

A European Renal Association (ERA) synopsis for nephrology practice of the 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension

Running Title: ERA synopsis of the 2023 ESH Guidelines

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ABSTRACT

In June 2023, the European Society of Hypertension (ESH) presented and published the new 2023 ESH Guidelines for the Management of Arterial Hypertension, a document that was endorsed by the European Renal Association (ERA). Following the evolution of evidence in recent years, several novel recommendations relevant to the management of hypertension in patients with chronic kidney disease (CKD) appeared in these Guidelines. These include recommendations for target office BP <130/80 mmHg in most and against target office BP <120/70 mmHg in all patients with CKD; recommendations for use of spironolactone or chlortalidone for patients with resistant hypertension with eGFR higher or lower than 30 ml/min/1.73m², respectively; use of an SGLT2-inhibitor for patients with CKD and eGFR ≥20 ml/min/1.73m²; use of finerenone for patients with CKD, type 2 DM, albuminuria, eGFR ≥25 ml/min/1.73m² and serum potassium <5.0 mmol/L; and revascularization in patients with atherosclerotic renovascular disease and secondary hypertension or high-risk phenotypes if stenosis ≥70% is present. The present report is a synopsis of sections of the ESH Guidelines that are relevant to the daily clinical practice of nephrologists, prepared by experts of ESH and ERA. The sections summarized are those referring to the role of CKD in hypertension staging and cardiovascular risk stratification, the evaluation of hypertension-mediated kidney damage and the overall management of hypertension in patients with CKD.

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

Introduction

In June 2023, the European Society of Hypertension (ESH) presented and published the new 2023 ESH Guidelines for the management of arterial hypertension [1], a document that was endorsed by the European Renal Association (ERA). Following recent evidence, several novel recommendations relevant to the management of hypertension in patients with chronic kidney disease (CKD) appeared in these Guidelines. The present report is a synopsis of the sections of the ESH Guidelines that are relevant to the daily clinical practice of nephrologists, prepared by experts of ESH and ERA. The sections summarized are those referring to the role of CKD in hypertension staging and cardiovascular risk stratification, the evaluation of hypertension-mediated kidney damage and, most importantly, the management of hypertension in patients with CKD. Of note, the 2023 ESH Guidelines and the present document do not discuss issues relevant to hypertension in patients with CKD G5 on chronic dialysis treatment; this field is extensively discussed in a previous joint consensus statement of the two societies [2,3].

Definition of hypertension and classification of BP

In the 2023 ESH Guidelines, hypertension is defined based on repeated office SBP values ≥ 140 mmHg and/or DBP ≥ 90 mmHg [1]. The document acknowledges that this definition is arbitrary and has mainly the pragmatic purpose of simplifying the diagnosis and decision on hypertension management, as there is a continuous relationship between BP and the risk of death from stroke or ischemic heart disease starting from an office SBP > 115 mmHg and a DBP > 75 mmHg [4]. In this context, the above office threshold BP values correspond to the level of BP at which the benefits of intervention (lifestyle interventions or drug treatment) exceed those of inaction, as shown by outcome-based RCTs. The classification of office BP and definition of hypertension grades remain the same from previous guidelines and are presented in Table 1. The evidence grading system used in the 2023 ESH Guidelines is depicted in Supplementary Figure 1.

In addition to grades of hypertension, which are based on BP values, the Guideline also distinguishes stages of hypertension as summarized below [Class of Recommendation (CoR) I, Level of evidence (LoE) C] [1]. The presence of CKD plays a crucial role in this staging.

- Stage 1: Uncomplicated hypertension [i.e. without hypertension-mediated organ damage (HMOD), established cardiovascular disease (CVD), and CKD G3 or higher].
- Stage 2: Presence of HMOD or CKD G3 or diabetes.
- Stage 3: Established CVD or CKD G4 or G5.

Recommendations relevant to the diagnosis of hypertension-mediated kidney damage and other diagnostic considerations

The 2023 ESH Guidelines list assessment of serum creatinine, estimation of glomerular filtration rate (GFR) with the 2009 CKD-Epidemiology Collaboration formula [5] and evaluation of urine albumin:creatinine ratio (ACR) measured from a spot urine sample (preferably early morning urine) as two of the three (the third being 12-lead electrocardiogram) basic tests to assess HMOD and stage hypertension. These examinations should be documented in all patients upon hypertension diagnosis, and at least annually thereafter [1]. Serum creatinine alone is identified as an insensitive marker of renal impairment, because a major reduction in kidney function can occur before serum creatinine rises. It is also suggested that a negative urinary dipstick test does not rule out A2 albuminuria, as many times it cannot detect ACR levels at the lower range [6], but it can offer information on other signs of kidney injury (i.e. microscopic hematuria, active urine sediment) and should be performed at least at the initial evaluation. The document endorses the currently universally used definition for CKD, involving an eGFR <60 ml/min/1.73 m² at any level of albuminuria or a 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.:

(a) normal/mildly increased, ACR <30 mg/g, (A1, formerly termed normoalbuminuria); (b)

moderately increased, ACR 30-300 mg/g, (A2, formerly termed microalbuminuria); and (c) severely increased, ACR>300 mg/g, (A3, formerly termed macroalbuminuria) [7].

Kidney ultrasound is listed among the extensive examinations for HMOD, due to its low cost, widespread availability, and useful information on renal morphology (kidney size and structure, roughness, adiposity, kidney stones) [8]. The role of spectral Doppler ultrasound with evaluation of renal resistive index (RRI), a reproducible measure of renal arterial impedance, as initial screening for renal artery stenosis is also emphasized. A RRI value lower than 0.7 is traditionally indicating normal impedance to renal blood flow, although considerable heterogeneity has been reported [9].

The clinical indications for performance of home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM) are not largely different between hypertensive patients with or without CKD. However, the guidelines highlight the increased prevalence of masked hypertension and high nighttime BP with abnormal dipping status in patients with CKD [10–13] as specific indications for HBPM and ABPM, respectively, in these individuals (CoR I, LoE B) [1].

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

Among several factors that influence cardiovascular risk in patients with hypertension, the 2023 ESH Guidelines promptly identify a lower eGFR and a higher albuminuria, indicating loss of kidney function and kidney damage, respectively, as independent and additive predictors of increased cardiovascular risk, in addition to being risk factors for progression of kidney disease [14,15]. CKD A2 (moderately increased albuminuria, ACR 30-300 mg/g) or CKD G3 (eGFR 30–59 ml/min/1.73m²) are listed as features identifying HMOD, while CKD A3 (severely increased albuminuria, ACR>300 mg/g) and CKD G4 and G5 (eGFR <30 mL/min/1.73m²) are listed among features identifying established kidney disease [1]. As such, the presence of CKD is exemplified as a main factor in the proposed system for overall cardiovascular risk stratification in patients with hypertension (Figure 1).

Treatment of hypertension in CKD

Initiation of treatment

The 2023 ESH Guidelines recommend that in patients 18 to 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) [1]. The exception to this rule is adult patients with a history of CVD, predominantly coronary artery disease (CAD), in whom drug treatment should be initiated in the high-normal BP range (SBP \geq 130 or DBP \geq 80 mmHg) (CoR I, LoE A). Nephrologists should note that many patients with CKD are falling in the later category. In patients \geq 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 2023 ESH Guidelines offer a detailed discussion on the issue of the best (most protective) BP targets in patients with CKD, including those with CKD and DM, recognizing that for more than a decade, there has been considerable debate in the scientific literature in this field [1]. Old observational data suggested an association between BP and the risk for kidney failure, starting from a SBP level of $>$ 120 mmHg [16]. More recent data from China obtained in CKD patients without antihypertensive therapy followed prospectively for 5 years indicated that a BP $>$ 130/90 mmHg was associated with a significantly increased risk of CV and kidney outcomes [17]. However, RCT evidence to fully delineate the target BP in CKD, is missing; ideally, this would be an RCT comparing different BP targets (i.e. SBP $<$ 140 vs $<$ 130 mmHg), including a CKD population with an appropriate mixture of kidney function levels, albuminuria levels and etiology, achieving corresponding BP levels during follow-up and being powered to investigate CV outcomes, hard kidney outcomes and mortality.

Current evidence in the field comes mainly from two previous trials in non-diabetic CKD that randomized patients to different levels or ranges of mean BP (MBP) and examined kidney outcomes. In the Modification-of-Diet-in-Renal-Disease (MDRD) study the projected GFR decline within 3 years, and the risk of ESKD and death were not significantly different between groups of low and usual BP target [18]. However, analyses by baseline proteinuria showed that those with proteinuria >1 g/day in the low-target group had a decrease in protein excretion and a slower GFR decline over time compared to patients in the usual-target group [19]. Similarly, in the African-American-Study-on-Kidney-Disease (AASK) no difference in outcomes between BP target groups was observed in the overall population [20]; in a post-hoc analysis, again, low BP was associated with better kidney outcomes in the small subset of patients with proteinuria >1 g/day [21]. Subsequent analyses of MDRD and AASK combined the randomized trial periods with subsequent observational follow-up phases. In MDRD long-term analysis, low-target BP was associated with overall reduced risk for ESKD and the composite of ESKD or death, but this was again mainly driven from a beneficial effect in patients with baseline proteinuria >1 g/day [22]. In the AASK long-term follow-up analysis, no difference in the risk of the composite outcome of doubling of serum creatinine, ESKD, or death was noted. However, for patients with urine protein-to-creatinine ratio (PCR) >0.22 g/g, which roughly equals proteinuria of 0.25-0.3 g/day and urine ACR >100 mg/g in most patients, there was a beneficial effect with low BP [23]. A subsequent analysis combining the trial and cohort periods of both these trials (adding up to 1907 patients and a median follow-up of 14.9 years), showed that low target BP was associated with significant reductions in the risks of ESKD and mortality in the total population; and this effect was mainly driven by changes in patients with urine PCR >0.44 g/g (urine ACR roughly >200 mg/g) [24]. Thus, sustainability of BP reduction and extent of proteinuria are major determinants of nephroprotection in patients with non-diabetic CKD.

The 2023 ESH Guidelines suggest that the results of the Systolic Blood Pressure Intervention Trial (SPRINT) have little relevance to the question discussed herein [1]. SPRINT randomized 9,361

hypertensive patients of increased cardiovascular burden to intensive (target SBP <120 mmHg) or standard treatment (target SBP <140 mmHg) [25]. Of these patients, about 28% had CKD with eGFR between 20 to 60 ml/min/1.73 m², but very few had albuminuria A2 or A3 as individuals with proteinuria >1 g/day or >1g/g were excluded. Importantly, diabetes mellitus, i.e. the most common cause of ESKD, and prior stroke were also exclusion criteria. In the overall trial, although the primary composite outcome of cardiovascular events as well as cardiovascular and total mortality were significantly lower in the intensive-treatment group compared with the standard-treatment group, kidney outcomes did not differ between the two groups. A sub-analysis of the SPRINT CKD subpopulation [26] showed no difference between groups in the primary outcome or in the pre-specified kidney outcome but a lower total mortality rate in participants in the intensive BP arm. The above results must be interpreted with caution, since 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).

Following the above, the 2023 ESH Guidelines indicate that a recommendation to target office SBP<120 mmHg in persons with CKD, cannot be made. The reasoning for this is that the only relevant findings are delivered by this 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) and had both the primary outcome and the main kidney outcome (with only few events) being not significantly different between treatment groups. Furthermore, although SPRINT according to protocol used a trial-specific automated BP measurement technique, during its execution no consistent universal methodology was followed with regards to personnel attendance (no attendance, attendance during rest periods, readings' period, or both), a fact that directly influenced the observed differences in outcomes [27]. 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) [28].

With regards to persons with 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 [29] and the sub-analysis of participants with DM of the Hypertension-Optimal-Treatment (HOT) [30] trials offered insight on the DBP 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 [31]. Apart from showing no difference in the primary outcome, most possibly due to interactions with other arms of the factorial design and the unexpectedly low event rate [32], ACCORD-BP excluded individuals with serum creatinine >1.5 mg/dL; thus, it can offer very little insight to the optimal BP in patients with CKD and DM. A post-hoc analysis of the Reduction-of-Endpoints-in-NIDDM-with-the-Angiotensin-II-Antagonist-Losartan (RENAAL) study showed that baseline SBP of 140-159 mmHg increased risk for ESKD or death by 38% compared to SBP<130 mmHg [33]. A relevant post-hoc analysis from the Irbesartan-Diabetic-Nephropathy-Trial (IDNT) showed that SBP>149 mmHg was associated with a 2.2-fold increase in the risk for doubling SCr or ESKD compared with SBP<134 mmHg; moreover, progressive lowering of SBP down to 120 mmHg improved kidney and patient survival, but below 120 mmHg, all-cause mortality increased [34]. Finally, although limited by the heterogeneity of the included studies [32], a recent meta-analysis in patients with CKD G3-G5 has reported a mortality benefit by a SBP reduction of 16 mmHg and an absolute SBP of <132 mmHg with a nonsignificant benefit at achieved SBP values of <125 mmHg [35]. In a more recent pooled analysis of four RCTs (AASK, ACCORD, MDRD and SPRINT), all-cause mortality showed a tendency to a reduction with intensive treatments (BP <130mmHg), but this finding was not statistically significant. However, after excluding patients with higher GFR and those undergoing intensive glycemic control, lowering BP to<130 mmHg decreased all-cause mortality (hazard ratio 0.79, 95% CI 0.63–1.00, P=0.048) when compared with a standard target of <140 mmHg [36].

Taking these largely indirect findings together and considering that, at least after development of proteinuria, progression of kidney injury tends to follow the same course in different situations, the 2023 ESH Guidelines suggest that: (i) the BP target for proteinuric nondiabetic CKD applies to patients with proteinuric diabetic kidney disease as well and (ii) for both patient categories, a target SBP of <130mmHg and DBP <80mmHg, if well tolerated, can be associated with protection against CKD progression in individuals with an albuminuria >30 mg/g. A similar target may be associated with a reduction in mortality in most patients with CKD. Particularly in patients with advanced CKD (G4 and G5), careful monitoring of eGFR is recommended as a further functional, but reversible, decline of GFR may occur on a lower BP. Finally, most of the patients with CKD have cardiovascular comorbidities that require respective target BP values to be taken into account, and thus these cardiovascular comorbidities and not CKD protection may primarily guide the target BP in an individual patient.

However, 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.

Overall, as shown in Figure 2, the guidelines 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 \geq 300 mg/g, high CV risk patients) office BP may be lowered to <130/80 mmHg if tolerated (CoR II, LoE B). To actively target an

office SBP target of <120 mmHg and DBP <70 mmHg cannot be recommended because of the absence of relevant evidence and the potential to induce harm (CoR III, LoE C).

Lifestyle interventions

The 2023 ESH Guidelines highlight a list of lifestyle interventions that are recommended in individuals with hypertension [1], including weight loss (CoR I; LoE A), 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), and smoking cessation (CoR I; LoE B). Dietary salt (NaCl) restriction to <5g (~2g sodium) per day is recommended for all patients (CoR I; LoE B), and is emphasized for patients with CKD as it can be particularly helpful for BP control and reduction of albuminuria [37]. Increased potassium consumption, preferably via dietary modification, is recommended for adults with elevated BP, except for patients with advanced CKD (CoR I; LoE B).

Antihypertensive agents

The 2023 ESH Guidelines comment that existing evidence suggests that BP reduction with any type of first-line antihypertensive agents can offer similar protection in individuals with and without CKD against major cardiovascular events (stroke, myocardial infarction, heart failure, or cardiovascular death) and all-cause death [38]. Achieving the recommended BP targets in CKD usually requires combination therapy, which should consist of a renin angiotensin system (RAS) blocker with a CCB or a thiazide/thiazide-like diuretic, if eGFR levels are ≥ 45 ml/min/1.73m² (up to CKD G3a), while in patients with an eGFR below 30 ml/min/1.73m² (CKD G4-G5), thiazide/thiazide-like diuretics should be generally replaced by loop diuretics, according to the updated algorithm presented in Figure 3. The transition from treatment with a thiazide/thiazide-like to a loop diuretic should be individualized in patients with eGFR values between 30 and 45

ml/min/1.73m², with effectiveness in these and lower eGFR levels being established at least for chlorthalidone.

Following seminal clinical trials, in people with diabetic [39–42] and non-diabetic CKD [20,43,44] an ACEI or an ARB is the treatment of choice, especially in those with moderate or severely increased albuminuria, where these agents were found to reduce proteinuria, the rate of GFR decline, and the risk of doubling of serum creatinine or ESKD (CoR I; LoE A). 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 [45,46]. In normoalbuminuric individuals with hypertension, ACEIs or ARBs are able to delay the progression to severely increased albuminuria compared to placebo [47], but no evidence exist for better preservation of kidney function with RAS blockers compared to other major antihypertensive classes [48]. Currently, there is no evidence to stop treatment with RAS blockers in advanced CKD, as in a recent open-label trial in which patients with an eGFR <30 mL/min/1.73 m² were randomized to either discontinuation or continuation of therapy with RAS inhibitors, discontinuation was not associated with a significant between-group difference in the long-term eGFR decline [49].

The 2023 ESH Guidelines highlight also the main therapeutic challenges with ACEI or ARB treatment [1]. As the vasodilating effect of ACEIs or ARBs on the efferent arteriole reduces intraglomerular pressure, eGFR drops commonly by an average of 10-15% in the first weeks of treatment with these agents (eGFR dip). A similar hemodynamic effect can be seen with large BP reductions offered by any antihypertensive agent. Thus, repeated monitoring of eGFR and blood electrolytes within 4-8 weeks (depending on baseline kidney function) is important when treatment is initiated. Clinicians should not be alarmed by this early GFR drop, but if the decline in GFR continues or is more severe (>30%), the RAS blocker should be stopped, and the patient should be

investigated for the presence of renovascular disease. Use of RAS blockers in CKD patients further increases in the risk of hyperkalemia [50]. Incident hyperkalemia is associated with increased mortality [51] and is the most frequent reason for dose reduction or discontinuation of ACEIs and ARBs in CKD patients [52,53]. However, reducing the dose or discontinuing RAS blockers has been associated with increased risk of CV events in large observational studies [53] and should be avoided. 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 [54,55]. Thus, these agents can be used to maintain serum potassium <5.5 mmol/L in individuals with CKD [56,57] (CoR II; LoE B).

The 2023 ESH Guidelines, emphasize that most individuals with CKD will not achieve target BP control with ACEI or ARB monotherapy, and dual combination by adding a dihydropyridine CCB or a diuretic should almost always be used to initiate the treatment in hypertensive patients with CKD as in most patients with hypertension [58,59]. Nevertheless, the majority of patients with CKD would need triple combination to achieve target BP (Figure 3) [1]. Dihydropyridine CCBs were shown to increase proteinuria when used in the absence of a RAS blocker in patients with proteinuric CKD [41,60]. However, in the general hypertensive population, where the majority of patients do not have moderately or severely increased albuminuria, dihydropyridine CCBs have similar effects on kidney outcomes with RAS blockers or diuretics [48]. Moreover, in a study of hypertensive patients of which 19% had moderately and 5% severely increased albuminuria at baseline, a combination of RAS blocker with a dihydropyridine CCBs was superior in reducing kidney outcomes compared to a RAS blocker-thiazide combination [61].

Diuretics are particularly useful in CKD patients, as these individuals are most often sodium-sensitive (especially if older, diabetic or obese) and have high prevalence of treatment resistant hypertension [59,62]. Furthermore, diuretics were shown to effectively reduce proteinuria when

added to RAS-blockers in proteinuric CKD [37]. When GFR falls $<45 \text{ mL/min/1.73 m}^2$, thiazide diuretics become less effective, as they cannot reach their tubular site of action due to competition for tubular secretion with other substances that accumulate in CKD [63]. This is theoretically also the case for thiazide-like diuretics, but recent RCT evidence indicated that at least chlortalidone is clinically effective in lowering BP in patients with G4 CKD [64]. In general, in patients with CKD G3b (eGFR $30\text{--}44 \text{ mL/min/1.73m}^2$), diuretic therapy should be modified and the dosing individualized, while in patients with CKD G4 (eGFR $<30 \text{ mL/min/1.73m}^2$), thiazides should be substituted with a loop diuretic. Within this class, torsemide might be preferred to furosemide because of its longer half-life, which allows a less frequent dosing scheme and a better adherence to treatment [65].

Finally, triple antihypertensive drug therapy may not control BP in a number of CKD patients. Hypertension is defined as resistant to treatment 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 $<140/90 \text{ mmHg}$ [1]. The inadequate BP control should be confirmed by uncontrolled 24h BP ($\geq 130/80 \text{ mmHg}$). Evidence of adherence to therapy and exclusion of secondary causes of hypertension are required to define true resistant hypertension. In patients with true resistant hypertension, the fourth line treatment should include the mineralocorticoid receptor antagonist (MRA) spironolactone, based on the evidence from the PATHWAY-2 trial [66] and relevant meta-analyses [67]. However, patients with an eGFR with eGFR $<45 \text{ mL/min/1.73m}^2$ or potassium above $>4.5 \text{ mmol/L}$ were excluded from this study [66] and, thus, the efficacy and safety of spironolactone in such individuals are not established. In the AMBER trial that used spironolactone with addition of placebo or patiromer in patients with treatment resistant hypertension and eGFR $25 \text{ to } \leq 45 \text{ mL/min/1.73 m}^2$, BP was effectively reduced in both groups, but the rates of hyperkalemia (potassium $\geq 5.5 \text{ mmol/L}$) were about 60% and 35%, respectively, at 12 weeks [68]. Based on the above, the 2023 ESH Guidelines have also updated the

treatment algorithm for true resistant hypertension depending on underlying renal function. Use of spironolactone as a fourth antihypertensive agent in patients with CKD G3b and treatment-resistant hypertension is generally recommended only when necessary (when BP control is not achieved with addition of other agents) and should be done with caution and frequent potassium monitoring. Use of novel potassium binders is advisable to maintain serum potassium <5.5 mmol/L. Spironolactone is not recommended in patients with CKD G4 or higher. Instead, in the recent CLICK randomized trial that included 160 patients with CKD G4 and resistant hypertension, the addition of chlorthalidone (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 [64]; as such, the algorithm now suggests the addition of chlorthalidone for this group of patients [1].

Beta-blockers and alpha-blockers can offer important help towards BP lowering in patients with CKD, since sympathetic activity is commonly increased [72]; however, their effects in CKD have not been tested in trials with hard kidney outcomes. Bisoprolol (5-10 mg/day), doxazosin extended release (4-8 mg/day) or a centrally acting agent such as the alpha-adrenergic receptor agonists (clonidine, 0.1-0.3 mg or moxonidine 0.2-0.3 mg twice daily) can be used [69]. However, bisoprolol and doxazosin reduced BP less effectively than spironolactone in the PATHWAY-2 trial [66], while clonidine has shown similar BP-lowering effects to spironolactone in resistant hypertension, with several side-effects [69]. Non-dihydropyridine CCBs (if used together with RAS blockers) were associated with reductions in proteinuria and decline of kidney function in proteinuric CKD [66,67], but when added to a RAS blocker in normoalbuminuric hypertensive subjects do not seem to offer additional nephroprotection [73]. Direct vasodilators, such as hydralazine or minoxidil, should be used parsimoniously because they may cause severe fluid retention and reflex sympathetic activation with tachycardia. Recent RCTs have shown that endovascular renal denervation (RDN) can be associated with a significant, albeit not marked, office and ambulatory BP reduction in patients with uncontrolled hypertension [70–72]. In a large registry of renal denervated patients, the

BP reduction was long-lasting and devoid of significant safety problems [73,74]. RDN can thus be proposed as an adjunctive therapy to patients with resistant hypertension provided eGFR >40 ml/min/1.73m², in whom BP control cannot be achieved or serious side effects cannot be avoided with antihypertensive medications [70,75].

Use of additional drugs that offer nephroprotection and cardioprotection in CKD

In addition to BP control at the targets and with the agents described above, the 2023 ESH Guidelines included for the first time a considerably detailed discussion and 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 [1].

The 2023 ESH guidelines discuss that early clinical studies in patients with T2DM with the oral antihyperglycemic class of sodium-glucose co-transporter-2 inhibitors (SGLT2is), suggested that these agents can offer office BP reductions of around 3-5/1-2 mmHg [76], that were later confirmed with ABPM studies [77]. Of interest, larger reductions were described in patients with CKD G4 (around 7 mmHg for SBP) [78]. The main mechanism is a mild natriuretic/diuretic effect occurring possibly from both inhibition of proximal sodium reabsorption and osmotic diuresis [76]. These agents were also shown to reduce urine ACR by 25-40%, depending on the baseline albuminuria levels [79], as well as plasma uric acid, which is also important in CKD patients [80]. The Guidelines refer to the fact that cardiovascular outcome trials with SGLT2is in patients with T2DM (that included also large proportions of patients with CKD), showed large and homogeneous reductions of around 40% in composite kidney endpoints [81–83]. The document also analyzes the results of the kidney outcome trials investigating SGLT2is on diabetic and non-diabetic CKD on top of standard therapy including an ACEI or an ARB on maximum tolerated doses the CREDENCE [84], DAPA-CKD [85], and EMPA-KIDNEY studies [86] to conclude that all three trials were

prematurely terminated due to benefit and showed significant reductions compared to placebo on composite kidney outcomes and individual endpoints such as doubling of SCr and progression to ESKD. In the EMPA-KIDNEY trial, the reduction in the composite kidney outcome was evident in patients across the whole range of eGFR and most striking in patients with severely increased albuminuria. The chronic rate of eGFR loss was lower with empagliflozin in all UACR subgroups [86]. A mild eGFR drop may also be present during the first weeks of treatment, but managed as in the case of RAS-blockers. The mild BP reduction is suggested as a contributor to the nephroprotective effect of SGLT2is. It is highlighted that in CREDENCE and DAPA-CKD, SGLT2is were also able to reduce the risk of some cardiovascular events and in DAPA-CKD the risk of mortality in patients with CKD [87], something that was not previously evident with RAS-blockade or any other drug treatment in this population [88–91].

The Guidelines report that addition of a steroidal MRA (spironolactone or eplerenone) on top of an ACEI or an ARB in patients with proteinuric diabetic CKD showed significant reductions in urine albumin or protein excretion [92–94], independently of the BP-lowering effect but their use was restricted in clinical practice due to absence of evidence from hard outcome trials and the increased risk of hyperkalemia [95]. The main mechanism of this action was inhibition of several deleterious genomic and non-genomic effects of aldosterone breakthrough, including kidney tissue inflammation and fibrosis mediated through MR overactivation [96]. Finerenone is a novel, non-steroidal MRA with different duration of action and tissue distribution than steroidal MRAs, that inhibits binding of different coregulatory molecules to MR receptors allowing reduction in inflammatory and fibrotic processes, with less interference with the classical MR-mediated actions in the distal tubule than steroidal MRAs [96,97]. The BP reduction observed with finerenone appears to be less than with spironolactone and does not seem to substantially contribute to its organ protective effects [98]. Following evidence showing dose-dependent reductions of albuminuria [99], the Guidelines discuss the effect of two RCTs, FIDELIO-DKD and FIGARO-DKD, that tested

finerenone in T2DM patients with CKD and moderately or severely increased albuminuria on top of ACEI or ARB treatment. In 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 cardiovascular outcome versus placebo [100]. The overall difference in BP over the course of the trial was 2.7/1.0 mm Hg favoring finerenone and these effects were consistent across all groups of baseline BP [98]. 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 [100]. In FIGARO-DKD, finerenone was associated with a 13% significant reduction in the risk of the primary cardiovascular outcome, with consistent beneficial effects on kidney outcomes and similar tolerability profile [101]. In the FIDELITY on-treatment analysis combining the patient population of both trials, finerenone reduced mortality by 18% compared to placebo [102]. Other non-steroidal MRAs (esaxerenone and apararenone) have also shown to significantly reduce albuminuria in CKD patients in phase 2 clinical trials [96], but are not yet tested in hard kidney outcome studies.

In view of the above evidence, the 2023 ESH Guidelines recommended to use SGLT2is or finerenone in patients with CKD in addition to lifestyle interventions and antihypertensive drug therapy. Use of an SGLT2i is recommended in patients with diabetic and in patients with nondiabetic CKD with a moderate or severe increase of albuminuria if eGFR is at least $20 \text{ ml/min/1.73m}^2$, 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 type 2 DM and moderate or severe albuminuria, if eGFR is at least $25 \text{ ml/min/1.73m}^2$ and serum potassium $<5.0 \text{ mmol/L}$ (CoR I, LoE A). The order of addition of an SGLT2is 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.

Hypertension in kidney transplant recipients

The 2023 ESH Guidelines also discuss in considerable length management of hypertension in kidney transplant recipients (KTRs) [1]. The guidelines discuss that kidney transplantation per se is associated with significant improvements in BP (8/5 mmHg in ambulatory BP) in the short- and mid-term post-transplant periods along with reduction in antihypertensive agents [103,104]; as such, ambulatory BP in KTRs is significantly lower than that in carefully matched hemodialysis patients and similar to patients with CKD with matched kidney function [105,106]. Despite these improvements, hypertension represents the most prevalent co-morbidity post transplantation, with ABPM studies estimating hypertension prevalence in >95% of KTRs [107]. Elevated BP is associated with kidney function decline, target-organ damage, cardiovascular events and reduced graft and patient survival [108–110]. As such, hypertension may play an important role towards the significantly higher residual cardiovascular risk in KTRs than in general population [111].

The Guidelines report evidence on commonly encountered misclassification of hypertension status by office BP in KTRs [112], mostly due to a particularly high proportion of masked hypertension (20-40%) [113]. This is associated with frequently impaired dipping status (around 50%) [113] and high rates of nocturnal hypertension (up to 70-80%) [114,115]. As ambulatory BP is a much stronger predictor of kidney function decline and target organ damage than office BP in KTRs [109], the guidelines advocated increasing the use of ABPM in KTRs for diagnosis and management of hypertension. With regards to the pathogenesis of hypertension in KTRs, the Guidelines highlight its multifactorial nature, involving traditional risk factors, factors related to CKD (most commonly, impaired sodium handling and activation of RAS and SNS) and factors related to transplantation and its treatment [116]. Among major immunosuppressive classes, purine pathway inhibitors (mycophenolate mofetil or azathioprine), and mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus) do not affect BP control [116,117]. The association of corticosteroid treatment with increased BP is emphasized, and partial activation of mineralocorticoid

receptors by cortisol causing sodium retention is suggested as a main mechanism [110], while glucocorticoid avoidance or withdrawal protocols in KTRs are associated with better BP profile [118,119]. Calcineurin inhibitors (cyclosporine or tacrolimus) are also associated with BP elevations, through increased sodium reabsorption via the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule and upregulation of vasoconstrictive substances leading to increased total peripheral resistance and vasoconstriction of afferent arterioles [116,117]. The effects of tacrolimus on BP appear less pronounced compared to cyclosporine.

As there are no specific RCTs that have tested different BP targets on major clinical endpoints in KTRs, BP targets for hypertension management in these individuals are extrapolated from data in CKD populations [1]. 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 CKD, and combinations of major antihypertensive agents should be employed in most patients. The benefits of ACEis/ARBs in KTRs are still not clearly established, since observational and outcome studies provided conflicting results [110,117]. In a recent meta-analysis of RCTs, the risk of graft loss was reduced by 38% with ACEi/ARBs, without any significant effects on non-fatal cardiovascular outcomes or death, whereas the incidence in hyperkalemia increased [120]. 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 [120]. 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 guidelines avoid to make any specific recommendation on preferred agents [1]. A notion is also made that transplant renal artery stenosis is not uncommon in KTRs and it should be

effectively sought for in cases of uncontrolled or abrupt onset hypertension [116]; percutaneous renal artery angioplasty has high success rates in these patients [121].

Renovascular disease

The 2023 ESH Guidelines also discuss the prevalence [122,123], prognosis [124] and management [125,126] of the two main causes of renovascular hypertension, atherosclerotic renal vascular disease (ARVD) and fibromuscular dysplasia (FMD) [1]. Revascularization with balloon angioplasty without stenting is emphasized as the treatment of choice for patients with FMD and critical renal artery stenosis [127], while for 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 documented high-grade stenosis ($\geq 70\%$) [1]. Medical therapy alone could be used for individuals with asymptomatic ARVD with stenosis $< 70\%$, patients with mild or moderate hypertension that is easily controlled with antihypertensive drugs and low-grade stenosis, or patient with non-viable kidney parenchyma, where revascularization has little to offer. In all the later cases, if treatment initiation with an ACEi or an ARB results in eGFR reduction of $\geq 30\%$, careful re-evaluation is warranted. Current strategies in the management of ARVD are detailed in a recent clinical practice document by ERBP and the Working Group “Hypertension and the Kidney” of ESH [128].

Conclusions

The 2023 ESH Guidelines for the Management of Arterial Hypertension document includes important information and several recommendation updates regarding the management of hypertension in CKD, following the evolution of evidence in recent years. Updated recommendations for daily nephrology practice that were briefly summarized in this text are relevant

to the optimal BP targets, the algorithm of antihypertensive drug use in patients with CKD G3b and G4, the use of nephroprotective and cardioprotective agents such as SGLT2is and finerenone, management of hypertension in KTRs, and current treatment of renovascular disease. Several other topics that are not discussed herein due to reasons of space can be also useful to practicing nephrologists, including management of hypertension in patient phenotypes that are commonly encountered (patients with diabetes, obesity, advanced CVD, sleep apnea), management of secondary hypertension, follow-up algorithms, the importance of adherence to treatment and the effects of the COVID-19 pandemic, among others. For all these topics, the reader is referred to the main Guideline document [1]. Implementation of the above recommendations in clinical practice is expected to help towards the improvement of BP control and reduction of hypertension-associated morbidity in patients with CKD.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared.

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Table 1. Classification of office BP and definition of hypertension grades in adults and adolescents ≥ 16 years old (from [1], with permission).

Category Systolic (mmHg) Diastolic (mmHg)

Optimal	SBP <120	and DBP <80 mmHg
Normal	SBP 120–129	and DBP 80–84 mmHg
High-normal	SBP 130–139	and/or DBP 85–89 mmHg
Grade 1 hypertension	SBP 140–159	and/or DBP 90–99 mmHg
Grade 2 hypertension	SBP 160–179	and/or DBP 100–109 mmHg
Grade 3 hypertension	SBP ≥ 180	and/or DBP ≥ 110 mmHg
Isolated systolic hypertension ^a	SBP ≥ 140	and DBP <90 mmHg
Isolated diastolic hypertension ^a	SBP <140	and DBP ≥ 90 mmHg

The BP category is defined by the highest level of BP, whether systolic or diastolic.

a) Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to systolic blood pressure (SBP) and diastolic blood pressure (DBP) values in the ranges indicated.

Table 2. Important changes and additions in recommendations relevant to hypertension in CKD patients in the 2023 ESH Guidelines in relation to previous Guideline versions (for Class or Recommendation and Level of Evidence grading, if available, see Figure 1 and text).

Therapeutic area	Recommendation
BP Targets in CKD	In all patients with CKD the primary goal is to lower office BP to <140/90 mmHg
	In most patients with CKD (especially, young patients, patients with an ACR \geq 300 mg/g, high CV risk patients) office BP should be lowered to <130/80 mmHg if tolerated.
	In kidney transplant patients with hypertension, office BP should be lowered to <130/80 mmHg.
	In patients with CKD, a BP target of <120/70 mmHg is not recommended.
Antihypertensive drug use in CKD	Step 1 of treatment includes combination of an ACEI or ARB + CCB or T_{12} Diuretic if eGFR \geq 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 ² *
	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 \geq 30 ml/min/1.73m ² and potassium within the normal range or chlortalidone if eGFR <30 ml/min/1.73 m ² *
Kidney and heart protection	SGLT-2 inhibitors are recommended for patients with diabetic and nondiabetic CKD, if eGFR is at least 20 ml/min/1.73m ² .
	The non-steroidal MRA finerenone is recommended in patients with CKD and albuminuria associated with type 2 DM, if eGFR is at least 25 ml/min/1.73m ² and serum potassium <5.0 mmol/L.
Potassium management	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
Atherosclerotic renovascular disease	Revascularization on top of medical therapy should be offered in patients with secondary hypertension due to ARVD or those with high-risk clinical phenotypes (flash pulmonary edema, refractory hypertension, or rapid loss of kidney function) with documented high-grade stenosis (\geq 70%)
	Medical therapy alone could be used for individuals with asymptomatic ARVD with stenosis <70%, patients with mild/moderate hypertension, easily controlled with antihypertensive drugs and low-grade stenosis, or patients with non-viable kidney parenchyma.

* excludes patients with CKD G5 on dialysis.

CKD: chronic kidney disease; ACR: albumin excretion ratio; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCB: calcium channel blocker; _{T/TL}Diuretic: thiazide or thiazide like diuretic; eGFR: estimated glomerular filtration rate; SGLT2i: sodium-glucose transporter 2 inhibitor; MRA: mineralocorticoid receptor antagonist; DM: diabetes mellitus RAS: renin-angiotensin system; ARVD: atherosclerotic renovascular disease

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Figure 1. Cardiovascular risk stratification according to grade and stage of hypertension (from [1], with permission).

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors ^a	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥4	Very high risk	Very high risk	Very high risk	Very high risk

■ <50 years	■ 60–69 years	■ ≥70 years	Complementary risk estimation in Stage 1 with SCORE2/SCORE2-OP
■ <2.5%	■ <5%	■ <7.5%	
■ 2.5 to <7.5%	■ 5 to <10%	■ 7.5 to <15%	
■ ≥7.5%	■ ≥10%	■ ≥15%	

HMOD: Hypertension mediated organ damage, defined as increased large artery stiffness, non-hemodynamically significant atheromatous plaque (stenosis) on imaging, left ventricular hypertrophy, CKD G1-G2/A2 (i.e., albuminuria 30–300 mg/g with eGFR ≥60 ml/min/1.73 m²) or G3 (i.e., eGFR 30–59 ml/min/1.73 m²), ankle–brachial index <0.9 or advanced retinopathy; CVD: cardiovascular disease; CKD: chronic kidney disease, BP: Blood pressure, SBP: systolic blood pressure; DBP: diastolic blood pressure;

Figure 2. Treatment strategies in patients with hypertension and chronic kidney disease (from [1], with permission).

Recommendations and statements	CoR	LoE
BP should be monitored at all stages of CKD, because hypertension is the most important risk factor for end-stage kidney disease (ESKD).	I	A
Non-dipping or elevated night-time BP are frequent in CKD patients and should be monitored by ABPM or HBPM.	I	B
In both diabetic and non-diabetic CKD with hypertension, BP-lowering treatment slows the decline of kidney function and reduces the risk of ESKD and CV outcomes.	I	A
Immediate lifestyle interventions and antihypertensive drug treatment are recommended in most patients with CKD independently of the CKD stage if SBP \geq 140mmHg or DBP \geq 90mmHg.	I	C
In all patients with CKD the primary goal is to lower office BP to <140 mmHg systolic and <90 mmHg diastolic.	I	A
In most CKD patients (young patients, patients with an albumin/creatinine ratio \geq 300 mg/g, high CV risk patients) office BP may be lowered to <130/80 mmHg if tolerated.	II	B
In kidney transplant patients with hypertension, office BP may be lowered to <130 mmHg systolic and <80 mmHg diastolic.	II	B
In patients with CKD, a BP target of less than 120/70 mmHg is not recommended.	III	C
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.	I	A

Dual combination of an ACEi with an ARB is not recommended.	III	A
SGLT2is inhibitors are recommended for patients with diabetic and non-diabetic nephropathies CKD if eGFR is at least 20 ml/min/1.73 ² . ^a	I	A
The non-steroidal MRA finerenone is recommended in patients with CKD and albuminuria associated with type 2 diabetes mellitus if eGFR is at least 25 ml/min/1.73 ² and serum potassium <5.0 mmo/L.	I	A
In CKD patients with hyperkalemia a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue.	II	B

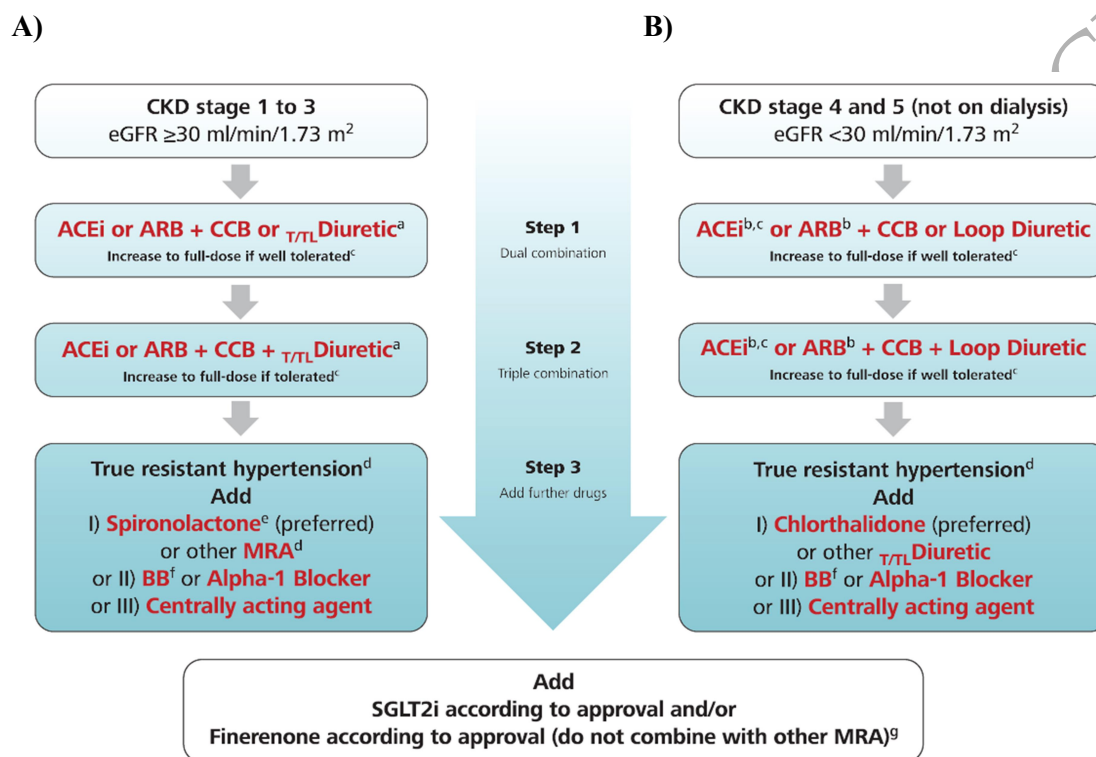
^aAdditional eGFR and albuminuria criteria apply for initiation of treatment with different SGLT2is

according to their respective approval.

CoR: Class of recommendation; LoE: level of evidence; BP: blood pressure; T/TL: thiazide/thiazide-like; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCB: calcium channel blocker; ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; SGLT2is: sodium-glucose transporter 2 inhibitors; RAS: renin-angiotensin system; MRA: mineralocorticoid receptor antagonists.

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Figure 3. BP-lowering therapy in patients with hypertension and chronic kidney disease (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) SGLT2is and Finerenone should be used according to their approval for CKD treatment (from [1], with permission).



BP: blood pressure; T/TL: thiazide/thiazide-like; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCB: calcium channel blocker; ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; SGLT2is: sodium-glucose transporter 2 inhibitors; MRA: mineralocorticoid receptor antagonist