Hypertension

REVIEW

Is the KDIGO Systolic Blood Pressure Target <120 mm Hg for Chronic Kidney Disease Appropriate in Routine Clinical Practice?

Indranil Dasgupta, Carmine Zoccali

ABSTRACT: Meticulous management of hypertension is important in chronic kidney disease (CKD) to reduce the risk of cardiovascular disease, mortality, and progression of CKD. The recently published Kidney Disease Improving Global Outcomes (KDIGO) guideline on blood pressure (BP) management in CKD stresses the importance of standardized BP measurement and strict control of BP. This is a useful document that will help to improve the management of hypertension in CKD globally. However, the recommendation of systolic BP target of <120 mm Hg by KDIGO is controversial. It is based on weak evidence derived mainly from a single randomized controlled trial and its CKD subgroup analysis. Here, we review the current evidence surrounding BP target in CKD. We argue that the target recommended by KDIGO is not generalizable to the majority of people with CKD. Standardized BP measurements are challenging to implement outside specialist hypertension and research clinics, and the target of <120 mm Hg BP systolic cannot be extrapolated to routine clinic BP measurements. If applied to routine BP measurement, this target will expose the multimorbid and frail CKD patients to the risk of adverse events including falls and fractures. Furthermore, it will not be achievable in the majority of CKD patients. The target recommended by KDIGO is an outlier among contemporary major international hypertension guidelines and is likely to perplex clinicians. We believe the KDIGO-recommended target systolic BP <120 mm Hg for CKD is inappropriate in the majority of CKD patients and it may even be harmful for patients managed in routine clinical practice.

Key Words: accidental falls ■ blood pressure ■ frail elderly ■ guideline ■ hypertension

Hypertension is an important risk factor for both cardiovascular disease (CVD) and chronic kidney disease (CKD).[1] It is also a major contributor to progression of CKD.[2,3] Furthermore, CKD is associated with a high risk of CVD, so much so that for a patient with stage 3 CKD, the risk of death due to CVD far exceeds that of end stage kidney disease.[3,4] Therefore, meticulous control of hypertension is crucial for reducing CVD risk in CKD and slowing the progression of CKD.

Kidney Disease Improving Global Outcome (KDIGO) is the global nonprofit organization that develops and helps to implement evidence-based clinical practice guidelines with a view to improving "the care and outcomes of patients with kidney disease worldwide." In March 2021, it published the Clinical Practice Guideline for the Management of Blood Pressure (BP) in CKD,[5] which is an update of their previous guideline of 2012[6]. The objective was to assess the current evidence pertaining to optimal means for measuring BP and management of high BP in CKD patients including diabetic and nondiabetic CKD, kidney transplantation, and CKD in pediatric population. This is a useful document of 92 pages that delves deep into the evidence base in the areas mentioned above. The guideline recommends that "adults with high BP and CKD be treated to a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using a standardized office BP." This recommendation has prompted debates among nephrologists across the globe as to how appropriate this target BP is in day-to-day clinical practice. In this article, we have gone through the available evidence and argue that this target is based on tenuous evidence, not generalizable, and raises significant safety concerns.

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Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
BP	blood pressure
CKD	chronic kidney disease
CVD	cardiovascular disease
HR	hazard ratio
KDIGO	Kidney Disease Improving Global Outcomes
RIISC	Renal Impairment in Secondary Care
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial

STRENGTH OF EVIDENCE

This recommendation has been graded by the guideline work group as level 2, that is, a recommendation that is "likely to require substantial debate and involvement of stakeholders before policy can be determined" and quality level B, which suggests it is underpinned by moderate-quality evidence. As a matter of fact, this recommendation is based on just one well-conducted randomized controlled trial (RCT) in the general population, SPRINT (Systolic Blood Pressure Intervention Trial),[7] and its CKD subgroup analysis.[8]

SPRINT randomized 9361 nondiabetic individuals, over 50 years of age and at least 1 CVD risk factor, to intensive (SBP, <120 mm Hg) and standard (<140 mm Hg) arms. The study was terminated early after average follow-up of 3.36 years because of substantial CVD and mortality benefit in the intensive BP arm. Participants in the intensive arm were found to be at 25% lower relative risk of the primary outcome—a composite of myocardial infarction, acute coronary syndrome, stroke, congestive heart failure, or CV death. There was a 27% relative risk reduction of all-cause death.[7] The CKD subgroup (n=2646) analysis, which was prespecified, showed 28% relative risk reduction of all-cause death but no risk reduction in the composite primary CVD outcome or the composite kidney outcome (drop in eGFR of ≥50% from baseline or end stage kidney disease). Furthermore, there was a more rapid decline in estimated glomerular filtration rate (eGFR) over the first 6 months in the intensive BP group, which continued, albeit at an attenuated rate, beyond the sixth month.[8]

SPRINT was not powered for subgroup analyses,[7] and it ended early. There was an increased risk of acute kidney injury in the intensive BP arm. Even though there was no formal effect modification by CKD, the risk reduction (−18%) of the primary CV outcome in the CKD subgroup was less pronounced than in the population without CKD (−30%). The guideline work group stated "the risk: benefit ratio for kidney outcomes in the intensive SBP arm may not be as favorable in this subgroup as in the subgroup with higher baseline eGFR."[7]

A post hoc analysis of SPRINT looking at eGFR and the risk-benefit profile of intensive BP control among nondiabetic patients found that the CV benefit of strict BP control is attenuated by lower eGFR whereas it did not modify the effect on AKI. In the 968 patients with eGFR <45 ml/min/1.73 m^2, there was no reduction in CV risk in the intensive BP group compared with standard BP group (hazard ratio [HR], 0.92 [95% CI, 0.62–1.38]), whereas it increased the risk of AKI (HR, 1.73 [95% CI, 1.12–2.66]).[9]

The only trial that compared the low BP target tested in SPRINT (SBP, <120 mm Hg) with standard BP control (<140 mm Hg) in diabetic patients was the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes).[10] This trial failed to show any benefit of intensive BP control except a reduction in the risk of developing nonfatal stroke. Moreover, ACCORD included few participants with significant CKD. Rightly, the guideline work group stated, "there is little evidence from ACCORD alone to guide a recommendation for patients with diabetes and CKD."[7]

Three recent systematic reviews and meta-analyses looked at the benefit of intensive BP control in CKD. The first one compared intensive BP control (<130/80 mm Hg) with standard BP control (<140/90 mm Hg) on major renal outcomes in patients with CKD without diabetes. It included 9 major hypertension trials with 8127 participants, including SPRINT, which looked at the progression of CKD. Over a median of 3.3 years of follow-up, there was no additional benefit of intensive BP control on renal outcomes.[11] The second carried out a meta-analysis of 18 randomized clinical trials (including SPRINT and ACCORD) comprising 15 924 patients with CKD, more intensive BP lowering (achieved mean SBP, 132 versus 140 mm Hg) was associated with significantly lower (HR, 0.86 [95% CI, 0.63–0.99]) risk of mortality compared with less intensive BP control.[12] The most recent of these studies pooled individual data on 4983 participants from 4 major hypertension and CKD trials, including SPRINT and ACCORD, testing the impact of intensive BP target (SBP, <130 mm Hg) compared with standard target (SBP, <140) on all-cause mortality. On primary analysis, there was no significant difference between the groups in the primary outcome of all-cause mortality or the secondary outcomes of CV composite end point and CV mortality.[13] After excluding those with eGFR >60 mL/min per 1.73 m^2 and intensive glycemic treatment, there appeared to be a lower risk of all-cause mortality in the intensive BP group (HR, 0.79 [95% CI, 0.63–1.00]). In these meta-analyses, the <120 mm Hg threshold was not tested, probably because ACCORD and SPRINT, that is, the two sole large trials testing such a threshold, produced highly heterogeneous results.

A network meta-analysis of 26 hypertension trials (including SPRINT, ACCORD, and all major CKD BP trials) evaluated the efficacy outcomes of stroke, myocardial infarction, death, cardiovascular death, heart failure, and safety outcomes of serious adverse effects including angioedema, hypotension, syncope, bradycardia/arrhythmia, or hypo/hyperkalemia. Trial arms were grouped into 5 SBP target categories: <160, <150, <140, <130, and <120 mm Hg. There was no difference in death, cardiovascular death, or heart failure when comparing any of the BP targets. The point estimates favored lower BP targets (<120 and <130 mm Hg) when compared with higher BP targets (<140 or <150 mm Hg). However, there were significantly higher incidence rates of serious adverse effects with lower BP targets. On-treatment SBP target of <130 mm Hg achieved optimal balance between efficacy and safety.[14] This has been further supported by a recent trial, which tested whether intensive BP control (SBP, 110–130 mm Hg) is superior to standard BP control (130–150 mm Hg) in reducing the risk of CV events in 9624 Chinese patients (19% diabetic, 196 patients with eGFR <60 mL/min per 1.72 m^2), aged between 60 and 80 years. The mean achieved BP in the two groups was 127.5 and 135.3 mm Hg, respectively. There was a 26% relative risk reduction (HR, 0.74 [95% CI, 0.60–0.92]) of primary composite CV end point, without increase in adverse events except more hypotension in the intensive BP control arm. Importantly, there was no difference between the groups in terms of renal outcomes.[15]

Taken together the evidence presented above, we would argue that there is insufficient evidence to support the recommendation that "adults with high BP and CKD be treated with target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using a standardized office BP." The quality of evidence underpinning this recommendation is perhaps low rather than moderate, that is, "the true effect of intensive BP control may be substantially different from the estimate of the effect."

GENERALIZABILITY

Per protocol, SPRINT excluded individuals <50 years of age, those with diabetes or proteinuria ≥1 g/ day, adult polycystic kidney disease, glomerulonephritis treated with or likely to be treated with immunosuppressive therapy, and those with eGFR <20 mL/min per 1.73 m^2. The mean eGFR in SPRINT was 48 mL/min per 1.73 m^2, and it included few patients with CKD stage 4.

Of the cases of CKD that were excluded in SPRINT, diabetes is the commonest cause of CKD accounting for 42% of cases across the world. Glomerulonephritis accounts for ≈20% followed by adult polycystic kidney disease (around 10%).[16,17] We have also seen that the ACCORD trial did not show any benefit of intensive BP control on CVD and death, except reduction in nonfatal stroke, in people with diabetes. Therefore, strictly speaking, the KDIGO-recommended target SBP <120 mm Hg may not apply to the vast majority of patients with CKD the nephrologists care for.

SAFETY OF THE LOW BP TARGET

The KDIGO BP guideline recommends that BP in people with CKD should be measured in a standardized manner. A standardized office BP essentially is an average of 2 or 3 BP measurements taken using a validated device, after a period of at least 5 minutes of rest in a quiet environment. The KDIGO guidance suggests that patients should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement. It also suggests ensuring that the patient has emptied their bladder before measurement.[5] In contrast, routine office BP measurement (also termed casual BP) does not include any preparation before taking the readings. SPRINT and other recent hypertension trials used standardized BP readings because it correlates well with out-of-office BP measurements. We believe the KDIGO recommendation to measure BP in a standardized manner is appropriate; an effort should be made to measure BP in a standardized manner every time BP is measured. However, more often than not, in clinical practice nephrologists rely on routine office BP. Office readings are often significantly higher than standardized BP measurements and ambulatory or home BP readings, mainly because of white-coat effect,[18] which affects over 50% patients with treated hypertension, average difference between clinic and ambulatory BP being 20 mm Hg.[19] Furthermore, standardized BP measurements correlate well with end organ damage.[20] A study looking at concordance between BP in SPRINT and that obtained in routine clinical practice, from electronic health records, demonstrated that there was low agreement between the two with wide agreement intervals ranging from −30 to +45 mm Hg. Interestingly, the difference was higher in the intensive treatment group compared with standard treatment group (mean difference, 7.3 versus 4.6 mm Hg).[21] In the context of CKD, standardized office BP has been shown to be, on average, 12.7 mm Hg lower than routine office BP, with wide limits of agreement (−46.1 to 20.7 mm Hg).[22] The wide limits of agreement between routine and standardized BP measurements emphasize the difference within individual patients. Consequently, no correction factor to estimate standardized BP can be applied to routine BP. Appropriately, the Guideline Work Group stated that it might be potentially hazardous to apply the SBP target <120 mm Hg nonstandardized BP measurements to office BP measurements, the most frequently used metric in nephrology clinics across the world, as there is risk of overtreatment.

The potential hazards of low target BP, especially when applied to routine BP measurement, include

increased risk of postural hypotension, recurrent falls and fractures, acute kidney injury, stroke in those with lower carotid reserve, and rapid decline in eGFR in those with renovascular disease.[23] CKD patients are at a much higher risk of these events than the general population as many of them are elderly, frail, and multimorbid.[14] The human and societal cost of falls is enormous. The human cost includes pain, injury, distress, loss of confidence, and a greater risk of death. One in 3 people with a hip fracture die within a year, although most of the deaths are not caused directly by fractures but rather the underlying ill health of which the fall may be a sign. In the United Kingdom, falls cost the UK National Health Service (NHS) £2 billion a year and 4 million bed days.[24] In the United States, in 2014, total personal health care spending for older adult falls ranged from $48 million in Alaska to $4.4 billion in California. Medicare spending attributable to falls in older adults ranged from $22 million in Alaska to $3.0 billion in Florida.[25]

Arguably, the AKI in SPRINT was mild and reversible and was ascribed to hemodynamic effect. However, we do not know what the long-term effect of AKI/eGFR decline with intensive BP lowering is especially in those with advanced CKD.[26] This is particularly so because the follow-up periods are relatively short in trials of intensive BP control. In SPRINT, AKI was significantly higher in those with eGFR <45 mL/min per 1.73 m^2 than in those with higher eGFR[9]; there were few participants with stage 4 CKD. Monitoring for electrolyte disturbances and AKI may also be less frequent in routine clinical practice compared with clinical trials. Therefore, the guideline should have highlighted the importance of close follow-up of these patients.

POTENTIAL HAZARDS OF DRIVING DIASTOLIC BP TOO LOW

Although the KDIGO guideline does not stipulate a diastolic target, in attempting to lower SBP <120 mm Hg in patients with CKD, there is also the risk of driving diastolic BP too low especially in older patients, who often have low diastolic BP because of advanced atherosclerosis.[27] Diastolic BP is important for adequate coronary artery filling. Many studies have demonstrated that low diastolic BP <70 mm Hg is associated with higher risk of CVD, recurrent CV events, and stroke compared with diastolic BP between 71 and 89 mm Hg.[27–30] People with CKD already have a high risk of CVD.[4]

The practice points of the KDIGO guideline in relation to the target BP recommendation highlight the potential hazards associated with the low BP target and suggest that clinicians can reasonably offer less intensive BP lowering therapy in those with symptomatic postural hypotension.

CHALLENGES OF IMPLEMENTATION OF STANDARDIZED BP MEASUREMENT IN ROUTINE CLINICAL PRACTICE

Standardized BP measurement as described in the preceding section requires significant resources including the need for staff training, additional clinic space, additional nurse time, ensuring the use of validated BP devices, etc. It is estimated that it adds at least 7 minutes to the consultation.[31] These require extra time, man power, and other resources necessitating restructuring of outpatient clinics. This begs the question whether standardized BP measurement can be routinely implemented outside research and specialist hypertension clinic settings, especially in busy nephrology clinics in large centers. Most of the early-stage CKD patients who are likely to benefit from low SBP target are cared for in primary care. Needless to say that this is likely to be even more difficult to implement in primary care clinics where the time allotted for each patient is much shorter than in specialist secondary care clinics. The time pressure in primary care clinics is known to compromise adherence to guidelines.[32] Similar time pressure exists in most European countries and in the United States.[33]

What we have described above are the challenges of implementing standardized BP measurement in the developed world, where it may necessitate widespread reform of health care to implement standardized BP measurement in routine care. The KDIGO guidelines are meant for the developing world as well, where we believe it will be even more challenging, if not impossible, to implement routine standardized BP measurement in CKD clinics in resource-poor settings.

The COVID-19 pandemic has led to significant changes in clinical practice across the world with reconfiguration of most outpatient services into virtual clinics. Moving forward, it is likely that many patients with chronic diseases will be followed up virtually through video or telephone consultation. It will be crucial to obtain reliable out-of-office BP readings, along with eGFR and electrolyte measurements, to monitor treatment in people with CKD. Therefore, there is an urgent need for recommendations based on home BP readings, obtained in a standardized manner, using validated monitors. Patients will need to be educated about correct monitoring technique and recording the readings that can be electronically transferred, where possible, to electronic patient records. This will improve patient engagement, but clinicians will need to be aware of the risk of suboptimal care being delivered to those without the resources. Home BP monitoring empowers patients and improves BP control.[34] Treating hypertension, for those with and without CKD, based on standardized home BP monitoring, we believe, is the way forward.

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POLYPHARMACY

Polypharmacy is defined as the use of ≥5 pharmacological agents in a person to treat multiple chronic conditions.[35] It is common in the elderly and multimorbid individuals. It is a major and growing public health problem and poses a huge prescribing challenge to clinicians especially in primary care.[36] Polypharmacy is common in people with CKD who are often multimorbid requiring multiple medications.[37] In a recent German study of people with mild-to-moderate CKD (eGFR, 30–60 mL/min per 1.73 m^2, >60 with proteinuria >500 mg/day), over two-thirds of them are on polypharmacy without taking into account over-the-counter medications, which are often used by many.[38]

In SPRINT, the participants in the intensive control group took 2.8 antihypertensive medications on average compared with the standard control group taking 1.8 antihypertensive medications.[7] However, as per protocol, SPRINT excluded nonadherent patients. Around 50% of people with treatment-resistant hypertension are either completely or partially nonadherent,[39] and nonadherence is a major issue in people with CKD.[40] The extra tablets prescribed to achieve the <120 mm Hg SBP goal is likely to further compound the problem of polypharmacy in people with CKD, which would probably have a negative impact on adherence to medications in these people who already have a high pill burden. Nonadherence increases steadily when the total number of prescribed drugs is over 3 to 4.[41]

Polypharmacy is associated with many problems that can affect patients seriously.[42] These include increases in adverse drug reactions, drug interactions, and, as discussed, medicinal nonadherence, the commonest cause of apparent treatment-resistant hypertension.[39] It is also associated with falls due to postural hypotension, urinary incontinence, poor nutrition, cognitive impairment, and poor functional status, all of which lead to poor quality of life. Additionally, polypharmacy is associated with higher direct and indirect health care cost.[42]

ACHIEVABILITY OF THE TARGET

A rule of halves operates in the management of hypertension in the general population—half of the people with hypertension are aware of the diagnosis, half of those aware get treatment, and of those treated approximately, half achieve the target BP (140/90 mm Hg conventionally).[43] The situation may not be significantly different in people with CKD. A study based on National Health and Nutrition Examination Survey (NHANES) of the United States 1999–2006 data suggested that around 50% of those with CKD achieve a target of 140/90 mm Hg, around 30%, a target of 130/80 despite the contemporary Joint National Committee (JNC) BP guideline for CKD became stricter over this period.[44]

Since the publication of the guideline, a study looked at how many (%) of the 35.3 million people with CKD in the United States meet various SBP targets by extrapolating from achieved targets in the NHANES population. They found that 69.5% have an SBP over 120 mm Hg, 49.8% over 130 mm Hg, and 31% over 140 mm Hg.[45] Our own experience in the RIISC study (Renal Impairment in Secondary Care)[46] cohort is remarkably similar. In this study, standardized BP measurement was done in 834 patients at baseline and at each follow-up visit over 3 years, ≈68% had an SBP ≥120 mm Hg, 47% systolic ≥130 mm Hg, and 30% systolic ≥140 mm Hg over the follow-up period (Indranil Dasgupta, unpublished data, 2021). Given <50% of patients achieve the modest target of 130/80 mm Hg recommended by other contemporary guidelines, we believe that the majority of people with CKD in the real world are unlikely to achieve the KDIGO SBP target of <120 mm Hg.

KDIGO TARGET IS AN OUTLIER AMONG MAJOR INTERNATIONAL GUIDELINE TARGET BP FOR CKD

Different expert guideline committees—namely the American College of Cardiology/American Hypertension Association,

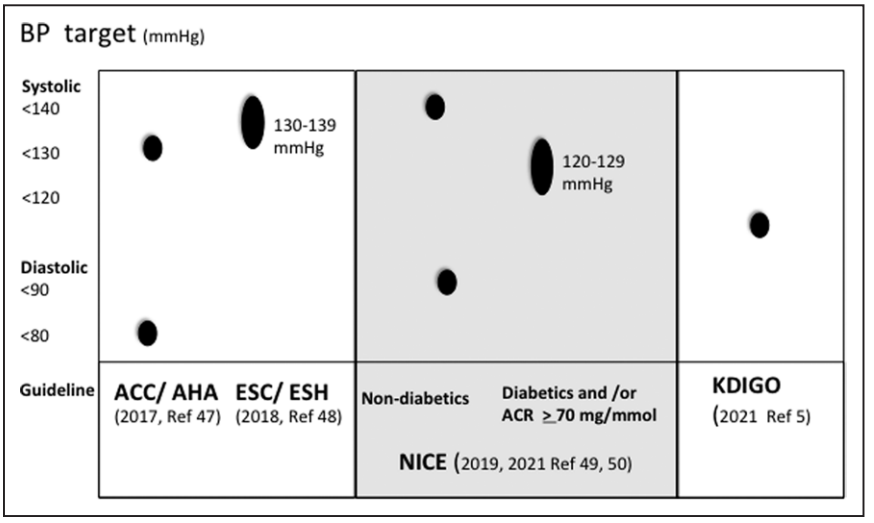

Figure 1. The blood pressure (BP) target for chronic kidney disease patients recommended by contemporary major international guidelines.
ACC indicates American College of Cardiology; ACR, urine albumin creatinine ratio; AHA, American Hypertension Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; KDIGO, Kidney Disease Improving Global Outcome; and NICE, National Institute for Health and Care Excellence.

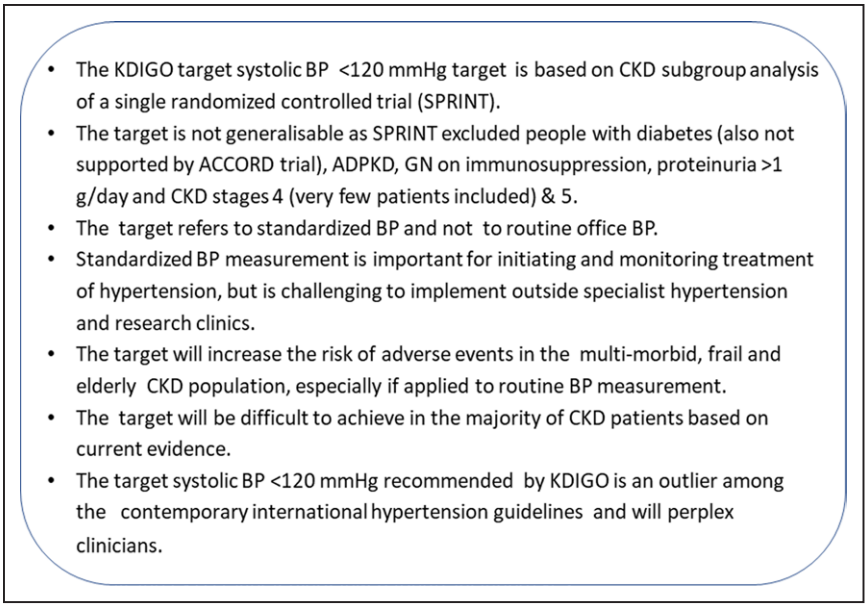

Figure 2. Key messages.
ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; ADPKD, adult polycystic kidney disease; BP, blood pressure; CKD, chronic kidney disease; GN, glomerulonephritis; KDIGO, Kidney Disease Improving Global Outcome; and SPRINT, Systolic Blood Pressure Intervention Trial.

European Society of Cardiology/European Society of Hypertension, National Institute for Health and Care Excellence, UK, and KDIGO—have assessed the same evidence, crucially including the SPRINT trial but have given different recommendations for target BP in CKD. The American College of Cardiology/American Hypertension Association guideline (2017) recommends a target of <130/80 mm Hg[47]; the European Society of Cardiology/European Society of Hypertension guideline recommends systolic BP of 130 to 139 mmHg[48]; National Institute for Health and Care Excellence Hypertension Guideline (2019)[49] recommends <140/90 mm Hg and systolic BP of 120 to 129 mm Hg for those with Diabetic Kidney Disease or ACR >70 mg/mmol while KDIGO (2021) recommends systolic BP of <120 mm Hg.[5] The National Institute for Health and Care Excellence CKD guideline,[50] which has been published more recently, recommends a BP target of <140/90 mm Hg in CKD and ACR <70 mmol/mol with the lowest SBP of 130 mm Hg and <130/80 mm Hg (lowest SBP, 120 mm Hg) for those with CKD with ACR >70 mmol/mol (Figure 1). Clearly, the KDIGO recommendation is an outlier among the major international hypertension guidelines. This is likely to confuse the clinician as to which target to follow while treating hypertension in a person with CKD.

In summary (Figure 2), the KDIGO BP guideline target of systolic <120 mm Hg is based on weak evidence from just 1 RCT (SPRINT) and its CKD subgroup analysis. SPRINT excluded people with a number of primary kidney diseases. As such, strictly speaking, this target does not apply to the majority of patients with CKD, including those with diabetes who form the largest group of CKD patients across the world. Furthermore, as the guideline work group admits, it is hazardous to apply this target without standardized BP measurement. A large proportion of CKD patients are elderly, infirm and multimorbid, and are likely to experience falls, fractures, AKI, and stroke leading to increased hospitalization and death. Standardized BP measurement is challenging to implement outside research and specialized hypertension clinics, especially in primary care and in resource-poor settings. In an effort to lower SBP <120 mm Hg, there is a risk of driving diastolic BP too low, which in turn is likely to further increase the risk of CV events in people with CKD, who are already at a high risk of developing CVD. This target is likely to promote polypharmacy, which increases the risks of drug nonadherence (the commonest cause of antihypertensive drug resistance), adverse drug reactions, drug interactions, falls, incontinence, and cognitive impairment. Lastly, recent hypertension guidelines by eminent international societies and guideline bodies have recommended differing targets, KDIGO being an extreme outlier. This may easily confuse physicians treating patients with CKD. Therefore, considering above, one would argue that lowering SBP <120 mm Hg in people with CKD is not underpinned by firm evidence of benefit, and it may even be hazardous to apply this target in the real-world clinical practice.

ARTICLE INFORMATION

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