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CKJ Review

CKJ REVIEW

Guidelines for the management of hypertension in CKD patients: where do we stand in 2024?

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ABSTRACT

Until recently, major bodies producing guidelines for the management of hypertension in patients with chronic kidney disease (CKD) disagreed in some key issues. In June 2023, the European Society of Hypertension (ESH) published the new 2023 ESH Guidelines for the management of arterial hypertension a document that was endorsed by the European Renal Association. Several novel recommendations relevant to the management of hypertension in patients with CKD appeared in these guidelines, which have been updated to reflect the latest evidence-based practices in managing hypertension in CKD patients. Most of these are in general agreement with the previous 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines—some reflect different emphasis on some topics (i.e. detailed algorithms on antihypertensive agent use) while others reflect evolution of important evidence in recent years. The aim of the present review is to summarize and comment on key points and main areas of focus in patients with CKD, as well as to compare and highlight the main differences with the 2021 KDIGO Guidelines for the management of blood pressure in CKD.

Keywords: albuminuria, blood pressure, chronic kidney disease, guidelines, hypertension

INTRODUCTION

Hypertension is the most common comorbidity accompanying chronic kidney disease (CKD), affecting about 80%–85% of individuals with CKD; its prevalence progressively increases with advancing CKD stages, reaching 95% in individuals with CKD category G4 or G5 before initiation of kidney replacement therapy [1, 2]. Elevated blood pressure (BP) is a strong and independent risk factor for development of CKD and progression to end-stage kidney disease (ESKD) [3, 4]. Hypertensive kidney disease *per se* is the second most common known cause of ESKD, after diabetic kidney disease [5, 6]. In addition, hypertension is also a typical consequence of many primary and secondary kidney diseases. Thus, high BP is by far the most common modifiable factor for CKD progression. Treatment-resistant hypertension, elevated nighttime BP and masked hypertension are common in patients with CKD, and are associated with lower eGFR, higher levels of albuminuria, progression to ESKD and hypertension-mediated organ damage (HMOD) [7–13], as well as with adverse cardiovascular (CV) outcomes [11–13].

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In June 2023, the European Society of Hypertension (ESH) published the new 2023 ESH Guidelines for the management of arterial hypertension [14], a document that was endorsed by the European Renal Association (ERA). The aim of the present review is to summarize and comment on the key points and main areas of focus in patients with CKD, as well as to compare and highlight the main differences with the previous 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for the management of BP in CKD (Table 1) [15]. The different evidence grading systems used in the Guidelines are presented in Supplementary data, Table S1.

DEFINITION OF HYPERTENSION AND BLOOD PRESSURE MEASUREMENTS

The 2023 ESH Guidelines define hypertension as the presence of repeated office systolic BP (SBP) values ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg [14]. The classification of office BP (optimal, normal, high normal) and definition of hypertension grades (Grade 1, 2 and 3 and isolated systolic and diastolic hypertension) are similar to previous guidelines [16].

Office BP measurements remain the first choice for diagnosis and management of hypertension. In both the 2023 ESH and the 2021 KDIGO guidelines, the use of standardized office BP readings are recommended, as they allow uniformity of the setting and the conditions of measurement, the patient position, the device, the measurement schedule and the interpretation of the results [14, 15]. The respective recommendations on proper office BP measurements are presented in Table 2.

In 2023 ESH Guidelines, the use of out-of-office BP measurements with ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) is strongly encouraged [14]. Both HBPM and ABPM are recommended to be used more extensively and complementarily to office BP readings for the management of high BP CKD, due to the increased prevalence of specific phenotypes (i.e. masked hypertension and nocturnal hypertension, abnormal dipping status) [9, 17–19] that apply as specific indications for HBPM and ABPM, respectively [Class of Recommendation (CoR) I, Level of Evidence (LoE) B] [14]. The corresponding ABPM and HBPM values used for hypertension diagnosis and management are presented in Supplementary data, Table S2. A similar suggestion for more extensive use of ABPM and HBPM for patients with CKD, if available, was also present in brief in the 2021 KDIGO Guidelines [15].

Primary advantages of ABPM include better reflection of BP readings in real-life scenarios, possible discrimination of various BP patterns such as white-coat hypertension or masked hypertension, morning BP surge or nighttime dipping pattern, or apparent or true resistant hypertension [20, 21]. Nevertheless, ABPM may not be suitable for population-based use in clinical practice due to limited availability in primary care centers, high cost and potential discomfort for patients especially during sleep [22].

DIAGNOSIS OF CKD AND HYPERTENSION-MEDIATED ORGAN DAMAGE

The 2023 ESH Guidelines list assessment of serum creatinine, estimation of glomerular filtration rate (eGFR) with the 2009 CKD-Epidemiology Collaboration formula [23] and evaluation of urine albumin:creatinine ratio (ACR) as two of the three (the third being 12-lead electrocardiogram) basic tests to assess HMOD and stage hypertension [14]. The document endorses the currently universally used definition for CKD, involving an eGFR <60 mL/min/1.73 m^2 at any level of albuminuria or an ACR >30 mg/g at any levels of eGFR persisting for more than 3 months and the current nomenclature for albuminuria, to highlight the risk associated to albuminuria increase, i.e. (i) normal/mildly increased, ACR <30 mg/g (A1, formerly termed normoalbuminuria); (ii) moderately increased, ACR 30–300 mg/g (A2, formerly termed microalbuminuria); and (iii) severely increased, ACR >300 mg/g (A3, formerly termed macroalbuminuria) [24]. In addition, kidney ultrasound is listed among the extensive examinations for HMOD, due to its low cost, widespread availability and useful information on renal morphology, while the role of spectral Doppler ultrasound is suggested as initial screening for renovascular disease [14].

However, integration of KDIGO CKD categories into 2023 ESH Guidelines is not full. The current international consensus definition of CKD (KDIGO 2012 and 2024) defines CKD as abnormalities of kidney structure or function, present for >3 months, with implications for health [24, 25]. CKD categories are recognized based on GFR (G categories G1 through G5) and on albuminuria (A categories A1 through A3). The combination of G and A categories provides an assessment of risk of CKD progression, all-cause or CV death, and acute kidney injury, that have been labeled mild, moderate (high CV risk) and severe CKD (very high CV risk) by the European Society of Cardiology in agreement with the ERA [26]. Category A2 [urinary ACR (UACR) 30–300 mg/g] or A3 (UACR >300 mg/g) albuminuria are by themselves diagnostic of CKD, even when GFR is preserved. The ESH Guidelines remain anchored in the 2002 Kidney Disease Outcomes Quality Initiative (K/DOQI) [27] nomenclature of CKD stages 3 through 5 based on GFR values, and have not yet adopted the KDIGO nomenclature of G and A categories. In this regard, they do not explicitly state that A2 or A3 albuminuria are diagnostic of CKD, although it is stated that CKD is classified according to eGFR and the presence and amount of albuminuria [14]. Rather, albuminuria is considered a criterion to assess HMOD [14]. A problem of the HMOD nomenclature is that it can convey the notion that CKD is secondary to hypertension, which may not always be the case.

TREATMENT OF HYPERTENSION IN CKD

Initiation of treatment

The 2021 KDIGO Guidelines did not specify thresholds for initiating antihypertensive medication [15]. As in previous versions, the 2023 ESH Guidelines set specific BP thresholds, based on age and CV risk. It is recommended that in patients aged 18–79 years, the office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP (CoR I, LoE A) [14]. The exception to this rule is adult patients with a history of CVD, predominantly coronary artery disease, in whom drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg) (CoR I, LoE A); the clinical nephrologists should not overlook that many CKD patients fall into the latter category and should be treated accordingly. In patients aged ≥80 years, the recommended office SBP threshold for initiation of drug treatment is 160 mmHg (CoR I, LoE A), but a lower SBP threshold of 140–159 mmHg may be considered (CoR II, LoE B).

Treatment targets

The BP targets of treatment is the area where the two guidelines under discussion do not meet. This is mostly due to the recommendation for an SBP target of <120 mmHg for patients

Table 1: Recommendations relevant to hypertension in CKD patients in the 2021 KDIGO and 2023 ESH Guidelines (the evidence grading systems used are displayed in Supplementary data, Table S1).

Therapeutic area	2021 KDIGO	2023 ESH	Agreement/differences
Treatment initiation		In patients 18–79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP, except for patients with a history of CVD, predominantly coronary artery disease, in whom drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg) (CoR I, LoE A)	Only in 2023 ESH
BP targets in CKD	In all adults with high BP and CKD the treatment target to lower standardized office SBP <120 mmHg (2B) In adult KTRs, standardized office BP should be lowered to <130/80 mmHg (not graded)	In all patients with CKD the primary goal is to lower office BP to <140/90 mmHg (CoR I, LoE A) In most patients with CKD (especially, young patients, patients with an ACR ≥300 mg/g, high CV risk patients) office BP should be lowered to <130/80 mmHg if tolerated (CoR II, LoE B) In kidney transplant patients with hypertension, office BP should be lowered to <130/80 mmHg (CoR II, LoE B) In patients with CKD, a BP target of <120/70 mmHg is not recommended (CoR III, LoE C)	• CKD: disagreement • KTRs: in general agreement
Antihypertensive drug use in CKD	• Starting an ACEi or ARB in all patients with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without DM, as well as in all diabetics with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) is recommended (1B) • Starting RASi (ACEi or ARB) in patients with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes, is suggested (2C)	An ACEi or an ARB, titrated to the maximum tolerated doses is recommended for patients with CKD and moderate (UACR 30 to 300 mg/g) or severe (UACR >300 mg/g) albuminuria (CoR I, LoE A) Step 1 of treatment includes combination of an ACEi or ARB + CCB or T/TL diuretic if eGFR ≥30 mL/min/1.73 m^2, or combination of an ACEi or ARB + CCB or loop diuretic if eGFR <30 mL/min/1.73 m^{2a} Step 2 of treatment includes combination of the 3 above drug classes to maximum tolerated doses Step 3 of treatment includes addition of spironolactone if eGFR ≥30 mL/min/1.73 m^2 and potassium within the normal range or chlortalidone if eGFR <30 mL/min/1.73 m^{2a}	• ACEi/ARB use: in general agreement • Specific algorithms and steps: only in 2023 ESH
Kidney and heart protection		SGLT2i are recommended for patients with diabetic and nondiabetic CKD, if eGFR is at least 20 mL/min/1.73 m^2 (CoR I, LoE A) The non-steroidal MRA finerenone is recommended in patients with CKD and albuminuria associated with T2DM, if eGFR is at least 25 mL/min/1.73 m^2 and serum potassium <5.0 mmol/L (CoR I, LoE A)	Recommendations on use of drugs to protect kidney and heart more detailed in 2023 ESH Recommendations on use of drugs to protect kidney and heart more detailed in 2023 ESH
Potassium management	Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi (not graded)	In CKD patients with hyperkalemia a potassium binder can be used to maintain potassium <5.5 mmol/L) to allow continuation of treatment with a RAS blocker or a MRA to continue (CoR II, LoE B)	In general agreement—use of potassium binders more detailed in 2023 ESH
Resistant hypertension	MRAs are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR (not graded)	- In patients with CKD stage 1–3 and true-resistant hypertension step 3 of treatment includes addition of spironolactone (preferred) or other MRA. B-Blockers, alpha-1 blockers or centrally actings agents can be used alternatively (CoR II, LoE B) - In patients with CKD stage 4–5[a] and true-resistant hypertension, step 3 of treatment includes the addition of chlortalidone (preferred) or other T/TL diuretic. B-Blockers, alpha-1 blockers or centrally actings agents can be used alternatively.(CoR II, LoE B)	In partial agreement

[a]Excludes patients with CKD G5 on dialysis.

T/TL diuretic: thiazide or thiazide-like diuretic.

Table 2: Standardized conditions for office BP measurement.

	2021 KDIGO	2023 ESH	Agreement/Differences
Patient preparation	– Have the patient relax, sitting in a chair (feet on floor, back supported) for > 5 min – The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement – Ensure patient has emptied his/her bladder – Neither the patient nor the observer should talk during the rest period or during the measurement – Remove all clothing covering the location of cuff placement – Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria	– Patients should be seated and relaxed in a quiet room for 3-5 min before BP measurements. – Conditions – Quiet room with comfortable temperature. – No smoking, caffeine, food, drug intake or exercise for 30 min before measurement. – Remain seated and relaxed for 3–5 min. – No talking during or between measurements. Posture – BP should be measured on a bare arm with the use of appropriate cuff size – Sitting with back supported by chair. – Legs uncrossed, feet flat on floor. – Arm resting on table; mid-arm at heart level.	In general agreement, except for: – Avoidance of food intake before the measurement (only in 2023 ESH) – Bladder emptying (only in 2021 KDIGO)
BP measurement technique	– Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically – Support the patient's arm (e.g, resting on a desk) – Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum) – 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 – Either the stethoscope diaphragm or bell may be used for auscultatory readings	– Office BP should be measured in standardized conditions using validated (www.stridebp.org) automatic electronic, upper-arm cuff devices. Hybrid manual auscultatory devices with LCD or LED display, or digital countdown, or shock-resistant aneroid devices can be used if automated devices are not available. Cuffless BP devices should not be used for the evaluation or management of hypertension in clinical practice – BP should be measured on a bare arm with the use of appropriate cuff size (selected according to the arm circumference of each individual (a single cuff cannot fit the range of arm sizes of all patients). For manual auscultatory devices, a cuff with an inflatable bladder length and width of 75–100% and 37–50% of the individual middle upper arm circumference, respectively, is required. For automated electronic devices, the cuff size should be selected according to the device instructions) – 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	In general agreement, except for: – preferrable BP measurement devices (1st choice in 2023 ESH automated electronic)
Take the proper measurements needed for diagnosis and treatment of elevated BP	– At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings – Separate repeated measurements by 1-2 min – For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds	– At the initial office visit, BP should be measured in both arms, ideally with electronic devices that can measure them simultaneously. An interarm SBP difference >10 mmHg must be confirmed with repeated measurements (a consistent interarm SBP difference > 15-20 mmHg should prompt further investigation for arterial disease). Use the arm with the higher value as the reference. – Three BP measurements should be recorded, 1-2 min apart, the average of the last two should be referred to as the representative value. – diagnosis of hypertension should not be based on a single office visit, unless office BP indicates grade 3 hypertension (180/110 mmHg) or the patient is at high or very high risk based on the presence of HMOD or CVD. In the vast majority of patients, an accurate evaluation of office BP requires at least two to three office visits at 1– 4-week intervals (depending on the BP level and CV risk).	In general agreement, except for: – number of BP recordings – requirement for repeated visits in 2023 ESH

Table 2: Continued

	2021 KDIGO	2023 ESH	Agreement/Differences
Properly document accurate BP 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 – Note the time of most recent BP medication taken before measurements	– When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.	In general agreement, except for: – noting the time of BP medication intake in 2021 KDIGO
Average the readings	Use an average of ≥ 2 readings on ≥ 2 occasions to estimate the individual's level of BP	– Triplicate measurements should be taken and the average of the last two should be referred to as the representative value.	Disagreement
Provide BP readings to patient	Provide patients with the SBP/DBP readings verbally and in writing		Only in 2021 KDIGO
Additional measurements		– In older persons (>65 years of age), treated hypertensive patients (especially very old patients), diabetic patients, patients with neurodegenerative disorders, or with symptoms suggesting postural hypotension, BP should also be measured 1 and 3 min after standing for detecting orthostatic hypotension.	Only in 2023 ESH

with CKD included in the 2021 KDIGO guidelines [15], with the specific notion that this refers to standardized office BP readings [15, 28]. As previously discussed, this recommendation, based on Systolic Blood Pressure Intervention Trial (SPRINT) results, was much different from any other relevant recommendation in major guideline documents [29, 30].

The 2023 ESH Guidelines provide a detailed discussion on the issue of most protective BP targets in patients with CKD, recognizing that for more than a decade, there has been considerable debate in the scientific literature in this field [14]. Overall, as shown in Fig. 1, it is recommend that in all patients with CKD the primary goal is to lower office SBP to <140 mmHg and DBP <90 mmHg (CoR I, LoE A) and that in most CKD patients (young patients, patients with a urine ACR ≥300 mg/g, high CV risk patients) office BP may be lowered to <130/80 mmHg, if tolerated (CoR II, LoE B).

Current evidence in the field derives from a few studies (Table 3); proper randomized controlled tials (RCTs) comparing different BP targets (i.e. SBP <140 vs <130 mmHg) in CKD population with different kidney function and albuminuria levels, achieving corresponding BP levels during follow-up and being powered to investigate hard outcomes are still missing. In the Modification of Diet in Renal Disease (MDRD) study, the two arms (low and usual BP target) showed similar projected GFR decline in 3 years, as well as risk of ESKD and death [31]; secondary analyses showed that patients with proteinuria >1 g/24 h in the low-target group had decrease in proteinuria levels and slower GFR decline over time than patients in the usual-target group [32]. Similarly, in the African American Study on Kidney Disease (AASK) no difference in outcomes between BP target groups was observed in the overall population [33]; however, in a *post hoc* analysis, low BP was again associated with better kidney outcomes in patients with proteinuria >1 g/24 h [34]. A subsequent analysis that combined trial and cohort periods of both these studies, showed that low target BP was associated with lower risk for ESKD and mortality in the total population; and this effect was mainly driven by changes in patients with urine protein:creatinine ratio >0.44 g/g (urine ACR roughly >200 mg/g) [35].

The SPRINT randomized 9361 non-diabetic, hypertensive patients to intensive or standard treatment (target SBP <120 vs <140 mmHg, respectively) [36]. From the total population, 28% had CKD (eGFR 20–60 mL/min/1.73 m^2), but very few had albuminuria A2 or A3, as individuals with proteinuria >1 g/24 h or >1 g/g were excluded. In the overall trial, the primary composite CV endpoint, CV and total mortality were significantly lower in the intensive than in the standard-treatment group, but kidney outcomes did not differ between groups. In a sub-analysis of the SPRINT in patients with CKD [37], in whom achieved BP was 123.3 ± 0.4/66.9 ± 0.3 mmHg in the intensive group (vs 136.9 ± 0.4/73.8 ± 0.3 mmHg in the standard group), no difference between groups in the primary outcome nor in the prespecified kidney outcome were detected, but mortality rate was lower in the intensive BP arm. The above results must be cautiously interpreted, as the SPRINT trial was not designed or powered to study kidney outcomes, and as such resulted in an extremely small number of kidney events (15 vs 16 in the two groups).

With regards to persons with diabetes mellitus (DM) and CKD, the 2023 ESH Guidelines identify no direct evidence to answer the question of optimal target BP. Older studies, including the United Kingdom Prospective Diabetes Study (UKPDS) [38] and the sub-analysis of participants with DM of the Hypertension Optimal Treatment (HOT) [39] trials offered insight on the DBP

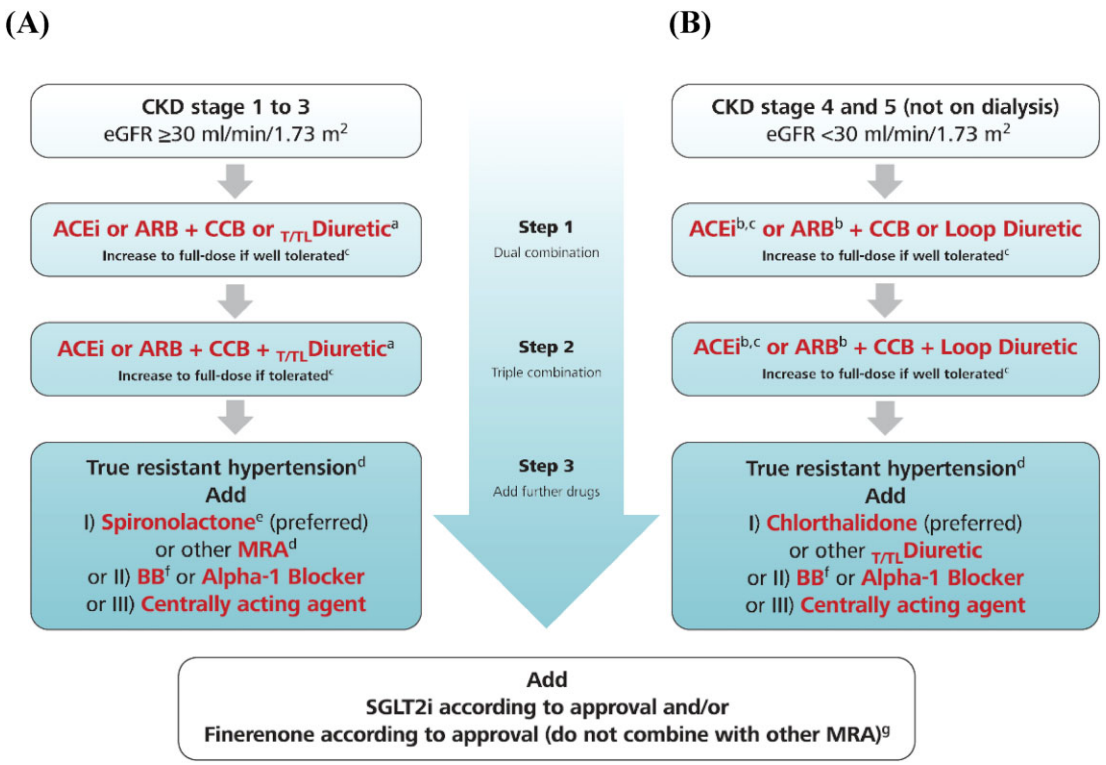

Figure 1: BP-lowering therapy in patients with hypertension and CKD. (**A**) Therapy for CKD G1–G3 (eGFR ≥30 mL/min/1.73 m²). (**B**) Therapy for CKD G4–G5 (eGFR <30 mL/min/1.73 m²) not on dialysis. (a) Transition from T/TL diuretic to loop diuretic should be individualized in patients with eGFR <45 mL/min/1.73 m². (b) Cautious start with low dose. (c) Check for dose adjustment according to renal impairment for drugs with relevant renal excretion rate. (d) When SBP is ≥140 mmHg or DBP is ≥90 mmHg provided that: maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a T/TL diuretic were used, adequate BP control has been confirmed by ABPM or by HBPM if ABPM is not feasible, various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded. (e) Caution if eGFR <45 mL/min/1.73 m² or serum potassium >4.5 mmol/L. (f) Should be used at any step as guideline directed medical therapy in respective indications or considered in several other conditions. (g) SGLT2i and finerenone should be used according to their approval for CKD treatment (from [14], with permission). T/TL: thiazide/thiazide-like.

target, since they randomized in different on-treatment DBP levels. The Action to Control CardiOvascular Risk in Diabetes (ACCORD)-BP trial randomized high-risk patients with T2DM to target SBP <120 or <140 mmHg [29, 40], but excluded individuals with serum creatinine >1.5 mg/dL, thus offering very little insight to the optimal BP in patients with CKD and DM. *Post hoc* analyses of major kidney outcome trials in DM [41, 42] showed benefits when SBP is reduced <130 mmHg, but not <120 mmHg. In a recent pooled analysis of the AASK, ACCORD, MDRD and SPRINT trials, all-cause mortality showed a tendency to a reduction with intensive treatments (BP <130 mmHg) [43]. In another meta-analysis of 18 RCTs ($n = 15\,924$ CKD patients), more intensive vs less intensive BP control (SBP 132 vs 140 mmHg) was associated with 14% lower risk of all-cause mortality [44].

Following the above, and in contrast to the 2021 KDIGO Guidelines, the 2023 ESH Guidelines indicate that a recommendation to target office SBP <120 mmHg in persons with CKD cannot be made (CoR III, LoE C). The reasoning for this is that the only relevant findings are delivered by a single, hypothesis-generating sub-analysis of the SPRINT trial, which included only a narrow range of the CKD population (non-diabetic, non-proteinuric CKD with eGFR 20–60 mL/min/1.73 m² without prior stroke) and had both the primary and the main kidney outcome (with only few events) being not significantly different between groups. In addition, and although SPRINT used a trial-specific automated BP measurement technique, the universal methodology followed during its execution was no consistent (no attendance, attendance during rest periods or readings period, or both), a fact that influenced the observed differences in outcomes [45]. It is also known that unattended SBP (assessed in about 42% of SPRINT participants) and conventional office SBP measurement can vary substantially in the individual (between 5 and 15 mmHg) [46].

The 2023 ESH Guidelines acknowledge that these recommendations have a number of limitations: (i) none of the trials comparing different BP targets included patients with diabetes and CKD, thus current evidence cannot be readily extrapolated to this subpopulation; (ii) MDRD and AASK trials randomized participants to different mean BP levels, which cannot be readily extrapolated to SBP and DBP values; (iii) MDRD and AASK trials recruited patient populations of a relatively young age (mean age 51.7 and 54.6 years, respectively), and thus, their findings cannot be readily extrapolated to older patients with CKD; and (iv) even for the long-term observational analyses, the benefits associated with lower BP targets were mainly apparent in individuals with proteinuria.

Lifestyle interventions

The 2023 ESH Guidelines highlight a list of lifestyle interventions that are recommended in all patients with hypertension, including those with CKD [14]; these are similar to the lifestyle

Table 3: Main characteristics and outcomes of major clinical trials and their long-term observational analyses including CKD patients that compared a low to a usual BP target.

Studies	Population	Type of analysis/comparison	Follow-up	Main results
MDRD [31]	Study A: 585 patients (GFR 25–55 mL/min/1.73 m^2); Study B: 255 patients (GFR 13–24 mL/min/1.73 m^2); mean age 51.7 years	Usual BP goal [MAP <107 mmHg for patients ≤60 years (roughly corresponding to <140/90) and <113 for patients ≥61 years] compared with a low goal [MAP <92 mmHg for patients ≤60 years (corresponding to <125/75) and <98 for patients ≥61 years]	2.2 years (mean)	No difference between groups in the projected GFR decline in 3 years (10.7 vs 11.5 mL/min/1.73 m^2), and the risk of ESKD and death (0.85; 95% CI 0.60–1.22 for low BP arm)
MDRD trial and cohort phase analysis [109]		MDRD trial period (1989–1993) and a cohort period (1993–2000) during which no specific target BP was recommended	10.7 years (median)	Low target BP was associated with reduced risk for ESKD (adjusted HR 0.68; 95% CI 0.57–0.82) and the composite of ESKD or death (HR 0.77; 95% CI 0.65–0.91), compared with usual target BP. The *P*-value for interaction of target BP with proteinuria was 0.09 for ESKD and 0.08 for the composite outcome
AASK [33]	1094 African-Americans with hypertensive CKD (GFR 20–65 mL/min/1.73 m^2, mean proteinuria 0.6 g/day); mean age 54.6 years	Usual BP goal (MAP 102–107) compared with a low BP goal (MBP ≤92 mmHg, corresponding to <125/75)	3.8 years (median)	No difference between groups in mean GFR slope (–2.21 ± 0.17 versus –1.95 ± 0.17 mL/min/1.73 m^2 per year; $P = .24$), or the composite outcome of reduction in GFR by 50% or more (or ≥25 mL/min/1.73 m^2), ESKD or death (risk reduction for intensive BP group 2%; 95% CI –22% to 21%; $P = .85$)
AASK trial and cohort phase analysis [110]		Trial period and a subsequent cohort period in which the BP target was <130/80 mmHg	Total follow-up 8.8–12.2 years	No difference between groups in the risk of the composite outcome of doubling of serum creatinine, ESKD or death (HR in low-BP group, 0.91; 95% CI 0.77–1.08). Significant interaction with the baseline level of proteinuria ($P = .02$). For patients with urine protein:creatinine ratio (UPCR) >0.22 mg/g, HR 0.73; 95% CI 0.58–0.93; for patients with UPCR ≤0.22, HR 1.18; 95% CI 0.93–1.50
MDRD and AASK trial and cohort phases combined [35]	1907 patients (mean age of 53 years, median GFR of 40 mL/min/1.73 m^2 and median urine protein excretion of 0.12 g/day at baseline	Trial period and subsequent cohort periods of both trials	14.9 years (median)	Low target BP was independently associated with lower risk of ESKD (HR 0.88; 95% CI 0.78–0.99) and death (HR 0.85; 95% CI 0.75–0.97). For patients with UPCR >0.44 g/g risk of ESKD (HR 0.77; 95% CI 0.64–0.92) and death (HR 0.77; 95% CI 0.62–0.96). For patients with UPCR <0.44 g/g no significant effects were shown
SPRINT sub-analysis in CKD patients [37]	2646 patients with eGFR 20–60 mL/min/1.73 m^2 (individuals with proteinuria >1 g/day or >1 g/g excluded); mean age 71.9 years	Intensive (SBP <120 mmHg) compared with standard (SBP <140 mmHg) BP-lowering treatment based on unattended automated office BP measurements	3.3 years (median)	No difference between groups in the risk of the primary outcome (MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated HF or death from CV causes) (HR 0.81; 95% CI 0.63–1.05), and the main kidney outcome (≥50% decrease in eGFR from baseline or ESKD) (HR 0.90; 95% CI 0.44–1.83); low target BP was associated with lower all-cause mortality (HR 0.72; 95% CI 0.53–0.99)

MAP, mean arterial pressure; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

modifications suggested by 2021 KDIGO [15] and other previous guidelines and include weight loss (CoR I, LoE A), healthy dietary pattern (CoR I, LoE A), daily physical activity and structured exercise (CoR I, LoE B), reduction of alcohol intake close to abstinence (CoR I, LoE B), smoking cessation (CoR I, LoE B) and reduction of stress via meditation, and mindfulness-based exercise or breathing exercise (CoR II, LoE C). Dietary salt restriction to <5 g (~2 g sodium) daily is recommended for all patients (CoR I, LoE B), and is emphasized for those with CKD, as it can be particularly helpful for improved BP control and decrease of albuminuria [47]. Increased potassium consumption via dietary modification, is recommended for adults with elevated BP, except for patients with advanced CKD (CoR I, LoE B) [14].

Antihypertensive agents

While the 2021 KDIGO Guidelines [15] mainly focused on recommending first-line agents, the 2023 ESH Guidelines [14] provides specific algorithms on antihypertensive agent selection for BP lowering in patients with hypertension and CKD (Fig. 1). Achieving the recommended BP targets in CKD usually requires combinations of two or more agents, which should consist of a renin–angiotensin system (RAS) blocker with a calcium channel blocker (CCB) or a thiazide/thiazide-like diuretic, if eGFR levels are ≥45 mL/min/1.73 m^2 (up to CKD G3a), while in patients with an eGFR <30 mL/min/1.73 m^2 (CKD G4–G5), thiazide/thiazide-like diuretics should be generally replaced by loop diuretics. Of note, this old general notion is not as strong given that a recent RCT reported that chlorthalidone was effective in reducing BP also in CKD patients with eGFR <30 mL/min/1.73 m^2 [48], as discussed below.

Treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-receptor blocker (ARB) remains the first choice for patients with CKD and albuminuria (CoR I, LoE A), based on evidence from seminal trials in people with diabetic [49–52] and non-diabetic CKD [33, 53, 54]. The ACEi or ARB monotherapy should be at maximum tolerated approved doses to achieve optimal nephroprotection. Dual combination of an ACEi with an ARB or combination of aliskiren with any of the two is not recommended (CoR III, LoE A), as two relevant outcome trials were prematurely terminated as combination therapy was associated with increased risk of adverse events [55, 56]. Of note, very recent evidence suggests against RAS blockers discontinuation in advanced CKD [57]. Treatment with RAS blockers is associated with different therapeutic challenges. It is of utmost importance to monitor eGFR and serum electrolytes within 4–8 weeks after treatment initiation. A consistent or severe (>30%) eGFR drop should prompt investigation for presence of renovascular disease and RAS blocker discontinuation. In addition, use of RAS blockers in CKD patients further increases the risk of hyperkalemia [58], which is the main reason for dose reduction or discontinuation [59, 60]. Novel potassium binders (patiromer and sodium zirconium cyclosilicate) were shown to effectively normalize elevated serum potassium and chronically maintain normal levels in CKD patients treated with ACEis, ARBs or spironolactone, with good tolerability [61, 62], and thus it is recommended to use these agents to maintain serum potassium <5.5 mmol/L in individuals with CKD in order to allow optimal treatment with a RAS blocker or a mineralocorticoid receptor antagonist (MRA) to continue [63, 64] (CoR II, LoE B).

In the 2023 ESH Guidelines, there is a detailed commentary on the role of diuretics in CKD patients with hypertension; this is partially related to the high prevalence of treatment resistant hypertension [65, 66]. Hypertension is defined as treatment resistant when appropriate lifestyle measures and treatment with optimal or best tolerated doses of three or more drugs (a thiazide/thiazide-like diuretic, a RAS blocker and a CCB) fail to lower office BP to <140/90 mmHg [14]. The inadequate BP control should be confirmed by uncontrolled 24 h BP (≥130/80 mmHg). Evidence of adherence to therapy and exclusion of secondary causes of hypertension are required to define true resistant hypertension.

Based on recent evidence, a specific algorithm for treatment of resistant hypertension in CKD is proposed depending on underlying renal function. Based on the evidence from the Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2) trial [67] and relevant meta-analyses [68], the fourth-line treatment in patients with resistant hypertension should include the MRA spironolactone; however, patients with an eGFR <45 mL/min/1.73 m^2 or potassium >4.5 mmol/L were excluded from this study [67] and, thus, the efficacy and safety of spironolactone in such individuals are not established. Indirect evidence comes from the Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER) trial that used spironolactone with addition of placebo or patiromer in patients with treatment resistant hypertension and eGFR 25 to ≤45 mL/min/1.73 m^2, in which BP was effectively reduced in both groups [69]. Based on the above, use of spironolactone as a fourth antihypertensive agent in patients with CKD G3b and treatment-resistant hypertension is generally recommended only when necessary and should be done with caution and frequent potassium monitoring. Spironolactone is not recommended in patients with CKD G4 or higher. Instead, in the recent Chlorthalidone in Chronic Kidney Disease (CLICK) randomized trial that included 160 patients with CKD G4 and uncontrolled hypertension, the addition of chlortalidone (mean dose 23 mg daily) on top of previous antihypertensive treatment (including a loop diuretic) was associated with 10.5 mmHg reduction in 24-h SBP [48]; as such, the algorithm now suggests the addition of chlorthalidone for this group of patients [14].

From the other antihypertensive drug classes, beta-blockers, alpha-blockers and centrally acting agent can offer important help towards BP lowering in patients with CKD. Direct vasodilators, such as hydralazine or minoxidil, should be used parsimoniously because they may cause severe fluid retention and reflex sympathetic activation with tachycardia. Finally, in patients with eGFR >40 mL/min/1.73 m^2, endovascular renal denervation (RDN) can be proposed as an adjunctive therapy to patients with resistant hypertension, in whom BP control cannot be achieved or serious side effects cannot be avoided with antihypertensive medications [70, 71], based on evidence from a few randomized clinical trials [70, 72, 73].

CARDIOPROTECTION AND NEPHROPROTECTION: A HOLISTIC APPROACH FOR PATIENTS WITH CKD

The position of CKD in assessing the overall CV risk in patients with hypertension

Among several factors that influence CV risk in patients with hypertension, the 2023 ESH Guidelines promptly identify a lower eGFR and a higher albuminuria, as independent and additive risk factors for CV disease and progression of kidney disease [74, 75]. CKD A2 or CKD G3 are listed as features identifying HMOD, while CKD A3 and CKD G4–G5 are listed among features identifying

established kidney disease [14]. As such, the presence of CKD is exemplified as a main factor in the proposed system for overall CV risk stratification in patients with hypertension.

Nephroprotective and cardioprotective medication use in CKD

The 2023 ESH Guidelines [14] included for the first time a considerably detailed discussion on nephroprotection and cardioprotection in CKD beyond the use of antihypertensive agents to lower BP. As such, they highlighted that progression of CKD and risk of CV events and mortality can be reduced in CKD patients by two novel drug classes that also have some BP-lowering effects, although they are not approved as antihypertensive agents [14]. In detail, the Guidelines recommended to use sodium-glucose cotransporter 2 inhibitors (SGLT2i) or finerenone in patients with CKD in addition to lifestyle interventions and antihypertensive drug therapy. Use of an SGLT2i is recommended in patients with type 2 DM (T2DM) and CKD and in patients with nondiabetic CKD with a moderate or severe increase of albuminuria if eGFR is at least 20 mL/min/1.73 m^2, with respect to current marketing authorizations of each agent (CoR I, LoE A), while use of finerenone is recommended in patients with CKD associated with T2DM and moderate (A2) or severe (A3) albuminuria, if eGFR is at least 25 mL/min/1.73 m^2 and serum potassium <5.0 mmol/L (CoR I, LoE A) [14]. The order of addition of an SGLT2i or finerenone has not been tested in clinical trials and can be based on the individual patient characteristics, including the need for improvement of glycemic control, potassium levels or persistent albuminuria. In this regard, use of SGLT2i can decrease the risk of hyperkalemia [76].

The evidence for the above derives from several seminal studies published in the last few years. Treatment with SGLT2i offers meaningful reductions in office BP of around 3–5/1–2 mmHg [77], which were later confirmed with ABPM studies [78]. Of interest, larger reductions (around 7 mmHg for SBP) were described in patients with CKD G4 [79]. CV outcome trials with SGLT2i in patients with T2DM (which included also large proportions of patients with CKD), showed large and homogeneous reductions of around 40% in composite kidney endpoints [80–82]. Moreover, in kidney outcome trials (Table 4), treatment with SGLT2i in diabetic and non-diabetic CKD showed significant reductions compared with placebo on composite kidney outcomes and individual endpoints such as doubling of serum creatinine (SCr) and progression to ESKD. The mild BP reduction is suggested as a contributor to the nephroprotective effect of SGLT2i. It is highlighted that in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) that SGLT2i were also able to reduce the risk of some CV events and in DAPA-CKD the risk of mortality in patients with CKD [83], something that was not previously evident with RAS blockade or any other drug treatment in this population [84–87].

As for non-steroidal MRAs, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trials tested the effects of finerenone in T2DM patients with CKD and moderately or severely increased albuminuria on top of ACEi or ARB treatment (Table 4). In the FIDELIO-DKD trial, finerenone was associated with significant reductions in the risk of the primary kidney outcome, as well as in the risk of the secondary composite CV outcome versus placebo [88]. The overall difference in BP over the course of the trial was 2.7/1.0 mmHg favoring finerenone and these effects were consistent across all groups of baseline BP [89]. Hyperkalemia leading to discontinuation of the trial regimen was 2.3% with finerenone and 0.9% with placebo, and no fatal hyperkalemia adverse events were reported [88]. In FIGARO-DKD, finerenone was associated with a 13% significant reduction in the risk of the primary CV outcome, with consistent beneficial effects on kidney outcomes and similar tolerability profile [90]. In the Finerenone in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis (FIDELITY) on-treatment analysis combining the patient population of both trials, finerenone reduced mortality by 18% compared with placebo [91]. Other non-steroidal MRAs (esaxerenone and apararenone) have also shown to significantly reduce albuminuria in CKD patients in phase 2 clinical trials [92], but have not yet been tested in hard kidney outcome studies.

SPECIAL POPULATIONS

Kidney transplant recipients

The ESH 2023 Guidelines [14] report that there are no completed randomized trials in kidney transplant recipients (KTRs) that examined different BP targets for major outcomes such as graft survival, CV events or mortality, to provide practice guidance. Consequently, BP targets for hypertension management in these individuals are extrapolated from data in CKD populations. In contrast to the overall CKD population, both 2023 ESH [14] and 2021 KDIGO Guidelines [15] use the same target for KTRs. A target BP of <130/80 mmHg is considered as a reasonable target for KTRs (CoR II, LoE B). Lifestyle modifications should be adopted on the basis of recommendations for the general CKD population. The 2023 ESH Guidelines discuss extensively the most appropriate agents for BP reduction in this population [14]. In most patients, combinations of major antihypertensive agents should be employed. The benefits of ACEis/ARBs in KTRs are still not clearly established, since observational and outcome studies provided conflicting results [93, 94]. In a meta-analysis, the risk of graft loss was reduced by 38% with ACEi/ARBs, without any significant effects on non-fatal CV outcomes or death [95]. CCBs have been consistently associated with benefits such as improved graft survival and minimization of the preglomerular vasoconstrictive effects of calcineurin inhibitors, especially in the early transplantation period. In the aforementioned meta-analysis, CCBs reduced the risk for graft loss by 42%, while in head-to-head comparisons with ACEis/ARBs, CCBs significantly increased GFR by 11 mL/min [95]. Thiazide/thiazide-like diuretics are also effective and useful in patients with kidney transplantation, because they block the cyclosporine-mediated sodium retention. As no data are currently available on the effect of antihypertensive drugs on long-term kidney outcomes in KTRs, the 2023 ESH guidelines avoid making any specific recommendation on preferred agents [14].

Furthermore, the latest ESH Guidelines highlight the important issue of misclassification of BP in KTRs [96]; this is mostly due to a particularly high proportion of masked hypertension (up to 40%) [97]. This is associated with abnormal dipping status [97] and high prevalence of nocturnal hypertension (reaching up to 70%–80%) [98, 99]. As ambulatory BP is a much stronger predictor of kidney function decline and target organ damage than office BP in KTRs [100], the guidelines advocated increasing the use of ABPM in KTRs for diagnosis and management of hypertension [14].

Table 4: Main outcome studies with (a) SGLT2i and (b) finerenone in patients with CKD.

Trial	Year	Treatment arms	Study population	Mean age at baseline (years)	Mean baseline eGFR (mL/min/1.73 m^2)[a]	Median baseline ACR (mg/g)	Primary endpoint	Prespecified CV endpoints
(a) SGLT2i								
CREDENCE trial [111]	2019	Canagliflozin 100 mg or placebo (1:1 ratio)	4401 patients with T2DM and CKD (eGFR 30–89 mL/min/1.73 m^2 and UACR 300–5000 mg/g	63	56.2 ± 18.2	927.0	Doubling of SCr, ESKD, or renal/CV death: HR, 0.70; (95% CI 0.59–0.82)	CV death or HHF (HR 0.69, 95% CI 0.57–0.83); CV death, MI, or stroke (HR 0.80, 95% CI 0.67–0.95); all-cause mortality (HR 0.83; 95% CI 0.68–1.02)
DAPA-CKD [112]	2020	Dapagliflozin 10 mg or placebo (1:1 ratio)	4304 patients with CKD (eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5000 mg/g)	61.8	43.1 ± 12.4	949.3	≥50% reduction in eGFR, ESKD, or renal/CV death: HR 0.61 (95% CI 0.51–0.72)	CV death or HHF (HR 0.71; 95% CI 0.55–0.92); all-cause mortality (HR 0.69; 95% CI 0.53–0.88)
EMPA-KIDNEY [113]	2022	Empagliflozin 10 mg or placebo (1:1 ratio)	6609 patients with CKD (eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 and UACR ≥200 mg/g)	63.8	37.3 ± 14.5	329	Progression of CKD (ESKD, eGFR <10 mL/min/1.73 m^2, ≥50% reduction in eGFR or renal death) or CV death: HR 0.72 (95% CI 0.64–0.82)	CV death or HHF (HR 0.84, 95% CI 0.67–1.07); CV death (HR 0.84, 95% CI 0.60–1.19); all-cause mortality (HR 0.87 95% CI 0.70–1.08)
(b) Finerenone								
FIDELIO-DKD [88]	2020	Finerenone (10 mg or 20 mg) vs placebo (1:1 ratio)	5734 T2DM and (a) UACR 300–5000 mg/g, eGFR 25–75 mL/min/1.73 m^2 or (b) UACR 30–300 mg/g, eGFR 25–60 mL/min/1.73 m^2, diabetic retinopathy	65.6 ± 9.1	44.3 ± 12.6	852 (446–1634)	kidney failure (ESKD or eGFR <15 mL/min/1.73 m^2), eGFR decrease of ≥40%, or renal death (HR 0.82; 95% CI 0.73–0.93)	CV death, nonfatal MI, nonfatal stroke or HHF (HR 0.86; 95% CI 0.75–0.99)
FIGARO-DKD [114]	2021	Finerenone (10 mg or 20 mg) vs placebo (1:1 ratio)	7437 T2DM and (a) UACR 30–300 mg/g, eGFR ≥25–90 mL/min/1.73 m^2, or (b) UACR 300–5000 mg/g, eGFR ≥60 mL/min/1.73 m^2	64.1 ± 9.8	67.8 ± 21.7	308 (108–740)	CV death, nonfatal MI, nonfatal stroke, or HHF (HR 0.87; 95% CI 0.76- 0.98)	Kidney failure (ESKD or eGFR <15 mL/min/1.73 m^2), eGFR decrease of ≥40% or renal death (HR 0.87; 95% CI 0.76–1.01)

[a]Mean ± standard deviation; [b]median (Q1, Q3).
HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; MI, myocardial infarction; RRT, renal replacement therapy.

Renovascular disease

In contrast to 2021 KDIGO Guidelines [15], the ESH 2023 Guidelines [14] offer insight in renovascular disease, which is a common cause of CKD, and it is associated with adverse CV and renal events, as well as increased mortality [101]. During the last few years, a progressive shift on the management of renovascular disease has been made, based on the best available evidence [102]. The 2023 ESH Guidelines [14] recommend to offer revascularization with balloon angioplasty without stenting in patients with fibromuscular dysplasia and critical renal artery stenosis [103], while for atherosclerotic renovascular disease (ARVD), the recommendation is to offer revascularization on top of medical therapy in patients with documented secondary hypertension due to ARVD or those with high-risk clinical presentations (flash pulmonary edema, refractory hypertension, or rapid loss of kidney function) with high-grade stenosis ($\geq$70%) [14]. Medical therapy alone could be used for individuals with asymptomatic ARVD with stenoses $<$70%, patients with mild or moderate hypertension that is easily controlled and low-grade stenosis, or patient with non-viable kidney parenchyma [101, 104], where revascularization has little to offer. As for transplant renal artery stenosis, it is recommended that all KTRs with uncontrolled or abrupt onset hypertension should be investigated for transplant artery stenosis [105]; percutaneous renal artery angioplasty has high success rates in these patients [106].

CONCLUSIONS

Until recently, major bodies producing guidelines for the management of hypertension in patients with CKD disagreed in some key issues [107]. Previous proposals to limit this disagreement between included formation of a shared group of individuals having expertise in both hypertension and in CKD to reach appropriate consensus. This strategy was recently employed in a successful documents discussing hypertension diagnosis in CKD patients [28]. The recent 2023 ESH Guidelines for the Management of Arterial Hypertension, endorsed by ERA, includes important information and several updated recommendations regarding the management of hypertension in CKD [14]. Most of these are in general agreement with the previous 2021 KDIGO Guidelines (Table 1), some reflect different emphasis on some topics (i.e. detailed algorithms on antihypertensive agent use), while others reflect evolution of important evidence in recent years. The only issue with a clear difference is that of BP target, in which the latest ESH Guidelines [14] comes in general agreement with AHA/ACC 2017 Hypertension Guideline [108] and other relevant documents, while the 2021 KDIGO Guideline is the only document favoring a very low SBP target [15]. Harmonization of relevant guidelines is expected to aid clinicians in their treatment decisions and proper implementation of research findings for the benefit of our patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

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CONFLICT OF INTEREST STATEMENT

A.O. is one of the former Editors-in-Chief of *CKJ*. M.K. is member of the *CKJ* Editorial Board.

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