Blood pressure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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In September 2017, KDIGO (Kidney Disease: Improving Global Outcomes) convened a Controversies Conference titled *Blood Pressure in Chronic Kidney Disease (CKD)*. The purpose of the meeting was to consider which recommendations from the 2012 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD should be reevaluated based on new evidence from clinical trials. Participants included a multidisciplinary panel of clinical and scientific experts. Discussions focused on the optimal means for measuring blood pressure (BP) as well as managing BP in CKD patients. Consistent with the 2012 Guideline, the conference did not address BP management in patients on maintenance dialysis.

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In patients with chronic kidney disease (CKD), the optimal blood pressure (BP) for minimizing the risk of CKD progression and systemic complications, particularly cardiovascular events, is unclear. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published a clinical practice guideline on the management of BP in nondialysis CKD.[1] Since then, new data from clinical trials, such as SPRINT (Systolic Blood Pressure Intervention Trial),[2] HALT-PKD (Halt Progression of Polycystic Kidney Disease),[3] and SPS3 (Secondary Prevention of Small Subcortical Strokes),[4] have expanded the evidence base. To examine how the new evidence may influence guideline updates, KDIGO convened a multidisciplinary Controversies Conference titled *Blood Pressure in CKD* in Edinburgh, Scotland in September 2017. Here, we summarize the points of consensus and controversy and identify knowledge gaps and research priorities. The conference agenda, discussion questions, and plenary session presentations are available at http://kdigo.org/conferences/controversies-conference-on-blood-pressure.

BLOOD PRESSURE MEASUREMENT

A major emphasis during the conference was on BP measurement methods. BP can differ widely depending on measurement setting (e.g., office or home) and the type of device used (e.g., manual or oscillometric sphygmomanometer).[5,6] Proper preparation prior to BP measurement is important (Table 1). Conference discussions focused primarily on the following 3 types of office-based BP measurements: (i) routine, or casual, office, which is conducted without following the recommended preparatory processes outlined in Table 1; (ii) standardized office,

Table 1 | Preparations for blood pressure measurement

Office or home[7–9]
- No talking or use of smartphone during the procedure
- No exercise, nicotine, or caffeine for at least 30 minutes prior to measurement
- Remove clothing covering location of cuff
- Seated comfortably with legs uncrossed and back and arm supported for at least 5 minutes prior to measurement
- Verify cuff size is correct
- Middle of the cuff should be placed at the level of the right atrium

Automatic oscillometric measurements[10,11]
- Average of 2–5 measurements at intervals of 1–2 minutes

which adheres to these processes but is performed with a manual technique; and (iii) automated oscillometric office, which includes a 5-minute rest followed by a series of 2 to 3 BP measurements that are averaged, as described, for example, in the SPRINT protocol.[12] Two types of out-of-office BP measurements were discussed: (i) home automated oscillometric, and (ii) 24-hour ambulatory. Pulse wave velocity and central aortic BP measurements were felt to be outside the scope of the conference. Non-cuff-based BP measurements are not sufficiently validated to guide practice[13] and were not discussed.

Comparisons of different types of BP measurements

Casual office BP is generally 5–10 mm Hg higher than both standardized office and automated oscillometric office BP,[14,15] whereas standardized office BP measurements are generally similar to those of automated oscillometric office BP.[14] Casual office BP is often higher than awake ambulatory BP; in contrast, standardized office BP may be lower than awake ambulatory BP.[14] In a subset of participants in the intensive treatment arm of the SPRINT study, mean automated office systolic blood pressure (SBP) was 119 mm Hg, whereas mean awake ambulatory SBP was 126 mm Hg.[16] The differences in BP obtained using different types of measurements in CKD appear similar to those in the general population, but the available data are limited.[6] The differences between methods as discussed are population means; in the individuals, those differences may vary drastically. Therefore, establishing conversion factors to translate a casual BP value into a standardized BP value is difficult.

Out-of-office BP measurements

Out-of-office BP measurement is required to diagnose white-coat hypertension (elevated office BP with controlled out-of-office BP) and masked hypertension (controlled office BP with elevated out-of-office BP; Figure 1). The prevalence of white-coat hypertension in patients with CKD from several countries ranges from 2% to 41%,[5,18–24] and the prevalence of masked hypertension ranges from 6% to 51%.[5,18,19,21–25] Ambulatory BP provides important information on nocturnal BP. Patients with CKD are more likely to have an absence or even a reversal of normal nocturnal dipping, with prevalence ranging from 14% to 75%,[18,20-22,26–34] which appears to increase with decreasing kidney function.[31]

In CKD, out-of-office BP may better predict kidney disease progression and cardiovascular events than office BP.[18,20,23,24,27,35–50] Nocturnal BP can be treated specifically but whether this strategy improves clinical outcomes is unclear. In an 8-week, uncontrolled study of 32 nondipping patients with CKD, shifting 1 antihypertensive drug from morning to evening restored normal nocturnal dipping in 88% of patients.[51] However, this study has yet to be replicated in a larger cohort with longer follow-up.

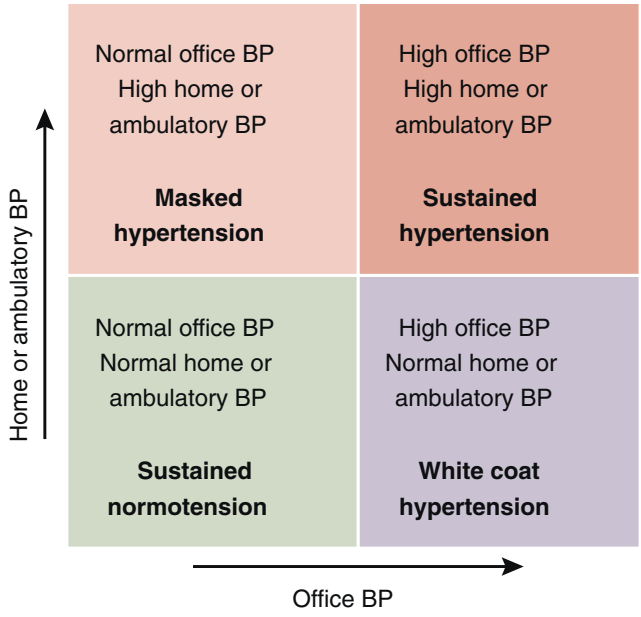

Figure 1 | Classification of patients based on the comparison of office blood pressure (BP) with home or ambulatory BP levels in untreated individuals. Large randomized trials with hard clinical outcomes have primarily targeted office BP values; therefore, clinical benefits of targeting home or ambulatory BP values are still unclear. Modified from Parati G, Ochoa JE, Bilo G, et al. Hypertension in chronic kidney disease part 1: out-of-office blood pressure monitoring: methods, thresholds, and patterns. *Hypertension.* 2016;67:1093–1101. Available at: https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.115.06895. Accessed February 22, 2019.[17] Copyright © 2016 American Heart Association, Inc.

No adequately-powered randomized controlled trials (RCTs) of BP control on clinical outcomes have targeted ambulatory or home BP in the CKD or general adult population. The sample size needed and the complexity of such a trial[52] raise questions about its feasibility. In addition, in many regions of the world, home BP or ambulatory BP monitoring are impractical.

Other BP variabilities

Orthostatic hypotension is usually defined as a decrease in SBP of at least 20 mm Hg or a decrease in diastolic BP (DBP) of at least 10 mm Hg within 3 minutes of standing up.[53] Orthostatic hypertension is usually defined as a rise in SBP of at least 20 mm Hg when standing. Estimates based on SPRINT study data indicate that among older, hypertensive patients, 5% have orthostatic hypotension and 5% have orthostatic hypertension.[54] Both groups carry an increased risk of cardiovascular events, as evidenced by multiple cohort studies.[55–57]

BP can vary in the short term (minute-to-minute), medium term (day-to-day), or longer term (visit-to-visit variability, VVV). More advanced CKD is associated with higher VVV of SBP,[58] and higher VVV in CKD is associated with adverse cardiovascular outcomes, adverse renal outcomes, and death. In a study of 114,900 patients with CKD,[58] higher VVV of SBP, independent of absolute levels of SBP, was associated with higher rates of heart failure, hemorrhagic stroke, and death. Despite the prognostic information provided by VVV of SBP, conference participants felt that its use in the clinical setting or as a target of therapy remains unclear.

Conclusions and ongoing controversies in BP measurement

Conference participants suggested that the future guideline work group should explicitly state which BP measurements should be used to diagnose and manage BP in CKD. Standardized office BP measurement is rarely performed in clinical practice.[7] Given that casual BP tends to provide higher values than other techniques, but more standardized techniques are often used in RCTs targeting BP, conference participants urged the future guideline work group to consider whether office BP should be measured using an automated oscillometric device with the appropriate preparations, as outlined as Table 1.

Conference participants also encouraged exploration of the evidence on out-of-office BP measurements in conjunction with office BP measurements in an updated guideline. More data are also needed regarding whether abnormal diurnal BP patterns can be restored in patients with CKD, and whether this strategy would improve clinical outcomes.

MANAGING BLOOD PRESSURE IN CKD PATIENTS WITH AND WITHOUT DIABETES

Salt intake

Lifestyle, including diet, is an integral component of BP management. Conference participants indicated that Recommendation 2.3.2 on salt intake (Chapter 2 of the 2012 KDIGO BP Guideline[1]) should be reviewed to identify new evidence specific to people with CKD, as debate about optimal salt intake in the general population is ongoing.[59] The conference participants questioned whether a level 1C recommendation is too strong based on the current evidence.[60,61]

Therapeutic thresholds and targets of BP

In light of new research findings, especially from SPRINT, each recommendation in the 2012 BP guideline regarding BP diagnosis thresholds and treatment targets[1] should be considered for revision. Whether separate recommendations are needed for diabetes mellitus and non-diabetes mellitus, and for different levels of albuminuria, depends in large part on where the threshold is set for lower-risk patients. For example, if the threshold is SBP <120 mm Hg for all patients, separate recommendations for higher-risk individuals would not be needed.

The extent to which SPRINT findings can and should be applied to persons with CKD G3b-G4 was debated. Impairment in the glomerular filtration rate (GFR) and albuminuria levels in the CKD subgroup in SPRINT were moderate (mean estimated GFR [eGFR] 48 ml/min per 1.73 m^2; mean urinary albumin-to-creatinine ratio 81 mg/g). It is unclear if the benefits and risks observed in SPRINT are applicable to patients with more advanced CKD or those with severely increased albuminuria, especially given that proteinuria >1 g/d was an explicit exclusion criterion in SPRINT. Indeed, a *post hoc* analysis of SPRINT suggested that the balance of risk and benefit from intensive BP lowering depended on the severity of CKD, with no apparent net benefit among patients with eGFR <45 ml/min per 1.73 m^2, a relatively small subgroup.[62]

There is biological basis for the potential unfavorable risk/benefit ratio of intensive SBP lowering in advanced CKD. Those patients frequently have increased arterial stiffness and increased pulse pressure.[63] Antihypertensive therapy could excessively decrease DBP, thus compromising coronary blood flow, although no RCT evidence of increased risks of myocardial infarction or heart failure at lower BP targets has been identified.[64,65] In fact, a recent *post hoc* analysis of SPRINT data showed no evidence that the cardiovascular benefits of intensive SBP lowering differed by baseline DBP, including the lowest DBP quintile of 61 ± 5 mm Hg.[66] Conference participants discussed whether limits of DBP for SBP reduction should be lower but doubted that evidence was sufficient to support a limit. Further, participants felt that the well-recognized phenomenon of "J" curves obtained when plotting DBP against risk of adverse outcomes was likely due to confounding by comorbidities. The literature needs to be critically reviewed before revised guidelines on DBP targets in the CKD population can be considered. Specific data on BP targets in advanced CKD (e.g., eGFR <45 ml/min per 1.73 m^2) and those with severely increased proteinuria are urgently needed.

Concerns that lowering BP in CKD G3a-G4 patients older than 69 years might lead to frequent hypotensive episodes have been discussed.[67] The recent SPRINT data in older patients[68] and a subgroup analysis of older patients with CKD[69] in SPRINT suggest, however, that intensive SBP lowering is generally safe. Whether safety depends on the number of drugs required to achieve the target SBP remains unclear.

A further area of controversy was the optimal BP target in people with diabetes, particularly because SPRINT excluded patients with diabetes. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which included patients with diabetes with SBP targets identical to those in SPRINT, failed to demonstrate statistically significant benefits in its primary cardiovascular outcome.[70] The lack of clear benefit in ACCORD might relate to its more complicated factorial study design, which included an intensive glucose-lowering intervention that increased the risk of death.[71] Conversely, a recent systematic review of BP lowering in people with diabetes in the general population[72] found clear cardiovascular benefit for BP lowering among individuals with baseline SBP over 140 mm Hg, but not for those with lower BP levels. The large amount of new data in this area requires careful review.

Changes in indicators of kidney function in patients receiving BP-lowering therapies

Albuminuria. Meta-analysis of data from clinical trials has suggested that albuminuria is a valid surrogate endpoint for end-stage kidney disease (ESKD) for certain types of kidney disease.[73] Conference participants agreed, however, that whether maximizing therapy to reduce albuminuria in addition to BP control, especially using agents that block the renin-angiotensin-aldosterone system (RAAS), is safe or effective in improving clinical outcomes is still unknown. The 2012 KDIGO BP Guideline also proposed a lower BP target and the use of RAAS inhibitors for people with albuminuria or proteinuria. Reassessment of these recommendations should be undertaken.

GFR. Conference participants debated whether the increased risk for acute declines in eGFR associated with lower BP goals in ACCORD, SPS3, and SPRINT is clinically important. A retrospective analysis of participants in the African American Study of Kidney Disease and Hypertension (AASK) and Modification of Diet in Renal Disease (MDRD) studies has indicated that patients who had acute eGFR declines ≥20% from baseline during intensive BP lowering were at increased risk of progression to ESKD.[74] On the other hand, acute declines of up to 30% in eGFR upon the initiation of RAAS inhibitors were deemed by some investigators to portend long-term renal benefit. The conference participants felt that statistical methodological issues complicate the interpretation of such data. Critical review of the literature and the statistical methodologies used in various studies are necessary to determine if recommendations can be formulated. Analyses from BP-lowering trials using active run-in periods where changes in eGFR can be assessed pre-randomization instead of post-randomization would be particularly helpful in resolving this controversy.

Apart from the acute change in GFR upon BP lowering, several recent BP outcome trials, such as ACCORD, SPRINT, and SPS3, have also demonstrated that GFR loss is slightly but consistently faster during chronic follow-up with a lower BP target. These observations need to be carefully considered in the revised BP guideline.

Choice of antihypertensive agents

The conference participants agreed that an angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) should be the agent of first choice among patients with severely increased albuminuria (i.e., >300 mg/g [>30 mg/mmol]) while some favor the preferential use of an ACEi or ARB for all CKD patients with diabetes and hypertension. The evidence favoring their preferential use for nondiabetic patients with CKD and moderately increased albuminuria (i.e., <300 mg/g (<30 mg/mmol) is less persuasive. The relative benefits of these agents compared with alternatives also depend on ethnic origin and the healthcare setting (given the need to monitor for hyperkalemia).

Hyperkalemia

RAAS blockers inhibit renal potassium excretion and therefore increase the risk of hyperkalemia, particularly in patients with CKD, hence limiting their utilization despite their proven benefits. In a large retrospective analysis from the Veterans Health Administration database, CKD and RAAS inhibitor prescriptions were the strongest predictors of hyperkalemia.[75] Several studies have shown a U-shaped relationship between serum potassium level and risk of death,[75–79] although the risks may be lower if patients are under the active care of a nephrologist.[80] The odds ratio of death from severe hyperkalemia (potassium >6.0 mmol/l) within 1 day of a measurement of serum potassium was very large, amounting to 31.6 for those without CKD, 19.5 for those with CKD G3, 11.6 for those with CKD G4, and 8.0 for those with CKD G5, suggesting the possibility of some degree of systemic adaptation to hyperkalemia with kidney impairment.[75] However, the absolute risks of death associated with hyperkalemia over an 18-month period were higher among those with CKD, heart failure, and diabetes.[76] In a cohort of patients managed by nephrologists, however, hypokalemia was associated with even higher risks of death than hyperkalemia.[77]

Novel potassium-binding drugs, such as patiromer and sodium zirconium cyclosilicate, could potentially change the pharmacotherapy for hypertension, but conference participants felt it was too early to evaluate the role of these drugs in routine clinical practice. Further research is needed to examine whether potassium binders allow better treatment of hypertension, for example, using RAAS blockers, and thus reduce cardiovascular and renal complications (Table 2).

Dual inhibition of the renin-angiotensin system

Post hoc analyses from the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and data from the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) and the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trials suggested that dual therapy with an ACEi, an ARB, and/or a direct renin inhibitor did not provide cardiovascular or kidney benefit compared with monotherapy in patients with low eGFR and elevated albuminuria, although BP was somewhat lower.[81] Additionally, the risks of hyperkalemia, acute kidney injury, and hypotension were greater with dual regimens.[82] In 2014, the European Medicines Agency endorsed restrictions on combining different classes of RAAS inhibitors in patients with diabetic nephropathy. A more recent meta-analysis suggested that dual ACEi and ARB treatments have efficacy in preventing ESKD in adults with diabetic kidney disease, if the treatments can be implemented safely.[83] Conference participants discussed the possibility that dual RAAS regimens have long-term benefits in specific subgroups of patients, particularly those with a substantially lower degree of albuminuria while they are on dual versus monotherapy of RAAS inhibitors or when dual blockers are used in combination with potassium binders. Combining an ACEi or ARB with mineralocorticoid receptor antagonist may also confer additional protection, but the absence of informative RCTs means that we cannot currently assess the relative risks (including acute kidney injury and hyperkalemia) and benefits.

Table 2 | Research recommendations for BP management in CKD

- Compare CKD G3a-G5 ND BP readings obtained using various BP measurement techniques, including casual office BP, standardized office BP, automated office BP, home BP and ambulatory BP measurements in adult and pediatric populations
- Relate different BP measurement techniques to cardiovascular and kidney outcomes in observational studies
- Investigate long-term clinical implications of acute lowering of glomerular filtration rate with intensive BP control and/or with renin-angiotensin-aldosterone system inhibitors
- Investigate whether oral potassium binders in CKD G3a-G5 ND with hypertension allow for the use of renin-angiotensin-aldosterone system inhibitors, and hence better treatment of hypertension and improvement in cardiovascular and kidney outcomes
- Determine whether subgroups within CKD G3a-G5 ND benefit from dual inhibition of the renin-angiotensin-aldosterone system in terms of cardiovascular and kidney outcomes and favorable benefit-to-risk ratio
- Determine the optimal management strategy for resistant hypertension in CKD G3a-G5 ND
- Address management of hypertension in older patients with CKD G3a-G5 ND, especially in terms of BP target, the role of nonpharmacological therapies, choice of antihypertensive agents, life expectancy, and bidirectional interactions between BP treatment and psychosocial environment
- Conduct randomized trials to evaluate the effects of various BP targets on cardiovascular and kidney outcomes in advanced CKD, diabetic CKD, severely increased proteinuria CKD, and kidney transplant patients
- Determine thresholds for initiating treatment and for BP targets in pediatric CKD patients

BP, blood pressure; CKD, chronic kidney disease; ND, nondialysis

This controversial area calls for RCTs to be studied in specific patient groups.

Resistant hypertension

Resistant hypertension is common in CKD. The conference participants discussed the possible role of mineralocorticoid receptor antagonists (e.g., spironolactone, epleronone) in the treatment of resistant hypertension (by extension from studies in the general population) and as add-on anti-proteinuric treatment, with or without the concomitant use of novel potassium-binding drugs. However, participants concluded that evidence is insufficient to define the role of these agents in practice for those with CKD.

MANAGING BLOOD PRESSURE IN OLDER PATIENTS WITH CKD

The 2012 KDIGO BP guideline assigned a chapter to older patients and noted that very little evidence is available to guide management in nondiabetic older patients with CKD. Conference participants agreed that, although the term "older patients" has no universal definition, treatment decisions should carefully take into account age, comorbidities, and other concomitant therapies, and that dose escalation of antihypertensive agents should be gradual, with close attention to adverse events.[1] The BP treatment target for older patients with advanced CKD is particularly controversial. Given the increasing incidence of ESKD in the older hypertensive population, study of the effects of antihypertensive therapy on cardiovascular and renal outcomes in older patients with advanced CKD remains an unmet need.

Initiating antihypertensive therapy and treatment targets in older patients with CKD

Conference participants recognized that for nonambulatory or nursing-home patient populations with CKD, no clinical trial data are available to inform decisions about antihypertensive therapy. Given that the aggregate benefits of antihypertensive therapy do not appear until 1–2 years after initiation of treatment, decisions regarding initiation of BP therapy and goals of treatment in persons with otherwise limited life expectancy should be based on shared decision-making with patients, family members, and caregivers, taking other medical and social conditions into consideration.

Based on available data,[2,68,69,84] conference participants discussed whether the target for SBP should vary by age in adult CKD patients. First, participants noted that most trials in the older population have targeted SBP instead of DBP, since SBP better predicts cardiovascular disease, and isolated diastolic hypertension is rare in older adults. The SPRINT trial did not capture the whole spectrum of CKD patients, as patients with diabetes mellitus, eGFR <20 ml/min per 1.73 m^2, or proteinuria >1 g/d were excluded.[2] Nonetheless, results from the SPRINT study suggest that cardiovascular and survival benefits are provided by an SBP target of <120 mm Hg (measured by automated oscillometric office BP) in the CKD population, including in those over 75 years old.[66] Intensive SBP lowering did not impair gait speed or self-reported mobility.[85] Less clear is whether older CKD patients with SBPs between 120 and 130 mm Hg (by standardized, not casual, BP measurement) should initiate treatment. A systematic review and perhaps future trials were suggested to provide insight into this issue. At the same time, such a systematic review should summarize methods of BP measurement in outcome trials.

Older patients commonly have CKD G3a without significant albuminuria.[69] Conference participants questioned whether the degree of albuminuria should influence BP targets in this population for renoprotective effects, as discussed above. Cardiovascular risk reduction should be a priority in this group, but no evidence to date suggests that the cardiovascular-protective effects of lowering BP depend on the degree of albuminuria.[86]

Choice of antihypertensive agents in older patients with CKD

The use of ACEis, ARBs, diuretics, and calcium channel blockers has been shown to be associated with improved cardiovascular outcomes in CKD patients.[87–89] The 2012 KDIGO BP Guideline recommended that, if the degree of albuminuria is higher than 300 mg/g, ACEis or ARBs be included in the antihypertensive regimen because of their renoprotective effects. In a subgroup analysis of an RCT in older hypertensive patients, cardiovascular events were more frequent with single high-dose ARB therapy, compared with combination therapies using an ARB plus a calcium channel

blocker.[90] Although the number of events was quite small, conference participants suggested that this study be considered in the guideline update.

Treatment monitoring in older patients with CKD

With antihypertensive therapy, the concern is that older patients are likely to have a higher incidence of serious adverse events than younger patients. However, among those aged 75 years or older, targeting SBP <120 mm Hg did not cause more serious adverse events than targeting SBP <140 mm Hg in the entire cohort[68] or in the CKD subgroup[69] in SPRINT. Nonetheless, BP management in older individuals with CKD should be individualized, taking into account comorbidities, polypharmacy, and other factors.[1]

MANAGING BP AMONG INDIVIDUALS WITH CKD AND PREVIOUS STROKE

This population is not specifically mentioned in the 2012 KDIGO BP guideline. The risk of stroke increases additively with declining GFR and increasing albuminuria, particularly in patients with an eGFR below 60 ml/min per 1.73 m^2,[91] and lowering BP generally reduces the risk for stroke and other cardiovascular events.[92] Currently, no evidence suggests that a history of prior stroke should change the chronic treatment of BP in patients with CKD, as shown in a subgroup analysis of the Perindopril Protection against Recurrent Stroke Study (PROGRESS),[93] although data are limited. In SPRINT, a history of stroke was an exclusion criterion. The SPS3 study[94] targeted SBP treatment to <130 mm Hg in patients with a history of prior stroke and included 474 patients with baseline eGFR <60 ml/min per 1.73 m^2. Compared with an SBP target of 130–149 mm Hg, a statistically nonsignificant reduction in the cardiovascular composite outcome occurred in the intensive SBP arm, with no effect modification by the baseline eGFR. Because of the paucity of data in this area, it is hoped that future RCTs of BP targets in people with prior stroke will include substantial numbers of individuals with CKD.[95] Systematic reviews, meta-analyses, and perhaps additional data from RCTs are needed to inform the best practices for managing BP in CKD patients acutely and chronically after a stroke. At present, formulating recommendations for this group of patients would be difficult.

MANAGING BP IN KIDNEY TRANSPLANT POPULATIONS

Treatment thresholds and targets in transplant recipients

The KDIGO 2012 BP guideline suggested that adult kidney transplant recipients who have an office SBP consistently >130 mm Hg or a DBP consistently >80 mm Hg be treated to maintain SBP <130 mm Hg and DBP <80 mm Hg, irrespective of the level of albuminuria,[1] largely because the work group believed that adult transplant recipients are at high risk for both graft loss and development of cardiovascular disease. Since 2012, evidence published from a *post hoc* analysis in the FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) Trial showed that SBP increases were associated with increased risk for cardiovascular disease in kidney transplant recipients.[96] This study did not address BP thresholds related to allograft failure. An important point to note is that BP was not a randomized intervention in FAVORIT. An earlier analysis of the Collaborative Transplant Study[97] demonstrated a close association of SBP and chronic allograft failure in a monotonic manner in the range of SBP down to 140 mm Hg and DBP down to 90 mm Hg. No RCTs have been conducted that could inform the optimal target BP with regard to cardiovascular or renal allograft outcomes in kidney transplant recipients.

A key issue is whether evidence regarding management of BP in nontransplant CKD patients can be extrapolated to transplant recipients. Conference participants felt that such extrapolation should be tempered because transplanted kidneys are denervated and therefore may not autoregulate glomerular perfusion in the same manner as nontransplanted kidneys. Further, kidney transplant recipients are at risk of transplant renal artery stenosis, and they are frequently prescribed calcineurin inhibitors, which raise BP and influence renal perfusion. Based on clinical experiences, concerns were expressed regarding targeting SBP to <120 mm Hg in transplant recipients. Adequately powered outcome trials in kidney transplant patients, with a design similar to that of SPRINT, are needed, but obtaining the required financial resources for such a trial will be challenging.

Choice of antihypertensive agents in transplant recipients

The 2012 KDIGO BP guideline did not specify preferred choices of antihypertensive agents.[1] Since 2012, reports have compared antihypertensive drugs in kidney transplant recipients. A 2016 meta-analysis by Hiremath *et al.*[98] suggested that ACEis or ARBs did not alter all-cause mortality or kidney outcomes but did increase the risk for hyperkalemia. Because of the small number of events and relatively short follow-up durations, the results of the meta-analysis were inconclusive.

In a randomized crossover trial of chlorthalidone versus amlodipine among kidney transplant patients treated with tacrolimus, patients in both arms experienced similar reductions in ambulatory SBP after 8 weeks.[99] Chlorthalidone reduced proteinuria by 30% but also temporarily reduced kidney function. In an RCT of 153 kidney transplant recipients, participants were randomized to losartan versus matched placebo for up to 5 years. Both arms had their BP treated to a goal of <130/80 mm Hg using other agents. Randomization to losartan did not have a significant influence on the time to a composite of ESKD, death, or doubling of creatinine level.[100]

Conference participants felt that this new evidence should be considered in the guideline update. The existing Recommendation 5.2 suggesting that choice of antihypertensive therapy take into account the time after transplantation, use of calcineurin inhibitors, presence or absence of albuminuria, and other comorbid conditions remains appropriate.

Living kidney donors

Living kidney donors were not specifically mentioned in the 2012 KDIGO BP guideline. In these individuals, each year of

age is associated with 9% greater odds of high BP requiring medication.[101] The KDIGO 2017 clinical practice guideline on living kidney donors suggests that donor candidates be informed that donation may accelerate a rise in BP and that they should have BP measured every year postdonation.[102] Conference participants agreed that although data linking close monitoring to improved clinical outcomes are not available, these recommendations are appropriate.

MANAGING BP IN PEDIATRIC CKD POPULATIONS

Thresholds for initiating treatment

Clinical trials assessing the effects of different BP targets on hard clinical endpoints in children who have CKD are limited. Applying BP guidelines in adults who have CKD to children who have CKD is not advisable because the normative BP values in children are dependent on age, gender, and height.

For the general pediatric population, the threshold for initiation of antihypertensive therapy has been the 95th percentile of normative BP values in the general pediatric population. Since the prior KDIGO CKD BP guideline was published, however, recognition of the effects of obesity on BP in children in general has increased. Thus, the American Academy of Pediatrics (AAP) guideline recently revised normative pediatric BP tables based on normal-weight children.[103] The AAP further recommends that children and adolescents with CKD be evaluated for hypertension using automated oscillometric equipment to measure BP in an office-based setting.[103] However, published normative BP values in children so far refer only to office auscultatory measurements. More normative data in children are needed for office-based and home-based automated oscillometric BP and ambulatory BP. Some normative data are available for ambulatory BP, but only in Western European populations.[104]

Recommendation 6.1 in the 2012 KDIGO BP guideline suggested that for children with CKD, treatment should be started when BP is consistently above the 90th percentile for a child's age, sex, and height.[1] This recommendation is consistent with guidance from Hypertension Canada[105] but at odds with that of the AAP[103] and the European Society of Hypertension,[106] which recommend that treatment be initiated if BP is consistently above the 95th percentile in the general pediatric population. A point to note is that these 3 guidelines are not specific to CKD patients. The AAP 2017 also recommends initiating treatment if BP is >130/80 mm Hg for children ages 13 years and above.[103] However, the cutoff age of 13 years in CKD patients was considered potentially problematic by conference participants because many pediatric patients with CKD have small stature and may have a lower BP than is typical for their age. The 2012 KDIGO BP guideline for pediatric CKD patients should be reconsidered in light of these new AAP normative data and other guidelines.

Treatment targets

Recommendation 6.2 in the 2012 KDIGO BP guideline suggests that SBP and DBP be lowered to values ≤50th percentile in children with CKD, particularly in those with proteinuria.[1] This recommendation was based primarily on the Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial, in which hypertensive pediatric CKD patients randomized to a mean arterial BP target of <50th percentile of normative values based on ambulatory BP measurements had fewer renal events than those randomized to the 50th–95th percentile.[107] Yet, the KDIGO recommendation has applied these targets to SBP and DBP measured using the auscultatory method. Therefore, conference participants felt that the 2012 KDIGO guideline should be revised accordingly. On the other hand, the fact that ambulatory BP monitoring may not be widely available was noted; therefore, guidance also should provide a target clinic BP using automated oscillometric devices as an alternative. Provision of this guidance would require new normative data on automated oscillometric office-based BP readings that correspond to specific ambulatory BP levels for any given age, sex, and height. Development of such data was felt to be an important research recommendation.

Choice of antihypertensive agent

The 2012 KDIGO guideline Recommendation 6.3 suggests that an ARB or ACEi be used in children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria.[1] This recommendation was based largely on preclinical data and data from adult studies. Only 4 small uncontrolled trials have shown that ACEis or ARBs reduce proteinuria in children with CKD.[107] Evidence indicates that losartan[108] and enalapril[109] each lowers proteinuria in children, and that their effects are comparable,[110] but data on end-organ consequences are unavailable. Conference participants also questioned whether the presence of proteinuria should be a consideration for the preferential use of ARBs or ACEis over other agents. Further research is needed on the long-term safety and efficacy of ARBs and ACEis in children with CKD.

Pediatric kidney transplant recipients

BP management in pediatric transplant recipients was considered to be an area without a sufficient evidence base to support guidelines. Additional research is warranted.

CONCLUSION

Overall, conference participants agreed that an update of the 2012 KDIGO BP guideline would be timely, particularly given the SPRINT data. In particular, BP thresholds and targets for treatment need to be reconsidered. Recommendations on where and how BP should be measured need to be emphasized. RCT data on the cardiovascular and survival benefits of diabetic kidney disease, advanced CKD, and severely increased proteinuric CKD are urgently needed for guidance regarding BP management in these CKD subgroups. Implementation of the updated guidelines was also recognized to be important, a process that

potentially can be facilitated by development of a patient decision aid for initiating antihypertensive treatment, with estimates of absolute risk and risk reduction from the treatment.

APPENDIX

Other conference participants

George L. Bakris, USA; Albertino Damasceno, Mozambique; Jamie P. Dwyer, USA; Linda F. Fried, USA; Richard Haynes, UK; Nobuhito Hirawa, Japan; Hallvard Holdaas, Norway; Hassan N. Ibrahim, USA; Julie R. Ingelfinger, USA; Kunitoshi Iseki, Japan; Arif Khwaja, UK; Paul L. Kimmel, USA; Csaba P. Kovesdy, USA; Elaine Ku, USA; Edgar V. Lerma, USA; Friedrich C. Luft, Germany; Jicheng Lv, China; Christopher B. McFadden, USA; Paul Muntner, USA; Martin G. Myers, Canada; Sankar D. Navaneethan, USA; Gianfranco Parati, Italy; Aldo J. Peixoto, USA; Ramesh Prasad, Canada; Mahboob Rahman, USA; Michael V. Rocco, USA; Cibele Isaac Saad Rodrigues, Brazil; Simon D. Roger, Australia; George S. Stergiou, Greece; Laurie A. Tomlinson, UK; Marcello Tonelli, Canada; Robert D. Toto, USA; Yusuke Tsukamoto, Japan; Robert Walker, New Zealand; Angela Yee-Moon Wang, Hong Kong; Jiguang Wang, China; Bradley A. Warady, USA; Paul K. Whelton, USA; Jeff D. Williamson, USA

DISCLOSURE

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