

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

Pantelis Sarafidis<sup>1</sup>, Roland Schmieder<sup>2</sup>, Michel Burnier<sup>3</sup>, Alexandre Persu<sup>4</sup>, Andrzej Januszewicz<sup>5</sup>, Jean-Michel Halimi<sup>6</sup>, Mustafa Arici<sup>7</sup>, Alberto Ortiz<sup>8</sup>, Christoph Wanner<sup>9</sup>, Giuseppe Mancina<sup>10</sup> and Reinhold Kreutz<sup>11</sup>

<sup>1</sup>1st Department of Nephrology, Aristotle University of Thessaloniki, Hippokraton Hospital, Thessaloniki, Greece

<sup>2</sup>Department of Nephrology and Hypertension, University Hospital Erlangen, Germany

<sup>3</sup>Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

<sup>4</sup>Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

<sup>5</sup>Department of Hypertension, National Institute of Cardiology, Warsaw, Poland

<sup>6</sup>Service de Néphrologie-Hypertension, Dialyses, Transplantation rénale, CHRU Tours, Tours, France and INSERM SPHERE U1246, Université Tours, Université de Nantes, Tours, France

<sup>7</sup>Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey

<sup>8</sup>Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain

<sup>9</sup>Division of Nephrology, University Hospital Würzburg, Germany

<sup>10</sup>University of Milano-Bicocca, Milan, Italy

<sup>11</sup>Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institut für Klinische Pharmakologie und Toxikologie, Berlin, Germany

Correspondence to: Pantelis A. Sarafidis; E-mail: [psarafidis11@yahoo.gr](mailto:psarafidis11@yahoo.gr)

## 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 blood pressure (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 chlorthalidone for patients with resistant hypertension with estimated glomerular filtration rate (eGFR) higher or lower than 30 mL/min/1.73 m<sup>2</sup>, respectively; use of a sodium-glucose cotransporter 2 inhibitor for patients with CKD and estimated eGFR ≥20 mL/min/1.73 m<sup>2</sup>; use of finerenone for patients with CKD, type 2 diabetes mellitus, albuminuria, eGFR ≥25 mL/min/1.73 m<sup>2</sup> 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 from 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 from ESH and ERA. The sections summarized are those referring to the role of CKD in hypertension staging and cardiovascular (CV) risk stratification, the evaluation of hypertension-mediated kid-

ney 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 systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg [1]. The document

Received: December 9, 2023; Editorial decision: December 15, 2023

© The Author(s) 2024. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

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

Category	Systolic and diastolic blood pressure (SBP and DBP)
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 $\geq 180$ and/or DBP $\geq 110$ mmHg
Isolated systolic hypertension <sup>a</sup>	SBP $\geq 140$ and DBP <90 mmHg
Isolated diastolic hypertension <sup>a</sup>	SBP <140 and DBP $\geq 90$ mmHg

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

<sup>a</sup>Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to SBP and DBP values in the ranges indicated.

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 randomized controlled trials (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 data, Fig. S1](#).

In addition to grades of hypertension, which are based on BP values, the Guidelines also distinguish 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 CV 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 (SCr), estimation of glomerular filtration rate (eGFR) 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 SCr 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 m<sup>2</sup> 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) [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 night-time 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 CV 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 CV 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/1.73 m<sup>2</sup>) 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/1.73 m<sup>2</sup>) 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 CV risk stratification in patients with hypertension (Fig. 1).










## TREATMENT OF HYPERTENSION IN CKD

### Initiation of treatment

The 2023 ESH Guidelines recommend 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) [1]. 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  $\geq 130$  or DBP  $\geq 80$  mmHg) (CoR I, LoE A). Nephrologists should note that many patients with CKD are falling in the latter category. In patients  $\geq 80$  years old, 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).

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 <sup>a</sup>	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

<b>&lt;50 years</b>	<b>60–69 years</b>	<b>≥70 years</b>	
 <2.5%	 <5%	 <7.5%	Complementary risk estimation in Stage 1 with SCORE2/SCOR2-OP
 2.5 to <7.5%	 5 to <10%	 7.5 to <15%	
 ≥7.5%	 ≥10%	 ≥15%	

**Figure 1:** CV risk stratification according to grade and stage of hypertension (from [1], with permission). 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 m<sup>2</sup>) or G3 (i.e. eGFR 30–59 mL/min/1.73 m<sup>2</sup>), ankle-brachial index <0.9 or advanced retinopathy.

## 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 diabetes mellitus (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 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 end-stage kidney disease (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 with 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 by 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 SCr, 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 9361 hypertensive patients of increased CV burden to intensive (target SBP <120 mmHg) or standard (target SBP <140 mmHg) treatment [25]. Of these patients, about 28% had CKD with eGFR between 20 and 60 mL/min/1.73 m<sup>2</sup>, but very few had albuminuria A2 or A3,

as individuals with proteinuria  $>1$  g/day or  $>1$  g/g were excluded. Importantly, DM, 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 CV events as well as CV 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 m<sup>2</sup>) and had both the primary outcome and the main kidney outcome (with only few events) be 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 type 2 diabetes mellitus (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 SCr  $>1.5$  mg/dL; thus, it can offer very little insight into 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 with 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  $<130$  mmHg), 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% confidence interval 0.63–1.00,  $P = .048$ ) 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  $<130$  mmHg and DBP  $<80$  mmHg, 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 CV comorbidities that require respective target BP values to be taken into account, and thus these CV 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 Fig. 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). Actively targeting 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  $<5$  g ( $\sim 2$  g 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

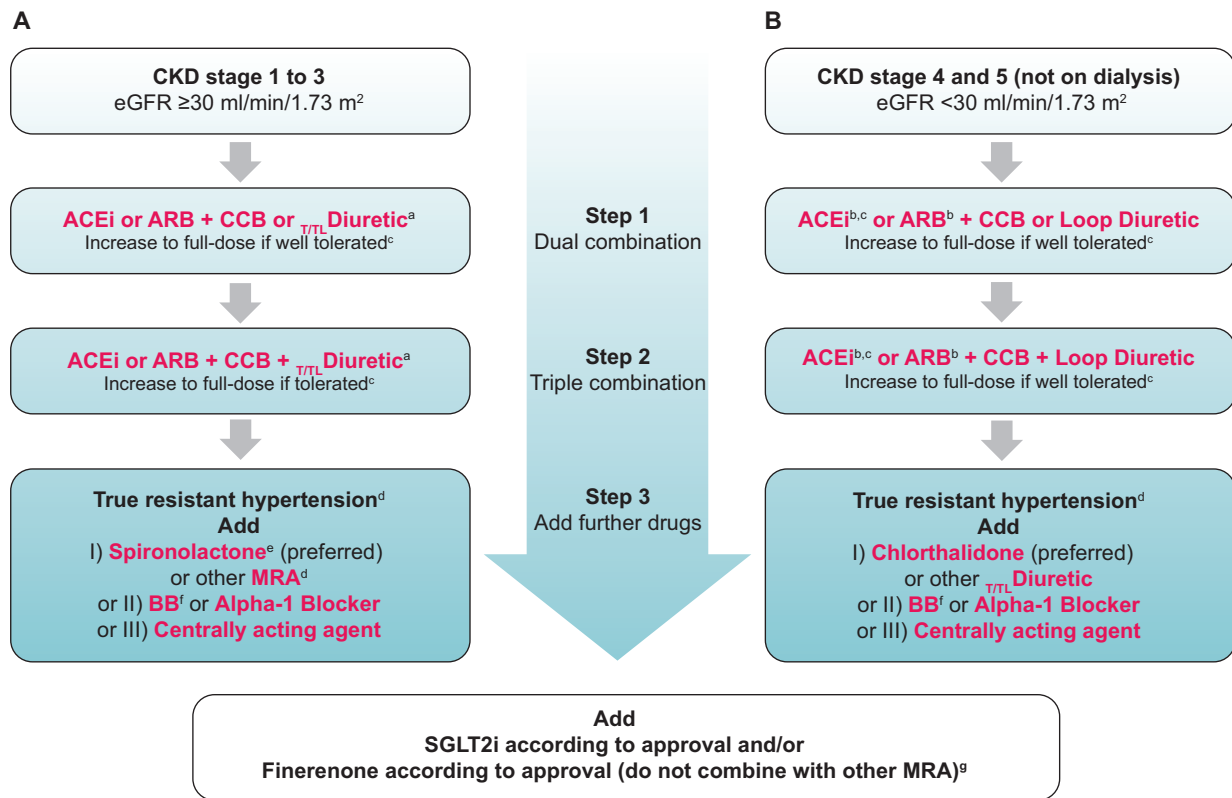
Recommendations and statements	CoR	LoE
BP should be monitored at all stages of CKD, because hypertension is the most important risk factor for end-stage kidney disease (ESKD).	I	A
Non-dipping or elevated night-time BP are frequent in CKD patients and should be monitored by ABPM or HBPM.	I	B
In both diabetic 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 $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg.	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 <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 >300mg/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 <sup>2</sup> <sup>a</sup>	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 <sup>2</sup> and serum potassium <5.0 mmol/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

<sup>a</sup>Additional eGFR and albuminuria criteria apply for initiation of treatment with different SGLT2is according to their respective approval.

**Figure 2:** Treatment strategies in patients with hypertension and CKD (from [1], with permission).

antihypertensive agents can offer similar protection in individuals with and without CKD against major CV events (stroke, myocardial infarction, heart failure or CV 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 calcium channel blocker (CCB) or a thiazide/thiazide-like diuretic, if eGFR levels are  $\geq$ 45 mL/min/1.73 m<sup>2</sup> (up to CKD G3a), while in patients with an eGFR <30 mL/min/1.73 m<sup>2</sup> (CKD G4–G5), thiazide/thiazide-like diuretics should be generally replaced by loop diuretics, according



**Figure 3:** BP-lowering therapy in patients with hypertension and CKD. (A) Therapy for CKD G1–G3 (eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>). (B) Therapy for CKD G4–G5 (eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>) not on dialysis. (a) Transition from thiazide/thiazide-like (T/TL) diuretic to loop diuretic should be individualized in patients with eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>. (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  $\geq 140$  mmHg or DBP is  $\geq 90$  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 m<sup>2</sup> 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). T/TL: thiazide/thiazide-like.

to the updated algorithm presented in Fig. 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/1.73 m<sup>2</sup>, 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 angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-receptor blocker (ARB) is the treatment of choice, especially in those with moderately or severely increased albuminuria, where these agents were found to reduce proteinuria, the rate of GFR decline, and the risk of doubling of SCr 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), because 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 with placebo [47], but no evidence exists for better preservation of kidney function with RAS blockers compared with 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 m<sup>2</sup> 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 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 (Fig. 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 with 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 below 45 mL/min/1.73 m<sup>2</sup>, 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 chlorthalidone is clinically effective in lowering BP in patients with G4 CKD [64]. In general, in patients with CKD G3b (eGFR 30–44 mL/min/1.73 m<sup>2</sup>), diuretic therapy should be modified and the dosing individualized, while in patients with CKD G4 (eGFR <30 mL/min/1.73 m<sup>2</sup>), 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 mmHg [1]. The inadequate BP control should be confirmed by uncontrolled 24-h BP ( $\geq$ 130/80 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 (Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension) trial [66] and relevant meta-analyses [67]. However, patients with an eGFR with eGFR <45 mL/min/1.73 m<sup>2</sup> or potassium >4.5 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 (Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease) trial that used spironolactone with

addition of placebo or patiromer in patients with treatment resistant hypertension and eGFR 25 to  $\leq$ 45 mL/min/1.73 m<sup>2</sup>, BP was effectively reduced in both groups, but the rates of hyperkalemia (potassium  $\geq$ 5.5 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 (Chlorthalidone in Chronic Kidney Disease) 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 [69]; 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 [70]. 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 [70]. 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 [71]. 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 [69, 72, 73]. In a large registry of renal denervated patients, the BP reduction was long-lasting and devoid of significant safety problems [71, 74]. RDN can thus be proposed as an adjunctive therapy to patients with resistant hypertension provided eGFR >40 mL/min/1.73 m<sup>2</sup>, in whom BP control cannot be achieved nor serious side effects cannot be avoided with antihypertensive medications [72, 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 CV outcome trials with SGLT2is 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 [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, i.e., the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) [84], DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) [85] and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) studies [86], to conclude that all three trials were prematurely terminated due to benefit and showed significant reductions compared with 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 urine ACR 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 CV 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 over-activation [96]. Finerenone is a novel, non-steroidal MRA with different duration of action and tissue distribution from steroidal MRAs, which 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 (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease), that tested

finerenone in T2DM patients with CKD and moderately or severely increased albuminuria on top of ACEi or ARB treatment. 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 [100]. 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 [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 CV outcome, with consistent beneficial effects on kidney outcomes and similar tolerability profile [101]. In the FIDELITY (Finerenone in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis) on-treatment analysis combining the patient population of both trials, finerenone reduced mortality by 18% compared with placebo [102]. Other non-steroidal MRAs (esaxerenone and aparenone) have also been shown to significantly reduce albuminuria in CKD patients in phase 2 clinical trials [96], but have not yet been tested in hard kidney outcome studies.

In view of the above evidence, the 2023 ESH Guidelines recommended using 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 mL/min/1.73 m<sup>2</sup>, 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 or severe albuminuria, if eGFR is at least 25 mL/min/1.73 m<sup>2</sup> and serum potassium is <5.0 mmol/L (CoR I, LoE A). 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.

## HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

The 2023 ESH Guidelines also discuss in considerable length the 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 comorbidity post transplantation, with ABPM studies estimating hypertension prevalence in >95% of KTRs [107]. Elevated BP is associated with kidney function decline, target-organ damage, CV events and reduced graft and patient survival [108–110]. As such, hypertension may play an important role towards the significantly higher residual CV 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 sympathetic nervous system 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 with 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 CV outcomes or death, whereas the incidence in hyperkalemia increased [120]. CCBs have consistently been 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 making 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

**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 Fig. 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 $T_{7/TL}$ Diuretic if eGFR $\geq$ 30 mL/min/1.73 m <sup>2</sup> , or combination of an ACEi or ARB + CCB or loop diuretic if eGFR <30 mL/min/1.73 m <sup>2a</sup> 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/1.73 m <sup>2</sup> and potassium within the normal range or chlortalidone if eGFR <30 mL/min/1.73 m <sup>2a</sup>
Kidney and heart protection	SGLT2is are recommended for patients with diabetic and nondiabetic CKD, if eGFR is at least 20 mL/min/1.73 m <sup>2</sup> 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 <sup>2</sup> 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
ARVD	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

<sup>a</sup>Excludes patients with CKD G5 on dialysis.  
 $T_{7/TL}$ Diuretic: thiazide or thiazide like diuretic.

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 patients with non-viable kidney parenchyma, where revascularization has little to offer. In all the latter 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 the European Renal Best Practice 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 (Table 2). 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.

## SUPPLEMENTARY DATA

Supplementary data are available at [ndt](https://academic.oup.com/ndt/article/39/6/929/7608518) online.

## ACKNOWLEDGEMENTS

The authors wish to thank Dr Marieta Theodorakopoulou for her help in editing and proofreading this manuscript.

## DATA AVAILABILITY STATEMENT

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

## CONFLICT OF INTEREST STATEMENT

P.S. reports research support to his institution from Boehringer Ingelheim, Genesis Pharma, and Vianex and advisor or speaker fees (personal or institutional) from Bayer, Astra-Zeneca, Primeview, Healthink, Recor Medical, Boehringer Ingelheim, Menarini, Baxter, Astellas, Genesis Pharma, Springer, Peervoice, WebMD, AICME and Science Collected R.S. reports grants to the Institution: Amgen, Ablative Solution, Boehringer Ingelheim, IPPmed, Medtronic, Novartis, NovoNordisk, Recor and Speaker or Advisor fees from Ablative Solutions, Apontis, AstraZeneca, Bayer, Boehringer Ingel-

heim, Daiichi Sankyo, Lilly, Kalos, Medtronic, Merck, NovoNordisk, Novartis, Recor, Servier, M.B. has received speaker fees from Servier, Menarini, Boehringer Ingelheim, Astra-Zeneca, and Tecnimede A.P. reports speaker or advisor fees from Ablative Solutions, Quantum Genomics, Servier and ReCor Medical A.J. reports speaker or advisor fees from Servier, Gedeon-Richter, Medtronic, KRKA, Novartis, AstraZeneca, Adamed, Bausch, Polfarma, Novartis, Berlin Chemie, Termedia, ViaMedica, Medycyna Praktyczna J-M.H. has received research funding from Astra Zeneca and Speaker Fees from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim France, Novartis, Servier, Vifor and Fresenius Pharma M.A. has received payment or honoraria for lectures, presentations, speakers' bureaus, publication writing or educational events from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, MSD, Novo Nordisk, Sandoz and Sanofi. A.O. has received grants from Sanofi and consultancy or speaker fees or travel support from Adviccene, Alexion, Astellas, AstraZeneca, Amicus, Amgen, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Lilly, Freeline, Idorsia, Chiesi, Otsuka, Novo-Nordisk, Sys-mex and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Catedra Mundipharma-UAM of DKD and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. He has stock in Telara Farma. C.W. reports speaker or advisor fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL-Vifor, Eli Lilly and Company, GSK, MSD, Novo Nordisk, and Sanofi G.M. has received compensations as speaker/chairman/consultant from Berlin Chemie, Exicon Consulting, Menarini Int, Merck Healthcare KGaA, Medtronic Inc USA, Recordati, Sanofi, Servier, and Sun Laboratories R.K. reports research support from Bayer; Speaker fees from Bayer, Boehringer Ingelheim, CinCor Pharma, Daiichi Sankyo, Ferrer, Merck, Menarini Group, MSD, Sanofi, Servier, Tecnimede; and Advisor fees from Bayer and Servier.

## REFERENCES

1. Mancia G, Kreutz R, Brunström M *et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;**41**:1874–2071.
2. Sarafidis PA, Persu A, Agarwal R *et al.* Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *J Hypertens* 2017;**35**:657–76.
3. Sarafidis PA, Persu A, Agarwal R *et al.* Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *Nephrol Dial Transplant* 2017;**32**:620–40.
4. Lewington S, Clarke R, Qizilbash N *et al.*; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–13.

5. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006>
6. McTaggart MP, Newall RG, Hirst JA et al. Diagnostic accuracy of point-of-care tests for detecting albuminuria: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**:550–7. <https://doi.org/10.7326/M13-2331>
7. Levin A, Stevens PE, Bilous RW et al. Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int (Suppl)* 2013;**3**:1–150.
8. Caroli A, Remuzzi A, Lerman LO. Basic principles and new advances in kidney imaging. *Kidney Int* 2021;**100**:1001–11. <https://doi.org/10.1016/j.kint.2021.04.032>
9. Ponte B, Pruijm M, Ackermann D et al. Reference values and factors associated with renal resistive index in a family-based population study. *Hypertension* 2014;**63**:136–42. <https://doi.org/10.1161/HYPERTENSIONAHA.113.02321>
10. Drawz PE, Alper AB, Anderson AH et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016;**11**:642–52. <https://doi.org/10.2215/CJN.08530815>
11. Gorostidi M, Sarafidis PA, de la Sierra A et al. Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: a 5,693-patient cross-sectional analysis from Spain. *Am J Kidney Dis* 2013;**62**:285–94. <https://doi.org/10.1053/j.ajkd.2013.03.025>
12. Parati G, Ochoa JE, Bilo G et al. Hypertension in chronic kidney disease part 1: out-of-office blood pressure monitoring: methods, thresholds, and patterns. *Hypertension* 2016;**67**:1093–101. <https://doi.org/10.1161/HYPERTENSIONAHA.115.06895>
13. Parati G, Ochoa JE, Bilo G et al. Hypertension in chronic kidney disease part 2: role of ambulatory and home blood pressure monitoring for assessing alterations in blood pressure variability and blood pressure profiles. *Hypertension* 2016;**67**:1102–10. <https://doi.org/10.1161/HYPERTENSIONAHA.115.06896>
14. Matsushita K, Mahmoodi BK, Woodward M et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012;**307**:1941–51. <https://doi.org/10.1001/jama.2012.3954>
15. Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and non-diabetic individuals. *JAMA* 2001;**286**:421–6. <https://doi.org/10.1001/jama.286.4.421>
16. Klag MJ, Whelton PK, Randall BL et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;**334**:13–8. <https://doi.org/10.1056/NEJM199601043340103>
17. Wu S, Li M, Lu J et al. Blood pressure levels, cardiovascular events, and renal outcomes in chronic kidney disease without antihypertensive therapy: a nationwide population-based cohort study. *Hypertension* 2023;**80**:640–9. <https://doi.org/10.1161/HYPERTENSIONAHA.122.19902>
18. Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in renal disease study group. *N Engl J Med* 1994;**330**:877–84. <https://doi.org/10.1056/NEJM199403313301301>
19. Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease study. *Ann Intern Med* 1995;**123**:754–62. <https://doi.org/10.7326/0003-4819-123-10-199511150-00003>
20. Wright JT, Bakris G, Greene T et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;**288**:2421–31. <https://doi.org/10.1001/jama.288.19.2421>
21. Lea J, Greene T, Hebert L et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005;**165**:947–53. <https://doi.org/10.1001/archinte.165.8.947>
22. Sarnak MJ, Greene T, Wang X et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005;**142**:342–51. <https://doi.org/10.7326/0003-4819-142-5-200503010-00009>
23. Appel LJ, Wright JT, Greene T et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**:918–29. <https://doi.org/10.1056/NEJMoa0910975>
24. Ku E, Sarnak MJ, Toto R et al. Effect of blood pressure control on long-term risk of end-stage renal disease and death among subgroups of patients with chronic kidney disease. *J Am Heart Assoc* 2019;**8**:e012749. <https://doi.org/10.1161/JAHA.119.012749>
25. SPRINT Research Group; Wright JT, Williamson JD, Whelton PK et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
26. Cheung AK, Rahman M, Reboussin DM et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**:2812–23. <https://doi.org/10.1681/ASN.2017020148>
27. Johnson KC, Whelton PK, Cushman WC et al. Blood pressure measurement in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 2018;**71**:848–57. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10479>
28. Drawz PE, Agarwal A, Dwyer JP et al. Concordance between blood pressure in the systolic blood pressure intervention trial and in routine clinical practice. *JAMA Intern Med* 2020;**180**:1655–63. <https://doi.org/10.1001/jamainternmed.2020.5028>
29. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**:703–13. <https://doi.org/10.1136/bmj.317.7160.703>
30. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;**351**:1755–62. [https://doi.org/10.1016/S0140-6736\(98\)04311-6](https://doi.org/10.1016/S0140-6736(98)04311-6)
31. ACCORD Study Group; Cushman WC, Evans GW, Byington RP et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–85.
32. Sarafidis PA, Lazaridis AA, Ruiz-Hurtado G et al. Blood pressure reduction in diabetes: lessons from ACCORD, SPRINT and EMPA-REG OUTCOME. *Nat Rev Endocrinol* 2017;**13**:365–74. <https://doi.org/10.1038/nrendo.2016.209>
33. Bakris GL, Weir MR, Shanifar S et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003;**163**:1555–65. <https://doi.org/10.1001/archinte.163.13.1555>
34. Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. *J Am Soc Nephrol* 2005;**16**:3027–37. <https://doi.org/10.1681/ASN.2004110919>

35. Malhotra R, Nguyen HA, Benavente O et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. *JAMA Intern Med* 2017;**177**:1498–505. <https://doi.org/10.1001/jamainternmed.2017.4377>
36. Aggarwal R, Petrie B, Bala W et al. Mortality outcomes with intensive blood pressure targets in chronic kidney disease patients. *Hypertension* 2019;**73**:1275–82. <https://doi.org/10.1161/HYPERTENSIONAHA.119.12697>
37. Vogt L, Waanders F, Boomsma F et al. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**:999–1007. <https://doi.org/10.1681/ASN.2007060693>
38. Blood Pressure Lowering Treatment Trialists' Collaboration; Ninomiya T, Perkovic V, Turnbull F et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ* 2013;**347**:f5680.
39. Strippoli GFM, Craig M, Deeks JJ et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004;**329**:828. <https://doi.org/10.1136/bmj.38237.585000.7C>
40. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9. <https://doi.org/10.1056/NEJMoa011161>
41. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60. <https://doi.org/10.1056/NEJMoa011303>
42. Barnett AH, Bain SC, Bouter P et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;**351**:1952–61. <https://doi.org/10.1056/NEJMoa042274>
43. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997;**349**:1857–63. [https://doi.org/10.1016/S0140-6736\(96\)11445-8](https://doi.org/10.1016/S0140-6736(96)11445-8)
44. Hou FF, Zhang X, Zhang GH et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**:131–40. <https://doi.org/10.1056/NEJMoa053107>
45. Parving H-H, Brenner BM, McMurray JJV et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**:2204–13. <https://doi.org/10.1056/NEJMoa1208799>
46. Fried LF, Emanuele N, Zhang JH et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. <https://doi.org/10.1056/NEJMoa1303154>
47. Haller H, Ito S, Izzo JL et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;**364**:907–17. <https://doi.org/10.1056/NEJMoa1007994>
48. Rahman M, Pressel S, Davis BR et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT). *Arch Intern Med* 2005;**165**:936–46. <https://doi.org/10.1001/archinte.165.8.936>
49. Bhandari S, Mehta S, Khwaja A et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;**387**:2021–32. <https://doi.org/10.1056/NEJMoa2210639>
50. Sarafidis PA, Blacklock R, Wood E et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;**7**:1234–41. <https://doi.org/10.2215/CJN.01150112>
51. Einhorn LM, Zhan M, Hsu VD et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**:1156–62. <https://doi.org/10.1001/archinternmed.2009.132>
52. Yildirim T, Arici M, Piskinpasa S et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? *Ren Fail* 2012;**34**:1095–9. <https://doi.org/10.3109/0886022X.2012.717478>
53. Epstein M, Reaven NL, Funk SE et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;**21**:S212–20.
54. Bakris GL, Pitt B, Weir MR et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA* 2015;**314**:151–61. <https://doi.org/10.1001/jama.2015.7446>
55. Roger SD, Spinowitz BS, Lerma EV et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *Am J Nephrol* 2019;**50**:473–80. <https://doi.org/10.1159/000504078>
56. Sarafidis PA, Georgianos PI, Bakris GL. Advances in treatment of hyperkalemia in chronic kidney disease. *Expert Opin Pharmacother* 2015;**16**:2205–15. <https://doi.org/10.1517/14656566.2015.1083977>
57. Valdivielso JM, Balafa O, Ekart R et al. Hyperkalemia in chronic kidney disease in the new era of kidney protection therapies. *Drugs* 2021;**81**:1467–89. <https://doi.org/10.1007/s40265-021-01555-5>
58. Sarafidis PA, Khosla N, Bakris GL. Antihypertensive therapy in the presence of proteinuria. *Am J Kidney Dis* 2007;**49**:12–26. <https://doi.org/10.1053/j.ajkd.2006.10.014>
59. Ott C, Schmieder RE. Diagnosis and treatment of arterial hypertension 2021. *Kidney Int* 2022;**101**:36–46. <https://doi.org/10.1016/j.kint.2021.09.026>
60. Adler AI, Stratton IM, Neil HA et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;**321**:412–9. <https://doi.org/10.1136/bmj.321.7258.412>
61. Bakris GL, Sarafidis PA, Weir MR et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010;**375**:1173–81. [https://doi.org/10.1016/S0140-6736\(09\)62100-0](https://doi.org/10.1016/S0140-6736(09)62100-0)
62. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol* 2008;**52**:1749–57. <https://doi.org/10.1016/j.jacc.2008.08.036>
63. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part I: mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. *Expert Opin Drug Saf* 2010;**9**:243–57. <https://doi.org/10.1517/14740330903499240>

64. Agarwal R, Sinha AD, Cramer AE et al. Chlorthalidone for hypertension in advanced chronic kidney disease. *N Engl J Med* 2021;**385**:2507–19. <https://doi.org/10.1056/NEJMoa2110730>
65. Loutradis C, Sarafidis P. Hypertension in patients with advanced chronic kidney disease. In: Mancia G, Grassi G, Tsioufis K et al. (eds), *Manual of Hypertension of the European Society of Hypertension*. Boca Raton, FL: CRC Press, 2019. <https://doi.org/10.1201/9780429199189>
66. Williams B, MacDonald TM, Morant S et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;**386**:2059–68. [https://doi.org/10.1016/S0140-6736\(15\)00257-3](https://doi.org/10.1016/S0140-6736(15)00257-3)
67. Chen C, Zhu X-Y, Li D et al. Clinical efficacy and safety of spironolactone in patients with resistant hypertension: a systematic review and meta-analysis. *Medicine (Baltimore)* 2020;**99**:e21694. <https://doi.org/10.1097/MD.00000000000021694>
68. Agarwal R, Rossignol P, Romero A et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019;**394**:1540–50. [https://doi.org/10.1016/S0140-6736\(19\)32135-X](https://doi.org/10.1016/S0140-6736(19)32135-X)
69. Böhm M, Kario K, Kandzari DE et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020;**395**:1444–51. [https://doi.org/10.1016/S0140-6736\(20\)30554-7](https://doi.org/10.1016/S0140-6736(20)30554-7)
70. Krieger EM, Drager LF, Giorgi DMA et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (Resistant Hypertension Optimal Treatment). *Hypertension* 2018;**71**:681–90. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10662>
71. Mahfoud F, Böhm M, Schmieder R et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPPLICITY Registry. *Eur Heart J* 2019;**40**:3474–82. <https://doi.org/10.1093/eurheartj/ehz118>
72. Azizi M, Sanghvi K, Saxena M et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet* 2021;**397**:2476–86. [https://doi.org/10.1016/S0140-6736\(21\)00788-1](https://doi.org/10.1016/S0140-6736(21)00788-1)
73. Azizi M, Schmieder RE, Mahfoud F et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;**391**:2335–45. [https://doi.org/10.1016/S0140-6736\(18\)31082-1](https://doi.org/10.1016/S0140-6736(18)31082-1)
74. Mahfoud F, Mancia G, Schmieder RE et al. Cardiovascular risk reduction after renal denervation according to time in therapeutic systolic blood pressure range. *J Am Coll Cardiol* 2022;**80**:1871–80. <https://doi.org/10.1016/j.jacc.2022.08.802>
75. Barbato E, Azizi M, Schmieder RE et al. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2023;**44**:1313–30. <https://doi.org/10.1093/eurheartj/ehad054>
76. Imprialos KP, Sarafidis PA, Karagiannis AI. Sodium-glucose cotransporter-2 inhibitors and blood pressure decrease: a valuable effect of a novel antidiabetic class? *J Hypertens* 2015;**33**:2185–97. <https://doi.org/10.1097/HJH.0000000000000719>
77. Papadopoulou E, Loutradis C, Tzatzagou G et al. Dapagliflozin decreases ambulatory central blood pressure and pulse wave velocity in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *J Hypertens* 2021;**39**:749–58. <https://doi.org/10.1097/HJH.0000000000002690>
78. Cherney DZI, Cooper ME, Tikkanen I et al. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int* 2018;**93**:231–44. <https://doi.org/10.1016/j.kint.2017.06.017>
79. Piperidou A, Sarafidis P, Boutou A et al. The effect of SGLT-2 inhibitors on albuminuria and proteinuria in diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019;**37**:1334–43. <https://doi.org/10.1097/HJH.0000000000002050>
80. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;**400**:1788–801. [https://doi.org/10.1016/S0140-6736\(22\)02074-8](https://doi.org/10.1016/S0140-6736(22)02074-8)
81. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28. <https://doi.org/10.1056/NEJMoa1504720>
82. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57. <https://doi.org/10.1056/NEJMoa1611925>
83. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–57. <https://doi.org/10.1056/NEJMoa1812389>
84. Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. <https://doi.org/10.1056/NEJMoa1811744>
85. Heerspink HJL, Stefánsson BV, Correa-Rotter R et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46. <https://doi.org/10.1056/NEJMoa2024816>
86. EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–27.
87. Sarafidis P, Ortiz A, Ferro CJ et al. Sodium-glucose co-transporter-2 inhibitors for patients with diabetic and non-diabetic chronic kidney disease: a new era has already begun. *J Hypertens* 2021;**39**:1090–7. <https://doi.org/10.1097/HJH.0000000000002776>
88. Sarafidis PA, Stafylas PC, Kanaki AI et al. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. *Am J Hypertens* 2008;**21**:922–9. <https://doi.org/10.1038/ajh.2008.206>
89. Sharma P, Blackburn RC, Parke CL et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. *Cochrane Database Syst Rev* 2011;**10**:CD007751.
90. Lin Y-C, Lin J-W, Wu M-S et al. Effects of calcium channel blockers comparing to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with hypertension and chronic kidney disease stage 3 to 5 and dialysis: a sys-

- tematic review and meta-analysis. *PLoS One* 2017;**12**:e0188975. <https://doi.org/10.1371/journal.pone.0188975>
91. Sarafidis P, Papadopoulos CE, Kamperidis V et al. Cardiovascular protection with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in chronic kidney disease: a milestone achieved. *Hypertension* 2021;**77**:1442–55. <https://doi.org/10.1161/HYPERTENSIONAHA.121.17005>
  92. Mehdi UF, Adams-Huet B, Raskin P et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 2009;**20**:2641–50. <https://doi.org/10.1681/ASN.2009070737>
  93. Epstein M, Williams GH, Weinberger M et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;**1**:940–51. <https://doi.org/10.2215/CJN.00240106>
  94. Alexandrou M-E, Papagianni A, Tsapas A et al. Effects of mineralocorticoid receptor antagonists in proteinuric kidney disease: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019;**37**:2307–24. <https://doi.org/10.1097/HJH.0000000000002187>
  95. Ortiz A, Ferro CJ, Balafa O et al. Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. *Nephrol Dial Transplant* 2023;**38**:10–25.
  96. Alexandrou M-E, Theodorakopoulou MP, Sarafidis PA. Role of mineralocorticoid receptor antagonists in diabetic kidney disease. *Kidney Dialysis* 2022;**2**:163–82. <https://doi.org/10.3390/kidneydial2020019>
  97. Agarwal R, Kolkhof P, Bakris G et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021;**42**:152–61. <https://doi.org/10.1093/eurheartj/ehaa736>
  98. Ruilope LM, Agarwal R, Anker SD et al. Blood pressure and cardiorenal outcomes with finerenone in chronic kidney disease in type 2 diabetes. *Hypertension* 2022;**79**:2685–95. <https://doi.org/10.1161/HYPERTENSIONAHA.122.19744>
  99. Bakris GL, Agarwal R, Chan JC et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;**314**:884–94. <https://doi.org/10.1001/jama.2015.10081>
  100. Bakris GL, Agarwal R, Anker SD et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–29. <https://doi.org/10.1056/NEJMoa2025845>
  101. Ruilope LM, Agarwal R, Anker SD et al. Design and baseline characteristics of the finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease trial. *Am J Nephrol* 2019;**50**:345–56. <https://doi.org/10.1159/000503712>
  102. Filippatos G, Anker SD, August P et al. Finerenone and effects on mortality in chronic kidney disease and type 2 diabetes: a FIDELITY analysis. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:183–91. <https://doi.org/10.1093/ehjcvp/pvad001>
  103. Buus NH, Carlsen RK, Hughes AD et al. Influence of renal transplantation and living kidney donation on large artery stiffness and peripheral vascular resistance. *Am J Hypertens* 2020;**33**:234–42. <https://doi.org/10.1093/ajh/hpz175>
  104. Xagas E, Sarafidis PA, Theodorakopoulou MP et al. A parallel evaluation of short- and mid-term changes of ambulatory blood pressure in kidney transplant recipients and kidney donors. *Clin Kidney J* 2022;**15**:2097–106. <https://doi.org/10.1093/ckj/sfac162>
  105. Korogiannou M, Sarafidis P, Alexandrou ME et al. Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against haemodialysis patients. *Clin Kidney J* 2022;**15**:951–60. <https://doi.org/10.1093/ckj/sfab275>
  106. Korogiannou M, Theodorakopoulou M, Sarafidis P et al. Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against chronic kidney disease patients. *Kidney Res Clin Pract* 2022;**41**:482–91. <https://doi.org/10.23876/j.krcp.21.250>
  107. Korogiannou M, Sarafidis P, Theodorakopoulou MP et al. Diagnostic performance of office versus ambulatory blood pressure in kidney transplant recipients. *Am J Nephrol* 2021;**52**:548–58. <https://doi.org/10.1159/000517358>
  108. Opelz G, Döhler B; Collaborative Transplant Study. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant* 2005;**5**:2725–31. <https://doi.org/10.1111/j.1600-6143.2005.01093.x>
  109. Pisano A, Mallamaci F, D'Arrigo G et al. Blood pressure monitoring in kidney transplantation: a systematic review on hypertension and target organ damage. *Nephrol Dial Transplant* 2021;**36**:1326–46. <https://doi.org/10.1093/ndt/gfab076>
  110. Alexandrou M-E, Ferro CJ, Boletis I et al. Hypertension in kidney transplant recipients. *World J Transplant* 2022;**12**:211–22. <https://doi.org/10.5500/wjt.v12.i8.211>
  111. Ying T, Shi B, Kelly PJ et al. Death after kidney transplantation: an analysis by era and time post-transplant. *J Am Soc Nephrol* 2020;**31**:2887–99. <https://doi.org/10.1681/ASN.2020050566>
  112. Halimi J-M, Ortiz A, Sarafidis PA et al. Hypertension in kidney transplantation: a consensus statement of the “hypertension and the kidney” working group of the European Society of Hypertension. *J Hypertens* 2021;**39**:1513–21. <https://doi.org/10.1097/HJH.0000000000002879>
  113. Pisano A, Mallamaci F, D'Arrigo G et al. Assessment of hypertension in kidney transplantation by ambulatory blood pressure monitoring: a systematic review and meta-analysis. *Clin Kidney J* 2022;**15**:31–42. <https://doi.org/10.1093/ckj/sfab135>
  114. Kooman JP, Christiaans MH, Boots JM et al. A comparison between office and ambulatory blood pressure measurements in renal transplant patients with chronic transplant nephropathy. *Am J Kidney Dis* 2001;**37**:1170–6. <https://doi.org/10.1053/ajkd.2001.24518>
  115. Mallamaci F, Tripepi R, D'Arrigo G et al. Long-term blood pressure monitoring by office and 24-h ambulatory blood pressure in renal transplant patients: a longitudinal study. *Nephrol Dial Transplant* 2019;**34**:1558–64. <https://doi.org/10.1093/ndt/gfy355>
  116. Loutradis C, Sarafidis P, Marinaki S et al. Role of hypertension in kidney transplant recipients. *J Hum Hypertens* 2021;**35**:958–69. <https://doi.org/10.1038/s41371-021-00540-5>
  117. Chatzikyrkou C, Schmieder RE, Schiffer M. Update on treatment of hypertension after renal transplantation. *Curr Hypertens Rep* 2021;**23**:25. <https://doi.org/10.1007/s11906-021-01151-8>
  118. Rice JB, White AG, Scarpati LM et al. Long-term systemic corticosteroid exposure: a systematic literature review. *Clin Ther* 2017;**39**:2216–29. <https://doi.org/10.1016/j.clinthera.2017.09.011>
  119. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation* 2010;**89**:1–14. <https://doi.org/10.1097/TP.0b013e3181c518cc>
  120. Pisano A, Bolignano D, Mallamaci F et al. Comparative effectiveness of different antihypertensive agents in kidney transplantation: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2020;**35**:878–87. <https://doi.org/10.1093/ndt/gfz092>

121. Ngo AT, Markar SR, De Lijster MS et al. A systematic review of outcomes following percutaneous transluminal angioplasty and stenting in the treatment of transplant renal artery stenosis. *Cardiovasc Intervent Radiol* 2015;**38**:1573–88. <https://doi.org/10.1007/s00270-015-1134-z>
122. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens* 2009;**27**:1333–40. <https://doi.org/10.1097/HJH.0b013e328329bbf4>
123. Persu A, Giavarini A, Touzé E et al. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens* 2014;**32**:1367–78. <https://doi.org/10.1097/HJH.0000000000000213>
124. Ritchie J, Green D, Chrysochou C et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis* 2014;**63**:186–97. <https://doi.org/10.1053/j.ajkd.2013.07.020>
125. Theodorakopoulou MP, Karagiannidis AG, Ferro CJ et al. Renal artery stenting in the correct patients with atherosclerotic renovascular disease: time for a proper renal and cardiovascular outcome study? *Clin Kidney J* 2022;**16**:201–4. <https://doi.org/10.1093/ckj/sfac140>
126. Pappaccogli M, Persu A, Fanelli E et al. Endovascular versus medical management of atherosclerotic renovascular disease: update and emerging concepts. *Hypertension* 2023;**80**:1150–61. <https://doi.org/10.1161/HYPERTENSIONAHA.122.17965>
127. Gornik HL, Persu A, Adlam D et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens* 2019;**37**:229–52. <https://doi.org/10.1097/HJH.0000000000002019>
128. Sarafidis PA, Theodorakopoulou M, Ortiz A et al. Atherosclerotic renovascular disease: a clinical practice document by the European Renal Best Practice (ERBP) board of the European Renal Association (ERA) and the Working Group Hypertension and the Kidney of the European Society of Hypertension (ESH). *Nephrol Dial Transplant* 2023;**38**:2835–50.