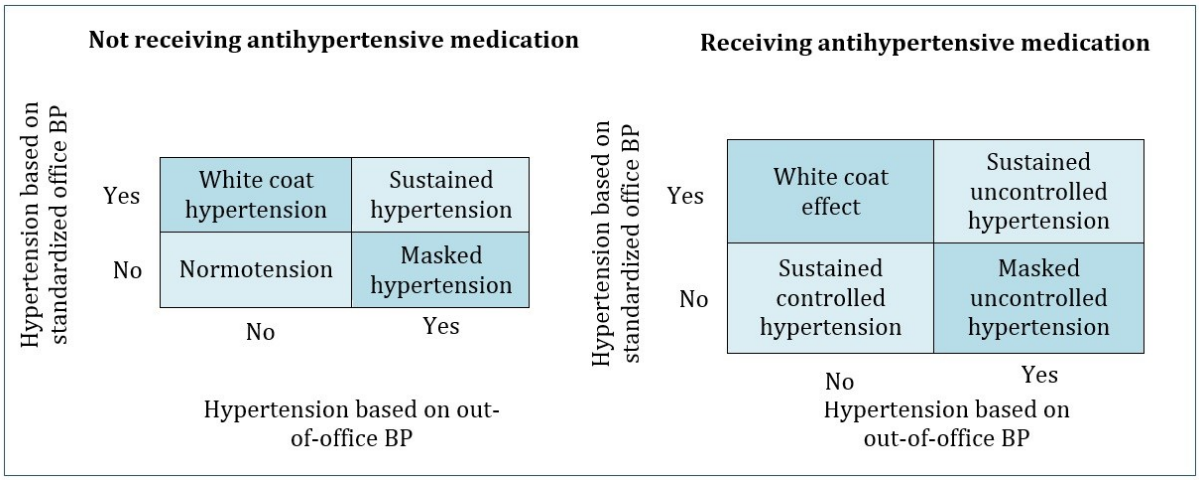
Key steps	Special instructions
1. Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. 3. Ensure patient has emptied his/her bladder. 4. 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 as 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 mmHg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mmHg 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.

A variety of BP measurement devices can be used for standardized office BP measurement, because the emphasis of standardization is on adequate preparation of patients for BP measurement, and not on the type of equipment [10]. However, there are several reasons why oscillometric devices are now considered a clinical standard for BP measurement [15, 18]: environmental concerns about mercury toxicity, the need for frequent calibration with aneroid sphygmomanometers, errors due to auscultation and inappropriately rapid deflation of the cuff, and greater

convenience and cost savings associated with use of oscillometric devices [18]. Oscillometric devices can be used to measure BP in patients with atrial fibrillation [10]. Given that large randomized studies have not found significant differences between standardized BP values measured using oscillometric and manual devices, manual BP devices are also considered acceptable when oscillometric devices are unavailable [19, 20]. Automated office BP devices may be the preferred method for standardized office BP measurement. They may increase the likelihood of adherence to proper preparation because they can be programmed to include a rest period, and they can also take multiple BP measurements and provide an average. Automated devices can measure BP either with or without a health worker in the room. The results of the SPRINT trial indicate attended or unattended automated office BP measurements result in similar BP values when the recommendations for accurate BP measurement are followed [21,22].

Out-of-office BP measurement techniques include home BP monitoring (HBPM) and 24-hour ambulatory BP monitoring (ABPM). In patients not taking BP-lowering medications, the following 4 groups can be categorized based on in-office and out-of-office BP measurements (Figure 1): normotension, white coat hypertension, sustained hypertension, and masked hypertension. In those taking BP lowering medications, 4 similar groups can be categorized: white coat effect, sustained controlled hypertension, sustained uncontrolled hypertension, and masked uncontrolled hypertension. [10].Approximately 30% of patients have discordant BP values in-office and out-of-office [23].Masked uncontrolled hypertension is more common in people with CKD compared to people without CKD [24]. Masked hypertension is associated with an increased risk of CVD and renal failure. In contrast, white coat hypertension is associated with a lower risk of adverse events than masked and sustained hypertension, but patients with untreated white coat hypertension have a higher risk of adverse events than patients with controlled office and out-of-office BP [25]. The high prevalence of white coat hypertension and masked hypertension, as well as the increased risk of adverse outcomes identified in observational studies, have resulted in the recommendation that ABPM and HBPM be used to complement standardized office BP for the management of high BP [10,15-17].

Figure 1. BP patterns based on out-of-office BP measurements in addition to standardized office BP measurements.



The KDIGO BP guideline recommends that ABPM be used initially to supplement standardized office BP measurement, while HBPM is further used for ongoing BP management. In areas where ABPM service is not available, HBPM may be used instead of ABPM as the initial procedure. Out-of-office BP measurement additionally burdens patients and clinic staff. For example, ABPM requires patients to wear a monitor for 24 hours, with the obligation to visit the clinic on 2 consecutive days for placement and removal of the monitor. On the other hand, HBPM is a more accessible method and can be particularly important for

the management of BP when a visit to the clinic is impossible or difficult for some reason. As with all BP measurements, out-of-office readings should be obtained using the standardized technique and a validated upper arm device.Notwithstanding the recommendations made, the KDIGO work group recognized the lack of randomized controlled trials comparing the effect of ABPM/HBPM to office-based BP management on cardiovascular or kidney disease outcomes, and therefore supports further research in this area [10].

LIFESTYLE INTERVENTIONS

According to the KDIGO guideline, the suggested sodium intake should be<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 [10]. Interventional studies in the general population have shown a gradual benefit in reducing of both BP and CVD risk with reduced dietary sodium intake [26]. Although the majority of the world's population consumes more than 2 g of sodium per day, even modest reductions in sodium intake that do not reach this goal are associated with BP and CVD benefits in the general population. However, there are no large and long-term randomized controlled trials evaluating the effects of dietary sodium restriction on clinical outcomes in CKD population.A recent meta-analysis that included only studies with CKD patients found that salt reduction in patients with CKD significantly reduced BP, and if such an effect were maintained in the long term it would result in a clinically significant reduction in CKD progression and CV events [28]. Finally, ACEI and ARB medications are commonly used in CKD population, and their kidney and cardiovascular benefits may be improved if accompanied by a low-sodium diet [29].

Considering that data on specific targets of sodium intake in CKD population with high BP are not firmly established, the KDIGO work group has adopted the recommended target for dietary sodium intake in the general population from the World Health Organization [30], which is in line with the recommendations of several recently published guides to hypertension [16, 17], but also consistent with KDIGO 2020 Guideline for Diabetes Management in CKD [31]. The WG also noted that there are circumstances in which recommendations from the general population cannot be applied to CKD population. The warnings relate to patients with CKD and salt-wasting nephropathy, for whom reduction in sodium intake may be inappropriate. The second warning relates to the dietary approach to the treatment of hypertension, taking into account that diets employed to lower BP are usually rich in potassium, and salt substitutes also contain potassium as the primary cation. These approaches may increase the risk of hyperkalemia, especially in advanced CKD [10].

As part of lifestyle changes, patients with high BP and CKD are 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. Studies in the general population have clearly demonstrated the beneficial effects of physical activity on BP-lowering, physical fitness and strength, weight loss and reducing the risk of dysglycemia and diabetes [10]. In the CKD population, the evidence is much more limited, but it also suggests that physical activity reduces BP and body weight and improves quality of life [32,33]. Observational data have shown a dose-response relationship between higher levels of physical activity and lower risk of mortality in patients with CKD [34]. On the other hand, the KDIGO work group recognizes a higher prevalence of comorbidities and frailty in the CKD population that might limit the level of physical activity by CKD patients and increase the risk of adverse events. Therefore, the degree of physical activity should be individualized in accordance with the patient's cognitive and physical conditions , which may change over time. Significant health benefits can be gained even if the level of physical activity falls below the proposed targets [10].

BLOOD PRESSURE TARGETS

In adults with high BP and CKD, the KDIGO guideline suggests a target SBP of <120 mmHg when tolerated, provided that a standardized office BP measurement is used. This recommendation pertains to patients with diabetes and without diabetes, and does not apply to patients with a kidney transplant or to those receiving dialysis [10].

For most patients with CKD, particularly those who are older, with low levels of albuminuria or are in the earlier stages of CKD, the risks for CVD and CV mortality are much

higher than those for kidney failure [35]. Therefore, this KDIGO recommendation relies heavily on the results of a high-quality and randomized SPRINT, that showed beneficial effects on CV and mortality outcomes in a study cohort of hypertensive subjects randomized to a target SBP <120 mmHg versus 140 mmHg [5].In this study, 90% of participants were receiving antihypertensive therapy at baseline, and beneficial effects were demonstrated in the group of patients with CKD [36], in the elderly [37] and in those with prediabetes [38]. Two meta-analyses also reported a risk reduction for CV events with intensive BP lowering in the CKD population, regardless of whether the reduction was equal to [39] or lower than in the general population [40].

The effects of intensive BP lowering on CKD progression toward kidney failure are less certain. There is a common perception that BP lowering is renoprotective, but only secondary analyses of some earlier randomized trials have shown that more intensive BP lowering reduces the rate of CKD progression among patients with greater baseline proteinuria [41,42]. However, the results of the two most frequently cited recent randomized trials, SPRINT and ACCORD, indicate that intense BP lowering leads to a small but consistent reduction in estimated glomerular filtration rate (eGFR) shortly after initiation, compared to less intensive controls (may be explained by hemodynamic effects), while the effects of intensive BP lowering on eGFR in the long term remain uncertain [36,43].

The original KDIGO 2012 BP guideline recommended a more intensive BP lowering for patients with albuminuria than those without [7]. With the adoption of an SBP target bellow 120 mmHg for all CKD patients in the revised guideline, separate targets for patients with and without albuminuria were no longer considered necessary. The KDIGO work group considered that the cardiovascular and survival benefits of intensive SBP control outweighed the observed increases in the risks for hyperkalaemia, hypokalaemia and acute renal injury [36].However, evidence supporting the SBP target <120 mmHg is less certain in some subpopulations, including patients with diabetes, advanced CKD (G4 and G5), significant proteinuria (> 1 g/day), baseline SBP 120-129 mmHg, in younger than 50 years or very old (age> 90 years), as well as those with "white coat" or severe hypertension [10], table 4. For example, the ACCORD trial studied exclusively patients with diabetes and randomized them to the same SBP targets as in SPRINT (<120mmHg, vs<140mmHg), but excluded those with a serum creatinine levels >132.6 umol/L and those with proteinuria >1g/day. Intensive BP control resulted in a lower risk for stroke, but without a statistically significant reduction in overall CV events. The analyses of ACCORD suggest a CV benefit of the lower BP target in the group with standard glucose control, but not in the group with intensive glucose control [8,43,44].However, for a similar SBP lowering, there was a greater risk of eGFR decline in patients with diabetes in ACCORD-BP than in patients without diabetes in SPRINT [45]. Therefore, the KDOQI (Kidney Disease Outcomes Quality Initiative) work group commented that the risk-benefit ratio of lower SBP target in patients with CKD and diabetes requires further research in randomized controlled trials, and currently considers an SBP target of <130 mmHg to be a more reasonable target in this subpopulation [46].

Table 4. Certainty of evidence supporting an SBP target of <120 mmHg 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 mmHg
Prior stroke
Very low DBP
Polycystic kidney disease
Severe hypertension – e.g., SBP >180 mmHg while receiving no treatment or ≥150 mmHg despite >4 antihypertensive agents

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure;
*CKD G4-G5 indicates estimated glomerular filtration rate <30 ml/min/1.73m^2.

Uncertainty about benefits and risks of intensive BP lowering in different subpopulations does not mean that intensive BP lowering is not warranted, but suggests that the potential adverse effects should be taken into consideration when deciding on the BP target for individual patients. Inconsistency in recommendations for treatment target SBP may contribute to physician confusion: ACC/AHA (American College of Cardiology/American Heart Association) BP guideline offers a target of<130/80 mmHg for patients with CKD, which is more aggressive than that recommended by the European Society of Cardiology/European Society of Hypertension (ESC/ESH; SBP target 130-139 mmHg), and different from that recommended by the National Institute of Health and Care Excellence (NICE; SBP target 120-139 mmHg) [15,16,47]. ESC also published a 2021 Clinical Guideline on Cardiovascular Disease Prevention in Clinical Practice that recommend office BP targets for people with CKD<140–130 mmHg SBP (lower SBP is acceptable if tolerated) and <80 mmHg DBP [48]. In practice, it should be borne in mind that it would be potentially hazardous to apply the recommended SBP target of <120 mmHg to BP measurements obtained in a non-standardized manner. It is also reasonable to use less intensive therapy for BP lowering in patients with very limited life expectancy or symptomatic orthostatic hypotension [10].

CHOICE OF ANTIHYPERTENSIVE DRUGS

Recommendations for the choice of antihypertensive therapy in CKD are based on evidence that renin-angiotensin system inhibitors (RASI), ACEI and ARB, reduce both CV events rates and kidney end points among patients with CKD. The strength of the evidence varies 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 need a combination of 2 or more antihypertensive drugs, but there are no randomized controlled trials comparing different combination therapies in CKD. Therefore, any algorithm for antihypertensive treatment in CKD is based on expert opinion, pathophysiological or pharmacodynamic considerations, or extrapolation from findings in the general population [10].

In patients with high BP, CKD(G1-G4) and severely increased albuminuria (A3) without diabetes, it is recommended to start RASI therapy (ACEI or ARB) [10]. Evidence supporting this view is based on the results of several placebo-controlled randomized trials, which confirmed the effects of this therapy on reducing the risks for both adverse renal outcomes and CV events [49-51].

In patients with high BP, CKD (G1-G4) and moderately increased albuminuria (A2) without diabetes, it is recommended to start

RASI therapy (ACEI or ARB) [10]. This is a weak recommendation, because there is no high-quality evidence from randomized controlled trials evaluating kidney outcomes in this subpopulation. The recommendation relies heavily on the results of the HOPE (Heart Outcomes and Prevention Evaluation) trial, which showed a CV benefit of ramipril compared to placebo, independent of BP, in patients with moderately increased albuminuria [52].

In patients with high BP, CKD (G1-G4) and moderate to severe albuminuria (A2 and A3) with diabetes, it is recommended to start RASI therapy (ACEI or ARB) [10]. Strong evidence from IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) indicates that RASI, compared with placebo or calcium channel blockers (CCBs), reduces risk for kidney events in diabetics with severely increased albuminuria [53,54]. MICROHOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes Substudy of Heart Outcomes Prevention Evaluation) found a reduction in CV risk in patients with diabetes and moderate albuminuria who were randomized to ramipril [55,56]. Meta-analysis by the KDIGO ERT (Evidence Review Team) showed that ACEIs compared with placebo had no effect on all-cause mortality but significantly reduced the risk for doubling of serum creatinine and progression of albuminuria from category A2 to A3 [10].

The KDIGO guideline highlights several practical points to pay attention to. The first point suggests that RASI (ACEI or ARB) would be a reasonable choice of therapy for people with high BP, CKD, and no albuminuria, with or without diabetes.Based on some research [57], the KDOQI work group believes that a diuretic or CCB would be equally reasonable choice as a first-line treatment for high BP in patients with CKD and without diabetes and no albuminuria [46], which is also recommended by the ACC/AHA guideline [15]. The need to use RASI (ACEI or ARB) in the highest approved dose that is tolerated is further emphasized, because the described benefits were achieved in trials using these doses. 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 eGFR and serum potassium. Hyperkalaemia associated with use of RASI can often be managed by measures to reduce serum potassium levels, rather than decreasing the dose or discontinuing RASI. ACEI or ARB therapy should be continued unless serum creatinine rises by more than 30% within 4 weeks of starting treatment or increasing the dose. Dose reduction or discontinuation of ACEI or ARB should be considered in the setting of either symptomatic hypotension or uncontrolled hyperkalaemia despite medical treatment, or to reduce uremic symptoms during treatment of kidney failure (eGFR <15 ml/min/1.73 m^2). Mineralocorticoid receptor antagonists (MRA) are effective for treatment of refractory hypertension, but may cause hyperkalaemia or reversible decline in kidney function, particularly in patients with low eGFR [10].

Special recommendation is to avoid any combination of ACEI, ARB, or direct renin inhibitors (DRI) in patients with CKD, with or without diabetes. This is a strong recommendation based on evidence from randomized controlled trials of sufficient duration to evaluate kidney and CV protection.There is growing evidence that dual RAS blockade does not lead to long-term CV or kidney benefit despite lowering proteinuria in the short term, and on the other hand increases the risks of hyperkalemia and AKI [10]. A large meta-analysis comparing the effects of monotherapy and dual RAS blockade in patients with CKD, with and without diabetes, found no significant differences in all-cause mortality, progression to end-stage CKD, and CV events between two groups [58]. In contrast, there is evidence that dual blockade of RAS in patients with CKD, with and without diabetes, increases the incidence of AKI by 40% compared to monotherapy [9,59]. Therefore, it can be considered justified that this recommendation places a higher importance on preventing hyperkalemia and AKI than on the potential benefits in reduction of albuminuria [46].

Most patients with CKD will require multiple antihypertensive therapy with ACEI or ARB in addition to CCB and diuretics to achieve target BP values. An instrumental variable analysis by Markovitz et al demonstrated an incremental reduction in SBP and cardiovascular risk with the addition of each additional antihypertensive agent in SPRINT [60]. Diuretics are often used in CKD patients with high BP due to pre-existing hypervolemia, but the literature on the effects of diuretics on major clinical

outcomes in this population is limited. Limited data have shown that the addition of an MRA, such as spironolactone, eplerenone, or finerenone, to an ACEI or ARB for renoprotection in CKD patients reduces blood pressure and urinary protein/albumin excretion with a quantifiable risk of hyperkalaemia [61]. The recent FIDELIO-DKD trial (The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) in CKD patients with diabetes showed a kidney and cardiovascular protection by finerenone, despite its modest effect on SBP and higher incidence of hyperkalemia-related events [62].

CONCLUSION

The updated 2021 KDIGO BP clinical practice guideline insists on standardized office BP measurement and recommends a target SBP <120 mm Hg in most subpopulations of CKD patients, provided this technique is used. The implementation of standardized BP measurement in a busy clinical practice is recognized as a challenge, but is fundamental to the practice of evidence-based medicine, because the available evidence for treatment recommendations is derived from the studies in which BP was measured in this way. That means the adoption of a target SBP <120 mmHg is inextricably linked to the technique of standardized office BP measurement, and kidney and cardiovascular benefits that would result from long-term intensive BP reduction in patients with CKD depend on it. Given the importance of these goals and the existing resistance to standardization of the method, it is possible that the new measures will require the regulatory enforcement of standardized BP measurement protocols in routine clinical practice.

Regardless of the recommended target SBP, the KDIGO work group warns of caution in certain subpopulations of CKD patients, pointing out that it is reasonable to apply less intensive BP targets in people with very limited life expectancy or symptomatic orthostatic hypotension. This suggestion supports physician autonomy and shared decision making, depending on patient characteristics, tolerability, and preferences, in order to select patients who are most likely to benefit from more intensive BP lowering. Large randomized controlled trials on the effects of intensive BP lowering for cardiovascular, kidney, and cognitive outcomes and/or survival in CKD patients are needed, particularly in subpopulations that were not adequately represented in previous studies. There is also an urgent need for randomized trials comparing the effects of different combinations of antihypertensive drugs on outcomes, which would contribute to the development of evidence-based algorithms for hypertension treatment in CKD.

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