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Editorial Comment



EDITORIAL COMMENT

# Blood pressure targets in CKD 2021: the never-ending guidelines debacle

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## ABSTRACT

In 2021, two updated clinical guidelines were published, providing guidance on blood pressure (BP) targets for people with chronic kidney disease (CKD). Kidney Disease: Improving Global Outcomes (KDIGO) updated its 2012 Clinical Practice Guideline for the Management of BP in CKD. Different systolic blood pressure (SBP) and diastolic blood pressure (DBP) targets for CKD (<130/80 and <140/90 mmHg, respectively, for people with a urinary albumin: creatinine ratio >30 mg/g or without pathological albuminuria) were replaced by a single number: an SBP target of <120 mmHg is suggested, when tolerated. This represents a major decrease in the SBP target and the abandonment of DBP targets. The European Society of Cardiology (ESC) also published a 2021 Clinical Guideline on Cardiovascular Disease Prevention in Clinical Practice that updates a prior 2016 guideline on prevention and the 2018 ESC/European Society of Hypertension Clinical Practice Guidelines for the Management of Arterial Hypertension. The 2021 ESC guideline was endorsed by 12 European scientific societies. The recommended office BP targets for people with CKD are <140–130 mmHg SBP (lower SBP is acceptable if tolerated) and <80 mmHg DBP. The question is: What should the practicing physician do now: treat hypertension in people with CKD to an SBP target of <120 mmHg or to a target of <140–130 mmHg? Major guideline bodies are aware of the activities of other major players. There is an urgent need for guideline bodies to establish communication channels, search consensus on major issues that impact the health of hundreds of millions of people worldwide and end individualism in guidelines generation.

**Keywords:** blood pressure targets, chronic kidney disease, European Society of Cardiology, guidelines, hypertension

Around 850 million people worldwide have chronic kidney disease (CKD) and >80% of them have hypertension [1]. A large proportion of people with hypertension, whose worldwide prevalence was estimated in 2000 at 972 million, may have concomitant CKD. Mortality from CKD is rapidly increasing and it is projected to become the fifth leading global cause of death by 2040 and the second leading cause of death before the end of the century in some countries with long life expectancies [2, 3]. Taking action to prevent these forecasts from materializing is a top healthcare priority [4]. Cardiovascular death is one of the largest contributors to mortality in CKD [5]. Thus setting targets for blood pressure (BP) control in CKD will affect the risk of premature death for hundreds of millions of people worldwide and has the potential to impact major causes of death

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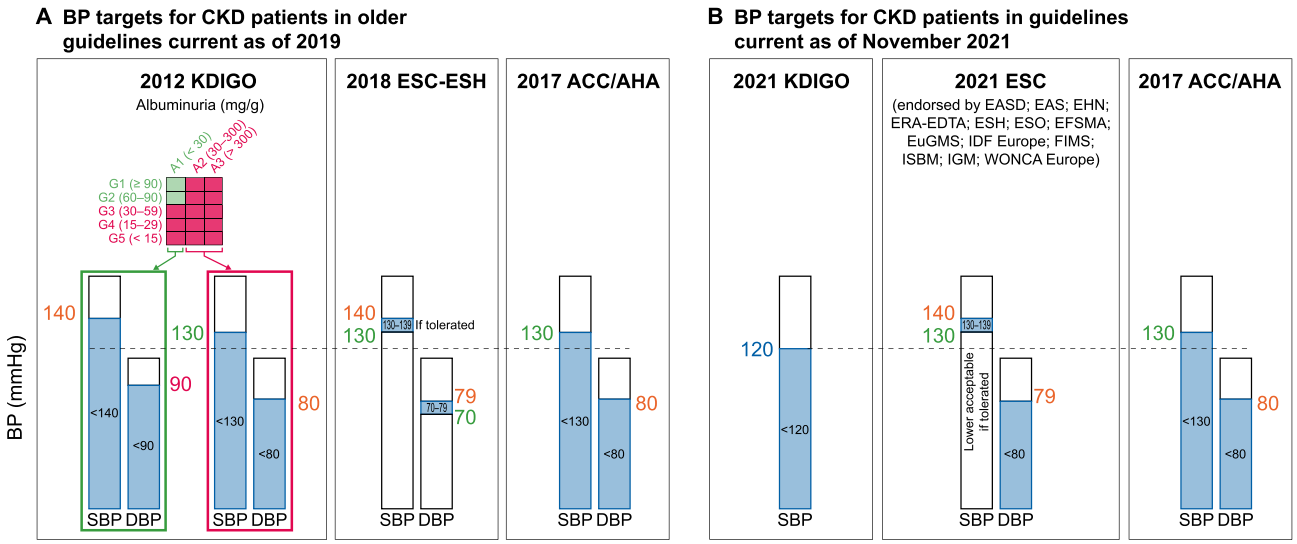


**FIGURE 1:** Different therapeutic targets in CKD patients as suggested or recommended by older (2012–18) or newer (2021 or not recently updated) guidelines. (**A**) Older guidelines: 2012 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease, 2017 ACC/AHA Guidelines and 2018 ESC/ESH Guidelines. (**B**) 2021 KDIGO and ESC Guidelines and 2017 ACC/AHA Guidelines that have not yet been updated and thus are deemed to remain current. Please note that therapeutic targets differ between guidelines, even between the two guidelines published in 2021. The blue colour of columns represents within the target BP. Individual numerical values in red represent the highest values of the three guidelines for the same concept (systolic or diastolic BP), in orange, intermediate values, and in green, the lowest values of the three guidelines for the same concept. Panel (A) is adapted from [8]. KDIGO targets are proposed for non-dialysis, non-transplant CKD. For kidney transplant recipients, KDIGO 2021 BP targets were only modestly modified to <130 mmHg SBP and <80 mmHg DBP. KDIGO 2021 provides no recommendations for patients on dialysis. ESC guidelines do not provide specific advice for kidney transplant recipients or patients on dialysis.

in the next decades. However, major guideline bodies do not agree on BP targets for CKD [6, 7]. Thus a situation that in 2019 was termed chaotic in the pages of *CKJ* will persist into the new decade [8]. While there might be justification for guidelines generated at different points in time examining different evidence to suggest/recommend different BP targets, there is little justification for two guidelines published over the span of 5 months using exactly the same evidence to provide highly divergent recommendations.

In 2021, two major guidelines updated prior (dating from 2012 and 2018, respectively) recommendations for BP targets for people with CKD: the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease [6] and the European Society of Cardiology (ESC) 2021 Clinical Guideline on Cardiovascular Disease Prevention in Clinical Practice [7]. Both new guidelines provide a simplified message that will favour uptake and implementation. Unfortunately, the suggested/recommended systolic blood pressure (SBP) targets were off by up to 20 mmHg. This creates confusion and will hinder implementation. There is an urgent need to reach consensus on such basic issues as the BP targets for hundreds of millions of people with CKD.

## FROM KDIGO 2012 TO KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF BLOOD PRESSURE IN CKD

The 2012 KDIGO guideline had a relatively complex set of BP targets based on the presence or absence of diabetes or pathological albuminuria [i.e. urinary albumin: creatinine ratio (UACR) > 30 mg/g] for adults with CKD not on dialysis (Fig. 1A) [9]:

- Recommendation: non-diabetic, UACR <30 mg/g; office SBP target ≤140 mmHg, DBP ≤90 mmHg (1B).
- Suggestion: non-diabetic, UACR 30–300 mg/g; office SBP target ≤130 mmHg, DBP ≤80 mmHg (2D for UACR 30–300 and 2C for UACR > 300 mg/g in non-diabetics, 2D for diabetics).

That is, for KDIGO 2012, a BP of 140/90 mmHg was adequate for patients with non-diabetic, normoalbuminuric CKD. There was no recommendation for patients on dialysis, while transplant patients had the same target as patients with pathological albuminuria [9].

The 2021 KDIGO guideline has a simpler message: 'We suggest that adults with high BP and CKD be treated with a target SBP of <120 mmHg, when tolerated, using standardized office BP measurement (2B)' (Fig. 1B) [6]. Additionally, it provides guidance on how to measure office BP (Table 1). The suggestion is based on the Systolic Blood Pressure Intervention Trial (SPRINT) [10]. SPRINT randomly assigned participants to an SBP target of <120 mmHg or <140 mmHg. Patients with an estimated glomerular filtration rate <20 mL/min/1.73 $m^2$, 24-h urine protein excretion >1 g, on dialysis or kidney transplant recipients were excluded. In the subgroup of patients with CKD, the achieved BP at 1 year was 123.3 ± 0.4/66.9 ± 0.3 mmHg versus 136.9 ± 0.4/73.8 ± 0.3 mmHg [11]. In patients with CKD, after a median follow-up of 3.3 years, the hazard ratio for the primary composite cardiovascular outcome was 0.81 [95% confidence interval (CI) 0.63–1.05] and for all-cause death it was 0.72 (95% CI 0.53–0.99), but patients with an SBP target of <120 mmHg lost GFR at a 47% faster rate (–0.47 versus –0.32 mL/min/1.73 $m^2$/year; $P < 0.03$). SPRINT measured BP in a standardized manner (Table 1). However, in SPRINT, there were four different groups of patients with regard to the presence of the doctor or study personnel during rest or during the actual BP readings (attended versus unattended BP) [12], a factor that can directly influence the levels of measured BP [13]. These four groups displayed no homogeneity with regard to the primary study outcome, a fact that makes the interpretation of the SPRINT results quite difficult.

**Table 1. Standardized conditions for office BP measurement**

| Conditions | SPRINT[a] | 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline reprinted on KDIGO 2021 | ESC 2021 |
|---|---|---|---|
| Patient preparation | • Sit quietly for 5 min, with back supported, legs uncrossed, in a quiet room<br>• Seated comfortably, feet flat on the floor with their back supported<br>• Ideally they should not have smoked or had any caffeine within the last 30 min prior to the BP determinations<br>• During the rest and BP measurement periods, the participants were not completing questionnaires, talking or texting<br>• Preferably, a chair with arm support for BP measurement or a chair and table. Table must provide for a comfortable resting posture of the arm with midcuff at heart level | • Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min<br>• The patient should avoid caffeine, exercise and smoking for at least 30 min before measurement<br>• Ensure patient has emptied his/her bladder<br>• Neither the patient nor the observer should talk during the rest period or during the measurement<br>• Remove all clothing covering the location of cuff placement<br>• Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria | • Patients should be seated comfortably in a quiet environment for 5 min before BP measurements<br>• Quiet room with comfortable temperature<br>• No smoking, caffeine, food or exercise for 30 min before measurement<br>• Remain seated and relaxed for 3–5 min<br>• No talking by patient or staff during or between measurements<br>• Sitting with back supported by chair<br>• Legs uncrossed, feet flat on floor<br>• Bare arm resting on table; mid-arm at heart level |
| BP measurement technique | • Preferred method: automated device<br>• Elbow and forearm resting comfortably on the armrest or table<br>• Proper cuff size<br>• Use right arm or arm with higher BP<br>• Bare arm | • Use a BP measurement device that has been validated and ensure that the device is calibrated periodically<br>• Support the patient's arm (e.g. resting on a desk)<br>• Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum)<br>• Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used<br>• Either the stethoscope diaphragm or bell may be used for auscultatory readings | • Office BP should be measured in standardized conditions using validated auscultatory or (semi)automatic devices<br>• Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients but use larger and smaller cuffs for larger (arm circumference >32 cm) and smaller (arm circumference <26 cm) arms, respectively<br>• The cuff should be positioned at the level of the heart with the back and arm supported, to avoid muscle contraction and isometric-exercise-dependent increases in BP<br>• Repeated automated office BP readings may improve the reproducibility of BP measurement. If the patient is seated alone and unobserved, an unattended automated office BP measurement may decrease or eliminate the 'white-coat' effect, and unattended automated office BP measurements are usually lower than conventional office BP measurements and more similar to ambulatory daytime BP or home BP values |

**Table 1. Continued.**

| Conditions | SPRINT[a] | 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline reprinted on KDIGO 2021 | ESC 2021 |
|---|---|---|---|
| Take the proper measurements needed for diagnosis and treatment of elevated BP | • Seated BP and pulse measured three times<br>• If large differences between the three measurements, one more set of measurements should be performed | • At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings<br>• Separate repeated measurements by 1–2 min<br>• For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff pressure 2 mmHg/s and listen for Korotkoff sounds | • Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference<br>• Three BP measurements should be recorded, 1–2 min apart, and additional measurements if the first two readings differ by >10 mmHg<br>• Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patients with AF, in whom manual auscultatory methods should be used, as most automated devices have not been validated for BP measurement in AF |
| Properly document accurate BP readings | • Record SBP, DBP and pulse readings obtained at each of the three readings and the average of the three readings | • 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<br>• Note the time of the most recent BP medication taken before measurements | • When using auscultatory methods, use phase 1 and 5 (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively |
| Average the readings | • The average of the three measurements constitutes the visit BP | Use an average of two or more readings on two or more occasions to estimate the individual's BP | • BP is recorded as the average of the last two BP readings |
| Provide BP readings to patient | | • Provide patients with the SBP/DBP readings verbally and in writing | |
| Additional measurements | • Standing (orthostatic) BP: after seated determinations, participants were asked to stand. Beginning when their feet touch the floor, BP should be taken 1 min later in the same arm used for the seated measurements, using the BP device. The BP change was calculated using the standing measurements minus the mean of the seated measurements | | • Record heart rate and use pulse palpation to exclude arrhythmia<br>• Measure BP 1 and 3 min after standing from the seated position in all patients at the first measurement to exclude orthostatic hypotension<br>• Lying and standing BP measurements should also be considered in subsequent visits in older people, in people with DM and in other conditions in which orthostatic hypotension may frequently occur. Initial orthostatic hypotension may occur <1 min after standing and may be difficult to detect with conventional measurement techniques |

AF: atrial fibrillation; DM: diabetes mellitus.

[a]However, in SPRINT there were four different groups of patients with regard to the presence of the doctor or study personnel during rest or during the actual BP readings (attended versus unattended BP) [12], a factor that can directly influence the levels of measured BP [13]. These four groups displayed no homogeneity with regard to the primary study outcome, a fact that makes interpretation of the SPRINT results quite difficult.

Patients with eGFR <20 mL/min/1.73 $m^2$, 24-h urine protein excretion >1 g, on dialysis or kidney transplant recipients were excluded from SPRINT.

**Table 2. Scientific societies that endorse the ESC 2021 SBP target of <140–130 mmHg for people with CKD**

| |
|---|
| European Association for the Study of Diabetes (EASD) |
| European Atherosclerosis Society (EAS) |
| European Heart Network (EHN) |
| European Renal Association (ERA) |
| European Society of Hypertension (ESH) |
| European Stroke Organization (ESO) |
| European Federation of Sports Medicine Association (EFSMA) |
| European Geriatric Medicine Society (EuGMS) |
| International Diabetes Federation Europe (IDF Europe) |
| International Federation of Sport Medicine (FIMS) |
| International Society of Behavioural Medicine (ISBM) |
| International Society of Gender Medicine (IGM) |
| World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA) Europe |

For kidney transplant recipients, BP targets were only modestly modified to <130 mmHg SBP and <80 mmHg DBP. Again, KDIGO 2021 provides no recommendations for patients on dialysis.

From 2018 ESC/European Society of Hypertension (ESH) Clinical Practice Guidelines for the Management of Arterial Hypertension to 2021 ESC Clinical Guidelines on cardiovascular disease prevention in clinical practice (endorsed by 12 European scientific societies, including the ESH) (Table 2).

The 2018 ESC/ESH guidelines contained a complex set of suggestions to determine whether to start therapy for hypertension, based on age [13]. Thus patients with CKD >80 years of age would not start pharmacological therapy for hypertension until their SBP was ≥160 mmHg or DBP ≥90 mmHg. In contrast, in younger patients, the threshold to start therapy was 140/90 mmHg. However, once therapy was started, the target was the same for adult CKD patients of all ages: 130–139 mmHg SBP and 70–79 mmHg DBP (Fig. 1A). The CKD target was higher than that for younger (18−65 years) people in the general population or for diabetics, in whom the target was 120–129 mmHg SBP, with a remark that it should not be <120 mmHg. This discrepancy in the target BP for patients with CKD versus those with diabetes or individuals from the general population was not supported by any kind of observational or clinical trial evidence.

ESC 2021 decreases differential SBP thresholds at which to initiate therapy based on age but still recommends a higher SBP target (130–139 mmHg) in adults with CKD of any age (Fig. 1B) than in younger people in the general population or in diabetics (120–130 mmHg if <70 years of age and 130–139 mmHg for those ≥70 years of age) [7]. A more subtle change to the 2018 document deemed a lower SBP acceptable in CKD, if tolerated. Additionally, the DBP target is universally <80 mmHg for all treated patients, independent of any associated comorbidity. The proposed BP assessment method is similar to that proposed by KDIGO 2021 (Table 1), ruling out that methodological differences explain the different BP targets.

ESC 2021 does not provide the rationale for target BP values in people with CKD and does not mention the SPRINT subanalysis of participants with CKD or the 2021 KDIGO guideline on BP and CKD, although it does cite other KDIGO guidelines on lipids and diabetes, one of which was accessed in June 2021 [7]. However, it does explain changes from the prior 2016 ESC prevention and 2018 ESC/ESH hypertension guidelines in the cut-off for identifying who is 'older' (from 65 to 70 years for reasons of consistency with other parts of the current guidelines), in BP targets for the elderly (based on the SPRINT subanalysis of people ≥75 years of age and others) and the rationale for BP targets for people with lower extremity artery disease [13–15].

## FUTURE DIRECTIONS

In conclusion, it is highly disappointing that two reference guideline bodies drastically disagree, without a detailed rationale, on guidance on such basic and universal items as BP targets for the 850 million people with CKD (Box 1) [16–18]. Strong bidirectional and/or multidirectional communication channels should be established between guideline bodies to prevent the future occurrence of such blatant discrepancies. The individualism that has presided over guidelines generation should become a thing of the past. In a worst-case scenario, guideline bodies should agree to disagree in a common document in which each guideline body explains the rationale for their choice of BP targets that may result from assigning different weights to different aspects of the evidence or impact that may range from emphasizing safety or efficacy, cost or implementation aspects, among others. These considerations should be clearly stated in the common document, helping national scientific societies, healthcare providers and payers and individual physicians to draw their own conclusions. Otherwise, we run the risk of compromising implementation, given the doubts raised by such different targets, and providing ammunition for guidelines and science skeptics. In a best-case scenario, consensus is reached on a single BP target. This may be facilitated by a body of experts in the field of hypertension in CKD representing and shared by different societies (Fig. 2).

### Box 1. Key questions and answers regarding the discrepancy in SBP targets between 2021 KDIGO and 2021 ESC guidelines that provide guidance on BP targets for people with CKD

Do the new guidelines cite different evidence for their BP targets in people with CKD?

- No. In fact, the 2021 ESC guideline does not cite any evidence to support its BP targets for people with CKD. However, the 2018 ESC/ESH guideline states that: 'the evidence with respect to BP targets in patients with CKD is complex' and cites a 2003 meta-analysis, a 2011 systematic review and a 2014 retrospective study [16–18]. While KDIGO 2021 cites evidence from SPRINT to support the new suggested SBP target, 2021 ESC acknowledges SPRINT for recommendations for people who do not have CKD but does not mention SPRINT in the discussion of BP targets for CKD.

Do the new guidelines recommend different methods to measure office BP?

- Not really. Standardized office BP measurement is the recommended method for evaluating BP in both (Table 1).

Does the most recent guideline (ESC 2021) acknowledge the guidelines published earlier in the same year (KDIGO) and discuss why they do not agree on the same BP targets?

- No.

Does the European guideline offer some explanation as to why the BP targets recommended by European scientific societies should differ from those suggested for the global population of people with CKD by KDIGO?

- No. In the 2021 ESC guidelines, there is no discussion on the evidence for BP targets in CKD.

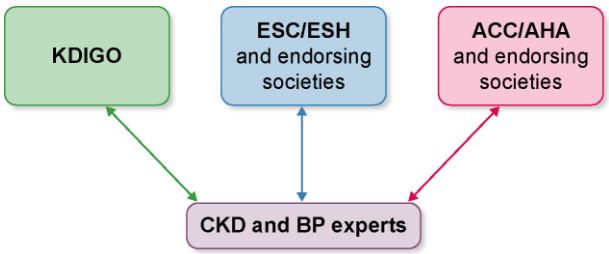


**FIGURE 2:** Proposal to limit the disagreement between clinical practice guidelines on BP targets for people with CKD. A shared group of experts who have an expertise in both hypertension and in CKD may represent the different societies/guideline bodies. These experts would be identified and selected based on internal rules by each guideline body and may undergo turnover as per these rules. The rules of engagement of this committee of experts may be decided in the future, e.g. whether consensus would be needed between all experts for a specific guideline from a single guideline body, but at least the integrated discussion between experts representing different guideline bodies would contribute to reach consensus between guidelines that limits the most egregious disagreements, or at least, to provide a rationale for choosing certain BP targets and not others.

## AUTHORS' CONTRIBUTIONS

All authors brainstormed for the concept of the manuscript. S.C. and A.O. generated the draft. All authors provided critical insights to the draft and approved the final version.

## CONFLICT OF INTEREST STATEMENT

A.O. has received consultancy or speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi Genzyme, Menarini, Kyowa Kirin, Alexion, Idorsia, Chiesi, Otsuka, Novo Nordisk and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of CKD and electrolytes. A.O. is the Editor-in-Chief of *CKJ*. P.S. has received consultancy or speaker fees or travel support from Elpen, Genesis Pharma, AstraZeneca, Menarini, Innovis Pharma, Winmedica, Bayer, Amgen, Boehringer Ingelheim, Winmedica and Genesis Pharma. S.C. has participated in an advisory board for Otsuka.

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