

SUPPLEMENT TO

# kidney

INTERNATIONAL



**KDIGO 2021 Clinical Practice Guideline for the  
Management of Blood Pressure in Chronic Kidney Disease**

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# **KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease**

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**KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease**

**S1 KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease**

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**KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE  
MANAGEMENT OF BLOOD PRESSURE  
IN CHRONIC KIDNEY DISEASE**



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# Reference keys

## NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A, B, C, or D**.

Grade	Implications		
	Patients	Clinicians	Policy
<b>Level 1 'Strong'</b> "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
<b>Level 2 'Weak'</b> "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.
Grade	Quality of evidence	Meaning	
<b>A</b>	High	We are confident that the true effect is close to the estimate of the effect.	
<b>B</b>	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	
<b>C</b>	Low	The true effect may be substantially different from the estimate of the effect.	
<b>D</b>	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.	

**CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE  
USED BY KDIGO**

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. GFR, glomerular filtration rate.

## CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Creatinine	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s

Note: Conventional unit × conversion factor = SI unit.

## ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 h)	ACR (approximate equivalent)		Terms <sup>a</sup>
		(mg/mmol)	(mg/g)	
<b>A1</b>	<30	<3	<30	Normal to mildly increased
<b>A2</b>	30–300	3–30	30–300	Moderately increased <sup>b</sup>
<b>A3</b>	>300	>30	>300	Severely increased <sup>c</sup>

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease.

<sup>a</sup>Formerly known as “normoalbuminuria,” “microalbuminuria,” and “macroalbuminuria.”

<sup>b</sup>Relative to young adult level.

<sup>c</sup>Including nephrotic syndrome (albumin excretion usually >2200 mg/24 h [ACR >2200 mg/g; >220 mg/mmol]).

## GLOSSARY OF TERMS FOR BLOOD PRESSURE MEASUREMENT

Terms	Definition
Standardized office blood pressure	This is the recommended method for measuring blood pressure in the current revised guideline. Blood pressure measurement following all guideline-recommended preparations as presented in <a href="#">Figure 2</a> . The device used is not part of the definition.
Routine office blood pressure	Blood pressure measured in the provider’s office. Preparation before measurement and the device used are not part of the definition. The values are often inconsistent between providers performing the measurements. In addition, it does not bear a reliable relationship with standardized office blood pressure.
Manual blood pressure	Blood pressure obtained using a manual auscultatory blood pressure cuff, instead of an automated method, with either a mercury or aneroid sphygmomanometer. Preparation before the measurement is not part of the definition.
Automated office blood pressure (AOBP)	Blood pressure obtained in the provider’s office using an automated device that is programmed to start only after a set resting period and measured several times with fixed intervals between measurements. An average reading is then provided as the output. Preparation before measurement and attendance by the provider are not part of the definition.
Ambulatory blood pressure monitoring (ABPM)	Blood pressure obtained on a frequent intermittent basis (i.e., 15–30 min per 24 h) using an automated wearable device, usually outside the provider’s office or medical facilities.
Home blood pressure monitoring (HBPM)	Blood pressure obtained at the patient’s home with an automated oscillometric or manual auscultatory device, usually excluding ABPM. Preparation before measurement, person taking the measurement, and the device used are not part of the definition, although they are often performed by the patient herself/himself with an automated device.

# Abbreviations and acronyms

ABPM	ambulatory blood pressure monitoring	HR	hazard ratio
ACEi	angiotensin-converting enzyme inhibitor(s)	i.v.	intravenous
ACR	albumin-creatinine ratio	KDIGO	Kidney Disease: Improving Global Outcomes
AOBP	automated office blood pressure	MACE	major adverse cardiovascular events
AKI	acute kidney injury	MAP	mean arterial pressure
ARB	angiotensin II receptor blocker	MI	myocardial infarction
BP	blood pressure	MRA	mineralocorticoid receptor antagonist
CCB	calcium channel blocker	NSAID	nonsteroidal anti-inflammatory drug(s)
CI	confidence interval	OR	odds ratio
CKD	chronic kidney disease	PCR	protein-creatinine ratio
CV	cardiovascular	p.o.	oral
DBP	diastolic blood pressure	RAS	renin-angiotensin system
DRI	direct renin inhibitor	RASi	renin-angiotensin system inhibitor(s)
eGFR	estimated glomerular filtration rate	RCT	randomized controlled trial
ERT	Evidence Review Team	RR	relative risk
ESKD	end-stage kidney disease	SBP	systolic blood pressure
GFR	glomerular filtration rate	SGLT2	sodium-glucose cotransporter-2
GI	gastrointestinal	T1D	type 1 diabetes
GRADE	Grading of Recommendations Assessment, Development, and Evaluation	T2D	type 2 diabetes
HBPM	home blood pressure monitoring	UKPDS	United Kingdom Prospective Diabetes Study Group
HF	heart failure		



# Notice

## SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in October 2018, supplemented with additional evidence through September 2019. The search was updated in April 2020 with additional analyses conducted as required. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health care professionals using these recommendations should decide how to apply them to their own clinical practice.

## SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

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# Foreword



*Kidney International* (2021) **99**, S1–S87; <https://doi.org/10.1016/j.kint.2020.11.003>

With the growing awareness that chronic kidney disease (CKD) is a major global health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with its stated mission to “improve the care and outcomes of patients with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.”

Since 2003, KDIGO has developed a catalog of clinical practice guidelines informing the care of patients with, or at risk of, developing kidney diseases. Currently, KDIGO is updating 2 existing guidelines on the Management of Blood Pressure in CKD and Glomerular Diseases, respectively. In addition, KDIGO has recently published its first guideline related to Diabetes Management in CKD.

High blood pressure (BP) is closely related to adverse kidney and cardiovascular outcomes in CKD. Thus, KDIGO published its first guideline for the management of BP in CKD in 2012. The guideline was derived from a significant effort by the Work Group to summarize the evidence on this topic available through 2011. Since 2011, new evidence has emerged, which has important implications to be considered for future guideline updates. To this end, KDIGO convened a Controversies Conference to examine this new evidence as it relates to the management and treatment of high BP in CKD.

The KDIGO Controversies Conference on Blood Pressure in CKD assembled a global panel of multidisciplinary clinical and scientific experts to identify key issues relevant to the updating of the KDIGO 2012 Blood Pressure guideline. The objective of this conference was to assess the current state of knowledge related to the optimal means for measuring BP, management of high BP in CKD patients, with and without diabetes (including older adults), as well as the pediatric and kidney transplant subpopulations. A guideline update was recommended and commissioned following this Controversies Conference.

In keeping with KDIGO’s policy for transparency and rigorous public review during the guideline development process, the guideline scope was made available for open commenting prior to the start of the evidence review. The feedback received on the Scope of Work draft was carefully considered by the Work Group members. The guideline draft was also released for public review by external stakeholders. The Work Group has critically reviewed the feedback from the public input and revised the guideline as appropriate for the final publication.

We thank Alfred K. Cheung, MD and Johannes F.E. Mann, MD for leading this important initiative, and we are especially

grateful to the Work Group members who provided their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from the independent Evidence Review Team (ERT) led by Jonathan Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD; Martin Howell, PhD; and David Tunnicliffe, PhD, who made this guideline possible.

KDIGO recently appointed Marcello Tonelli, MD, SM, MSc, FRCPC as its first Guideline Methods Chair. He was tasked with improving KDIGO guideline methodology by reinforcing the linkage between the recommendations and the corresponding evidence, standardizing the guideline format, reducing unnecessary length, and enhancing the utility of the guideline for its users.

To meet these goals, Dr. Tonelli suggested KDIGO work with MAGICapp, a web-based publishing platform for evidence-based guidelines. The program uses a predefined format and allows for both direct linkage of the evidence to the recommendation statement, and the generation of patient decision aids directly from the evidence syntheses used to support the guideline. In addition, he also introduced the concept of practice points, a new form of guidance in addition to recommendations. For cases in which a systematic review was not done, or was performed but did not find sufficient evidence to warrant a recommendation, a practice point was used to provide guidance to clinicians. Practice points do not necessarily follow the same format as recommendations—for example, they may be formatted as tables, figures, or algorithms—and are not graded for strength or evidence quality.

With Dr. Tonelli’s guidance and expertise, and through the use of MAGICapp, and the adoption of practice points, KDIGO has aligned the update of the Blood Pressure in CKD Guideline with the current state of the evidence, creating a highly useful document that is rich in guidance while maintaining the high-quality standards and rigor for which KDIGO is best known. The update to the KDIGO guideline format is discussed below in greater detail by Dr. Tonelli (Figure 1).

In summary, we are confident that this guideline will prove useful to clinicians around the world who are treating people with high BP and kidney disease. Once again, we thank the Work Group members and all those who contributed to this very important KDIGO activity.

Michel Jadoul, MD  
Wolfgang C. Winkelmayer, MD, ScD  
KDIGO Co-Chairs

# Updates to the KDIGO guideline format



KDIGO guidelines continue to use the GRADE methodology, but we have strengthened the link between the recommendation statements and underlying evidence base.

Guidelines now include a mix of recommendations and “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice points are a new addition to KDIGO guidance, and may be formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and simultaneously posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below is an FAQ outlining the rationale for this shift along with an example recommendation in the new format.

## Practice Points are used when

- No systematic review was conducted
- There is insufficient evidence
- Evidence is inconclusive
- The alternative option is illogical
- Guidance is discretionary for the physician
- Consensus statements providing guidance are needed in the absence of evidence. Benefits and harms will not be explicitly discussed
- Guidance does not require an explicit discussion of values and preferences or of resource considerations, although it is implied that these factors were considered
- The guidance may be more useful as a table, figure, or algorithm

## Recommendations are provided when

- Systematic review was conducted
- Ample/significant evidence is available
- Evidence shows a clear preference for one action over the alternatives
- Guidance is always actionable
- Consensus statements are supported with evidence and explicit discussion of their balance of benefits and harms, values and preferences is necessary
- Application of guidance requires explicit discussion of values and preferences or on resource considerations
- The guidance requires a more thorough explanation in text (i.e., rationale)

## Information on Guideline Development Process

### Who

- A Work Group of experts is convened to develop KDIGO guidelines based on evidence and clinical judgment.
- A designated Evidence Review Team will systematically review and analyze the evidence.
- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is used to analyze certainty in the evidence and strength of guideline recommendations.

**Figure 1 | Updates to the KDIGO guideline format.** CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAQ, frequently asked questions; GFR, glomerular filtration rate; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial.

### How

- Where the Work Group determines that the quality of evidence or strength/ importance of the statement warrants a graded recommendation, the text will be organized into structured sections (see below).
- Strength, quality, and magnitude of evidence (published or empirical) will indicate grading of the recommendation.
- Where the Work Group judges that there is a lack of evidence or consensus-based clinical practice statements are more appropriate, they may choose to develop a practice point.

## What are the structured sections that are included in a recommendation?

Following each recommendation, there is a short remark of one to two sentences **summarizing the most important factors** considered when making the recommendation statement.

Next, the **Key Information** write-up is comprised of five specific subsections representing factors that the Work Group considered both in developing and grading the recommendation. The sections are:

1. Balance of benefits and harms,
2. Quality of evidence,
3. Values and preferences,
4. Resource use and costs, and
5. Considerations for implementation.

The final section of the write-up is a **Rationale** section which serves two purposes. First, the rationale expands on the short remark that immediately follows the recommendation summarizing how the Work Group considered the five factors of the Key Information section when drafting the recommendation.

Second, the rationale may be used to describe any key differences between the current KDIGO recommendation and recommendations made in the previous guideline or by other guideline producers.

## How should I use practice points when caring for my patients?

- As noted, practice points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quantity of evidence was identified.
- Note that practice points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, practice points are not graded for strength of recommendation or quality of evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.

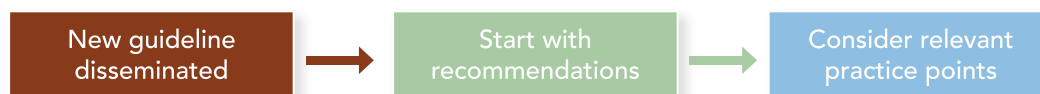


Figure 1 | (Continued)

## What happened to the previous “ungraded statements”?

Ungraded statements were often useful to clinicians, but some were not strictly necessary, and their format (i.e., as imperative statements) was not suitable for every situation.

The added flexibility to present practice points in alternative formats such as tables, figures, and algorithms should make them more useful to clinicians. Since shorter documents are easier to use, we have tried to eliminate superfluous statements from the guideline and to retain only those that are necessary for providing patient care.

## Why did KDIGO make these changes?

The main rationale for the changes was to improve rigor (better linkage of evidence to recommendations; standardized and consistent format), reduce unnecessary length, and enhance utility to practitioners (clinically useful guidance through practice points; visually appealing tables, figures and algorithms that are easier to use at point of care).

## Example of new recommendation and practice point format

### Treatment

**Recommendation 1.** We recommend treating patients with T2D, CKD, and an eGFR  $\geq 30$  ml/min per 1.73 m<sup>2</sup> with metformin (1B).

Why was this formatted as a recommendation?

- Balance of benefits and harms (all based on published, scientific studies):
  - Benefits: HbA1c reduction, greater weight reduction compared to other drugs, protective against cardiovascular events in general population, etc.
  - Harms: potential for lactic acid accumulation.
- Quality of evidence: this recommendation was based on clinical data extracted from RCTs, systematic reviews performed in the general population, and outcomes from observational studies were considered.
- Resources and other costs: metformin is least expensive, widely available, and affordable.
- Considerations for implementation: dose adjustments are required, no safety data for patients with eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>, and must be discontinued when this level is reached.

**Practice Point 1.** Treat kidney transplant recipients with T2D and an eGFR  $\geq 30$  ml/min per 1.73 m<sup>2</sup> with metformin according to recommendations for patients with T2D and CKD.

Why was this formatted as a practice point?

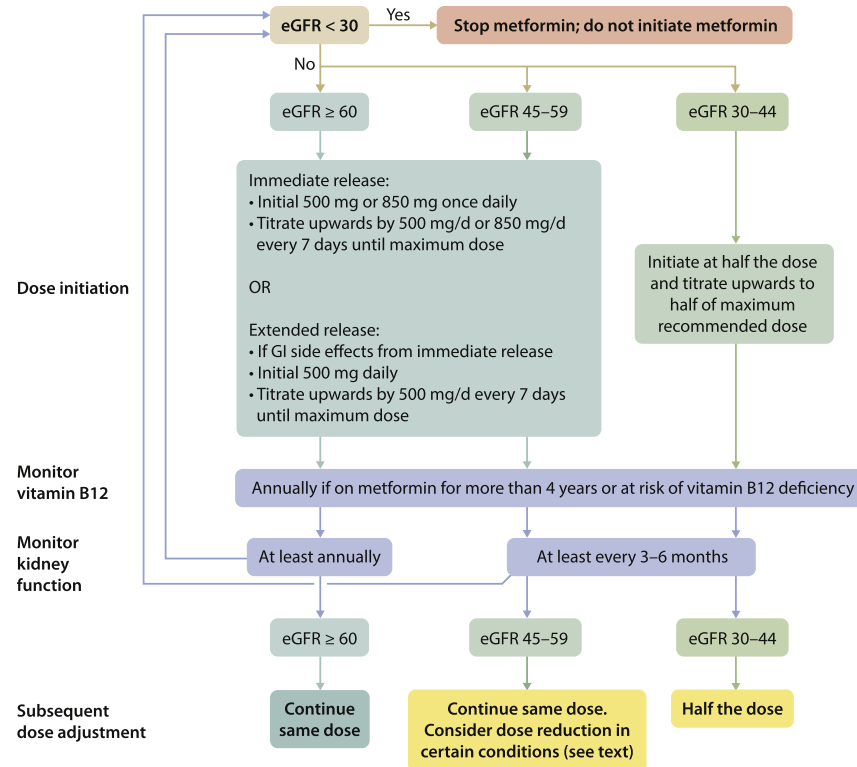
- Less robust data than recommendation; no systematic review was conducted.
- Few studies found; most data were from registry and pharmacy claims. This evidence cannot be considered conclusive.
- Based on the limited evidence available, the Work Group decided to base their guidance to use metformin in the transplant population on the eGFR, the same approach as for the CKD group.

Figure 1 | (Continued)

Practice Points may also have accompanying algorithms to aid in implementation

For example:

**Practice Point 2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is < 60 ml/min per 1.73 m<sup>2</sup>**



Why was this formatted as a practice point?

- Limited evidence to support the guidance but monitoring eGFR in these patients is necessary.
- No systematic review was conducted.
- The Work Group believes a graphic would be more useful to the reader since an algorithm offers a clearer visual presentation of the approach to monitoring than a series of statements.

Figure 1 | (Continued)

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Cochrane Kidney and Transplant recognizes the contribution of authors (Elisabeth Hodson, Emma McMahon, Patrizia Natale, Narelle Willis) who have updated their reviews for this guideline.

**MAGICAPP LIAISON**

Lyubov Lytvyn, BSc, MSc



# Abstract

The *Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (CKD)* represents an update to the 2012 KDIGO guideline on this topic. The scope includes topics covered in the original guideline, such as optimal blood pressure targets, lifestyle interventions, and antihypertensive therapies in CKD patients not receiving dialysis, including special populations such as kidney transplant recipients and children. In addition, this guideline introduces a chapter dedicated to proper blood pressure measurement. The goal of the guideline is to serve as a useful resource for clinicians and patients by providing actionable recommendations with useful infographics based on a rigorous formal systematic review. Another aim is to propose research recommendations for areas in which there are gaps in knowledge. The guideline targets clinicians treating high blood pressure and CKD, while taking into account policy and resource implications. Development of this guideline update followed an explicit process of evidence review. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Limitations of the evidence are discussed, and areas of future research are presented.

**Keywords:** albuminuria; ambulatory blood pressure monitoring; angiotensin-converting enzyme inhibitor; angiotensin II receptor blocker; antihypertensive agents; automated office blood pressure; blood pressure measurement; blood pressure targets; children; chronic kidney disease; creatinine; diabetes; dietary sodium; evidence-based; guideline; home blood pressure monitoring; hyperkalemia; KDIGO; kidney transplant recipient; lifestyle; mineralocorticoid receptor antagonist; office blood pressure; physical activity; potassium; proteinuria; renin-angiotensin system; standardized office blood pressure; systematic review; weight loss

## CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int.* 2021;99(3S):S1–S87.

This guideline, including all statements and evidence, will be published simultaneously on MAGICapp (<https://kdigo.org/guidelines/blood-pressure-in-ckd/>). This online format will facilitate rapid updates as new evidence emerges.

# Introduction

The original KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease in the chronic kidney disease (CKD) population not receiving dialysis was published in 2012. Since then, completion of the SPRINT trial and the revision of blood pressure (BP) guidelines by many guideline task forces around the world have prompted the re-examination of the KDIGO 2012 Guideline for the Management of Blood Pressure. Upon invitation by the KDIGO Executive Committee, a Work Group consisting of a subset of the members of the original guideline panel and some new members was formed in 2018. The Cochrane Kidney and Transplant group from Australia was selected as the Evidence Review Team (ERT) for the update, and a new online publishing software, MAGICapp, was introduced with the aim to create a “living” guideline that is consistently kept up-to-date.

A Controversies Conference was held in Edinburgh in September 2017 to help better identify the emerging evidence, ongoing controversies, and unsettled questions in relation to BP management in CKD. The conclusions from this conference helped to frame the Scope of Work for the Guideline update. It was decided that since the definition, management, and nuances of high BP in the maintenance dialysis population are significantly different from those in the CKD population not receiving dialysis, the Work Group should confine its purview to the latter population in keeping with the 2012 guideline.

The chapters from the original guidelines have been reorganized. The section on pharmacologic agents in the original chapter on “Lifestyle and pharmacologic treatments for lowering blood pressure in CKD ND patients” has been significantly streamlined and separated. The lifestyle chapter, Chapter 2, now focuses on dietary sodium restriction and physical activities. The use of renin-angiotensin inhibitors (RASi) is now included in the current Chapter 3 under the broad topic of BP management in CKD patients, while readers are referred to standard textbooks for descriptions of various BP-lowering drugs. The original Chapter 3 on BP management in CKD patients without diabetes and the original Chapter 4 on CKD patients with diabetes are now consolidated into the current Chapter 3, which covers both subgroups, with the literature on patients with diabetes and without, combined and synthesized. The current Chapter 3 also includes guidance related to older adults with CKD, which was in a separate chapter in the original guideline. Since older adults comprised a substantial proportion of the cohort in the SPRINT trial, it forms a major basis for the current recommendation of the BP target. Finally, the respective chapters on kidney transplant recipients and children with CKD have both been retained and updated.

The Work Group has identified 2 major areas that warrant particular attention in this guideline update because of new evidence and interests that have emerged since the publication of the original guideline. These 2 areas are: (i) BP measurement (Chapter 1) and (ii) BP targets within the domain of BP management in CKD patients not receiving dialysis (Chapter 3). These 2 issues are closely related as the systolic BP (SBP) target of <120 mm Hg recommended in Chapter 3 is contingent upon proper BP measurement technique following recommended rigorous procedures.

This lower SBP target is largely based on its cardioprotective, survival, and potential cognitive benefits. There are no new data supporting the renoprotective benefits of targeting SBP <120 mm Hg. The overall evidence for kidney protection at this low SBP level is almost non-existent, but it is somewhat more convincing for CKD patients with proteinuria and long-term follow-up.

There are certain subpopulations in CKD in which the evidence supporting the SBP target of <120 mm Hg is less rigorous; hence, the risk–benefit ratios in those instances are less certain. These subpopulations include those with diabetes, advanced CKD (G4 and G5), significant proteinuria, very low diastolic blood pressure (DBP), “white-coat” hypertension, and at extreme ages (younger or older). Thus, randomized controlled trials (RCTs) in these subpopulations are necessary.

The term “high BP” is used throughout the document to denote BP above the target. For most patients with CKD not receiving dialysis, the target is SBP <120 mm Hg. For kidney transplant recipients (Chapter 4), the target SBP is <130 mm Hg, and target diastolic BP (DBP) is <80 mm Hg. For children with CKD (Chapter 5), a mean arterial pressure (MAP, calculated as  $DBP + 1/3 \times \text{pulse pressure}$ )  $\leq$ 50th percentile for age, sex, and height is the primary target.

The Work Group fully emphasizes that individualization of management, including consideration of the patient’s characteristics, tolerability, and preferences is crucial, as it is in other areas of medical management. However, the Work Group also feels that some guidance should be provided to practitioners and that these practitioners should be aware of the strengths and weaknesses of the evidence underlying the recommendations. Evidence in all chapters has been carefully gathered and scrutinized by the ERT, including areas in which the Work Group decided that update or revision of the guideline is unnecessary. This guideline focuses exclusively on high BP and does not discuss other health-related issues of CKD, such as smoking or obesity. We also do not discuss benefits and harms of physical activity or diet beyond their effects on BP. As in many other KDIGO guidelines, recommendations for further research are an integral component as it will facilitate the update and revision of future guidelines on BP management in CKD.

The Co-Chairs would like to recognize all the efforts of the Work Group, ERT, and KDIGO staff. We greatly appreciate the dedication and work of the entire team, as well as the public comments, and the collaboration of the KDIGO Diabetes guideline team. Our goal is to help improve the care of patients with high BP and CKD, and we hope this update to

the guideline will succeed in doing so for the global nephrology community.

Alfred K. Cheung, MD  
Johannes F.E. Mann, MD  
Blood Pressure Guideline Update Co-Chairs

# Summary of recommendation statements and practice points

The term “high BP” is used throughout the document to denote BP above the target for a particular population under consideration. For most adult patients with CKD not receiving dialysis, the target is SBP <120 mm Hg (Chapter 3). For adult kidney transplant recipients, the target remains SBP <130 mm Hg/DBP <80 mm Hg (Chapter 4). For pediatric populations, MAP (calculated as DBP +  $1/3 \times$  pulse pressure) targets are age-dependent (Chapter 5). Given that these targets vary according to the subpopulation of interest, we have avoided the term “hypertension” when referring to treatment decisions, as the term “hypertension” requires a single numerical definition and does not necessarily facilitate BP management.

## Chapter 1: Blood pressure measurement

**Recommendation 1.1: We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (1B).**

**Practice Point 1.1:** An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes adequate preparations for BP measurement, not the type of equipment.

**Practice Point 1.2:** Automated office BP (AOBP), either attended or unattended, may be the preferred method of standardized office BP measurement.

**Practice Point 1.3:** Oscillometric devices can be used to measure BP among patients with atrial fibrillation.

**Recommendation 1.2: We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP (2B).**

## Chapter 2: Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis

### 2.1. Sodium intake

**Recommendation 2.1.1: We suggest targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD (2C).**

**Practice Point 2.1.1:** Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.

**Practice Point 2.1.2:** The Dietary Approaches to Stop Hypertension (DASH)-type diet or use of salt substitutes that are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism or other causes of impaired potassium excretion because of the potential for hyperkalemia.

### 2.2. Physical activity

**Recommendation 2.2.1: We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).**

**Practice Point 2.2.1:** Consider the cardiorespiratory fitness status, physical limitations, cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.

**Practice Point 2.2.2:** The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.

### Chapter 3: Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis

#### 3.1. Blood pressure targets

**Recommendation 3.1.1:** We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).

**Practice Point 3.1.1:** It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a non-standardized manner.

**Practice Point 3.1.2:** Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.

#### 3.2 Treatment with antihypertensive drugs, including RAS inhibitors (RASi)

**Recommendation 3.2.1:** We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (1B).

**Recommendation 3.2.2:** We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (2C).

**Recommendation 3.2.3:** We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).

**Practice Point 3.2.1:** It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).

**Practice Point 3.2.2:** RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

**Practice Point 3.2.3:** Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

**Practice Point 3.2.4:** Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

**Practice Point 3.2.5:** Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

**Practice Point 3.2.6:** Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m<sup>2</sup>).

**Practice Point 3.2.7:** Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR.

#### 3.3. Role of dual therapy with RASi

**Recommendation 3.3.1:** We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes (1B).

## Chapter 4: Blood pressure management in kidney transplant recipients (CKD G1T–G5T)

Practice Point 4.1: Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).

**Recommendation 4.1: We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).**

## Chapter 5: Blood pressure management in children with CKD

**Recommendation 5.1: We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to  $\leq$ 50th percentile for age, sex, and height (2C).**

Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 months with standardized auscultatory office BP in children with CKD.

Practice Point 5.2: In children with high BP and CKD, when ABPM is not available, manual auscultatory office BP obtained in a protocol-driven standardized setting targeting achieved SBP <90th percentile for age, sex, and height of normal children is a reasonable approach.

Practice Point 5.3: Use ACEi or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated, but they carry the risk of hyperkalemia and have adverse fetal risks for pregnant women.

# Chapter 1: Blood pressure measurement

This chapter makes recommendations on how to measure BP among adults aged  $\geq 18$  years with CKD. Please refer to Chapter 5 for details of BP measurement in children.

The evidence review for this chapter encompassed only a search for existing systematic reviews on BP measurement in the general population. An independent systematic review was not undertaken by the ERT.

Throughout this chapter, standardized office BP refers to measurements obtained according to recommended preparation procedures (Figure 2<sup>1,2</sup>), regardless of the type of equipment used. In contrast, routine office BP refers to measurements obtained without following these recommended preparation procedures and is often also called casual office BP.

Once the appropriate preparations for standardized office BP have been made, BP may be measured by an automated oscillometric device or manually using an auscultatory method. An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement (see Practice Point 1.1.), but the main emphasis is on the importance of measuring BP according to recommended preparation procedures (Figure 2). Manual BP may be measured with either a mercury or aneroid sphygmomanometer. However, aneroid devices require frequent calibration: every 6 months for wall-mounted and every 2–4 weeks for handheld devices.<sup>3,4</sup> Oscillometric devices generally require less-frequent calibration (e.g., every 1–2 years, based on manufacturer recommendations), than aneroid devices.<sup>3</sup>

<b>1 Properly prepare the patient</b>	<ol style="list-style-type: none"> <li>1 Have the patient relax, sitting in a chair (feet on floor, back supported) for &gt; 5 min</li> <li>2 The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement</li> <li>3 Ensure patient has emptied his/her bladder</li> <li>4 Neither the patient nor the observer should talk during the rest period or during the measurement</li> <li>5 Remove all clothing covering the location of cuff placement</li> <li>6 Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria</li> </ol>
<b>2 Use proper technique for BP measurements</b>	<ol style="list-style-type: none"> <li>1 Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically</li> <li>2 Support the patient's arm (e.g., resting on a desk)</li> <li>3 Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum)</li> <li>4 Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used</li> <li>5 Either the stethoscope diaphragm or bell may be used for auscultatory readings</li> </ol>
<b>3 Take the proper measurements needed for diagnosis and treatment of elevated BP</b>	<ol style="list-style-type: none"> <li>1 At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings</li> <li>2 Separate repeated measurements by 1–2 min</li> <li>3 For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level</li> <li>4 For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds</li> </ol>
<b>4 Properly document accurate BP readings</b>	<ol style="list-style-type: none"> <li>1 Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number</li> <li>2 Note the time of most recent BP medication taken before measurements</li> </ol>
<b>5 Average the readings</b>	<p>Use an average of <math>\geq 2</math> readings obtained on <math>\geq 2</math> occasions to estimate the individual's level of BP</p>
<b>6 Provide BP readings to patient</b>	<p>Provide patients with the SBP/DBP readings verbally and in writing</p>

**Figure 2 | Checklist for standardized office blood pressure measurement.** BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. Modification for pediatrics: BP in infants should be taken while supine and the use of the bell is recommended.<sup>1</sup> Reprinted from the *Journal of the American College of Cardiology*, Volume 71, Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Pages e127–e248, © 2018 with permission from the American College of Cardiology Foundation and the American Heart Association, Inc.<sup>2</sup>

Some oscillometric devices can be programmed to automatically provide a period of rest followed by multiple BP readings with a single activation, a method known as automated office BP (AOBP). AOBP can be performed either with the patient alone (i.e., unattended) or with a healthcare provider/technician present (i.e., attended), whereas the other office BP methods all require a healthcare provider to be present to perform the measurement. We suggest that AOBP is the preferred method of standardized office BP measurement (see Practice Point 1.2), but we have no preference for unattended versus attended measurement.

**Recommendation 1.1: We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (1B).**

*This recommendation places a relatively higher value on consistency with the BP measurement methods used to define BP targets in prior large clinical outcome trials. It also places a higher value on avoidance of misclassification to prevent overtreatment or undertreatment of high BP. This recommendation places a lower value on the increased burden to patients, providers, and staff. This recommendation is strong because, in the Work Group's opinion, the importance of office BP measured using a standardized versus a routine, non-standardized approach outweighs any potential burden to its implementation.*

#### Key information

**Balance of benefits and harms.** This recommendation relies heavily on the importance of standardized office BP measurement protocols that are consistent with large randomized controlled trials (RCTs) with clinically important outcomes that have been used to define BP targets. Standardized office BP measurements allow for extrapolation of the RCT findings to clinical practice and avoid overtreatment or undertreatment of high BP that may occur if non-standardized measurements are used. The negative aspects of standardized office BP measurement, including the increased burden on patient, provider, staff time, and clinic space, are outweighed by the benefits.

**Quality of evidence.** There is moderate-quality evidence that routine office BP is generally, but not invariably, higher than standardized office BP, regardless of whether manual or oscillometric devices are used. However, there is strong evidence that the relationship between routine office BP and standardized office BP is highly variable among individuals. Thus, it is not possible to apply a correction factor to translate a given routine BP value to standardized office BP.

**Values and preferences.** Appropriate BP management requires proper BP measurements. All large randomized BP outcome trials used standardized office BP measurements. In the opinion of the Work Group, the importance of measuring BP in a manner that is consistent with the RCTs far outweighs the additional burdens and costs for providers, staff, and

patients. Increased costs are due to personnel and clinic time utilization.

Routine office BP measurements are generally higher than standardized office BP measurements.<sup>5,6</sup> Therefore, the use of routine office BP measurements for BP management could lead to overtreatment of BP and possibly result in a higher incidence of hypotension-related adverse events. Conversely, for some persons for whom routine office BP is lower than standardized office BP, use of routine office BP could lead to undertreatment of high BP and result in a higher risk of future cardiovascular (CV) events. Routine and standardized BP measurements have poor agreement, including those in the CKD population.<sup>5,6</sup> It is therefore not possible to convert a routine office BP into a standardized office BP using a correction factor in an individual. Thus, in the opinion of the Work Group, most well-informed patients would accept the additional time required for standardized office BP measurement.

**Resource use and costs.** Standardized office BP does not necessarily require additional equipment beyond the existing BP measurement devices. However, standardized office BP takes longer to perform than routine office BP, given the need to follow proper preparatory procedures (Figure 2). Therefore, there may be an increased time burden on patients, providers, and staff. This approach also requires staff training and retraining to ensure that a standardized BP measurement approach is followed. Adequate access to a quiet clinic space that allows for an adequate rest period prior to BP measurement may also be an issue in certain settings. However, in the opinion of the Work Group, this recommendation is likely to be cost-effective as it may avert consequences of overtreatment and undertreatment, though an economic analysis has not been published.

**Considerations for implementation.** The use of standardized office BP over routine office BP holds true for all patients, regardless of age, sex, race, or CKD severity.

#### Rationale

This chapter is an addition since the KDIGO 2012 BP guideline. This recommendation places a relatively higher value on consistency with BP measurement methods used in prior outcome trials examining different BP targets, and on minimizing overtreatment or undertreatment of BP that may result from routine, non-standardized office BP measurements. This recommendation places a lower value on the increased time required to perform standardized BP measurements.

This recommendation is consistent with other recent guidelines that also underscore the importance of standardized office BP measurement (e.g., American College of Cardiology [ACC]/American Heart Association [AHA],<sup>2,7</sup> and European Society of Cardiology [ESC]<sup>8</sup>).

**Practice Point 1.1: An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes adequate preparations for BP measurement, not the type of equipment.**



Oscillometric BP devices may be preferred over manual BP devices, as the former minimizes potential sources of inaccuracies in BP measurements that can occur with human errors associated with manual BP measurement such as those resulting from hearing impairment, an improper deflation rate, or terminal-digit bias.<sup>9</sup>

Manual BP devices are also acceptable when oscillometric devices are unavailable. The main emphasis is on the importance of obtaining standardized BP measurements that are made according to recommended preparation procedures (Figure 2).

RCTs and prospective cohort studies used standardized office BP measured with either oscillometric (in newer studies) or manual devices (in older studies; Figure 3<sup>10–13</sup>). Studies that directly compared standardized office BP measured using an oscillometric device versus a manual device do not suggest overt differences in readings between these 2 types of devices (Supplementary Table S4<sup>14–16</sup>). Moreover, all BP measurement devices are validated and calibrated against mercury sphygmomanometers, so they would be expected to give similar BP readings. Therefore, BP levels from trials that have used different types of standardized office BP measurements should, in general, be comparable.

The negative aspects of oscillometric BP devices are the potentially higher cost of the device compared with a manual device, the requirement of an electric power source, and lack of availability in some settings. In choosing a device, one that has been validated for accuracy and precision against a mercury sphygmomanometer should be selected. Several national medical or hypertension associations have established a validated device listing that has information on oscillometric devices that are suitable for use.<sup>17–19</sup> Providers working in areas where oscillometric BP devices are not available may use

a manual BP device, but proper calibration of these BP devices is required as noted above.

Regardless of the type of BP device used, proper preparation and BP measurement techniques are paramount (Figure 2).

**Practice Point 1.2: Automated office BP (AOBP), either attended or unattended, may be the preferred method of standardized office BP measurement.**

In the opinion of the Work Group, AOBP may increase the likelihood of adherence to proper preparation measures, as the AOBP devices can be programmed to include a rest period. AOBP devices can also automatically take multiple BP measurements and provide an average BP measurement. Thus, BP measured with AOBP can be either attended (i.e., with a healthcare provider in the room) or unattended (i.e., without a provider in the room). Although a recent meta-analysis suggested that unattended AOBP measurements result in lower average BPs than attended measurements,<sup>20</sup> the differences were notably small when restricted to studies that randomized the order in which unattended and attended standardized measurements were made.<sup>18,21–25</sup>

Several large trials, including Systolic Blood Pressure Intervention Trial (SPRINT), Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), and Action to Control Cardiovascular Risk in Diabetes (ACCORD), used AOBP as the BP measurement method (Figure 3). Of note, the SPRINT protocol did not specify whether AOBP should be performed while attended or unattended. A *post hoc* analysis of SPRINT data found that while a majority of sites did perform unattended AOBP, many performed attended AOBP or some combination of

Study	Year	Population	Type of study	Method/device
Framingham	1970s	General	Observational	Manual
MDRD	1994	CKD (eGFR < 55 ml/min/1.73 m <sup>2</sup> )	Clinical trial	Manual
UKPDS	1998	T2D (baseline SCr 1.06 mg/dl [94 μmol/l])	Clinical trial	Automated
AASK	2002	CKD (GFR 20–65 ml/min/1.73 m <sup>2</sup> )	Clinical trial	Manual
ADVANCE	2007	T2D (baseline SCr 0.97 mg/dl [86 μmol/l]; 19% CKD) <sup>†</sup>	Clinical trial	Manual
CRIC	2009	CKD (eGFR < 70 ml/min/1.73 m <sup>2</sup> )	Observational	Manual and automated
ACCORD	2010	T2D (baseline SCr 0.9 mg/dl [80 μmol/l]; 37% CKD)	Clinical trial	Automated/Omron™
SPS3	2011	Recent lacunar stroke (baseline eGFR 80 ml/min/1.73 m <sup>2</sup> ; 16% CKD) <sup>§</sup>	Clinical trial	Automated/Colin electronic device
ONTARGET <sup>†</sup>	2012	CVD or T2D (baseline SCr 1.05 mg/dl [93 μmol/l]; 24% CKD, eGFR < 60 ml/min/1.73 m <sup>2</sup> )	Clinical trial	Automated/Omron™
CKD-JAC	2013	CKD (eGFR < 60 ml/min/1.73 m <sup>2</sup> )	Observational	Manual
SPRINT	2015	High CVD risk (baseline SCr 1.07 mg/dl [95 μmol/l]; 28% CKD, eGFR 20–< 60 ml/min/1.73 m <sup>2</sup> )	Clinical trial	Automated/Omron™

**Figure 3 | Blood pressure measurement method and device used in select RCTs and prospective observational studies.** AASK, African American Study of Kidney Disease and Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; CKD-JAC, Chronic Kidney Disease Japan Cohort; CRIC, Chronic Renal Insufficiency Cohort; MDRD, Modification of Diet in Renal Disease; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; SPRINT, Systolic Blood Pressure Intervention Trial; SPS3, Secondary Prevention of Small Subcortical Strokes Trial; UKPDS, United Kingdom Prospective Diabetes Study. Adapted with modifications with permission of the American Society of Nephrology from BP measurement in clinical practice: time to SPRINT to guideline-recommended protocols. Drawz PE, Ix JH, volume 29, Copyright © 2018, permission conveyed through Copyright Clearance Center, Inc.<sup>10</sup> <sup>†</sup>ONTARGET was published in 2008.<sup>11</sup> The BP measurement approach used in the trial was subsequently published in the 2012 article referenced above. <sup>‡</sup>de Galan *et al.*<sup>12</sup> <sup>§</sup>Peralta *et al.*<sup>13</sup> CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial; SCr, serum creatinine; T2D, type 2 diabetes.

unattended and attended measurements.<sup>26</sup> Nonetheless, similar BP levels and CV disease risk reduction were observed in the intensive group in SPRINT participants, whether the measurement technique used was primarily attended or unattended.

Unattended AOBP measurements may have some practical advantages over attended standardized BP measurements, such as discouraging talking by the patients and freeing clinic staff to complete other duties during the BP measurement process.

**Practice Point 1.3: Oscillometric devices can be used to measure BP among patients with atrial fibrillation.**

It is a misperception that oscillometric devices do not measure BP accurately among patients with atrial fibrillation. Prior studies comparing BP measured using oscillometric devices versus auscultatory techniques suggest that oscillometric devices provide a valid systolic BP (SBP) assessment in patients with atrial fibrillation.<sup>27</sup> Although oscillometric devices may be less accurate for estimating diastolic BP (DBP) than auscultatory techniques, the population with atrial fibrillation is, on average, older, and the emphasis in older adults has been on SBP.<sup>28</sup>

**Recommendation 1.2: We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP (2B).**

*This recommendation places a relatively higher value on detecting a potential difference in BP status based on office versus out-of-office BP (Figure 4). In the judgment of the Work Group, the potential benefits of additional information obtained from out-of-office BP measurements outweigh the additional costs and increased patient burden that these measurements impose. We suggest using an initial ABPM to supplement standardized office BP and HBPM for ongoing management of BP. Although ABPM may be the better measurement method, HBPM is more practical for routine out-of-office assessment. HBPM may be particularly important for the management of BP when a clinic*

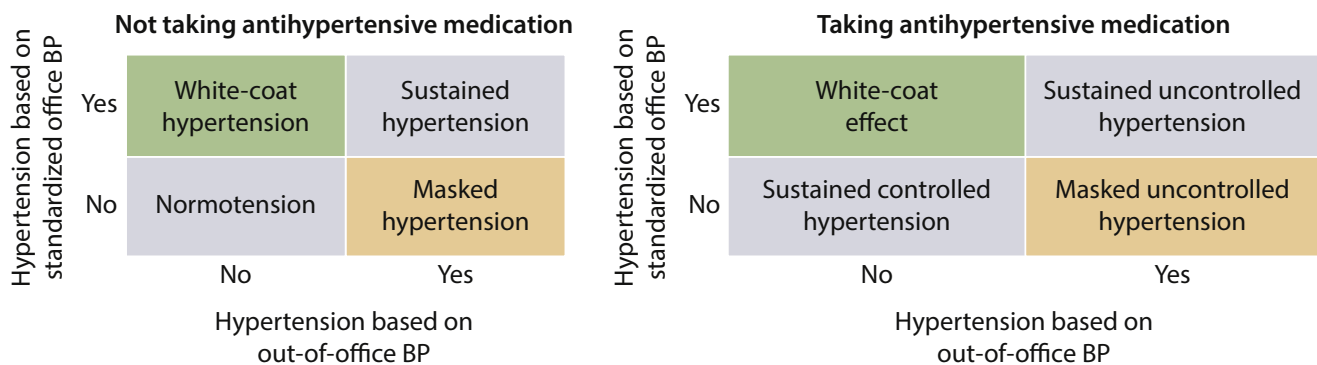
*visit is not practical, for example, in the coronavirus disease 2019 (COVID-19) pandemic. For individuals not taking antihypertensive medication identified as having “white-coat” hypertension, annual out-of-office BP assessments may be useful. For individuals taking antihypertensive medication, 1 week of daily HBPM prior to each office visit may be useful to complement standardized office BP for clinical management decisions.*

*This is a weak recommendation according to GRADE, since there are no large RCTs comparing the effects of lower versus higher BP goals on clinical outcomes in adults that used out-of-office measurements to guide the BP intervention. Hence, the BP target using out-of-office measurements is unknown. Furthermore, it may not be feasible to implement ABPM and HBPM in many settings. Providers working in areas where ABPM is not available may choose to use HBPM instead of an initial ABPM procedure. Patients who find ABPM and HBPM to be uncomfortable and inconvenient may prefer not to use such devices.*

**Key information**

**Balance of benefits and harms.** This recommendation places a relatively higher value on assessing a patient’s broader BP profile than relying solely on standardized office BP measurements. Observational studies indicate that the diagnosis of high BP and BP control status differs for a high proportion of adults when BP is measured in the office versus outside the office, which can lead to detection of masked hypertension, masked uncontrolled hypertension, “white-coat” hypertension, and the “white-coat” effect (Figure 4). Further, observational studies indicate a stronger association of out-of-office BP measurements with CV and kidney outcomes than office BP measurements in the general population and CKD.<sup>29–31</sup>

Masked hypertension and masked uncontrolled hypertension are present among 9%–30% of adults without high BP based on office measurements and are associated with higher risk for CV disease and kidney outcomes compared with sustained normotension and sustained controlled hypertension, respectively. “White-coat” hypertension and the “white-coat” effect are present among 15%–30% of adults with high BP based on office measurements. In a recent meta-analysis, “white-coat” hypertension was associated with a



**Figure 4 | Blood pressure patterns informed by out-of-office blood pressure measurements in addition to standardized office blood pressure measurement.**

modest increased risk for CV disease, compared to sustained normotension.<sup>29</sup> However, this risk was substantially lower than the risk for participants with sustained hypertension.<sup>31</sup> Additionally, the “white-coat” effect was not associated with increased risk for CV disease when compared to the risk for people with sustained controlled hypertension.<sup>29</sup>

The prevalences of “white-coat” hypertension, masked hypertension, the “white-coat” effect, and masked uncontrolled hypertension are each high among patients with CKD.<sup>5,32–35</sup> Identification of “white-coat” hypertension and masked hypertension for patients not taking antihypertensive medication, and the “white-coat” effect and masked uncontrolled hypertension for patients taking antihypertensive medication may have potential treatment implications (see Rationale section). However, it remains to be determined whether initiation of antihypertensive medication among patients with “white-coat” hypertension and masked hypertension, or intensification of antihypertensive medication among patients with the “white-coat” effect and masked uncontrolled hypertension improves outcomes (see Research Recommendations).

This recommendation places a relatively lower value on the potential lack of device availability, costs, and patient and staff burden.

**Quality of evidence.** There are systematic reviews in the general population showing that high out-of-office BP is associated with CV disease risk independent of office BP.<sup>36</sup> Although there are no systematic reviews in CKD patients, the results from individual studies in CKD are generally consistent with the general population data in that BP differs when measured outside the office versus in the office setting, and out-of-office readings provide additional prognostic information.<sup>32,34</sup> Therefore, there is no reason to suspect that findings in the general population would not apply to patients with CKD also. The systematic reviews and meta-analyses of general population studies provide moderate-quality evidence because of the inherent limitations of observational studies, but the evidence quality is upgraded from low because of the strength of associations of out-of-office BP measurements with critically important outcomes. However, no single outcome trial targeting out-of-office BP has been reported so far in CKD populations.

**Values and preferences.** This recommendation places a relatively higher value on providing complementary information to standardized office BP that may affect clinical decisions. There is a modest correlation between BP measured in the office and outside of the office using ABPM or HBPM. However, these BP measurements should not be considered interchangeable. Importantly, there have been no large RCTs with clinical outcomes using ABPM or HBPM to define BP targets. Therefore, at present, ABPM and HBPM cannot be used alone to guide therapy. The recommendation places a relatively lower value on the potential lack of device availability, costs, and patient burden. In the opinion of the Work Group, many but not all patients and providers will value the information provided by ABPM and HBPM. Prior studies

have found that a majority of patients prefer HBPM to ABPM. HBPM has been reported by patients to result in fewer disturbances in their daily activities and to be more comfortable than ABPM.<sup>37–39</sup> The Work Group recognizes that some patients will find both ABPM and HBPM to be uncomfortable and/or inconvenient, and such patients may choose to forgo measurement using these devices.

**Resource use and costs.** This recommendation stems from studies showing that ABPM is cost-saving and cost-effective for the management of high BP in the general population. Although studies were not conducted in CKD, there is no reason to expect that the cost-savings would be any different in the CKD population.<sup>40,41</sup> In contrast, the cost-effectiveness of HBPM for management of high BP is unclear.<sup>40,41</sup> Persons with limited financial resources, or those treated in health systems where ABPM and HBPM are less available or affordable, may be less inclined to follow this recommendation.

**Consideration for implementation.** The use of ABPM or HBPM will depend on the resources available. Staff should be trained to conduct ABPM and to teach patients proper HBPM techniques. This recommendation holds true for all patients, regardless of age, sex, race, or CKD severity.

ABPM requires recalibration every 1–2 years, based on manufacturer recommendations.<sup>3</sup> There are no standardized protocols for calibrating HBPM devices; however, when it is suspected that home measurements are inaccurate, providers should ask their patients to bring their HBPM device to the office to compare BP values on these devices with those obtained from a calibrated device.<sup>42</sup>

## Rationale

This recommendation places a high value on informing an individual’s overall BP profile and identifying persons with high CV disease risks related to high BP. This recommendation places a relatively lower value on the potential lack of device availability, cost, and patient burden.

Observational studies indicate that the diagnosis of high BP and BP control status differs for a high proportion of adults when BP is measured in the office versus outside the office. Also, observational studies indicate a stronger association of out-of-office BP measurements with CV and kidney outcomes than office BP measurements in the general population and CKD.

Identification of “white-coat” hypertension, masked hypertension, the “white-coat” effect, and masked uncontrolled hypertension has potential treatment implications. Antihypertensive medication initiation and intensification may be considered for patients with substantial masked hypertension and masked uncontrolled hypertension, respectively, whereas for those with substantial “white-coat” hypertension and the “white-coat” effect the choice may be made to defer initiation and defer intensification of antihypertensive medication, respectively, especially in individuals with symptoms associated with documented out-of-office hypotension. However, the Work Group acknowledges the lack of RCTs that

specifically address whether and how best to treat BP profiles identified by out-of-office BP measurements. HBPM also has the advantage of empowering individuals to take ownership of their medical care, hence promoting adherence to therapy.

#### Research recommendations

There are several areas in which more research is needed specifically for the CKD population:

- Identify if procedures for standardized BP measurement can be simplified, such as using a shorter rest period (e.g., 1 or 2 minutes) or a shorter interval between BP measurements (e.g., 15 or 30 seconds).
- Compare standardized unattended versus standardized attended AOBP in routine clinical practice.
- Determine the optimal interval for repeating ABPM and HBPM among individuals not taking and taking antihypertensive medications.
- Determine the proportion of CKD patients with “white-coat” hypertension, masked hypertension, the “white-coat” effect, and masked uncontrolled hypertension using a BP threshold of 120 mm Hg instead of 140 mm Hg, and whether these phenotypes are associated with increased risk for CV disease.
- Assess the cost-effectiveness of ABPM and HBPM, separately, for identifying “white-coat” hypertension, masked hypertension, the “white-coat” effect, and masked uncontrolled hypertension.
- Conduct RCTs comparing treatment based on ABPM or HBPM versus standardized office BP measurements. Treatment based on ABPM or HBPM includes not treating patients with “white-coat” hypertension, not intensifying treatment for the “white-coat” effect, treatment of masked hypertension, and intensifying treatment for masked uncontrolled hypertension.

# Chapter 2: Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis

## 2.1 Sodium intake

**Recommendation 2.1.1: We suggest targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD (2C).**

*This recommendation places a relatively high value on data from both the CKD population and the general population demonstrating that reductions in dietary sodium intake induce short-term reductions in BP and other evidence suggesting that these benefits will reduce the need for antihypertensive medications. The Work Group placed lower value on the limited available data evaluating the effects of dietary sodium intake on clinical outcomes, including kidney failure, mortality, and CV disease endpoints in CKD patients. The recommendation is weak according to GRADE because of the low-quality evidence supporting the benefits of low-sodium intake specifically in the hypertensive CKD population; yet, many well-informed patients would agree to follow the guidance. This represents a change from the recommendation (1C) in the 2012 guideline based on the opinion of the current Work Group members, but it is consistent with the KDIGO 2020 Guideline for the Management of Patients with Diabetes and CKD.*

### Key information

**Balance of benefits and harms.** In most populations worldwide, estimated average sodium intake is much higher than the proposed target of sodium intake <2 g (<90 mmol) per day for the general population. Recent meta-analyses of RCTs in non-CKD populations demonstrate a graded benefit in both BP and CV disease risk reduction with reductions in sodium intake. Importantly, even more-modest reductions in sodium intake that did not reach the <2 g per day target were associated with these benefits.<sup>43</sup> Indeed, achieved mean sodium intake typically was in the 3.0–3.5 g/d range, and the low target of <2 g/d was reached in few participants. In CKD populations, this recommendation is driven by short-term studies of moderate-quality evidence evaluating SBP and DBP, but not CV events, as endpoints. It is unknown whether sodium intakes far below 2 g per day are safe or not.

The Work Group notes that there are instances in which recommendations in the general population may not apply to the CKD population. For example, rarely, CKD patients may have salt-wasting kidney disease in which case this recommendation may not apply. In some instances, salt substitutes

are used for the purpose of maintaining food-taste preferences in people practicing dietary sodium restriction. These substitutes often replace sodium with potassium salts. Clinical trials of potassium-containing salt substitutes systematically exclude patients with CKD, so benefits and harms of potassium-containing salt substitutes in CKD are not available. Potassium-containing salt substitutes differ from foods rich in potassium, as such foods may have other health benefits, thus extrapolating data from potassium intake in the diet may not be informative to potassium-containing salt substitutes. Although there is still controversy about the risk-benefit ratio of potassium intake, observational studies often found that a higher potassium intake may be associated with a lower risk for all-cause death, CV disease, and CV death. However, at advanced stages of CKD (G4 and G5), a high potassium intake may be associated with higher risk.<sup>44–46</sup> The Work Group suggests caution in using potassium-containing salt substitutes in CKD populations, especially in those with advanced CKD, hyporeninemic hypoaldosteronism, or hyperkalemia from other causes until more data on the safety and efficacy of their use in CKD become available (see Practice Point 2.1.2).

**Quality of evidence.** The Cochrane systematic reviews updated for this guideline found low-to-moderate-quality evidence demonstrating that dietary sodium reduction results in short-term reductions in BP in CKD populations.<sup>47,48</sup> This was evident for both SBP and DBP in CKD without diabetes (moderate; [Supplementary Table S5](#)<sup>49–58</sup>); Type 1 diabetes (T1D) and CKD (low; [Supplementary Table S6](#)<sup>59–63</sup>); Type 2 diabetes (T2D) and CKD (low; [Supplementary Table S7](#)<sup>64–69</sup>); and diabetes and severely increased albuminuria (low; [Supplementary Tables S8 and S9](#)<sup>63,66,68,69</sup>). These data were considered in the context of a substantial body of evidence confirming short-term benefits in SBP and DBP reduction in the general population. In the general population, the magnitude of BP lowering may be greater in persons with high BP, which is more prevalent in CKD patients.<sup>43</sup>

There is also moderate strength of evidence from systematic reviews that lowering of sodium intake reduces CV disease in the general population.<sup>43</sup> The systematic review conducted for this guideline found no RCT data evaluating the effects of dietary sodium reduction on clinical outcomes, including kidney failure (formerly known as end-stage kidney disease [ESKD]), CV disease, or mortality in CKD populations. However, the Work Group agrees that there is no reason to believe that the epidemiologic findings in the general population would be different in CKD populations.

Further, persons with CKD frequently take angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) compared to non-RASi therapy, and the kidney and CV benefits of these medications may be enhanced if accompanied by a low-sodium diet compared to a high-sodium diet.<sup>70</sup>

**Values and preferences.** This recommendation places a relatively high value on the benefits of using a non-pharmacologic method to lower BP and minimize additional medications. The recommendation places a relatively high value on data from the general population, demonstrating that reductions in dietary sodium intake induce short-term reductions in BP, and other evidence suggests that these benefits likely extend to people with CKD. The Work Group placed lower value on the limited available data evaluating the effects of dietary sodium reduction on clinical outcomes, including kidney failure, mortality, and CV disease endpoints in CKD patients. The Work Group also considered the secondary benefits of dietary sodium reduction in reducing pill burden and medication-related side effects. However, in the judgment of the Work Group, some individuals may prefer additional medications to the burden and decreased palatability of foods when following a low-sodium diet. Although fortified salt is an important treatment for iodine deficiency in some countries, the Work Group judged that the benefits of implementing this recommendation in CKD patients likely outweigh its risks. The recommendation is weak because, in controlled trials, only a minority of patients reached a target intake of <2 g (<90 mmol) of sodium per day, and effects on important clinical outcomes in CKD are uncertain. However, the Work Group believes that the benefits of the recommendation likely exceed the harms and that many well-informed patients would try to follow the advice.

**Resource use and costs.** Processed foods are generally higher in salt and often are less expensive than fresh food alternatives. Yet, a higher sodium intake associated with processed foods is likely to necessitate additional antihypertensive medications, greater pill burden, and associated healthcare costs. The Work Group also recognizes that, although feasible, following a low-sodium diet is challenging in many Western food environments. However, this recommendation may not only benefit individual patients, but also may influence public health interventions and policymakers to consider targeting reductions of sodium in the food supply. Although this may require buy-in from key stakeholders, policy changes, and investment of public health resources, the Work Group believes that the health benefits of such changes are also likely to be experienced by a wider population than those with CKD alone.

**Considerations for implementation.** This recommendation places high value on evidence linking short-term changes in sodium intake with reductions in BP in CKD populations, and extrapolation of long-term benefits from the general population. Although there is limited evidence from RCTs about the long-term benefits or harms of sodium reduction

in CKD populations *per se*, the Work Group agrees, with few exceptions, that there is little evidence or likelihood that health benefits observed in the general population should not apply to CKD patients. On the contrary, there is reason to believe that the health benefits of dietary sodium reduction may be particularly beneficial in CKD patients. Persons with CKD are commonly hypertensive, and systematic reviews have suggested that the magnitude of BP reduction for a given degree of reduction in dietary sodium intake is magnified in hypertensive individuals, particularly if usual sodium intake is high.<sup>43</sup> CKD populations also have high risk of CV disease and may therefore have a greater absolute risk reduction of such events with dietary sodium reduction, if the relative benefits in the general population are indeed applicable to CKD. Finally, ACEi and ARBs are commonly used in CKD patients, and *post hoc* analyses of RCTs demonstrate that low-sodium intake may enhance the effects of these medications on kidney and CV outcomes.<sup>70</sup>

The Work Group agrees that decreasing dietary sodium intake is likely to also be appropriate in children with CKD, albeit with modified targets. Specific targets are not available from prior studies for children with CKD, but the Work Group believes that adjusting the <2 g (<90 mmol) daily target for body weight in children would be reasonable.<sup>71</sup>

The Work Group considered the specific target of sodium intake of <2 g (<90 mmol) daily and found no evidence showing different health benefits or harms at different sodium intake targets in CKD populations *per se*. Existing intervention studies targeting BP in CKD populations typically targeted <2 g or <2.3 g daily in the low-sodium arms, which are similar to targets recommended for the general population.<sup>43,71,72</sup> Therefore, the present guideline was created in the absence of data suggesting superiority or inferiority of other targets in CKD populations. Further, for concordance across guidelines from various organizations that might facilitate policy decisions, Work Group members agree a target of <2.0 g per day should be recommended for CKD populations.

### Rationale

This recommendation places a relatively higher value on studies in CKD populations demonstrating that short-term dietary sodium reduction interventions lower BP, and consistency with findings of similar interventions in the general population. The recommendation also places a higher value on dietary sodium-reduction strategies as a readily available, non-pharmacologic intervention to lower BP in CKD populations. Relatively lower value was placed on the challenges in following a low-sodium diet in many current food environments. This recommendation is made despite low-to-moderate-quality evidence in CKD populations *per se*, especially for hard clinical endpoints, because in the judgment of the Work Group, relative benefits of efforts to lower dietary sodium intake will outweigh risks and healthcare costs in most patients.

Although there is a lack of RCT data on use of potassium-containing salt substitutes in CKD populations, Work Group members are concerned about the risk of hyperkalemia that

these salt substitutes may pose to persons with advanced CKD, as well as observational data suggesting that higher dietary potassium intake may be associated with increased risk of CV and kidney outcomes in CKD populations.<sup>45,46</sup> The Work Group acknowledges that there is also evidence to the contrary in people at high CV risk in the general population.<sup>73,74</sup> Therefore, the present recommendation for sodium reduction refers to dietary sodium reduction without substitution with potassium until further studies can discern risks and benefits of salt-substitution strategies specifically in CKD.

**Practice Point 2.1.1: Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.**

**Practice Point 2.1.2: The Dietary Approaches to Stop Hypertension (DASH)-type diet or use of salt substitutes that are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoadosteronism or other causes of impaired potassium excretion because of the potential for hyperkalemia.**

(For Rationale of above practice points, please see text of Recommendation 2.1.1.)

## 2.2 Physical activity

**Recommendation 2.2.1: We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).**

*This recommendation places a relatively higher value on evidence suggesting that physical activity lowers BP, improves quality of life, and improves CV health in CKD patients. The recommendation places lower value on the time investment required for physical activity and the potential for physical activity to cause adverse events in CKD patients. The recommendation is weak according to GRADE because of the low quality of evidence supporting the benefits of physical activity, specifically in hypertensive CKD populations.*

### Key information

**Balance of benefits and harms.** The recommendation is driven by low-quality evidence demonstrating that physical activity may decrease BP and body weight and improve quality of life in CKD patients. The recommendation was also supported by the larger body of evidence in the general population, demonstrating the BP-lowering and other health benefits of regular physical activity. The Work Group recognizes a higher prevalence of comorbidity and frailty in CKD compared to the general population and is uncertain about whether regular physical activity increases or decreases adverse events. Nonetheless, the Work Group believes that most CKD patients would benefit from regular physical activity.

**Quality of evidence.** Intervention studies and systematic reviews in the general population have firmly established the effects of regular physical activity on BP lowering, improved strengthening, physical fitness, lower body weight, and lower risks of dysglycemia and diabetes. In populations with CKD, however, the evidence is much more limited. Our systematic review in CKD populations found low-quality evidence from 1 study conducted over 12 months showing that physical activity may improve SBP and DBP, and low-quality evidence from the same study showing that physical activity may improve eGFR over 12 months.<sup>75</sup> These findings, however, were inconsistent with other studies suggesting little or no differences.<sup>76–82</sup> The updated Cochrane systematic review finds that physical activity decreases weight and improves the mental components of quality of life in CKD.<sup>83</sup> Evaluating 282 patients from 6 studies, the systematic review found very low-quality evidence supporting the association of physical activity with increased study-reported adverse events (including pain, kidney infection, hypotension, dizziness, etc.), an important consideration given the high burden of comorbidity and frailty in CKD populations ([Supplementary Table S10](#)<sup>75–83</sup>). Observational data also show a dose-response relationship between greater levels of physical activity and lower risk of mortality in CKD patients.<sup>84</sup> Overall, the available literature did not allow differentiation between resistive and aerobic physical activity, or between supervised and unsupervised physical activity programs, leading to uncertainty about the critical elements of physical activity interventions in CKD populations. Nevertheless, it was the opinion of the Work Group that recommendations for the general population are likely to apply in CKD.

**Values and preferences.** This recommendation places a relatively high value on physical activity as a nonpharmacologic intervention, with substantial evidence for BP lowering, improvements in dysglycemia, and other CV and health benefits in the general population. The high prevalence of hypertension, dysglycemia, and CV disease in CKD populations suggests that the absolute benefit of physical activity may be especially high in people with CKD if the established relative benefits in the general population are indeed applicable to CKD. The higher potential for benefit is possibly offset by the high prevalence of comorbidity and frailty in CKD populations, which might limit the level of physical activity CKD patients can achieve and increase the risk of adverse events. However, the data on critical outcomes are not available, and those for other health benefits and risks are limited in CKD populations, leading to a weak recommendation.

The Work Group recognizes that some patients may have limited ability to exercise due to severe cardiorespiratory illnesses and physical or cognitive limitations, and may not be able to achieve physical activity levels recommended for the general population. In such individuals, targets can be individualized by patients and healthcare providers. The Work Group judged that most patients would benefit from efforts to perform physical activity regularly, even if not achieving the targets set for the general population. Patients in whom

physical activity is less feasible due to comorbidity may be less inclined to follow the recommendation, as with those who place a lower potential value on the uncertain benefits associated with physical activity.

**Resource use and costs.** Although a formal cost–benefit analysis has not been performed, the Work Group judged that encouraging physical activity is likely to be a good use of resources. Some individuals may choose to perform physical activity in structured environments such as a gymnasium with guidance and supervision from exercise professionals, which could incur costs. However, simple and widely available recreational and leisure-time activities are likely to lead to health benefits for CKD patients as well.

**Considerations for implementation.** Moderate physical activity may include recreational and leisure-time activities such as walking and cycling, household chores, and playing sports in the context of daily family and community life. Some patients with musculoskeletal limitations, frailty, high risks of falls, cognitive impairment, or severe cardiorespiratory disease may not be able to achieve physical activity targets set for the general population, but efforts to increase physical activity levels to modified targets, in the Work Group’s opinion, are likely to translate to health benefits nonetheless. The specific type, frequency, duration, and intensity of physical activity that maximizes health benefits in CKD patients are unknown. However, the Work Group found no reason to believe that interventions with proven health benefits in the general population would not also provide health benefits in CKD populations.

### Rationale

There are limited data in CKD populations on the risks and benefits of physical activity interventions. The quality of evidence is low or very low. Nonetheless, short-term studies suggest that physical activity interventions lower BP, decrease weight, and improve the mental aspects of quality of life. These data are consistent with a substantial body of evidence demonstrating that physical activity improves BP, dysglycemia, cardiopulmonary fitness, physical function, and mood in the general population. Prevalence of hypertension and diabetes, and risk of CV disease are extremely high in CKD populations, suggesting that the absolute benefit of physical activity interventions may be enhanced in CKD if the relative benefits are equivalent to those observed in the general population. Exercise programs have also been shown to improve health outcomes in other chronic disease conditions, including CV disease and chronic obstructive pulmonary disease. These factors led the Work Group to believe that physical activity is likely to be beneficial in CKD populations as well, despite the low-quality direct evidence currently available.

There are limited data on the optimal type or intensity of physical activity in CKD populations. The Work Group reviewed physical activity targets set forth by the World Health Organization (WHO)<sup>71</sup> and the recently released AHA/ACC lifestyle guidelines for primary prevention of CV disease.<sup>7</sup> These targets were not developed to specifically

address physical activity in populations with chronic diseases; however, the Work Group believes there is no evidence or plausibility to suggest that these recommendations are not applicable to CKD patients. The Work Group also consulted with the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD. In an effort to align guidelines, the target set forth by the AHA/ACC guidelines of moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week was adopted. This target is applicable to hypertensive CKD patients if their healthcare providers consider that the individual patient’s comorbidities and exercise tolerance allow it. For others, the degree of physical activity should be individualized according to their cognitive, CV, and physical tolerance, and adjusted, as these limitations change over time.

**Practice Point 2.2.1: Consider the cardiorespiratory fitness status, physical limitations, cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.**

**Practice Point 2.2.2: The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.**

(For Rationale of above practice points, please see text of Recommendation 2.2.1.)

### 2.3 Other lifestyle interventions

The Work Group recognizes that several other lifestyle interventions, including weight loss among those who are overweight or obese, reducing alcohol consumption among those who drink heavily, and adopting a heart-healthy diet pattern have been demonstrated in RCTs to lower BP in the general population. These lifestyle interventions may also have BP-lowering benefits in patients with CKD, and it may be reasonable to consider them when they can be applied safely and without side effects. Insufficient data on the risks or benefits of these interventions on BP in CKD populations *per se* precluded specific recommendations in this guideline.

#### Research recommendations

- Conduct clinical trials evaluating different dietary sodium reduction strategies for prevention of clinical endpoints of critical importance for CKD populations, including kidney failure, CV disease, and mortality.
- There are inconsistencies among the studies examining the relationship of dietary sodium intake with health outcomes in persons with diabetes.<sup>45,46,85</sup> Additional research is required to investigate the consistency of effects of dietary sodium changes on health benefits and harms across different causes and severities of CKD.
- It is unknown if there is a minimum dietary sodium level in CKD below which health risks are increased. Most of these



data derive from studies evaluating sodium intake using spot urine sodium measurements. There is current controversy about the accuracy of assessing sodium intake using random “spot” urine specimens, and potential increased risk of adverse health outcomes at the low-sodium intake range when assessed by this method.<sup>86</sup> Additional research is required in both sodium-intake assessment methodology in CKD, and to evaluate the health impacts of very low-sodium intakes in CKD populations.

- Recent small, single-center clinical trials evaluating chronic oral sodium bicarbonate supplementation versus placebo have not found changes in BP.<sup>87–89</sup> These findings raise the possibility that the anion associated with sodium intake may influence the BP response. Future research is required to determine if relationships of sodium intake with BP are influenced by the accompanying anion.
- In the general population, potassium-containing salt substitutes have been demonstrated to lower BP. Persons with CKD have been systematically excluded from clinical trials evaluating potassium-based salt substitutes, and some, albeit not all, observational data in CKD populations demonstrate that higher potassium intake is associated with higher risk of CKD progression and CV disease. Whether using potassium-containing salt substitutes may have health benefits or unique risks when applied to CKD populations requires future study.
- Persons of African ancestry are disproportionately represented in CKD populations. Prior systematic reviews suggest that reductions in sodium intake may result in larger reductions in BP in persons of African and Asian ancestry, compared to Caucasians.<sup>90</sup> Whether such racial differences can also be found in CKD populations is uncertain and should be evaluated in future studies.
- There is a paucity of data on factors that could identify individual CKD patients who have the greatest or least BP benefit from physical activity interventions, and also those that are at greater risk for harm. Identification of these factors and algorithms to tailor physical activity intensity and supervision to individual CKD patients is needed.
- Iodine supplements are added to salt in some countries. Future studies are required to determine whether restricting sodium intake in CKD populations may contribute to iodine deficiency in these settings.

# Chapter 3: Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis

## 3.1 Blood pressure targets

**Recommendation 3.1.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).**

*The recommendation is based on a single high-quality RCT with important benefits in the study cohort that included a substantial number of CKD patients, even though the recommendation is considered weak by GRADE standards. This recommendation assumes that standardized office BP measurement has been taken according to Recommendation 1.1. The recommendation suggests that the majority of people would want the recommended course of action, but some, particularly in the subgroups mentioned below, may not, because adjusting BP-lowering therapy to achieve this target SBP causes potential benefits and harms that may vary with comorbidities, severity of CKD, existing treatment burden, and the presence of “white-coat” or masked hypertension. The statement is weak because it is based primarily on a subgroup from 1 RCT; however, the subgroup was prespecified from a very high-quality trial. This recommendation does not apply to patients with CKD who have a kidney transplant; this guideline does not apply to those receiving dialysis.*

### Key information

**Balance of benefits and harms.** There is evidence that targeting SBP to <120 mm Hg, when measured under standardized conditions, reduces CV events and all-cause mortality in CKD (Supplementary Table S11<sup>91–93</sup>). In most people with high BP, including the frail and elderly, these benefits appear to outweigh the risks of harm (e.g., hypotension and acute kidney injury [AKI]). However, empirical evidence demonstrating how individuals would weigh these benefits and harms is lacking. These benefits extend to patients with or without CKD. Still, there is less certainty that the benefits outweigh the harms with the following scenarios:

- CKD G4 and G5: For people with a lower GFR, there is less certainty around the benefit of lower BP target and potential risk of harm, compared to people with higher GFRs.
- Diabetes: The benefits of intensive BP lowering are less certain among patients with concomitant diabetes and CKD, compared to patients with CKD without diabetes.

- Individuals with SBP of 120–129 mm Hg: Observational data suggest that individuals with SBP of 120–129 mm Hg are at higher CV risk than those with SBP <120 mm Hg.<sup>94</sup> Lowering the SBP from 120–129 mm Hg to <120 mm Hg may therefore be beneficial hypothetically. However, RCTs in CKD targeting SBP <120 mm Hg have not included individuals with SBP of 120–129 mm Hg. Therefore, the recommendation of lowering SBP from 120–129 mm Hg to <120 mm Hg by pharmacologic or non-pharmacologic means is tentative.
- People with very low baseline DBP (e.g., <50 mm Hg), particularly in the presence of coronary artery disease: In theory, it is possible that intensive BP lowering will increase the risk of myocardial infarction (MI) in this subgroup because coronary perfusion depends on DBP. However, in SPRINT, the subgroup with the lowest DBP at baseline had similar CV and survival benefits from intensive SBP reduction as those with higher baseline DBP.
- Etiology of CKD: There is no evidence that CV benefits of a lower target BP in CKD varies with its etiology. However, kidney benefits in autosomal dominant polycystic kidney disease may be greater with an SBP of 95–110 mm Hg than with 120–130 mm Hg.<sup>95</sup>
- Proteinuria: Proteinuria may no longer be an effect modifier of BP target with an SBP target of <120 mm Hg.
- Older age: The ratio of benefits to harms of intensive BP reduction in CKD patients at the upper spectrum of age (e.g., >90 years old) is less certain, although people with a mean age of  $83 \pm 3$  years seemed to derive CV, survival, and cognitive benefits.<sup>96</sup>
- Younger age: The ratio of benefits to harms of intensive BP reduction in people at the younger spectrum of age (e.g., <50 years old), who may have low absolute risks of CV disease and all-cause death, is less certain.
- The very frail and those residing in a nursing home: Frailty did not appear to modify the beneficial effects of intensive SBP lowering.
- “White-coat” hypertension: If office BP, even when measured under standardized conditions, is higher than daytime ambulatory or home BP, the risks of additional BP-lowering treatment to achieve office BP <120 mm Hg may be higher, with less certainty of benefits. Nonetheless, it should be noted that patients with “white-coat” hypertension were not excluded in SPRINT and other major outcome trials.

- Severe hypertension, such as SBP  $\geq 180$  mm Hg on no or 1 antihypertensive drug, or  $\geq 150$  mm Hg on  $>4$  antihypertensive drugs, because such patients were not included in SPRINT.

Uncertainty in risk–benefit ratios in the various scenarios above does not necessarily imply that intensive SBP lowering is not warranted. It only reflects the lack of RCT data to support or refute the ratios. If the patient cannot tolerate SBP  $<120$  mm Hg despite a slow, gradual decrease in SBP over months, efforts should be made to maintain SBP  $<130$  mm Hg,  $<140$  mm Hg, or an even higher tolerated SBP goal. Individualization based on trial and error prevails, as in many aspects of medical practice. The importance of standardized BP measurement when applying this guideline cannot be overemphasized. Routine, non-standardized office BP measurements often, but not invariably, overestimate BP compared to measurements under standardized conditions (Chapter 1). Importantly, the extent to which routine measurements overestimate or underestimate standardized office BP is highly variable between and within patients; therefore, no correction factor can be used to convert routine BP to standardized BP measurement by calculation. The use of routine measurements to adjust BP-lowering therapy confers a serious risk of overtreatment and sometimes undertreatment. It should be emphasized that the most important aspect of standardized BP measurement is preparation prior to the measurement and not the equipment used (Chapter 1).

**Heterogeneity in primary outcomes among various RCTs.** It should be noted that the medium-sized trials that exclusively enrolled CKD patients and examined target BP levels, such as the Modification of Diet in Renal Disease (MDRD) trial,<sup>97</sup> the African American Study of Kidney Disease and Hypertension (AASK) trial,<sup>98</sup> and the Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) trial,<sup>99</sup> had used kidney events as the primary outcomes and had relatively few non-kidney events during the trial. In contrast, the larger trials that did not exclusively enroll CKD patients, such as the Systolic Hypertension in the Elderly Program (SHEP) trial,<sup>100</sup> the Secondary Prevention of Small Subcortical Strokes (SPS3) trial,<sup>101</sup> the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,<sup>92</sup> and the Systolic Blood Pressure Intervention Trial (SPRINT),<sup>93</sup> used CV events as the primary outcomes and had relatively few kidney events, although there might be a sizeable number of CKD patients in the latter trials. These dichotomies and the heterogeneity in the characteristics of the study cohorts create challenges in data synthesis to provide an evidence base for practice recommendations in CKD.

**Cardiovascular outcomes. General population.** In the general population, there is extensive evidence that the reduction in the risk of CV events is proportional to the SBP reduction achieved, with the absolute benefits being greater in those with higher baseline risk of CV disease, and with no difference in proportional risk reductions across groups defined according to higher or lower baseline SBP.<sup>102–106</sup> The meta-

analysis of 21 RCTs by Xie *et al.* concluded that the absolute benefits of lowering SBP were greater and the number-needed-to-treat was smaller in trials where all enrolled patients had vascular disease, diabetes, or kidney disease.<sup>106</sup> In this meta-analysis, on-treatment BP averaged 133/76 mm Hg on intensive treatment and 140/81 mm Hg on less-intensive treatment. Outcomes in patients with and without albuminuria at baseline were not reported separately.

SPRINT provides further evidence that intensive SBP lowering reduces CV events and death in those at high CV risk. Those benefits targeting SBP  $<120$  mm Hg compared to  $<140$  mm Hg in SPRINT extended to CKD, the elderly, and those with frailty.<sup>91,107</sup> In a prespecified analysis, the benefits of targeting SBP  $<120$  mm Hg in SPRINT included a significant reduction in the combined endpoint of probable dementia and mild cognitive impairment, with no interaction with baseline CKD.<sup>108</sup> Secondary analyses further suggest that the beneficial effect of intensive BP lowering on the incidence of mild cognitive impairment *per se* may extend to those with CKD<sup>107</sup> and those who are aged 80 years or older.<sup>96</sup>

A recent meta-analysis of 74 RCTs with broader inclusion criteria than those discussed above<sup>102,105,106</sup> concluded that the effect of BP lowering differed by baseline BP with no clear effect on death or CV disease in participants with no prior coronary heart disease and SBP  $<140$  mm Hg at baseline.<sup>109</sup> This finding has been used by some guideline groups, such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom, to justify a more conservative approach to BP-lowering therapy than that advocated in the present guideline. However, the inclusion of large numbers of trials comparing antihypertensive drugs versus placebo, not lower versus higher BP target, and importantly, those in which BP measurement technique was less precisely specified makes drawing conclusions challenging.<sup>109</sup>

**Adults with CKD.** A meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, which included trials of antihypertensive drugs versus placebo and trials of different BP targets, found that the proportional reduction in CV events with more intensive BP treatment was independent of the presence or absence of CKD.<sup>110</sup> In their meta-analysis, Ettehad *et al.* also reported a risk reduction for CV events with intensive BP lowering in those with CKD, but the size of the risk reduction was less than that in those without CKD.<sup>105</sup>

SPRINT intentionally included a CKD subgroup *a priori* and examined an SBP target of  $<120$  mm Hg, as recommended in the present guideline, versus  $<140$  mm Hg. In the primary analysis of the entire cohort of 9361 participants, SPRINT demonstrated benefits for the primary CV outcome (hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.64–0.89) and for all-cause death (HR: 0.73; 95% CI: 0.60–0.90) across all subgroups with no heterogeneity, including those with or without CKD defined as eGFR 20 to  $<60$  ml/min per 1.73 m<sup>2</sup>, with proteinuria  $<1$  g/d.<sup>91,93</sup> Indeed, in the subgroup with CKD (median albumin-creatinine ratio [ACR]: 13.3 mg/g [1.33 mg/mmol] [IQR: 6.4–43.1 {0.64–4.31}] and mean eGFR: 47.9  $\pm$  9.5 ml/min per 1.73 m<sup>2</sup>), the CV benefit

missed significance of  $P < 0.05$  (HR: 0.81; 95% CI: 0.63–1.05), while the mortality benefit was nominally significant. That said, SPRINT was not powered for subgroup analyses, especially given that it ended early because of the substantial CV disease and mortality benefit. It should be noted that large RCTs with major clinical outcomes are rarely powered for a specific subgroup, even for age or sex. Trial results should be interpreted for the entire study cohort, with effect modification by factors defining subgroups examined in secondary analysis. Such effect modification was not noticed for CKD in SPRINT. Regardless, SPRINT is the largest trial testing 2 BP targets in CKD with approximately 2600 CKD patients. Although SPRINT excluded patients with diabetes, polycystic kidney disease, or proteinuria  $\geq 1$  g/d, those with glomerulonephritis not taking immunosuppressive medications were not excluded.

Three other trials comparing different BP targets, powered for kidney outcomes as primary outcomes, generated far too few CV events or death outcomes (MDRD, AASK, REIN-2). However, a meta-analysis by Malhotra *et al.*, examining death as an outcome exclusively in the CKD subgroups of the large hypertension treatment RCTs, also found a benefit of lower target BP.<sup>111</sup>

Older adults with or without CKD. There are meta-analyses and systematic reviews based on the general population of older adults, including patients with CKD, addressing the impact of lower BP targets. Garrison *et al.* analyzed RCTs conducted in hypertensive adults aged 65 years or older and reported outcomes for higher SBP (150–160 mm Hg) or DBP (95–105 mm Hg), compared to a lower treatment target of  $\leq 140/90$  mm Hg.<sup>112</sup> SPRINT was excluded from this analysis because its lower target was lower than the inclusion criteria of the meta-analysis. Its inclusion may have changed the results of the meta-analysis. Based on this meta-analysis, there was insufficient evidence to determine whether a lower SBP target provides meaningful differences in benefits or harms to older adults. However, there are very few major trials and relatively few events in this meta-analysis. In contrast, Bavishi *et al.* included RCTs in a meta-analysis comparing intensive versus standard or less-intensive BP control in older adults ( $\geq 65$  years) and provided long-term CV and safety outcomes.<sup>113</sup> SPRINT met the inclusion criteria for this review. There were reductions in major CV events, CV mortality, and heart failure (HF), but a possible increase in AKI and serious adverse events. No analysis of the older population with CKD was described in these studies.

There is only one large study analyzing the effects of lower BP targets in CKD patients older than 75 years. A *post hoc* analysis of that specific subgroup in SPRINT showed that the low BP target (SBP  $< 120$  mm Hg) reduced the primary CV outcome (HR: 0.64; 95% CI: 0.45–0.92), all-cause death (HR: 0.64; 95% CI: 0.43–0.96), and the composite of primary CV disease outcome or all-cause death (HR: 0.66; 95% CI: 0.49–0.90).<sup>91</sup> There was no description of potential harm of achieving lower targets in this subgroup of older adults with CKD, although the risk–benefit ratio in the entire CKD

cohort and in the entire subcohort older than 75 years in SPRINT was favorable. Even in the age group 80 years and older, subgroup analysis in SPRINT showed that intensive BP lowering decreased the risk of CV events (HR: 0.66; 95% CI: 0.49–0.90) and all-cause mortality (HR: 0.67; 95% CI: 0.48–0.93).<sup>96</sup>

Adults with diabetes and CKD. Among patients with concomitant diabetes and CKD, the benefits of intensive BP lowering are less certain than those with CKD without diabetes. All previous studies in diabetes with and without CKD have favored more, instead of less, intensive BP reduction (UKPDS-38,<sup>114</sup> SHEP,<sup>100</sup> Syst-Eur,<sup>115</sup> ABCD,<sup>116</sup> HOT<sup>117</sup>). In their meta-analysis, Ettehad *et al.* reported that the reduction in major CV events remained proportional to the BP reduction achieved among trial participants with diabetes, but that the proportional risk reductions were smaller than the reductions in those without diabetes.<sup>105</sup> In contrast, in the meta-analysis of intensive versus less-intensive BP-lowering therapy among patients with CKD, Malhotra *et al.* found no evidence of heterogeneity in beneficial effects on mortality with respect to the presence or absence of diabetes.<sup>111</sup> Brunström *et al.* conducted a systematic review and meta-analysis of RCTs that included at least 100 patients with diabetes, and found that BP reduction decreased MI, stroke, CV mortality, ESKD, and all-cause mortality if baseline SBP was  $> 150$  mm Hg; there was decreased MI, HF, and all-cause mortality if baseline SBP was 140 to 150 mm Hg, but paradoxically, increased CV mortality was observed if baseline SBP was  $< 140$  mm Hg.<sup>118</sup>

Two major caveats should be noted regarding these meta-analyses in diabetes. First, these meta-analyses differ substantially from each other in their respective inclusion criteria. Brunström *et al.* and Ettehad *et al.* included RCTs that compared antihypertensives to placebo, and different BP targets. Ettehad *et al.* included RCTs of head-to-head comparisons of antihypertensive agents to examine the effect of 10 mm Hg reduction in SBP on clinical outcomes. Second, none of the trials conducted prior to ACCORD and SPRINT examined an SBP target as low as  $< 120$  mm Hg. Nonetheless, they collectively suggest that SBP lowering decreases the CV event rate and perhaps mortality and kidney outcomes.

The ACCORD trial that enrolled exclusively patients with diabetes did not show a difference in the prespecified primary endpoint of composite CV events between the intensive SBP target ( $< 120$  mm Hg) and standard SBP target ( $< 140$  mm Hg), but it did demonstrate a significant reduction in stroke (HR: 0.59; 95% CI: 0.39–0.89), a prespecified secondary outcome, with intensive SBP lowering.<sup>92</sup> However, ACCORD included few patients with CKD, as patients with serum creatinine  $> 1.5$  mg/dl (132  $\mu$ mol/l) were excluded, and those with CKD were mostly proteinuric with well-preserved eGFR.<sup>119</sup> Therefore, there is little direct evidence from ACCORD alone to guide a recommendation for patients with diabetes and CKD. Nonetheless, there was no statistical interaction between CKD and intensive BP lowering on the reduction in stroke risk.<sup>119</sup>

In contrast to ACCORD, SPRINT included a substantial number ( $n = 2646$ ) of participants with CKD. Although SPRINT specifically excluded patients with diabetes, 42% ( $n = 3898$ ) of the cohort had prediabetes, defined as baseline fasting serum glucose  $>100$  mg/dl [ $5.6$  mmol/l]. A *post hoc* analysis of SPRINT comparing participants with and without prediabetes found that the CV and survival benefits of intensive SBP reduction ( $<120$  mm Hg) were similar in the 2 subgroups.<sup>120</sup>

Other secondary analyses of ACCORD data further suggest that intensive SBP lowering is beneficial. A combined *post hoc* analysis of SPRINT and ACCORD suggested similar CV benefits of intensive BP-lowering therapy in the presence or absence of diabetes.<sup>121</sup> ACCORD was not only a BP trial, but it also employed a rather complex study design. The participants were randomized first to intensive versus less-intensive glycemic control, and then either to intensive versus less-intensive BP control or to the addition of fenofibrate versus placebo on a background of a statin. The trial of glycemic control was terminated early because of higher all-cause mortality with intensive glycemic control.<sup>92</sup> This adverse effect of intensive glycemic control was also demonstrated in the CKD subgroup of ACCORD.<sup>119</sup> The ACCORD BP trial reported no statistical interaction between glycemic control and BP control on prespecified primary and secondary CV outcomes. However, a more detailed combined analysis of data from ACCORD and SPRINT found that the beneficial effects of intensive SBP control (with both trials targeting  $<120$  mm Hg) on combined CV endpoints and on all-cause mortality were similar in the standard glycemia arm of ACCORD and in SPRINT.<sup>122,123</sup> In contrast, intensive SBP control increased CV death, HF, and MI in the intensive glycemia arm. These interactions lessened after discontinuation of the glycemic intervention.<sup>122</sup> In another *post hoc* analysis among ACCORD participants in the standard glycemia arm who had additional CV risk factors that would have met the SPRINT inclusion criteria, intensive BP control provided CV benefits similar to those seen in SPRINT.<sup>124</sup>

Similarly, a pooled analysis of individual patient data from 4983 patients with CKD from AASK, MDRD, ACCORD, and SPRINT found a non-significant trend to decreased mortality with intensive BP-lowering therapy, but a statistically significant reduction in mortality in a subgroup with eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup> who were not assigned to intensive glycemic control.<sup>125</sup> Collectively, these aforementioned *post hoc* analyses support the notion that intensive BP control improves clinical outcomes even in patients with diabetes and CKD, but glycemic control modulates the effects of intensive BP control on CV outcomes. This evidence is indirect, hence diminishing the certainty of the benefits and strength of recommendation of targeting SBP  $<120$  mm Hg.

**Low diastolic blood pressure.** Numerous observational studies,<sup>126,127</sup> including those that examine data from RCTs in a *post hoc* observational manner,<sup>128</sup> although not all studies, have suggested a J-shaped curve with very low DBP being associated with an increased risk of CV events, particularly MI

among patients with pre-existing coronary artery disease.<sup>94</sup> The validity of these observations is supported by biological plausibility, as low DBP in the setting of coronary stenosis could lead to impaired subendocardial blood flow during diastole. However, this association is heavily confounded, as patients with very low DBP inherently have high CV risks. Beddhu *et al.* recently showed that in SPRINT participants, baseline DBP indeed bore a U-shaped relationship with mortality. However, the CV-protective benefits of intensive SBP lowering were independent of baseline DBP, including the lowest DBP quintile at baseline with a mean DBP of  $61 \pm 5$  mm Hg.<sup>129</sup> Whether this beneficial effect of SBP lowering persists at even lower DBP levels (e.g.,  $<45$  mm Hg) cannot be determined from these data.

**Kidney outcomes.** Rate of decline in GFR. The effects of intensive BP lowering on GFR are often complicated by an exaggerated early acute GFR decline that is also seen with inhibitors of the renin-angiotensin system (RAS) and the sodium–glucose cotransporter-2 (SGLT2) system. This acute eGFR decrease with BP lowering may be mediated, at least in part, by intrarenal hemodynamic changes. This hypothesis is supported by the following observations:

- (i) Single-nephron GFR decreases when glomerular blood flow rate drops below the level that can be sustained by arteriolar autoregulation.<sup>130</sup>
- (ii) Urinary excretion of various tubular biomarkers during intensive SBP treatment in SPRINT was not indicative of tubular damage.<sup>131,132</sup>
- (iii) Albuminuria during follow-up was lower, instead of higher, in the intensive SBP arm than in the standard SBP treatment arm in SPRINT. Similar observations have been reported in ACCORD participants.<sup>133</sup>

Nonetheless, the overall rate of decline of eGFR was higher rather than lower on intensive treatment in SPRINT in both CKD<sup>91</sup> and non-CKD subgroups,<sup>134</sup> ACCORD,<sup>92</sup> and SPS3.<sup>12</sup> In both ACCORD and SPRINT, participants assigned to intensive BP target also developed more incident CKD during follow-up than those assigned to standard BP target.<sup>128,134</sup>

There was no difference in the rate of doubling of serum creatinine between intensive and standard SBP treatment in SPRINT, but the small number of these discrete events precludes firm conclusions. The difference in the rate of decline of eGFR in SPRINT after the initial 6 months was small ( $0.47$  vs.  $0.32$  ml/min per  $1.73$  m<sup>2</sup>/yr in the intensive and standard arms, respectively). If this slope persisted long-term, it would take 20 years to cause a  $3$  ml/min per  $1.73$  m<sup>2</sup> difference in eGFR between intensive and standard SBP treatment. Taking both the beneficial effect on albuminuria and the adverse effect on eGFR into account, the long-term effects of intensive SBP lowering on the kidney cannot be determined from these relatively short-term, on-treatment observations.

Progression to kidney failure and effect modification by proteinuria. Prior to SPRINT, the largest RCTs addressing the effects of intensive BP control in CKD were MDRD,<sup>97</sup> AASK,<sup>135</sup> and REIN-2.<sup>99</sup> The primary outcome of these 3 trials was progression of kidney disease. During the trial phase, when the

participants were under their respective randomized interventions, none of these trials showed benefits or harms on kidney function by intensive BP lowering in the primary analysis of the entire cohort. A caveat of MDRD and AASK is that both trials targeted mean arterial BP (MAP, calculated as  $DBP + 1/3 \times \text{pulse pressure}$ ), rather than SBP or DBP. The lower target was a MAP of  $<92$  mm Hg (equivalent, for example, to 125/75 mm Hg, 140/68 mm Hg, 160/58 mm Hg, or many other combinations of SBPs and DBPs), whereas the higher target was a MAP of  $<107$  mm Hg (equivalent to 140/90 mm Hg, 125/98 mm Hg, etc.). Further, the MAP targets varied in MDRD, depending on the age of the patients.<sup>136</sup>

A meta-analysis in 2011 conducted by the ERT of the KDIGO 2012 BP guideline found only these 3 studies (MDRD, AASK, and REIN-2) pertinent to the discussion of whether a lower BP target reduced the risk of progression to kidney failure in the presence of proteinuria. They concluded that the evidence was inconclusive.<sup>137</sup> Similarly, the current ERT review found no effect modification according to the presence of proteinuria (Supplementary Table S12<sup>97–99,135,138</sup>). The evidence that intensive BP reduction reduces the risk of progression to kidney failure is derived mainly from a predefined subgroup analysis of MDRD (only 54 patients with proteinuria  $>3$  g/d, but large effect size)<sup>97,139</sup> and long-term post-treatment follow-up from MDRD<sup>138</sup> and AASK.<sup>135</sup> A more recent meta-analysis of 11 RCTs of lower versus higher BP goals found that intensive BP reduction was associated with a reduction in kidney failure events (defined as the composite of doubling of serum creatinine and a  $>50\%$  reduction in eGFR or ESKD), with effect modification by baseline proteinuria.<sup>140</sup> Intensive BP control reduced the risk of kidney failure only among those with baseline proteinuria, defined as a protein-creatinine ratio (PCR)  $>220$  mg/g (22 mg/mmol). The MDRD and AASK studies were major contributors to this evidence base.

The REIN-2 study compared a higher DBP target of  $<90$  mm Hg with a lower BP target of  $<130/80$  mm Hg by adding felodipine to baseline ramipril therapy in patients with proteinuric CKD (mean eGFR and proteinuria approximately 35 ml/min and 3 g/d, respectively) without diabetes.<sup>99</sup> REIN-2 found no benefit of intensified BP control over a mean follow-up of approximately 19 months. However, the study was underpowered with a total of only 338 participants and had very small differences in achieved SBP and DBP of only 4 mm Hg and 2 mm Hg, respectively, during the intervention phase.

The effects of intensive SBP lowering with target  $<120$  mm Hg are only available in ACCORD and SPRINT. In ACCORD, which had few CKD patients, there was no difference in progression to ESKD between intensive (59 cases/2362 patients) and standard (58 cases/2371 patients) SBP groups. SPRINT excluded patients with proteinuria  $>1$  g/d, and the baseline median ACR was only 13 mg/g (1.3 mg/mmol) in the CKD subgroup. ESKD events were rare in SPRINT, with a total of only 16 cases in 9361 patients. No reliable conclusions can therefore be reached on the effects of an SBP target  $<120$  mm Hg on progression to kidney failure

in patients with CKD from ACCORD or SPRINT (Supplementary Table S11<sup>91–93</sup>).

Previous guidelines, including the KDIGO 2012 BP guideline, recommended more aggressive BP lowering for patients with albuminuria than for those without albuminuria.<sup>141</sup> These recommendations were based largely on the subgroup findings of the MDRD,<sup>97</sup> AASK,<sup>98</sup> as described above, and in the pediatric population, the ESCAPE trial (Chapter 5).<sup>142</sup> With the adoption of an SBP target  $<120$  mm Hg for all patients with CKD in the present revised guideline based on the evidence for CV and survival benefits, separate targets for patients with and without albuminuria are no longer required. There is no evidence supporting an even lower target (e.g.,  $<110$  mm Hg) for patients with severely increased proteinuria.

**Mortality.** The ERT found 5 RCTs examining the effects of intensive versus less-intensive BP control on mortality in patients with CKD without diabetes (Supplementary Table S14<sup>91,97–99,135,138,143</sup>). Over a mean follow-up of 3.23 years of the 9351 participants in these 5 studies, 84 deaths per 1000 participants were seen in the standard BP control arm, and 66 per 1000 participants in the intensive BP control arm (18 fewer deaths per 1000; 95% CI: 26 fewer—8 fewer deaths per 1000 participants). Secondary analyses of the MDRD and AASK cohorts using administrative databases have also suggested long-term survival benefits from a lower MAP target.<sup>144,145</sup> The mortality rates were low in these studies, and the conclusions can only be interpreted as hypothesis-generating.

When results of studies in patients with CKD without diabetes are combined with those in patients with diabetes and CKD, the effect of intensive BP lowering on all-cause mortality was attenuated. In 9 studies with 13,367 participants and a mean of 3 years of follow-up, intensive BP targets, compared with higher BP targets, resulted in 23 fewer deaths per 1000 patients, but the 95% CI indicated 49 fewer to 33 more deaths per 1000 (Supplementary Table S13<sup>91,92,97–99,116,135,138,143,146–148</sup>).

A recent individual patient-level meta-analysis of 18 trials comprising 15,294 patients with CKD (defined as an eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup>) found that intensive BP lowering resulted in a significantly lower risk of mortality compared to less-intensive BP lowering; this benefit was consistent across multiple subgroups.<sup>111</sup> This meta-analysis included RCTs that compared a range of target BPs, but it also included trials comparing antihypertensive agents with placebo or no treatment.

Evidence of the effects of an SBP target of  $<120$  mm Hg versus  $<140$  mm Hg in patients with CKD without diabetes is available only from SPRINT.<sup>91</sup> There were 53 deaths per 1000 participants in the standard BP control arm, and 40 deaths per 1000 participants in the intensive BP control arm, resulting in a statistically significant difference of 13 fewer per 1000 participants (95% CI: 23 fewer—1 fewer deaths per 1000 participants; Supplementary Table S11<sup>91,93</sup>). This difference is also evident when the CKD subgroups in both ACCORD (comprised all patients with diabetes) and SPRINT (comprised no patients with diabetes) are combined.

**Adverse effects.** Some practitioners may be concerned about adverse events associated with the low SBP target. Although the Work Group cautions about these possibilities, regardless of the level of SBP, age, and comorbidities, the available evidence shows that the SBP target of <120 mm Hg is generally safe. In a patient with severe carotid stenosis, an SBP <120 mm Hg may be insufficient to maintain cerebral perfusion, and even an SBP of 150 mm Hg may be insufficient. Diligence in monitoring the patient and taking the appropriate actions of adjusting BP, administration of anticoagulants, or surgical correction of the stenosis may be necessary. Such scenarios do not refute the notion that an SBP target <120 mm Hg in most adults is beneficial and not associated with increased significant adverse events.

**Clinical events.** Within the CKD subgroup, SPRINT reported no significant difference in serious adverse events, and in adverse events associated with hypotension, postural hypotension, syncope, bradycardia, and injurious falls between the intensive (<120 mm Hg SBP) and standard (<140 mm Hg SBP) BP arms. Among the participants aged  $\geq 75$  years or even  $\geq 80$  years at baseline, of which approximately 44% and 50%, respectively, had an eGFR <60 ml/min per 1.73 m<sup>2</sup>, the risk profile for clinical adverse events with intensive BP lowering was also quite favorable.<sup>96,107</sup> There were no differences in serious adverse events and injurious falls between the intensive and standard BP arms. In SPRINT, standing BP was measured at prespecified visits.<sup>149</sup> Intensive BP lowering reduced, rather than increased, the risk of orthostatic hypotension. Further, orthostatic hypotension was not associated with a higher risk of CV disease events, falls, or syncope.<sup>93</sup> However, it is reasonable to consider a change in medications or less-intensive therapy if the patient is symptomatic or BP is excessively low (e.g., SBP <100 mm Hg).

**Electrolyte abnormalities.** Within the CKD subgroup, SPRINT reported no significant difference in adverse events associated with hyponatremia or hypernatremia between standard and intensive BP arms. However, there were increased risks for hypokalemia (HR: 1.87; 95% CI: 1.02–3.43) and hyperkalemia (HR: 1.36; 95% CI: 1.01–1.82), presumably because of the greater use of antihypertensive medications in the intensive BP arm.

**Acute kidney injury.** In the entire ACCORD cohort and SPRINT cohort (and in the SPRINT CKD subgroup), there were higher rates of AKI in the intensive SBP arms, although most of these were AKI Stage 1 and showed full recovery.<sup>150</sup> The biomarker data described above suggest that at least some of the fall in eGFR seen with intensive BP treatment could be due to intrarenal hemodynamic changes rather than structural damage. In a *post hoc* analysis of SPRINT, there was a significant interaction between baseline eGFR and SBP lowering, such that patients with a baseline eGFR <45 ml/min per 1.73 m<sup>2</sup> had an increased risk of AKI in the intensive BP arm but no reduction in the primary CV outcome.<sup>151</sup> Hence, the risk–benefit ratio for kidney outcomes in the intensive SBP arm may not be as favorable in this subgroup as in the subgroup with higher baseline eGFR. However, caution should be used in interpreting these non-prespecified *post hoc* findings in relatively small subgroups. In 2 other *post hoc* analyses of SPRINT, the

respective risks of AKI were marginally increased with the intensive BP target in people  $\geq 75$  years old (HR: 1.41; 95% CI: 0.98–2.04) and increased in people  $\geq 80$  years old (HR: 2.12; 95% CI: 1.37–3.26). These data collectively suggest that intensive BP lowering increased the risk of AKI in people with moderate CKD and advanced age, but the episodes were rather infrequent, affecting less than 4% of SPRINT participants and tended to be mild and reversible (Supplementary Table S11<sup>91–93</sup>).<sup>96,107</sup>

**Polypharmacy.** Most participants in SPRINT were taking 1 or 2 BP-lowering therapies before randomization. The benefits of intensive SBP lowering are unclear among patients who require 4 or more BP-lowering medications to achieve SBP <120 mm Hg. In a *post hoc* analysis of the SPRINT database, the number of additional BP-lowering medications was an independent predictor of poorer survival.<sup>152</sup> However, the requirement for multiple medications to achieve SBP <120 mm Hg may reflect the patient's underlying characteristics and does not imply that intensive SBP lowering is not beneficial. Indeed, in another study using the SPRINT database and more advanced statistical techniques that account for confounding by indication, the addition of a new antihypertensive drug class led to significant reductions in SBP and major CV event rates but no difference in serious adverse events. These incremental effects appeared to be consistent regardless of the level of baseline drug use.<sup>153</sup> Hence, at present, there is no clear evidence that people who require multiple medications to achieve an SBP of <120 mm Hg would have an unfavorable risk–benefit ratio. Nonetheless, polypharmacy also adds to treatment burden and is often associated with reduced adherence, which may be attenuated by the use of single-pill combinations.

**Quality of evidence.** The evidence on the effects of intensive BP lowering, namely the <120 mm Hg SBP target, on critical clinical outcomes such as CV events and all-cause mortality is considered to be moderate due to study limitations, while the effect on kidney failure is weak. For CV events and all-cause mortality, the evidence is primarily derived from SPRINT, in which the sample size was large, the effects of intensive BP lowering on clinical outcomes were strong, and there was no heterogeneity in the effects between the CKD and non-CKD subgroups. Results from the subgroup analysis of ACCORD, as well as the joint analysis of the ACCORD and SPRINT data, lend further support, although there were relatively few participants with CKD in ACCORD (Supplementary Table S11<sup>91–93</sup>).

The renoprotective effects of BP lowering in CKD are primarily derived from MDRD and AASK trials. The evidence is considered to be of low quality due to study limitations and inconsistency. The effects were seen in only the proteinuric subgroups, and in the case of AASK, the effects were seen only during the long-term post-trial follow-up (Supplementary Table S12<sup>97–99,135,138</sup> and Supplementary Table S13<sup>91,92,95,97–99,135,138,143,146–148</sup>). Further, SPRINT showed a short-term acute decline in eGFR and no long-term beneficial effect on eGFR with intensive SBP lowering. Therefore, collectively, these studies did not show convincingly that intensive BP lowering is renoprotective.

**Values and preferences.** The Work Group places high value on decreasing the risks of CV events and all-cause mortality by intensive SBP lowering, although the renoprotective effects are more tenuous. The reduction in the absolute risk of all-cause mortality in the CKD subgroup in SPRINT was 0.6% per year (1.61% and 2.21% in the intensive and standard SBP group, respectively). If this trend continues linearly, the risk reduction would be substantial over 20 or 30 years.

The Work Group also places higher value on increased pill burden, more clinic visits, electrolyte abnormalities, hypotension, syncope, injurious falls, and AKI that may be caused by targeting an SBP <120 mm Hg. However, intensive SBP lowering in CKD patients did not cause more serious adverse events, orthostatic hypotension, syncope, or injurious falls than targeting SBP <140 mm Hg in SPRINT. The Work Group places lower values on the higher risks of mild AKI, hyperkalemia, and hypokalemia seen in the intensive SBP lowering in CKD patients because they are largely mild, transient, and manageable. We found no informative studies of how patients with CKD would balance these potential benefits with potential harms.

The adoption of an SBP target <120 mm Hg is an ideal topic for shared decision-making between individual patients and clinicians. There is likely to be marked variability in how individual patients weigh and value the potential benefits and harms of intensive BP control. This may vary with age, culture, number of drugs (both BP-lowering and other drugs), and other factors. Decision aids to support shared decision-making are available on the online version of this guideline (see link to MAGICapp at <https://kdigo.org/guidelines/blood-pressure-in-ckd/>). These aids are based on the evidence syntheses compiled by the ERT that were used to develop the guideline and can be used online or to generate printable summaries of the evidence relating to each decision (e.g., differences in absolute mortality or in AKI per 1000 patients with standard vs. intensive SBP target).

**Resource use and costs.** The implications for resource utilization for standardized office BP measurement, as recommended in this guideline, are discussed in Chapter 1. Costs of additional antihypertensive drugs are relatively small in view of the benefits; however, there may be additional costs for monitoring. The Work Group does not consider that resource implications would have significant impact on the recommendation. Indeed, economic analysis using SPRINT data suggest that intensive SBP treatment is cost-effective.<sup>154</sup> Nonetheless, it is possible that there will be difficulties in implementing these recommendations in countries in which resources are limited; in those settings, it is probably more important to ensure that all eligible patients have at least reasonable BP control (e.g., SBP <140 mm Hg) than to focus efforts on achieving intensive BP control in a smaller fraction of the population.

**Considerations for implementation.** Although there is strong evidence that home BP measurements are predictive of long-

term adverse clinical outcomes, no adequately powered trial for guiding antihypertensive medication based on home BP targets has been reported. Nonetheless, HBPM may help to improve patient motivation and adherence to treatment and can also be used to identify patients with masked hypertension, masked uncontrolled hypertension, “white-coat” hypertension, and the “white-coat” effect as an adjunct for diagnosis and potential management of BP (see Chapter 1).

The use of standardized office measurements for BP management may require additional equipment, clinic space, time, training, and/or change in culture, habits, or policies (see Chapter 1). Practitioners would benefit from understanding the guidelines and the underlying data and rationale, and can tailor the target and treatment strategy for individual patients according to overall health conditions, response and tolerability to SBP lowering, as well as their preferences. Shared decision-making with individual patients is essential. The practitioners should provide general information and individualized considerations of the pros and cons of the treatment option and explain that the evidence for intensive SBP targets is more certain in some groups (e.g., those who would have been eligible for SPRINT) and less certain in others (e.g., people with diabetes, advanced CKD with eGFR <30 ml/min per 1.73 m<sup>2</sup>, older adults aged >90 years, and those with severe hypertension [e.g., SBP >180 mm Hg or >150 mm Hg on >4 antihypertensive drugs]).

As worded, the recommendation states that clinicians should target an SBP <120 mm Hg. In practice, adoption of this recommendation in a population of patients with CKD will result in a median SBP around 120 mm Hg, meaning that 50% of patients will have SBP >120 mm Hg at any one time. A more stringent recommendation would be that all patients should achieve an SBP <120 mm Hg. This would require an even lower target or threshold for intervention. However, adoption of this more stringent recommendation would go beyond the available evidence. SPRINT targeted an SBP <120 mm Hg; the mean achieved SBP was 121.4 mm Hg.

### Rationale

This recommendation replaces the target recommendations from Chapters 3 and 4 of the KDIGO 2012 recommendation on BP management in CKD.<sup>141</sup> The most important differences are: (i) the adoption of standardized office measurement as the preferred technique; (ii) the adoption of a lower SBP target (<120 mm Hg); and (iii) the adoption of the same SBP target irrespective of the presence or absence of proteinuria, diabetes, or older age. The current guideline also specifies only an SBP target and not a DBP target (see below).

The recommendation of standardized office measurement is crucial because this technique was used in large RCTs with clinically important outcomes, and values obtained using other techniques cannot be readily translated to values obtained using standardized office measurement. If BP is not measured using the standardized technique, the SBP target goal does not apply. The adoption of a lower SBP



target for patients with CKD without diabetes is based largely on the CV and survival benefits in the CKD subgroup in SPRINT, although subgroup analysis and long-term follow-up in the MDRD and AASK studies also suggest kidney benefits at BP levels that may be similar to the lower BP goal in SPRINT.

The KDIGO 2012 guideline reversed previous recommendations from other organizations that called for more-aggressive BP-lowering therapies among CKD patients with diabetes, largely because ACCORD-BP failed to demonstrate statistically significant benefits for the primary CV endpoint in the intensive BP-lowering arm. Since then, SPRINT and further analyses of ACCORD, together with combined analyses of these 2 trials, have supported the conclusion that intensive BP-lowering therapy might well confer similar benefits among patients with diabetes and CKD as in patients with CKD alone. However, the quality of evidence for BP target among CKD patients with concomitant diabetes is low, especially among those with advanced CKD.

The recommendation of SBP <120 mm Hg is classified as weak (in the dichotomous classification of strong and weak in GRADE), raising concerns that clinicians and patients may decide to ignore the guidance and opt for less-intensive treatment. The Work Group debated whether to provide a strong recommendation for an SBP target of at least <140 mm Hg for all patients with CKD, together with separate recommendations for lower SBP (<120 mm Hg) targets in specified subgroups. This more complex alternative was eventually rejected, on the basis that it would probably persuade clinicians to continue to adopt an SBP target of <140 mm Hg for all CKD patients, thus denying many patients the potential advantages of tighter control. A strong recommendation implies that most patients and caregivers would want the recommended course of action, whereas a weak recommendation states that the majority of people would want the recommended course of action, but some would not. Regardless of the strength of recommendations, but especially for weak recommendations, clinicians should understand the nature and rationale of the recommendations and engage in shared decision-making with the patients, as discussed above.

**Diastolic blood pressure as a target.** The Work Group chose not to provide a target for DBP alongside the targeted SBP <120 mm Hg, although other guidelines often advocate targets for both SBP and DBP. The reasons for this decision are two-fold. First, for young patients with diastolic hypertension, it is essential to target DBP. Indeed, a number of earlier trials in the general population (e.g., ALLHAT) had explicit DBP as an inclusion criterion. However, wide pulse pressure, which is common in CKD implies that achievement of SBP <120 mm Hg will almost certainly result in DBP <70 mm Hg in the great majority of patients, making the provision of a separate DBP target redundant.<sup>141,155,156</sup> Second, literature on RCTs targeting DBP with clinical outcomes is scarce, especially in the CKD population. Both MDRD and AASK studies employed a target MAP of <92 mm Hg, instead of an

SBP and a DBP target, in the intensive BP arm, which is often considered equivalent to 125/75 mm Hg, but it is also equivalent to 116/80, 135/70, 140/68, 145/65, or other figures, depending on the pulse pressure.

As discussed earlier, these studies suggest that this intensive MAP target may provide renoprotective effects in proteinuric patients. Hence, it seems reasonable to target DBP of young patients with CKD and diastolic hypertension to <80 mm Hg, in addition to an SBP target <120 mm Hg. However, the Work Group is hesitant to recommend a DBP target because of the lack of evidence.

**Comparison with ACC/AHA guideline.** The Work Group discussed extensively the 2017 ACC/AHA guideline that offered a target of <130/<80 mm Hg for patients with CKD and analyzed the reasons provided in that guideline for this more conservative target, although the SBP target of <130 mm Hg is still more aggressive than those proposed by the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) (target: 130-139 mm Hg) and by NICE (target: 120-139 mm Hg).<sup>2,8,157,158</sup> One of the reasons was a concern that clinicians might apply the target to routine office BP readings. The KDIGO Work Group shares this concern but takes the view that patients should not be penalized for suboptimal clinical practice. One should not rely on routine office BP to adjust BP-lowering therapy. It should be noted that Hypertension Canada recommends an SBP target of <120 mm Hg using standardized BP measurement,<sup>159</sup> consistent with the present guideline.

The ACC/AHA guideline provides a table of equivalent BP values among standardized office, home, daytime ambulatory, night-time ambulatory, and 24-hour ambulatory measurements. These equivalents were established using an outcome-based approach that determines the BP threshold with each measurement technique that is associated with similar long-term outcomes in study populations.<sup>160</sup> However, differences in BP values obtained using different measurement techniques vary greatly among individual persons and even within a given individual over time. Thus, for any given individual patient, the KDIGO Work Group found no evidence that one can reliably estimate the BP that would be obtained under standardized office conditions from measurements taken in any other settings. As a result, the Work Group decided that the best evidence-based approach is to use standardized office BP for management (see Chapter 1).

**Practice Point 3.1.1: It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a non-standardized manner.**

Non-standardized BP measurements frequently yield values that are substantially higher, but sometimes lower, than standardized measurements, in an unpredictable manner for individual patients. Basing BP-lowering therapy decisions on non-standardized BP measurements therefore often risks overtreatment and sometimes undertreatment. In these situations, the risk-benefit ratio of BP therapy may not be favorable.

**Practice Point 3.1.2: Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.**

Individualization based on patient characteristics and preferences with an understanding of the literature, including caveats, is important for proper BP goals and therapy.

**Research recommendations**

- Information is needed on how patient values and preferences influence decisions related to BP-lowering therapy. This would be an ideal topic for the Standardised Outcomes in Nephrology (SONG) initiative.
- Conduct adequately powered RCTs to examine the effects of intensive BP control among patients with CKD: (i) with concomitant diabetes; (ii) with concomitant severely increased proteinuria (>1 g/d); or (iii) with very low GFR (<30 ml/min per 1.73 m<sup>2</sup>). ACCORD included only small numbers of patients with CKD, most of whom qualified for CKD because of albuminuria, and it is therefore uninformative for patients with CKD G3–G5. On the other hand, SPRINT explicitly excluded patients with diabetes.
- In some Asian countries, stroke is more common than cardiac diseases as the cause of CV deaths. Whether intensive SBP control has similar, greater, or less CV-protective effects in the Asian CKD population is unclear and may require confirmation.
- Although there is strong evidence that ambulatory or home BP measurements are better predictors of adverse outcomes than office BP, all large RCTs on BP targets in adults employed standardized office BP. RCTs targeting home or ambulatory BP measurements are needed.
- SGLT2 inhibitors have major CV, kidney, and survival benefits among patients with CKD. In addition to reducing BP, they cause an early, acute fall in GFR, a pattern that is also observed in intensive SBP lowering. The effects of these drugs, in combination with intensive BP-lowering therapy on CV outcomes, all-cause mortality, cognition, as well as acute and chronic changes in kidney function, require further examination.
- There is a strong need for implementation research on locally acceptable strategies to increase adherence to guideline-based BP-lowering treatment (e.g., polypills).

**3.2 Treatment with antihypertensive drugs, including RAS inhibitors (RASi)**

This section makes recommendations on which medications to use for treatment of high BP in patients with CKD, with and without diabetes, with and without albuminuria. The recommendations presented in this section governing initiation of RASi apply only to CKD G1–G4 since there is currently no RCT evidence on the use of these agents in CKD G5. The benefits and harms of initiation, continuation, or discontinuation of RASi in CKD G5 have not been tested in RCTs. The evidence review included an assessment of subgroups based on the amount of albuminuria (A1 [ACR <30 mg/g or 3 mg/mmol],

A2 [30–300 mg/g or 3–30 mg/mmol], A3 [>300 mg/g or 30 mg/mmol], respectively). The outcomes evaluated, where available, include all-cause mortality; CV outcomes, such as MI, stroke, and HF; and kidney outcomes, such as kidney failure (ESKD) and doubling of serum creatinine, as well as adverse effects including AKI and hyperkalemia.

There are no well-powered trials examining CV outcomes or survival comparing various antihypertensive classes with each other or with placebo in people with high BP and CKD, although there was a CKD subgroup analysis in the ALLHAT study.<sup>161</sup> A few such trials examined kidney outcomes. For example, AASK and IDNT, which enrolled only patients with high BP, were powered for kidney outcomes and compared the antihypertensive drug classes ACEi/ARB, beta-blockers, and calcium channel blockers (CCBs) while treating to target BP. ACEi/ARB demonstrated a slower decline in kidney function in AASK for those with hypertensive nephrosclerosis and in IDNT for those with diabetes and kidney disease with severely increased albuminuria.<sup>98,162</sup>

A fair number of trials examined RASi as agents used to reduce kidney disease progression in people with and without high BP, and/or with and without diabetes. Similarly, at least 3 large trials (HOPE,<sup>163</sup> EUROPA,<sup>164</sup> and PEACE<sup>165</sup>) examined ACEi as CV protective agents in people with and without high BP and included a minority with CKD. Lowering of BP was explicitly not the aim of those trials. Kidney disease progression was reduced with RASi compared to placebo or other antihypertensive agents with a suggestion of effect modification by urine protein excretion.<sup>166</sup> RASi also reduced CV outcomes as compared to placebo in high-risk populations, particularly in subgroups with CKD,<sup>166,167</sup> independent of the presence or absence of high BP.<sup>165,167,168</sup>

That said, there is limited evidence to use specific antihypertensive agents to treat high BP to target in CKD, and almost no evidence comparing antihypertensive combination therapies in CKD from outcome trials. Many people with CKD and BP of at least 20 mm Hg above the target will need combinations of several antihypertensive drugs. Starting antihypertensive therapy in such people with antihypertensive drug combinations is suggested. There are, however, no RCTs comparing different drug combinations in CKD, as there are no RCTs on antihypertensive classes other than RASi, beta-blockers, and CCBs.

A recent network meta-analysis by Xie *et al.*, including 119 RCTs (n = 64,768), examined the benefits of treating with RASi compared to placebo or active therapy in patients with CKD for kidney and CV outcomes and included studies with and without diabetes and albuminuria (A1–A3). The results demonstrated improved precision with narrower confidence intervals than smaller meta-analyses reported below.<sup>169</sup> Both ACEi and ARBs reduced the risk of kidney failure (defined as a composite of any of the following: doubling of serum creatinine, 50% decline in GFR, or ESKD) by 39% and 30%, respectively, compared to placebo with high certainty; and 35% and 25%, respectively, against active controls with moderate certainty. Although both ACEi and ARB reduced major CV events to the same degree compared to placebo (18% for ACEi and 24% for ARB), ACEi,

compared to ARBs, were consistently associated with higher probabilities of reducing kidney failure and CV death. ACEi, but not ARB, reduced the odds of all-cause death compared to active control. Results of the network analysis were not subdivided by diabetes or albuminuria status.

Therefore, any antihypertensive treatment algorithm in CKD beyond monotherapy depends on expert opinion, pathophysiologic or pharmacodynamic considerations, extrapolation from findings in primary hypertension in the absence of CKD, and small studies in CKD with surrogate outcomes, namely change in BP over the short term or meta-analyses of underpowered studies.

In people with high BP and CKD, and mildly or moderately increased albuminuria (A1 or A2), there is limited evidence on CV or kidney outcomes from RCTs comparing specific antihypertensive drugs to placebo or active comparators. There are, however, data from RCTs specifically in those with severely increased albuminuria (A3), statistically powered for kidney outcomes comparing specific antihypertensive drugs to placebo or active comparators. Those trials included people with and without high BP, apart from a few studies that excluded people with normal BP.<sup>98,162</sup> There are also secondary analyses of subgroups based on level of albuminuria (A1–A3) or eGFR <60 ml/min per 1.73 m<sup>2</sup>, comparing specific antihypertensive drugs to placebo or to active comparators from CV and kidney outcome trials.

In RCTs of primary hypertension examining the effect of antihypertensive drugs on CV outcomes that included participants with CKD, CV benefits have been most consistent with ACEi, ARBs, thiazide-like diuretics, and CCBs. The data are less consistent with beta-blockers, which have been inferior to these above classes in some but not all trials and in many meta-analyses. However, beta-blockers are often indicated for specific conditions, such as angina pectoris, post-MI, and systolic heart failure with reduced ejection fraction (HFrEF). For CV disease prevention in those with high BP, unless there is a strong indication for 1 specific class, it seems reasonable to begin with 1 or more drugs among ACEi or ARB, CCB, and thiazide-like diuretic. Non-dihydropyridine CCBs have the apparent additional benefit of reducing proteinuria.<sup>170</sup> If a 3-drug combination of RASi, CCB, and diuretic at recommended doses is not adequate to control BP, additional therapy including a mineralocorticoid-receptor antagonist (MRA), long-acting alpha antagonist, or beta-blocker can be used, as well as dihydropyridine, hydralazine, minoxidil, or centrally acting agents.<sup>171</sup>

Higher BP due to fluid overload is common in CKD; therefore, diuretics are, in general, logical agents at appropriate dose to lower high BP, with or without the concomitant use of RASi. Outcome data in primary hypertension favor chlorthalidone and indapamide over hydrochlorothiazide,<sup>2</sup> although this has been questioned and there is an ongoing trial.<sup>172–174</sup> Thiazide diuretics lose efficacy in diuresis and BP lowering as GFR worsens, but several, including chlorthalidone, metolazone, and indapamide appear to remain effective at GFRs <30 ml/min per 1.73 m<sup>2</sup>. Loop diuretics are often effective at lower GFRs (i.e., <30 ml/min per 1.73 m<sup>2</sup>). When combined

with a loop diuretic, thiazides are particularly effective in inducing diuresis, but they often lead to hypokalemia and hypomagnesemia.<sup>175</sup> There are no data on clinical outcomes with loop diuretics in the treatment of high BP with or without CKD.

The most common side effects of each antihypertensive drug class for patients with CKD include: for both ACEi and ARBs, hyperkalemia as well as AKI, the latter when compounded by volume depletion or renal artery stenosis; for diuretics, hypokalemia; for dihydropyridine CCBs, edema; for non-dihydropyridine CCBs, constipation and bradyarrhythmias when used in conjunction with beta-blockers; cough with ACEi; fatigue and limited exercise tolerance with beta-blockers; somnolence or dry mouth with central alpha-agonists; rebound hypertension if clonidine is stopped suddenly without taper; dizziness with alpha-blockers; hyperkalemia with MRA; headache with hydralazine; and edema and hirsutism with minoxidil, to name some examples.

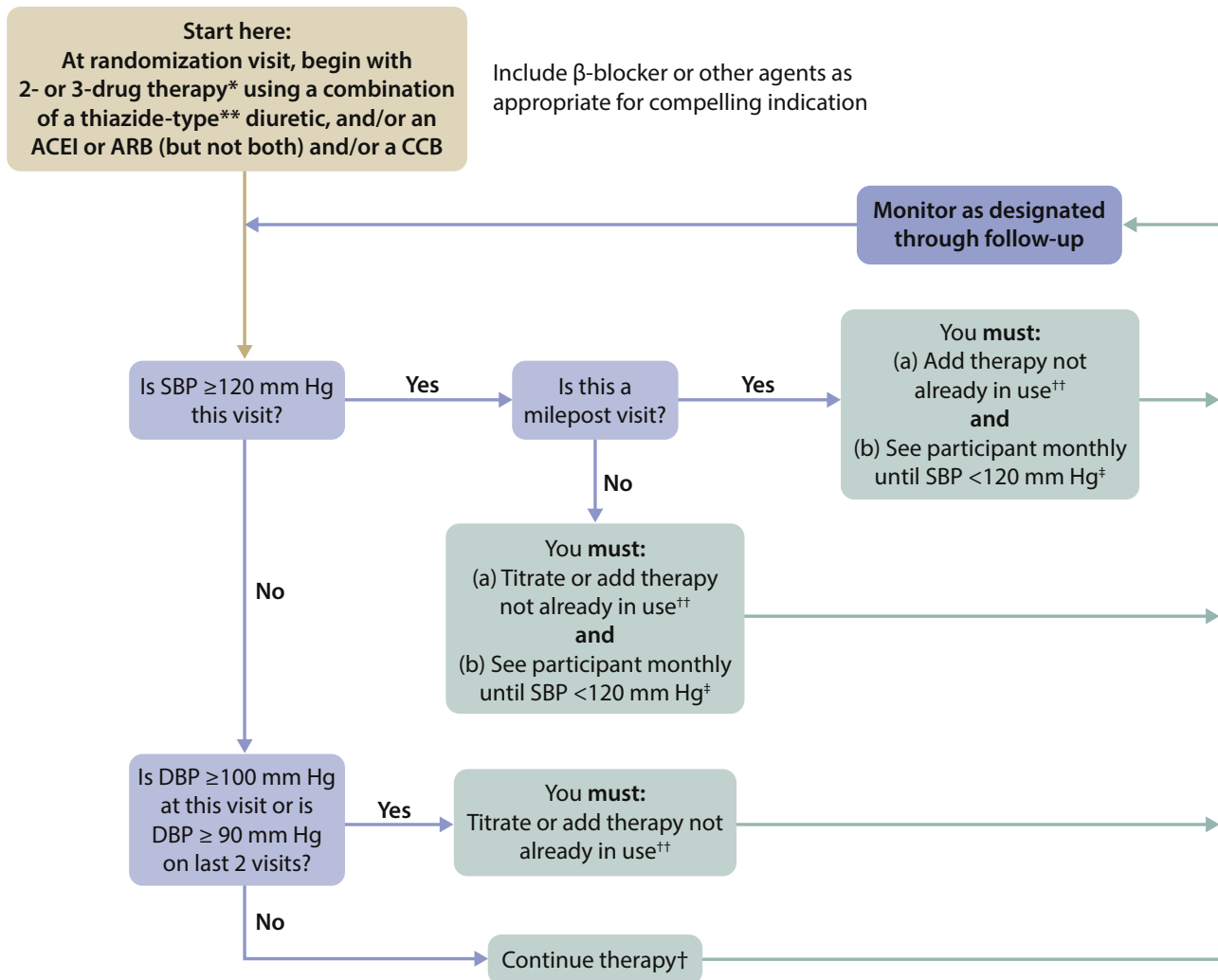
The SPRINT research algorithm for BP management is presented in Figure 5 with slight modifications of the footnotes. Clinicians should use this as a reference and modify it as they see fit. More detailed descriptions and recommendations about the use of antihypertensive drugs, various drug combinations, potential advantages, or adverse effects is beyond the scope of this guideline; readers are referred to standard textbooks and guidelines.

**Recommendation 3.2.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (1B).**

*This recommendation is strong according to GRADE, based on 3 moderate-quality RCTs with important benefits in CKD patients. The recommendation suggests that the majority of people would want the recommended course of action. This recommendation does not apply to patients with CKD who are receiving dialysis or have a kidney transplant.*

#### Key information

**Balance of benefits and harms.** Kidney benefits of RASi in CKD without diabetes and severely increased proteinuria were demonstrated in the Ramipril Efficacy In Nephropathy (REIN) study which compared ramipril to placebo to assess the effect of RASi on CKD progression independent of BP lowering. The Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN; [REIN Stratum-2]) study of 166 patients with proteinuria ≥3 g per 24 hours was stopped early due to efficacy of ramipril in slowing eGFR decline.<sup>176</sup> The monthly decline in GFR was significantly lower in the ramipril group (0.88 ml/min) than the placebo group (0.53 ml/min). The composite of doubling of serum creatinine or ESKD was reached in 18 versus 40 participants (ramipril vs. placebo,  $P = 0.02$ ).<sup>176</sup> In the REIN Stratum-1 of 186 patients with proteinuria of >1 to <3 g/d, the decline in GFR was not different, but ESKD events were less with ramipril



**Figure 5 | SPRINT research treatment algorithm for the intensive group (goal SBP <120 mm Hg).** From *The New England Journal of Medicine*, the SPRINT Research Group, A Randomized Trial of Intensive Versus Standard Blood-Pressure Control, Volume 373, Pages 2103–2116, Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.<sup>93</sup> \*May begin with a single agent for participants aged  $\geq 75$  years with SBP <140 mm Hg on 0–1 medications at study entry. A second medication should be added at the 1-month visit if participant is asymptomatic and SBP  $\geq 130$  mm Hg. \*\*May use loop diuretic for participants with advanced CKD. <sup>†</sup>Unless side effects warrant change in therapy. <sup>††</sup>Consider adding a fifth antihypertensive medication. <sup>‡</sup>Or until clinical decision made that therapy should not be increased further. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

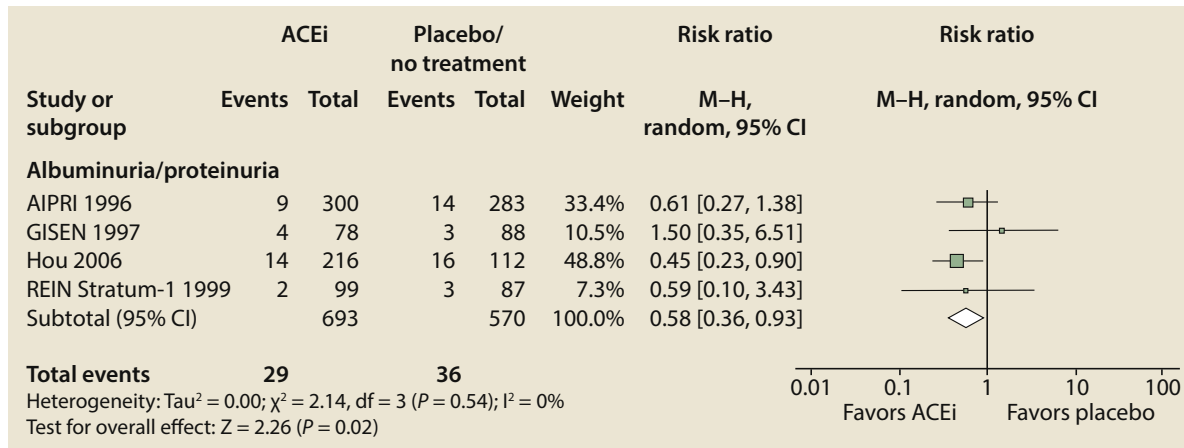
(9 cases/99 patients) than with placebo (18 cases/87 patients).<sup>177</sup> The Angiotensin-Converting Enzyme Inhibitors and Kidney Protection (AIPRI) trial compared benazepril to placebo in patients with CKD mostly without diabetes to assess its effect on CKD progression (doubling of serum creatinine or ESKD as the primary outcome). Benazepril also caused a 53% reduction of the primary outcome (RR: 0.47; 95% CI: 0.27–0.70).<sup>178</sup> A meta-analysis of these 2 trials found a 49% decrease (RR: 0.51; 95% CI: 0.38–0.69) in the composite outcome, ESKD and a doubling of serum creatinine with 769 participants (Supplementary Table S15).<sup>177,178</sup>

CV benefit from ACEi in these 3 aforementioned studies was assessed by meta-analysis, with the addition of the study by Hou *et al.*<sup>179</sup> A reduction of CV events of 42% was found (RR: 0.58; 95% CI: 0.36–0.93; Figure 6<sup>176–179</sup>). There are several meta-analyses reporting greater benefits of ACEi or

ARBs on kidney outcomes with increasing albuminuria, as for example, from Jafar *et al.*<sup>166,180</sup>

The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study directly compared benazepril (ACEi) to losartan (ARB) in 360 patients with CKD without diabetes and mean proteinuria of 1.4–2.0 g/d.<sup>181</sup> No differences were found in kidney outcomes (primary outcome) or CV events between the 2 classes of RASi.

Many of the above trials examined RASi versus placebo in people on background antihypertensive therapy. Few trials also tested active comparators to RASi (e.g., AASK, IDNT). There is sparse evidence of the effect of antihypertensive agents other than RASi on clinical outcomes in the setting of CKD with high BP and severely increased proteinuria, with the exception of AASK and IDNT. A number of smaller trials assessed changes



**Figure 6 | Cardiovascular events in patients with CKD G3–G4, A3 without diabetes.** Meta-analysis was conducted by the Cochrane Kidney and Transplant Evidence Review Team as part of the guideline evidence review. GISEN reported data from the REIN Stratum-2 group (baseline proteinuria ≥3 g/24 h), in contrast to REIN Stratum-1 (baseline proteinuria 1-3 g/24 h). A3, severely increased albuminuria; ACEi, angiotensin-converting enzyme inhibitor; AIPRI, Angiotensin-Converting Enzyme Inhibitors and Kidney Protection; CI, confidence interval; CKD, chronic kidney disease; events, number of events; GISEN, Gruppo Italiano di Studi Epidemiologici in Nefrologia; M-H, Mantel-Haenszel; REIN, Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease; total, number of participants.

in proteinuria. Whether those changes translate to changes in hard outcomes is uncertain. In particular, we have no RCT evidence that, for example, targeting a proteinuria of <1 g compared to >2 g leads to fewer hard kidney or CV outcomes. Due to the imprecision in the studies from a low number of events, beta-blockers (Supplementary Table S18<sup>182,183</sup>) and CCBs (Supplementary Table S19<sup>184–186</sup>) were found to have little or no difference compared to placebo or RASi for the CV and kidney outcomes (ESKD, doubling of serum creatinine, GFR decline) in patients with CKD with and without diabetes and severely increased levels of albuminuria. Only RASi has been extensively studied in appropriately powered trials. There was only 1 relevant direct renin inhibitor study, comparing aliskiren to the ARB losartan in patients without diabetes and varying levels of albuminuria, and there were no events in either arm (Supplementary Table S20<sup>187</sup>).

**Quality of evidence.** The overall quality of the evidence comparing ACEi or ARB with placebo or standard of care in patients with CKD and severely increased albuminuria without diabetes is moderate. The quality of the evidence was downgraded because of study limitations, such as small numbers of events, inadequate reporting of sequence generation, and allocation concealment (Supplementary Table S15<sup>176–179,188,188a,189</sup> and Supplementary Table S16<sup>190,191</sup>).

For studies of ACEi versus placebo or standard of care, some outcomes (ESKD, doubling of serum creatinine, and CV events) exhibited moderate quality of the evidence, downgraded because of study limitations (Supplementary Table S15<sup>176–179,188,188a,189</sup>).

The quality of evidence for other antihypertensive therapies in the population of CKD patients without diabetes and severely increased albuminuria was lower than the evidence for RASi, as it has only been examined in a limited number of RCTs for MRA of rather short duration and powered for surrogate outcomes (Supplementary Table S17<sup>192–195</sup>).

**Values and preferences.** The presence of severely increased albuminuria and CKD is associated with a higher prevalence of CV disease, progressive CKD, and attendant loss of quality of life.<sup>196</sup> In the opinion of the Work Group, most well-informed patients with CKD and severely increased albuminuria would place emphasis on preventing CV outcomes in addition to preventing CKD progression.

**Resource use and costs.** The risks, benefits, resource use, and costs of RASi therapy should be considered when treating patients with CKD. The costs of generic RASi medication are generally low. However, the use of RASi in patients with CKD G1–G4 with A3, especially those with G4, necessitates patient education (e.g., when to pause RASi), repeat lab testing, vigilance to prevent hyperkalemia and AKI due to volume depletion and other events, as well as repeat visits to restart RASi if it has been stopped during a hospitalization. On the other hand, there is moderate evidence for RASi treatment with the goal of preventing progressive loss of kidney function, which likely justifies the additional costs and visits required for monitoring.

**Considerations for implementation.** There is insufficient information to differentiate between men and women for this recommendation, and insufficient evidence that there are different outcomes by race.

**Rationale**

We make this recommendation for RASi because the benefits of kidney and CV protection outweigh the potential adverse risks; therefore, most well-informed patients with CKD not on dialysis with severely increased albuminuria but without diabetes will opt for treatment with RASi. We feel that patients put a large value on the cardio- and renoprotective benefits of RASi and are willing to tolerate its potential harms, including hyperkalemia and AKI. These side effects, however, may lead to higher healthcare costs from additional visits and laboratory testing.

**Recommendation 3.2.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (2C).**

*This recommendation is weak according to GRADE, based on limited evidence from RCTs of sufficient duration to evaluate kidney protection. However, the Work Group judged that most well-informed patients would value the cardio- and renoprotective benefits of RASi over potential harms from AKI or hyperkalemia.*

**Key information**

**Balance of benefits and harms.** The HOPE study,<sup>163</sup> one of the largest RASi studies, found in a prespecified subgroup analysis of those with CKD and normal-to-moderately increased albuminuria (creatinine clearance <65 ml/min, estimated by the Cockcroft Gault formula; n = 3394; mean follow-up 4.5 years) that ACEi versus placebo reduced the risk for all-cause mortality by 20% (HR: 0.80; 95% CI: 0.67–0.96), MI by 26% (HR: 0.74; 95% CI: 0.61–0.91), stroke by 31% (HR: 0.69; 95% CI: 0.49–0.90).<sup>167</sup> It should be noted that approximately one-third of patients in the HOPE study had diabetes, and only half had high BP. In the overall HOPE study, the CV benefits of ramipril versus placebo were also present in those with moderately increased albuminuria (approximately 1900 cases/9360 patients).<sup>197</sup>

There were no studies specifically evaluating the effect of RASi on slowing kidney disease progression in patients with CKD without diabetes and A2; therefore, HOPE provides the best guide for this subpopulation. Cinotti *et al.* examined the role of lisinopril on progression of kidney disease assessed by inulin clearance in 131 patients without diabetic nephropathy over 22.5 months.<sup>189</sup> The mean baseline proteinuria per day was 506 mg, thus including A2 and A3, and progression to dialysis or ESKD was reduced by 66% but with very wide 95% confidence intervals (HR: 0.34; 95% CI: 0.01–7.92). The TRANSCEND study compared telmisartan to placebo in high-risk patients with and without high BP. It reported a benefit of the ARB on the composite of doubling of serum creatinine or ESKD in those with moderately increased albuminuria, but detrimental kidney effects in those with normal or mildly increased albuminuria (*P* for interaction 0.006).<sup>198</sup> Limitations of subgroup data on tertiary outcomes with low event numbers apply.

There is sparse evidence for agents other than RASi used as initial therapy for high BP in people with CKD and moderately increased albuminuria (A2) without diabetes. In the AASK trial (mean PCR approximately 0.33 g/g [33 mg/mmol]), metoprolol and amlodipine were not significantly different from ramipril for the few CV events that occurred, but they were inferior to ramipril for clinical kidney outcomes for which the trial was powered.<sup>98</sup>

For MRAs, there were 3 RCTs with a total of 1426 participants mainly from HF, not hypertension, trials with defined CKD subgroups. Patients had varying levels of albuminuria.<sup>192,194,195</sup> With relatively few events for the individual trial outcomes,<sup>192,194,195</sup> there was a 29% risk reduction (HR:

0.71; 95% CI: 0.58–0.87) for the composite outcome of CV events and CV mortality based on data from 1 study with 912 CKD participants and a mean follow-up of 21 months (Supplementary Table S17<sup>192–195</sup>).

**Quality of evidence.** The overall quality of the evidence for kidney outcomes comparing ACEi or ARB with placebo or standard of care in patients with CKD and moderately increased albuminuria without diabetes is low, due to imprecision because of a lack of data. The quality of the evidence for CV outcomes in patients with A2 without diabetes was rated as low. HOPE provided indirect evidence, as only two-thirds of the population had no diabetes.

**Values and preferences.** In the opinion of the Work Group, many well-informed patients would place more emphasis on the potential for preventing CKD progression.

**Resource use and costs.** When treating patients with CKD (G1–G4, A2) where the indication for ACEi or ARB therapy is not strong, consideration should be given to the clinical impact on the patient and the costs of starting RASi, including additional clinic visits and the need for additional lab testing

**Considerations for implementation.** There is insufficient information to differentiate between men and women for this recommendation. However, data from ALLHAT demonstrated that ACEi as initial therapy for high BP in patients of African origin was inferior to chlorthalidone for stroke and combined CV outcomes.<sup>199</sup> ALLHAT did not measure urine protein or albumin.

**Rationale**

We make this recommendation, albeit weak, because the CV benefits appear to outweigh the potential adverse risks; therefore, many well-informed patients with CKD not on dialysis with moderately increased albuminuria but without diabetes will opt for treatment with RASi. We feel that patients would put a large value on the CV benefits of RASi and are willing to tolerate its potential harms, including hyperkalemia and AKI. These side effects, however, may lead to higher healthcare costs from additional visits and laboratory testing.

**Recommendation 3.2.3: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).**

*This is a strong recommendation based on evidence from RCTs of sufficient duration to evaluate kidney protection in patients with diabetes and CKD. This recommendation places a relatively higher value on preventing long-term progression of CKD and a relatively lower value on the risks of AKI or hyperkalemia, which are often transient. Where data are available, analyses by albuminuria subgroup are provided.*

**Key information**

**Balance of benefits and harms.** The 2 main studies demonstrating kidney benefit from RASi independent of BP control in diabetes were the three-arm IDNT<sup>162</sup> and the two-arm

RENAAL<sup>200</sup> studies where ARB was compared with placebo<sup>200</sup> or with placebo and with CCB in a double-blinded manner.<sup>162</sup> IDNT excluded participants with normal BP; RENAAL included those with and without high BP. Both studies included only participants with severely increased albuminuria. Irbesartan in the IDNT study resulted in a 20% (RR: 0.80; 95% CI: 0.66–0.97) risk reduction in the primary composite endpoint (doubling of serum creatinine, ESKD, death from any cause) versus placebo and a 23% reduction versus amlodipine (RR: 0.77; 95% CI: 0.63–0.93); while losartan in the RENAAL study caused a 16% (RR: 0.84; 95% CI: 0.72–0.98) reduction in the composite outcome of death, dialysis, and doubling of serum creatinine compared to placebo. These studies demonstrated that RASi therapy improved the composite outcome in patients with diabetes, significant albuminuria (IDNT: 2.9 g/d proteinuria, baseline serum creatinine of 1.67 mg/dl [148 µmol/l]; RENAAL: albumin–creatinine ratio 1237 mg/g [124 mg/mmol], baseline serum creatinine 1.9 g/dl [168 µmol/l]), and G3–G4, A3. Further, the RENAAL study demonstrated that in patients who have already doubled their serum creatinine during the study, remaining on RASi therapy significantly delayed the onset of dialysis by a mean of 6 months. In the IDNT study, hyperkalemia necessitating a stop in therapy occurred in only 2% of patients with RASi, versus 0.5% of patients in the other arms. Overall, serious adverse events were actually lower in the RASi group than in the control group. Therefore, in those with diabetes and CKD G3–G4, A3, there is strong evidence supporting the treatment with RASi because of their renoprotective effects.

Data for people with diabetes and CKD G1–G3, A2 comes from the Micro-HOPE study, in which people with diabetes, moderately increased albuminuria, and higher CV risks had improved CV outcomes when randomized to ACEi therapy compared to placebo.<sup>201</sup> Specifically, for the composite outcome of MI, stroke, and CV death, there was a relative risk reduction of 28.6% (HR: 0.71; 95% CI: 0.6–0.9) based on 1140 patients with diabetes from the Micro-HOPE study, with a mean follow-up of 4.5 years. Kidney benefit in this group was largely limited to reducing progression from moderately increased albuminuria to severely increased albuminuria. Only 18 cases in total developed ESKD–10 on ramipril and 8 on placebo.<sup>163</sup> In the Micro-HOPE study, baseline serum creatinine was 1.06 mg/dl (94 µmol/l), and 474 (14%) of 3238 people progressed to a serum creatinine level of  $\geq 1.4$  mg/dl (124 µmol/l) over the 4.5 years (231 on ramipril and 243 on placebo).<sup>202</sup>

In a meta-analysis performed by the ERT, we found that, for patients with diabetes (including patients with and without albuminuria [A1, A2, and A3]), ACEi compared to placebo or standard of care did not reduce the risk for all-cause mortality, based on data from 7561 patients in 22 studies with a mean follow-up of 32 months (Supplementary Table S21<sup>163,203–223</sup>). The absolute difference was 26 fewer events per 1000 (95% CI: 57 fewer–20 more) and was not statistically significant. The risk of doubling of serum creatinine was reduced by 30% (RR: 0.70; 95% CI: 0.46–1.05) based on 6759 patients from 8 studies with a mean follow-up of 32 months and an absolute difference

of 12 fewer events per 1000 (95% CI: 22 fewer–2 more), and was not statistically significant.<sup>163,207,213,215,221,222</sup> However, in patients with severely increased albuminuria, ACEi reduced doubling of serum creatinine by 42% (RR: 0.58; 95% CI: 0.37–0.90) based on 441 participants in 2 studies.<sup>219,224</sup>

ACEi also reduces albuminuria in the CKD population with diabetes. The risk of progression from moderately increased albuminuria to severely increased albuminuria decreased by 55% (RR: 0.45; 95% CI: 0.29–0.69) based on 2036 patients from 17 studies with a mean follow-up of 34 months and an absolute difference of 123 fewer events per 1000 patients (95% CI: 159 fewer–69 fewer).<sup>163,206,208,210,213,221,222,225–233</sup>

Compared to placebo or standard of care in 8 studies of 4106 participants, ARBs did not show a difference in all-cause mortality in patients with diabetes and CKD (RR: 0.99; 95% CI: 0.85–1.16). Similarly, there was no benefit in CV mortality, MI, HF, stroke, or CV benefit in diabetes and CKD. There was a kidney benefit with a reduction of doubling of serum creatinine of 16% (RR: 0.84; 95% CI: 0.72–0.98) based on 3280 patients from 4 studies with a mean follow-up of 34 months (Supplementary Table S22<sup>162,200,234,235</sup>).

There were no differences between ACEi and ARB for the discrete outcomes of all-cause mortality, CV mortality, MI, stroke, HF, and kidney function in people with diabetes and albuminuric or non-albuminuric CKD subpopulations (Supplementary Table S23<sup>217,236–239</sup>). When compared to placebo or standard of care, ACEi improves CV outcomes, but for ARB, there is no improvement. Studies comparing ACEi to ARB in patients with CKD and diabetes may have had an insufficient number of patients to find a difference.

There has been little evidence to support the use of other agents such as MRA, beta-blockers, and CCBs as the initial therapy in patients with diabetes and albuminuria for CV or kidney protection beyond albuminuria reduction. For MRA compared to placebo, there were 3 small short-term studies powered for changes in albuminuria (Supplementary Table S24<sup>235,240,241</sup>). Albuminuria was lowered by MRA; however, in a meta-analysis by the ERT, there was no beneficial effect in RCTs on all-cause mortality, MI, and stroke, and very few events to determine the effect on kidney outcomes. However, those trials were not powered for CV or kidney outcomes. Similarly, meta-analysis showed no evidence of benefits on CV or kidney outcomes for beta-blockers (Supplementary Table S25<sup>242–249</sup>) and CCBs (Supplementary Table S26<sup>210,230,250–256</sup>) compared to placebo or standard of care. However, the studies were not properly powered for kidney or CV outcomes.

The importance of diuretic therapy for lowering BP is suggested by the ADVANCE study comparing treatment with a combination of an ACEi plus diuretic (perindopril plus indapamide) to usual care without a thiazide-type diuretic in 11,140 people aged  $\geq 55$  years with diabetes, CV risk, or increased albuminuria (A2 or A3) over a mean of 4.3 years.<sup>257</sup> The main outcomes were death from CV disease, non-fatal stroke or non-fatal MI, and new or worsening kidney or diabetic eye disease. The relative risk of a major macrovascular or

microvascular event was reduced by 9% (HR: 0.91; 95% CI: 0.83–1.00); the relative risk of death from CV disease was reduced by 18% (HR: 0.82; 95% CI: 0.68–0.98); and death from any cause was reduced by 14% (HR: 0.86; 95% CI: 0.75–0.98). These improvements in clinical outcomes were associated with a fall in BP of SBP 5.3/DBP 2.1 mm Hg in patients with CKD G1 or G2, and SBP 4.5/DBP 1.8 mm Hg in patients with CKD G3–G5. There was no effect modification by the presence of baseline albuminuria. It should be noted that in the ADVANCE study, 49% of the placebo group were already treated with RASi at baseline, which further increased to 73% by the end of the study, while 25% were on diuretics at baseline, which decreased to 21% in the placebo group at the final visit. This finding suggests that the benefits seen in ADVANCE might have been due to the addition of the diuretic and/or greater BP lowering in the active treatment group.

There is emerging evidence that MRA have beneficial effects on clinical kidney outcomes. The FIDELIO-DKD study, an RCT of 5734 participants, demonstrated that finerenone, a nonsteroidal MRA, on the background of an ACEi or ARB in patients with diabetes, CKD, and albuminuria reduced the risk of composite primary endpoint of GFR decline, kidney failure, or renal death when added to standard of care.<sup>258</sup> Finerenone also reduced the risk of CV events. However, its effect on SBP lowering was modest (2–3 mm Hg), and there was a higher risk of hyperkalemia-related events. At the writing of this guideline, finerenone has not been approved for clinical use. The trial was published after the evidence review cut-off for the guideline but will be assessed in future updates.

**Quality of evidence.** The ERT updated a Cochrane systematic review on antihypertensive therapies in patients with diabetes and CKD, A2 and A3.<sup>259</sup> The overall quality of the evidence was rated as moderate, as the studies examining the use of RASi therapy exhibited study limitations with unclear allocation concealment for critical and important outcomes. The quality of the evidence was lower for CV outcomes, owing to there being fewer events and inconsistent reporting of these outcomes in trials (Supplementary Tables S21–S30).

In the ADVANCE study of patients with CKD G1–G3, A2, the quality of evidence is low according to GRADE.<sup>260</sup> The quality of the evidence was downgraded due to serious risk of bias, with unclear allocation concealment, and imprecision, as the beneficial results of diuretics were seen only in the CKD subgroups, when the results were negative in the entire cohort (Supplementary Table S27).

The best evidence for renoprotective effects of RASi therapy independent of BP control in patients with diabetes, CKD G3–G4, and severely increased albuminuria comes from the IDNT<sup>162</sup> with its active comparator arm, and from the RENAAL<sup>200</sup> trial. For CV outcomes, the Micro-HOPE study provides the best evidence for patients with moderately increased albuminuria.<sup>163</sup> There are no RCTs in those with moderately increased albuminuria (A2) powered for hard kidney outcomes. Published meta-analyses for patients with diabetes, hypertension, and CKD provided mixed results. One found a reduction of all-cause mortality, CV mortality, and

major CV events in 32,827 people with diabetes treated with ACEi, but this was not found in 23,867 patients treated with ARBs.<sup>261</sup> A meta-analysis comparing RASi to other antihypertensive medications, excluding placebo-controlled trials, in people with diabetes, did not find CV outcome improvement.<sup>262</sup> There was also no improvement in kidney failure, but the vast majority of included studies enrolled people with normal urine albumin or did not measure albumin at all. These meta-analyses included patients with diabetes and CKD G1 and G2, A1–A3, and G3 and G4, A1–A3, respectively. It is likely that including the low-risk and high-risk groups together led to the lack of statistical significance for CV outcomes. Although it is tempting to extrapolate the beneficial CV effects of RASi to all people with diabetes, in the absence of high BP, CV risks, and lower GFR (G3 and G4, A2 and A3), the evidence is weak at best. For treatment with RASi, there is, therefore, a gradation of evidence from strong in the CKD subpopulation with low eGFR and severely increased albuminuria, to weak or absent in the subpopulation with normal eGFR without albuminuria.

**Values and preferences.** In the opinion of the Work Group, this recommendation for people with diabetes and CKD with severely increased albuminuria places higher value on the ability of RASi to prevent CV and CKD events, such as doubling of serum creatinine and dialysis. It places less value on the risks of hyperkalemia and AKI.

**Resource use and costs.** The costs of the RASi medications are probably low in most countries. However, adding RASi to patients with diabetes and severely increased albuminuria will require more laboratory testing and visits to healthcare providers, especially in those with low GFR. It will also likely lead to greater incidence of hyperkalemia and AKI—hence the associated costs of monitoring and treating these complications.

**Considerations for implementation.** There is insufficient information to differentiate between men and women for this recommendation, and there is insufficient evidence that there are different outcomes by race.

### Rationale

We issue a strong (1B) recommendation for treatment with ACEi or ARB for patients with diabetes, increased albuminuria, and normal-to-low GFR (G1–G4; A2 or A3), because their desirable benefits in kidney and CV protection outweigh the adverse risks associated with therapy. Nonetheless, these side effects, such as hyperkalemia and rises in serum creatinine, may lead to higher costs from additional visits and laboratory testing.

**Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).**

Patients with CKD, high BP, and no albuminuria are at lower risk of CKD progression. In this subpopulation, existing evidence does not demonstrate clear clinical benefits of RASi for CKD progression, and other antihypertensive agents are as appropriate for BP management. However, we feel that some patients would put a large value on the CV protection from RASi and would be willing to tolerate the potential harms, particularly patients with higher GFR and a relatively low risk of harm.



The HOPE study, one of the largest RASi studies, reported CV benefits with an ACEi versus placebo in people at high CV risk with or without high BP.<sup>163</sup> In a prespecified CKD subgroup (CrCl <65 ml/min by the Cockcroft-Gault formula) of 3394 patients with no or mildly increased albuminuria (approximately one-third of whom had diabetes), ACEi reduced the risk for all-cause mortality by 20% (HR: 0.80; 95% CI: 0.67–0.96), MI by 26% (HR: 0.74; 95% CI: 0.61–0.91), and stroke by 31% (HR: 0.69; 95% CI: 0.49–0.90) during a mean follow-up of 4.5 years.<sup>167</sup> In the overall HOPE study, 3577 patients had diabetes, and 2437 of them (roughly two-thirds) did not have albuminuria.<sup>163</sup> The PEACE sub-study in those with CKD confirmed this notion.<sup>165</sup>

**Practice Point 3.2.2: RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.**

The Work Group judged that a large majority of physicians would be comfortable initiating RAS blockade treatment and titrating it to the maximum dose approved by regulatory agencies and tolerated by the patient because of its benefits in kidney protection, their familiarity with this drug, and its good safety profile. The benefits from RASi administered in less than maximally recommended doses are less certain. However, if for whatever reason (e.g., hyperkalemia) the patient cannot tolerate the maximum dose, a smaller dose may still be reasonable. It should be noted that the maximum dose of RASi allowed by the regulatory agency varies by country, and the practitioners are advised to follow their respective national guidance.

**Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.**

ACEi and ARBs are potent antihypertensive agents that counteract the vasoconstrictive effects of angiotensin II. Moreover, blocking the action of angiotensin II causes selectively greater vasodilatation of the efferent arterioles of the glomeruli, resulting in a decline of the intraglomerular filtration pressure, and not unexpectedly, a decrease in the GFR and a rise in the serum creatinine. In addition, RAS blockade inhibits the action of aldosterone, resulting in a greater propensity for hyperkalemia. In patients at risk for hyperkalemia, measuring serum potassium before and at 1–2 weeks after initiation of RASi is recommended, based on expert opinion.<sup>44</sup> An increase in serum creatinine level, if it occurs, will typically happen during the first 2 weeks of treatment initiation, and it should stabilize within 2–4 weeks in the setting of normal sodium and fluid intake.<sup>263</sup> Therefore, patients should be monitored for symptomatic hypotension, hyperkalemia, and serum creatinine within 2–4 weeks after initiating or changing the dose of the drug, with the time interval depending on baseline BP, serum creatinine, and serum potassium. A shorter time interval is indicated if the baseline serum creatinine is high, or serum potassium is already high-normal, or there is a

history of hyperkalemia or an acute rise in serum creatinine with BP lowering or RASi.

**Practice Point 3.2.4: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.**

In observational cohorts, hyperkalemia is often associated with a subsequent reduction in dose or discontinuation of RASi.<sup>44,264,265</sup> Pseudo-hyperkalemia needs to be first ruled out. Then, there are multiple measures that can be taken to mitigate the hyperkalemia.<sup>44</sup> Improvement in potassium control could lead to increased use of RASi in patients with an evidence-based indication. Strategies to control chronic hyperkalemia include dietary potassium restriction; discontinuation of potassium supplements, certain salt substitutes, and hyperkalemic drugs; adding potassium-wasting diuretics, and oral potassium binders.<sup>44</sup> In CKD patients receiving RASi who develop hyperkalemia, the latter can be controlled with newer oral potassium binders in many patients, with the effect that RASi can be continued at the recommended dose.<sup>266,267</sup> Whether the latter therapeutic strategy improves CV or kidney outcomes is being examined in RCTs, such as the ongoing DIAMOND trial (NCT03888066). Side effects of the newer potassium binders are reported to be moderate.

**Practice Point 3.2.5: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.**

This practice point reiterates a common expert opinion and may be a reasonable option for many patients treated with RASi. However, there is not a single trial that compared meaningful clinical outcomes in patients who were continuing versus discontinuing versus reducing the dose of RASi upon a fast increase in serum creatinine by 10%, 20%, 30%, 40%, etc. Observational data relating acute changes in serum creatinine shortly after RASi initiation to subsequent long-term outcomes are equivocal and contradictory.<sup>263,268–270</sup> An increase of <30% in serum creatinine from the baseline value does not mandate a dosage decrease or discontinuation of RASi, as long as the serum creatinine increase is not associated with other complications, such as hyperkalemia and fluid retention.

**Practice Point 3.2.6: Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m<sup>2</sup>).**

The dose of ACEi or ARBs should be reduced or discontinued in patients with hyperkalemia after other measures have failed to achieve a normal serum potassium level. In general, similar efforts should be made to discontinue other concurrent BP medications before attempting to reduce the dose of ACEi or ARBs in patients who experience symptomatic hypotension and has a specific indication for RASi,

such as severely increased albuminuria or heart failure. Which BP medication to discontinue or which ones to retain would depend on the relative indication of each medication.

When these drugs are used in patients with eGFR <30 ml/min per 1.73 m<sup>2</sup>, close monitoring of serum potassium is required. On the other hand, withholding these drugs solely on the basis of the level of kidney function will unnecessarily deprive many patients of the CV benefits, and perhaps even protection of the residual kidney function, that they otherwise would have received, particularly when measures could be undertaken to mitigate the risk of hyperkalemia.<sup>179,271</sup> However, in patients with advanced CKD who are experiencing uremic symptoms or uncontrolled hyperkalemia, it is reasonable to discontinue ACEi and ARB temporarily to allow time for kidney replacement therapy preparation.<sup>272</sup>

**Practice Point 3.2.7: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR.**

The steroidal MRAs spironolactone and eplerenone have, in small and short-term studies, been found to reduce BP in resistant hypertension (defined as uncontrolled hypertension on 3 antihypertensive agents including a diuretic) in a population that included CKD and non-CKD<sup>171,273</sup> and to lower albuminuria in patients with diabetes and elevated urinary albumin excretion.<sup>193</sup> Side effects, particularly hyperkalemia and decline in kidney function,<sup>274</sup> are however a concern when added to background therapy with an ACEi, ARB, or diuretic, particularly among patients with eGFR <45 ml/min per 1.73 m<sup>2</sup>.<sup>275</sup> Thus, MRAs should not be used in patients with high risk of hyperkalemia (e.g., hypoaldosteronism or type 4 renal tubular acidosis). Results from the AMBER trial showed that in patients with resistant hypertension and advanced CKD (25 to <45 ml/min per 1.73 m<sup>2</sup>), concomitant use of the oral potassium binder patiromer compared with placebo allowed a larger proportion of patients using spironolactone at 12 weeks.<sup>276</sup> A recent trial, FIDELIO, examining the impact of the nonsteroidal MRA finerenone showed kidney protection; however, the effect on BP was modest and the risk of hyperkalemia-related events was increased.<sup>258</sup>

**Research recommendations**

- RASi in patients with CKD G3–G4, A1 and A2 with or without diabetes have not been adequately studied. Future studies should examine if RASi, in the presence or absence of other renoprotective agents such as SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, provide kidney, CV, and survival benefits to this important subgroup.
- There are insufficient data on the role of diuretics as first-line therapy for the treatment of high BP in patients with CKD. It would be helpful to clarify the role of diuretics as initial therapy in this population.

**3.3 Role of dual therapy with RASi**

RASi have been shown to both lower BP and slow the progression of certain types of kidney diseases independently of BP

control. The strongest data come from studies of patients with CKD and diabetes with albuminuria, in which therapy with ACEi or ARB has shown improvement of kidney outcomes and potentially CV outcomes, as discussed above in Section 3.2. Some investigators have advocated the use of dual therapy with ACEi, ARB, and/or aliskiren to enhance the antiproteinuric and renoprotective effects. However, compared to monotherapy with ACEi or ARB, dual RASi therapy appears to cause more adverse effects, including hyperkalemia and AKI, that may outweigh any potential CV or kidney benefit.

**Recommendation 3.3.1: We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes (1B).**

*This is a strong recommendation based on evidence from RCTs of sufficient duration to evaluate kidney and CV protection. There is growing evidence that dual RAS blockade with an ACEi, ARB, or DRI does not lead to long term CV or kidney benefit despite lowering proteinuria in the short term, but it leads to an increased risk of harm from hyperkalemia and AKI. This recommendation places a higher value on preventing harm from hyperkalemia and AKI than on lowering proteinuria. The combination of ACEi or ARB with MRA was beneficial in 1 large outcome trial; thus, our recommendations on combination therapy do not apply in this scenario.*

**Key information**

**Balance of benefits and harms.** In patients with CKD with and without diabetes, a large network meta-analysis compared dual blockade to monotherapy and included 17,750 participants. Two of these studies excluded participants with diabetes.<sup>169</sup> There was no significant difference in all-cause mortality from dual blockade versus monotherapy in 7 studies of 16,862 patients with a mean follow-up of 3.4 years. There was also no difference in progression to ESKD and no improvement of CV events based on 7 studies of 16,507 patients with a mean follow-up of 40 months.

On the other hand, a traditional pair-wise meta-analysis performed by the ERT demonstrated harm for dual blockade compared to monotherapy. In studies of patients with CKD with and without diabetes, dual blockade compared to monotherapy caused a slightly higher risk of all-cause mortality of borderline significance (HR: 1.09; 95% CI: 1.00–1.20) based on data from 10,615 patients in 4 studies with a mean follow-up of 31 months: VALERIA,<sup>277</sup> ONTARGET,<sup>278</sup> PRONEDI,<sup>279</sup> and VA-NEPHRON-D<sup>280</sup> (Supplementary Table S31).

Importantly, in studies of patients with CKD with or without diabetes, there was evidence that dual therapy increased the incidence of AKI by 40% (RR: 1.60; 95% CI: 1.26–2.04), compared to monotherapy, based on data from 6139 patients in 2 studies—VA-NEPHRON-D<sup>280</sup> and ONTARGET<sup>278</sup>—with a mean follow-up of 39 months (Supplementary Table S31).

Combining data for patients who have both CKD and diabetes (and excluding those without diabetes) from 3 large RCTs, there was no benefit in all-cause mortality; there were

9% fewer deaths with monotherapy RASi compared to dual RASi therapy (RR: 0.92; 95% CI: 0.84–1.01) based on data from 10,486 patients with a mean follow-up of 52 months (PRONEDI,<sup>279</sup> VA-NEPHRON-D,<sup>280</sup> ONTARGET 2011<sup>278</sup>). There was a marginal reduction of 20% (RR: 0.80; 95% CI: 0.65–1.00) in doubling of serum creatinine by dual therapy, compared to monotherapy, during the study of 10,486 patients from 3 studies with a mean follow-up of 37 months (PRONEDI,<sup>279</sup> VA-NEPHRON-D,<sup>280</sup> and ONTARGET 2011<sup>278</sup>). However, the lower confidence interval reaches the null, indicating high uncertainty.

The data analysis of the meta-analysis cited above is echoed by the individual large RCTs, including ONTARGET, VA-NEPHRON D, ALTITUDE, and ORIENT.

Although dual therapy with ACEi and ARB (or DRI in ALTITUDE) moderately reduces albuminuria and BP compared to monotherapy with either drug, dual therapy does not confer important clinical kidney or CV benefits, and it causes more hyperkalemia and AKI.

**Quality of evidence.** The overall quality of the evidence for harm was moderate. The network meta-analysis that compared dual RASi with mono RASi exhibited moderate quality of the evidence because of concerns regarding inconsistency for all-cause mortality and CV events and serious imprecision for ESKD due to wide CIs that indicated appreciable benefits and harms (Supplementary Table S32).<sup>169</sup> The ERT review (including Cochrane reviews that were updated<sup>259,281</sup>) rated the quality of evidence to be moderate for studies that compared dual with mono RASi because of study limitations, with unclear reporting for Cochrane risk of bias<sup>282</sup> domains, random sequence generation, and allocation concealment (Supplementary Table S31<sup>234,277–279,283,284</sup>). The ERT updated a Cochrane review protocol on the addition of aliskiren to RASi therapy with mono RASi.<sup>285</sup> The quality of the evidence was moderate for most outcomes (Supplementary Table S29<sup>286–291</sup>). For CV mortality, ESKD, moderately increased albuminuria, and doubling of serum creatinine, the quality of the evidence was downgraded because of serious imprecision due to only 1 study reporting these outcomes, and all-cause mortality was downgraded due to wide confidence intervals that indicate appreciable benefits and harms. Finally, for the serious adverse events, the quality of the evidence was downgraded to moderate because of study limitations (unclear random sequence generation, allocation concealment, and a lack of blinding of outcome assessors).

**Values and preferences.** In the opinion of the Work Group, this recommendation places a higher importance on preventing hyperkalemia and AKI than on the benefits in reduction of albuminuria. The significance of these beneficial effects on albuminuria is unclear, in view of the absence of effects in GFR, at least during the follow-up period of the trials. Although some benefit has been found for dual therapy in HF, this has not been confirmed so far in patients with CKD with or without diabetes. The Work Group believes that patients and providers would

want to avoid hyperkalemia and AKI because of the associated downstream risks as well as the need for more frequent laboratory tests, office and emergency department visits, additional short-term therapies, and adjustment in diet.

**Resource use and costs.** Resource utilization and costs increase, instead of decrease, by instituting dual RASi therapy compared to monotherapy.

**Considerations for implementation.** Given that dual RASi therapy decreases proteinuria, practitioners might be tempted to institute dual therapy to treat very high levels of albuminuria in selected patients, even recognizing the risks of hyperkalemia and AKI.<sup>292</sup> There is, unfortunately, no RCT data on safety or kidney efficacy of dual therapy in patients with very elevated proteinuria.<sup>293</sup> There is a report that dedicated clinics for remission of progression of kidney disease are superior to historical controls.<sup>294</sup> There is insufficient information to differentiate between men and women for this recommendation, and there remains insufficient evidence that there are different outcomes by race or age. In summary, dual therapy should be discouraged for patients with CKD with or without diabetes, with or without albuminuria.

### Rationale

The belief that dual therapies of RASi are beneficial, compared to monotherapies, stemmed only from the improvement in albuminuria with dual therapy.

**Addition of an MRA to ACEi or ARB.** Limited data have shown that the addition of an MRA, such as spironolactone, eplerenone, or finerenone, to an ACEi or ARB for renoprotection in patients with diabetes and kidney disease resulted in a reduction of albuminuria but a higher risk of hyperkalemia. Beyond albuminuria, no adequately powered study examining GFR and kidney failure outcomes has been completed with spironolactone or eplerenone.<sup>295</sup> However, the recent FIDELIO trial showed kidney and cardiovascular protection by finerenone despite its modest effect on SBP (2–3 mm Hg lower) and a higher incidence of hyperkalemia-related events.<sup>258</sup> Results of the FIGARO cardiovascular trial, which is also testing finerenone on the background of an ACEi or ARB in patients with diabetes and kidney disease, are forthcoming.

### Research recommendations

- The benefits of dual versus monotherapy on major kidney outcomes in people with CKD without diabetes and severely increased proteinuria (e.g., >2–3 g/d) have not been well studied. Future trials should examine this important subgroup, while curtailing the risks of hyperkalemia and AKI.
- Conduct studies examining the addition of endothelin blockers or GLP-1 receptor agonists to concomitant RASi monotherapy for potential kidney benefits in the advanced CKD (G4–G5) population and the nonproteinuric CKD populations.
- In the era of personalized medicine, research should be directed to identify individuals who will benefit or experience harm from these combinations in all CKD populations.

## Chapter 4: Blood pressure management in kidney transplant recipients (CKD G1T–G5T)

This chapter makes recommendations for BP management in adult (age  $\geq 18$  years) kidney transplant recipients (CKD G1T–G5T). The evidence review for this chapter included an update of a previous Cochrane review<sup>296</sup> in addition to a new search of the Cochrane Kidney and Transplant Registry for all RCTs.

The term “high BP” is used throughout the document for BP above the target. For kidney transplant recipients, the target is SBP  $<130$  mm Hg/DBP  $<80$  mm Hg.

**Practice Point 4.1: Treat adult kidney transplant recipients with high BP to a target BP of  $<130$  mm Hg systolic and  $<80$  mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).**

This practice point is identical to the original recommendation put forward in the KDIGO 2012 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease.<sup>141</sup> The target is also consistent with the recommended target of  $<130/80$  mm Hg as defined in the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients.<sup>297</sup>

There are no completed RCTs in kidney transplant recipients that have tested different BP targets on clinically important outcomes such as graft survival, CV events, or mortality. There is only 1 RCT on intensified BP control in kidney transplant recipients that compared to standard blood pressure (MAP between 50th and 99th percentiles) versus intensified BP control (MAP  $<50$ th percentile), and it did not report on any clinical outcomes.<sup>298</sup>

The Work Group judged that a target of  $<130$  mm Hg systolic, using standardized office measurement, remained a reasonable goal for kidney transplant recipients. A higher target SBP, such as 140 mm Hg, was in the opinion of the Work Group too high given the preponderance of evidence from RCTs demonstrating survival and CV benefits of targeting SBP  $<130$  mm Hg in the general population.<sup>299–301</sup> In contrast, the Work Group judged that a lower SBP goal, such as 120 mm Hg (see Recommendation 3.1.1), may not be appropriate for kidney transplant recipients without further data on the risks and benefits of targeting this level of BP in this population. This concern for the lower SBP goal of  $<120$  mm Hg partly stems from observations from the SPRINT trial showing that, compared to the standard arm (SBP target  $<140$  mm Hg), patients in the intensive BP arm had modestly higher rates of eGFR decline within the

3-year follow-up of the trial,<sup>91,302</sup> AKI (albeit mild in intensity),<sup>150</sup> and incident CKD,<sup>134</sup> which may be of concern to kidney transplant recipients and clinicians (see *Values and preferences* below). It is conceivable that kidney transplant patients with a solitary, denervated kidney could be at an even higher risk for such adverse events with intensive BP lowering, although this has not been substantiated by clinical data. Data from RCTs involving kidney transplant recipients will be needed to provide a clearer profile of the true risks and benefits of a SPRINT-like goal in this population.

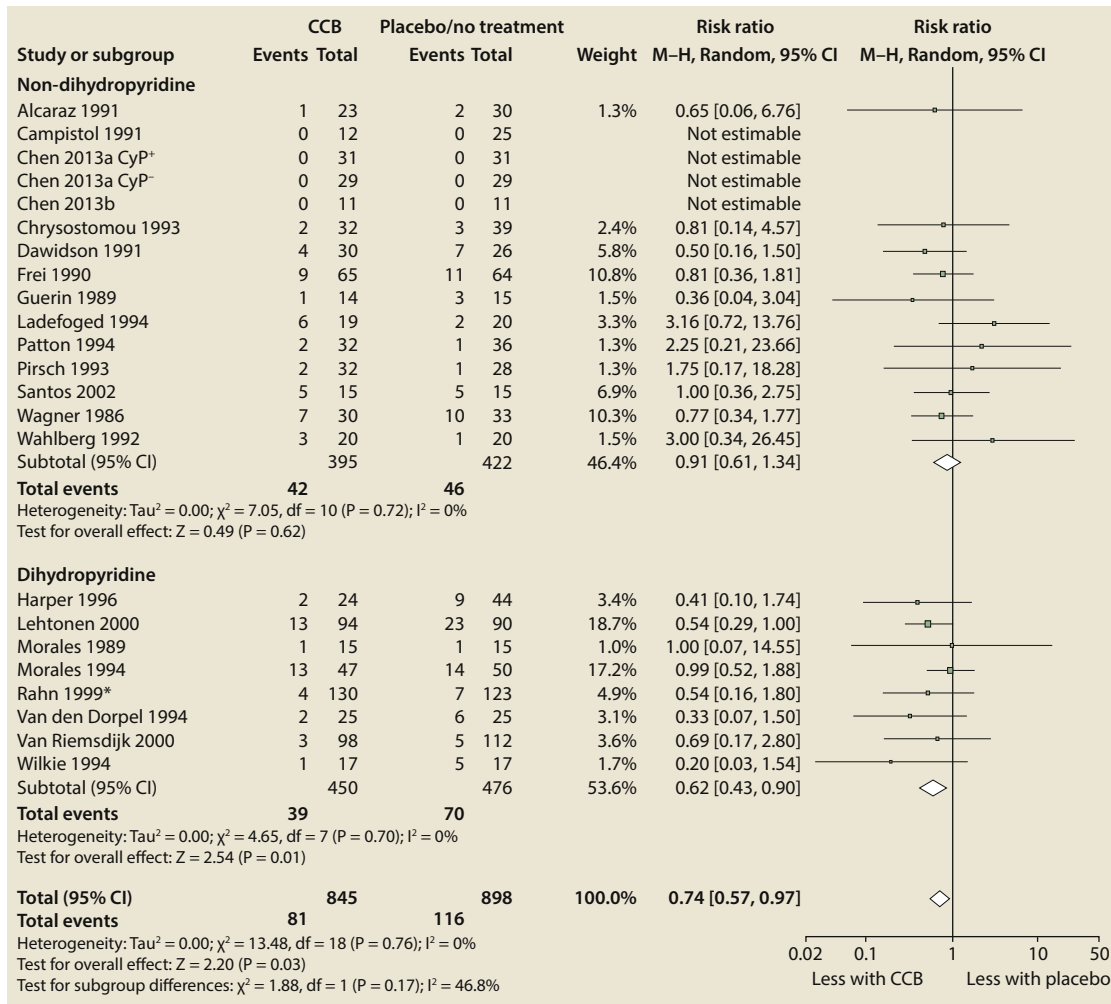
Similar to the non-transplant CKD population (Recommendation 1.2), ABPM or HBPM may be used to complement standardized office BP readings for the diagnosis and management of high BP in the kidney transplant population. As with the general population, classification of BP status using out-of-office BP is often different from classification using standardized office BP in kidney transplant recipients; the complementary use of out-of-office BP measurements may lead to more appropriate therapeutic decisions.<sup>303,304</sup> Again, it should be noted that there have been no completed RCTs targeting different BP values using either office BP readings or out-of-office BP readings in the kidney transplant population.

**Recommendation 4.1: We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).**

*This recommendation places a relatively higher value on preventing kidney allograft loss and a relatively lower value on the risk of a possible medication-related side effect. This recommendation is strong because in the judgment of the Work Group, the potential prevention of transplant failure outweighs potential risks of burden associated with its implementation. The Work Group also judged that all or nearly all well-informed transplant patients would choose to receive a CCB or an ARB given the potential benefit.*

### Key information

**Balance of benefits and harms.** This recommendation relies heavily on the importance of preventing graft loss to kidney transplant recipients and clinicians.<sup>305,306</sup> The evidence review, including both hypertensive and normotensive



**Figure 7 | CCB versus placebo/no treatment for the outcome of graft loss.** Meta-analysis was conducted by the Cochrane Kidney and Transplant Evidence Review Team as part of the guideline evidence review. \*Includes patients both with and without high blood pressure. CCB, calcium channel blocker; CI, confidence interval; CyP, cytochrome P450 3A5 polymorphism; M-H, Mantel-Haenszel.

patients, has found that, compared to placebo, CCB use caused a mean 26% reduction in graft loss (RR: 0.74; 95% CI: 0.57–0.97; [Supplementary Table S33](#); [Figure 7<sup>307–326</sup>](#) [Santos AF, Keitel E, Bittar A, et al., eds. Long-term results of diltiazem use associated to cyclosporin in renal transplantation {abstract}. XIXth International Congress of the Transplantation Society; August 25–30, 2002; Miami, FL, USA]). This evidence is derived from a meta-analysis of 22 RCTs involving 1745 patients conducted by the ERT for this guideline. These 22 trials, however, evaluated both dihydropyridine CCBs (e.g., amlodipine, nifedipine) and non-dihydropyridine CCBs (e.g., diltiazem, verapamil). From a pharmacologic perspective, non-dihydropyridine and dihydropyridine CCBs are very different medications with distinct effects and adverse effects and should not be combined in a meta-analysis. When these medication classes were examined separately, only the dihydropyridine CCB group caused a 38% reduction in graft loss (RR: 0.62; 95%

CI: 0.43–0.90) over a mean of 25 months compared to placebo ([Figure 7<sup>307–326</sup>](#)). This evidence was derived from 8 RCTs involving 926 participants followed for a mean of 25 months.<sup>314,316–318,321–323,326</sup> In contrast, the reduction in graft loss caused by the non-dihydropyridine CCB group was not statistically significant (RR: 0.91; 95% CI: 0.61–1.34) compared to placebo ([Figure 7<sup>307–326</sup>](#)). The evidence review has also found that ARB use compared to placebo caused a 65% reduction in graft loss (RR: 0.35; 95% CI: 0.15–0.84; [Supplementary Table S34](#)). This evidence was derived from 3 RCTs involving 786 participants followed for a mean of 37 months.<sup>327–329</sup>

The evidence review found no benefit of CCB or ARB use on all-cause mortality or CV events such as MI or stroke. Dihydropyridine CCB use, but not ARB use, however, caused a lower serum creatinine concentration (mean difference: 16.01 μmol/l [0.18 mg/dl] lower; 95% CI: 24.97 lower–7.05 lower) and a higher GFR (mean difference: 5.27 ml/min

higher; 95% CI: 2.79 higher–7.74 higher) compared to placebo over a mean follow-up of 15.3 months (Supplementary Table S33<sup>314,317,318,321,322,330–334</sup>).

The tradeoff or harms with these interventions include well-known adverse events for both dihydropyridine CCB (e.g., edema<sup>335</sup>) and ARB (e.g., anemia, acute decline in kidney function, hyperkalemia<sup>336</sup>).

The evidence review found that, compared to placebo or no treatment, ACEi, alpha-blockers, beta-blockers, and MRAs had no significant effect on mortality, graft loss, or CV events (Supplementary Table S35,<sup>332,337–349</sup> Supplementary Table S36,<sup>350</sup> Supplementary Table S37,<sup>351</sup> Supplementary Table S38<sup>352</sup>). With regard to ACEi there was trial evidence showing that these agents were effective at reducing BP and proteinuria in kidney transplant recipients (Supplementary Table S35). However, there was no significant effect of ACEi on all-cause mortality or graft loss, and their use was associated with a significant increase in adverse events in the kidney transplant population, including angioedema, cough, hyperkalemia, and anemia (Supplementary Table S35).

**Quality of evidence.** The ERT updated a Cochrane systematic review<sup>296</sup> and evaluated the quality of the evidence based on RCTs only (Supplementary Tables S33–S39). The evidence for the use of an ARB or CCB compared to placebo or no treatment is considered low quality because of a serious risk of bias (unclear randomization sequence generation and allocation concealment) and imprecision around the effect estimates. Overall, there were very few graft failure events, which introduces greater fragility in the effect estimates. For example, there were only a total of 25 graft failure outcomes among the 786 participants over a mean of 37 months of follow-up in the ARB trials.

**Values and preferences.** Kidney transplant recipients place a high priority on allograft survival. The SONG–Kidney Transplantation (SONG–Tx) group was established to determine which outcomes to measure in transplant trials.<sup>305</sup> The SONG–Tx methodology included a Delphi survey that was completed by 461 patients or caregivers and 557 health professionals from 79 countries. They also held 3 consensus conferences in which patients and caregivers participated.<sup>305,306</sup> Kidney allograft survival was unequivocally the dominant priority for patients, caregivers, and health professionals.<sup>305,306</sup> From the patient's perspective, there was a prevailing dread of returning to dialysis, and they focused on well-being.<sup>305</sup> Preventing graft loss was the top priority, even over death, as the patients were more concerned with quality than quantity of life.<sup>305</sup>

The SONG–Tx work provides strong rationale for the use of interventions that will reduce graft failure. It is the opinion of the Work Group that most well-informed transplant patients would have the same values and preferences for the avoidance of graft loss, as was evident from the SONG–Tx

work. Thus, we believe that nearly all well-informed transplant patients would accept the tradeoffs of side effects of a CCB or an ARB in exchange for the possible benefit of prolonged graft survival.

**Resource use and other costs.** This recommendation assumes that an antihypertensive agent will be started for the treatment of high BP, and the guideline is to facilitate the decision on the choice of the agent. In most countries, generic CCBs and generic ARBs are inexpensive. In resource-limited settings, these drugs are most likely to be available at even lower cost. Given the high financial and human cost of graft failure, and the relatively low cost of CCB or ARB, it is likely that the initiation of a CCB or ARB would be cost-effective.<sup>353</sup> However, a formal economic analysis evaluating different antihypertensive agents in the kidney transplantation setting has not been performed.<sup>354</sup>

**Considerations for implementation.** High BP can be difficult to control in kidney transplant recipients, and most patients will require more than 1 antihypertensive agent.<sup>299–301</sup> This recommendation is for the selection of an initial antihypertensive agent with the understanding that other medications may be required to achieve BP control. Patients with evidence of volume overload and high BP should be treated with diuretics before considering an ARB or CCB. Women trying to conceive or who are pregnant should be treated with a CCB, which is generally safe during pregnancy and lactation, whereas ARB is contraindicated in these conditions. In kidney transplant recipients with proteinuria and high BP, ARB should be considered first given the known proteinuria-lowering effects of these medications.<sup>296</sup> In the early posttransplant period, ARBs should be avoided until kidney transplant function stabilizes, as the acute negative effect of an ARB on GFR can be confused with other causes of graft dysfunction (e.g., rejection). For most other subgroups of transplant patients (e.g., elderly, diabetic), an ARB or CCB should be considered as the first-line antihypertensive agent. Most, if not all patient subgroups, would value graft survival as a high-priority outcome. The choice of class (i.e., ARB vs. CCB) and specific agent should be based on local availability and cost.

### Rationale

This recommendation places a higher value on preventing kidney allograft loss and a lower value on the risk of medication-related side effects. There are many advantages of using an ARB or CCB for high BP in kidney transplant recipients, including physician familiarity with these agents, well-known side-effect profiles, availability, and low costs.

This recommendation is strong because, in the judgment of the Work Group, the potential prevention of transplant

failure far outweighs potential risks and burden associated with its implementation. The Work Group also judged that most transplant patients would take a CCB or an ARB given the potential benefit, and only a small proportion would not. Finally, the Work Group judged that the majority, if not all, of clinicians would be comfortable in starting a CCB or ARB due to the familiarity with these agents and their well-known safety profiles.

**Research recommendations**

Future research should include:

- Adequately powered RCT to evaluate CV and kidney effects of targeting SBP <120 mm Hg versus <130 mm Hg SBP among patients with kidney transplants.
- Adequately powered RCT to evaluate CV and kidney effects of ARB versus dihydropyridine CCB among patients with kidney transplants.

# Chapter 5: Blood pressure management in children with CKD

**Recommendation 5.1: We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to  $\leq$ 50th percentile for age, sex, and height (2C).**

*This recommendation is weak, according to GRADE, because the potential risks for adverse events from BP lowering may vary depending on the underlying cause of CKD in children. In particular, risks of dehydration, hypotension, and possible AKI may be greater in children with underlying urologic disease that may be associated with fixed urine output despite intercurrent gastrointestinal (GI) illness and fluid loss or decreased fluid intake. There may also be burden due to limitations in available resources associated with BP monitoring via 24-hour ABPM. It places a high value on reduction in kidney disease progression and kidney failure and use of the same BP measurement technique by ABPM as in the single RCT that forms the evidence base. It places a relatively low value on the lack of evidence demonstrating that the clinical benefits of BP lowering extend to populations characterized by different causes of CKD, level of albuminuria, race and ethnicity, and on the costs and inconvenience associated with BP monitoring using ABPM.*

## Key information

**Balance of benefits and harms.** This recommendation relies heavily on the data from a single trial (the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients [ESCAPE] trial) of 385 participants in which intensified BP control (targeting 24-hour MAP  $<$ 50th percentile of normal children) was compared to standard BP control (targeting 24-hour MAP 50th–99th percentile of normal children; [Supplementary Table S40<sup>1,142,355</sup>](#)). This study showed a probable benefit in slowing kidney disease progression and no greater risk of adverse events, such as hypotension or acute decrease in GFR. This study in children was not powered for, and did not demonstrate, differences in the critical outcome of all-cause mortality. In the ESCAPE trial, targeting the intensified BP control required a larger number of antihypertensive agents than the conventional target, which may be a burden for some children. Certain subgroups, those with glomerular disorders, GFR  $<$ 45 ml/min per 1.73 m<sup>2</sup>, and those with PCR  $>$ 1.5 g/g (150 mg/mmol) seemed to benefit the most. Of note, based on this observation, the 2016 European Society of Hypertension guideline recommends targeting the 75th percentile of MAP of normal children in a CKD patient with no proteinuria, and

the 50th percentile if an individual has proteinuria.<sup>356</sup> This is based on a subgroup analysis of the ESCAPE data, which suggested that those children with a PCR  $<$ 0.5 g/g (50 mg/mmol) did not have a significant benefit from strict BP control. Therefore, the risk–benefit ratio associated with this treatment strategy may differ in different subpopulations. There may be a higher risk of adverse events with aggressive BP control in individuals who are prone to become dehydrated and are at risk of AKI. This is especially relevant to children with CKD and congenital anomalies of the kidney and urinary tract (CAKUT) who may be unable to concentrate urine and have a salt-losing nephropathy.<sup>357</sup> On the other hand, there are potential CV end-organ benefits, such as less left ventricular hypertrophy.<sup>358</sup>

The single RCT of BP control and kidney failure outcomes in the pediatric CKD population utilized 24-hour MAP as the BP target.<sup>142</sup> Additionally, the AHA Scientific Statement on pediatric ABPM currently considers ABPM as the gold standard metric for the assessment of BP in children, as stronger associations have been reported between ABPM and target organ damage in children compared with clinic BP values.<sup>359</sup> Targeting BP control by ABPM in children with CKD is also recommended by the American Academy of Pediatrics (AAP).<sup>1</sup> However, in clinics that do not have the capacity to provide ABPM, performance of standardized, protocol-driven manual BP measurement using an aneroid sphygmomanometer is a reasonable alternative. Such standardized manual BP measurement provides prognostic information similar to that provided by ABPM.<sup>360,361</sup> Data from the Chronic Kidney Disease in Children Study (CKiD) further demonstrate that manual auscultatory clinic BPs taken in a protocol-driven setting are not inferior to ambulatory BP in the discrimination of BP-related adverse outcomes in children with CKD.<sup>360</sup> However, it must be emphasized that, despite their prognostic utility, RCTs targeting standardized manual BP with meaningful clinical outcomes are not available in children.

Proper technique is essential for BP measurement. BP should be measured in the right arm using standard practices, similar to the method used for adults (see [Figure 2](#) in Chapter 1). The AAP 2017 Clinical Practice guidelines also provide considerable detail on correct BP measurement methods.<sup>1</sup> When possible, in the clinic, the use of auscultatory BP is preferred, as normative BP data in children are obtained using this technique, and there are significant differences between values obtained by oscillometric and auscultatory measurements, with oscillometric measures being slightly



higher on average.<sup>1,3,362</sup> Regardless, RCT data targeting either oscillometric or auscultatory BP measurements obtained in the clinic setting in children are lacking.<sup>363</sup> For practical purposes, the initial BP measurement in a clinic setting may be oscillometric using a calibrated machine that has been validated for use in the pediatric population.<sup>1,3</sup> However, conversion from oscillometric to auscultatory measurement on an individual basis is difficult. In individuals at particularly high risk for elevated BP (e.g., those with glomerular disease),<sup>364</sup> readings should then be confirmed by auscultation.

Use of HBPM in children requires further study and has not been endorsed for the diagnosis of hypertension by the AAP Clinical Practice Guideline. When performed, electronic upper-arm cuff monitors, which have been clinically validated in children, should be used with appropriate cuff size. Validation status for oscillometric BP devices in the pediatric age group can be checked at [stridebp.org](http://stridebp.org). HBPM should be performed for 7 days (not less than 3), with duplicate morning and evening measurements after 5 minutes of sitting at rest and 1 minute between measurements (total of at least 12 readings per week). These preparations have been suggested to be useful in the initial evaluation of untreated children with suspected hypertension, and for children with treated hypertension before each follow-up visit to the healthcare provider.<sup>365</sup> The advantages of HBPM include the ability to obtain multiple BP measurements outside the office setting, its relative ease of use, and perhaps higher acceptance by patients and families. Similar to standardized office BP measurements and in contrast to ABPM, however, no prospective RCTs targeting HBPM to improve clinical outcomes are available in children. Reliable factors converting standardized office BP to home BP or ABPM are also not available in children. Additionally, clinical validation of newer, more automated BP devices in children is necessary.

**Quality of evidence.** The quality of the evidence is low for the outcomes of annual GFR loss and ESKD, as the recommendation of a target of <50th percentile MAP by ABPM in children was based on a single RCT with study limitations ([Supplementary Table S40](#)<sup>142</sup>). The quality of the evidence for the mortality outcome was very low because of study limitations and very serious imprecision because death is a rare event in children. Nonetheless, multiple smaller interventional trials and observational studies with multiple meaningful outcomes for children have consistently shown benefits of BP lowering. For example, observational data from CKiD, published in abstract form, suggest that MAP targets at <90th percentile are beneficial for children with either glomerular or non-glomerular causes of CKD, and lower MAP at <50th percentile may have an additional benefit.<sup>366</sup> Therefore, a range of MAP targets, including the 50th–90th percentile, may also be considered.

**Values and preferences.** The Work Group judged that the prevention of kidney failure and progressive kidney function loss would be of high value to nearly all well-informed patients or caregivers. Published patient-reported outcome data from

the SONG–Kids study reported that children with kidney disease and caregivers rated kidney function as an important outcome, whereas BP control was also rated as an important outcome by caregivers.<sup>367</sup> In the judgment of the Work Group, most patients would value these clinical benefits despite the inconvenience and potential risk of harms associated with aggressive BP management (e.g., multiple medications, more-frequent dosing, possible adverse events if dehydrated, and the burden of monitoring with 24-hour ABPM). Patients for whom medication burden or the burden of ABPM monitoring are particularly important concerns may be more inclined not to follow this recommendation.

**Resource use and costs.** In the judgment of the Work Group, the potential benefits associated with ABPM outweigh the costs and inconvenience associated with its implementation. Patients and families in areas where ABPM is unavailable or less affordable will be less inclined to follow this recommendation and may choose to use clinic-based auscultatory BP monitoring instead.

**Consideration for implementation.** There are no data that suggest differences in beneficial effects of BP lowering between males and females, or children of different ethnic backgrounds or races. However, compared to nonproteinuric kidney diseases, children with proteinuria may derive more clinical benefits from intensive BP lowering.<sup>142</sup>

Implementation of ABPM for monitoring treatment of hypertension is challenging.<sup>368</sup> Some children have difficulty wearing the monitors and completing the full 24 hours of measurements. Monitors are not always available when needed; they require time from a parent or other adult to return the monitor to the clinic and are expensive. With this in mind, there are certain situations in which there is a low probability of finding elevated BP by ABPM. For example, individuals with clinic BP at  $\leq$ 25th percentile are unlikely to have elevated ABPM. Individual practitioners may, therefore, consider less-frequent ABPM monitoring if this level of clinic BP is achieved.<sup>360</sup>

There are additional challenges on how these guidelines apply to children who are too young to undergo ABPM or to children <120 centimeters in height, for whom no normative ABPM data exist. Additionally, for those on ACEi or ARB, it is important for families to understand how to monitor their children to prevent complications, such as dehydration, hypotension, and AKI.

### Rationale

The Work Group considered the balance between benefits and harms, evidence quality, values and preferences, as well as resource utilization in making this recommendation. Primary evidence comes from the ESCAPE trial in which children with baseline CKD with eGFR 20–80 ml/min per 1.73 m<sup>2</sup> and 24-hour average ambulatory MAP >95th percentile were randomized to <50th percentile versus 50th–90th percentile of MAP in the nomogram of healthy children. Both arms received ramipril. The primary composite endpoint of 50%

GFR decline and ESKD favored the intensive BP arm (HR: 0.65; 95% CI: 0.44–0.94).<sup>142</sup>

Existing guidelines from other organizations include the 2016 ESH guidelines for management of high BP in children and adolescents, which promote the use of auscultatory office measurements and BP targets in children with CKD of <75th percentile of normal children (and <50th percentile if proteinuric). This recommendation is based on a *post hoc* analysis from the ESCAPE study.<sup>142</sup> Observational data on standardized auscultatory office monitoring in the CKiD cohort suggest achieved office SBP and DBP <90th percentile offers protection against kidney function decline, compared to office SBP and DBP >90th percentile in children with CKD, with potential additional benefit of even lower office BP levels in children with non-glomerular forms of CKD.<sup>369</sup> Additionally, observational data illustrate that higher levels of proteinuria are most strongly associated with poor BP control and worsening BP over time.<sup>370</sup>

Targeting BP control by ABPM in children with CKD is also recommended by the AAP. The AAP 2017 Pediatric Hypertension guideline recommends that children or adolescents with both CKD and hypertension should be treated to lower 24-hour MAP to <50th percentile of the distribution of BP of healthy children, as measured using ABPM. They further recommend that, regardless of apparent control of BP according to office measurements, children and adolescents with CKD and a history of hypertension should have BP assessed by ABPM at least yearly. Additionally, this guideline recommends that children and adolescents with CKD, hypertension, and proteinuria should be treated with an ACEi or ARB, largely based on observational data.<sup>1</sup> In the ESCAPE trial, children in both arms of the trial were given a fixed-dose ACEi; therefore, the effect of ACEi *per se* could not be delineated.

Key differences between the current and prior KDIGO recommendations in children with CKD include that the prior KDIGO guideline made a recommendation for the initiation of antihypertensive medication when the office SBP or DBP is consistently above the 90th percentile for age, sex, and height, whereas in the current guideline, all children with CKD and MAP consistently above the 50th percentile should be treated. The use of medications is included in this update only as a practice point, as direct trial evidence supporting

their use does not exist, and the prior recommendation was based on limited indirect evidence, primarily data from CKiD that showed better BP control with use of ACEi or ARB.<sup>371</sup> Compared to standard-of-care therapy, ACEi in children with CKD did not lower BP or protect against GFR decline, although it has been reported to have a beneficial effect on proteinuria and left ventricular hypertrophy in small RCTs.<sup>372,373</sup>

**Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 months with standardized auscultatory office BP in children with CKD.**

**Practice Point 5.2: In children with high BP and CKD, when ABPM is not available, manual auscultatory office BP obtained in a protocol-driven standardized setting targeting achieved SBP <90th percentile for age, sex, and height of normal children is a reasonable approach.**

**Practice Point 5.3: Use ACEi or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated, but they carry the risk of hyperkalemia and have adverse fetal risks for pregnant women.**

(For Rationale of above practice points, please see text of Recommendation 5.1.)

#### Research recommendations

- Develop normative reference values for ABPM in pediatric populations that include various races and ethnicities, as differences in normative values by race or ethnicity might inform appropriate targets for BP treatment in childhood CKD.
- Identify the best BP measurement technique and setting to define hypertension and BP targets for pediatric CKD patients.
- Ascertain when antihypertensive medications should be initiated.
- Conduct RCTs that define targets for treatment when ABPM cannot be obtained repeatedly, for example, with home-based or office-based auscultatory or oscillometric BP, with kidney disease progression and CVD as outcomes.

# Methods for guideline development

## Aim

This is an update of the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (CKD) published in 2012.<sup>141</sup> In September 2017, KDIGO held a Controversies Conference to determine whether there was sufficient new evidence to support updating any of the guideline recommendations. It was decided that a guideline update was required.<sup>374</sup>

The objective of this project was to update the evidence-based clinical practice guideline for the management of BP in patients with CKD. The guideline development methods are described below.

## Overview of the process

This guideline adhered to international best practice for guideline development ([Appendix B: Supplementary Tables S2 and S3](#)).<sup>375,376</sup> This guideline has been conducted and reported in accordance with the AGREE II reporting checklist.<sup>377</sup> The processes undertaken for the development of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope and topics of the guideline
- Formulating clinical questions—identifying the Population, Intervention, Comparator, Outcome, Methods (PICOM)
- Selecting topics for systematic evidence review and linking to existing Cochrane Kidney and Transplant systematic reviews
- Developing and implementing literature search strategies
- Selecting studies according to predefined inclusion criteria
- Data extraction and critical appraisal of the literature
- Evidence synthesis and meta-analysis
- Grading the quality of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the quality of the evidence, and other considerations
- Finalizing guideline recommendations and supporting rationale
- Public review in January 2020
- Guideline update
- Finalizing and publishing the guideline

The development process was followed in the majority of the guideline chapters. Some chapters, in particular Chapter 3, required an iterative process, whereby the initial evidence review deliverables were revised to reflect issues raised during the Work Group meeting in January 2019. These additional reviews and clarifications were provided to the Work Group coauthors to ensure that the draft of the Chapter reflected available evidence.

**Commissioning of Work Group and ERT.** The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult and pediatric nephrology, blood pressure management, epidemiology, and public health. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in

guideline development methodology. The ERT consisted of adult and pediatric nephrologists, and methodologists with expertise in evidence synthesis, and guideline development. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the quality of the evidence per outcome, and grading the quality of the evidence for the recommendations. The Work Group was responsible for writing the recommendations and underlying rationale, as well as grading the strength of the recommendation.

The KDIGO Co-Chairs, KDIGO Methods Chair, Work Group Co-Chairs, and the ERT had a one-day meeting in Houston, Texas, USA in February 2018 to discuss the previous guideline and the findings from the KDIGO Controversies Conference on Blood Pressure in Chronic Kidney Disease,<sup>374</sup> and finalize the guideline development process. Guideline topics from the previous guideline and new guideline topics were linked with appropriate clinical questions to underpin the systematic evidence review. The draft guideline topics and review topics were finalized with feedback from the Work Group.

**Defining scope and topics and formulating key clinical questions.** The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline<sup>141</sup> and the KDIGO Controversies Conference on Blood Pressure in CKD.<sup>374</sup> Logical frameworks were developed to present a visual representation of the clinical question and facilitate discussion about the scope of the guideline. The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. However, for questions of critical importance, systematic reviews of the general population were included. Clinical questions adhered to the PICOM format (a list of critical and important outcomes was compiled after voting from the Work Group [[Table 1](#)]). The Work Group and the ERT further refined the clinical questions to finalize inclusion and exclusion criteria to guide literature searching and data extraction. Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map with any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.<sup>141</sup> Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in [Table 2](#). All evidence reviews were conducted in accordance to the Cochrane Handbook,<sup>383</sup> and guideline development adhered to the standards of GRADE.<sup>384</sup>

**Literature searches and article selection.** Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of the Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE

**Table 1 | Hierarchy of outcomes**

Hierarchy	Outcomes
Critical outcomes	<ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Cardiovascular mortality</li> <li>• Kidney failure (formerly known as ESKD)</li> <li>• Cardiovascular events (MI, stroke, HF)</li> <li>• Dementia or cognitive impairment</li> </ul>
Important outcomes	<ul style="list-style-type: none"> <li>• Doubling serum creatinine</li> <li>• AKI</li> <li>• Falls</li> <li>• Fatigue</li> <li>• Body weight</li> <li>• Blood pressure</li> </ul>
Outcomes of limited importance	<ul style="list-style-type: none"> <li>• eGFR or creatinine clearance</li> <li>• Proteinuria</li> </ul>

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MI, myocardial infarction.

The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes median was rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including [clinicaltrials.gov](http://clinicaltrials.gov) and the International Clinical Trials Register search portal. The updated search examined the medical databases MEDLINE, Cochrane Central Registry of Controlled Trials, and Embase.

For review topics that matched existing Cochrane Kidney and Transplant systematic reviews, an updated search for the review using the Cochrane Kidney and Transplant Registry of studies was conducted. The Cochrane Kidney and Transplant Registry of studies was searched for clinical questions that included only RCTs and were not linked to any existing Cochrane systematic review. For clinical questions that included other study types, such as systematic reviews on non-CKD populations, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in [Appendix A: Supplementary Table S1](#).

The titles and abstracts resulting from the searches were screened by 2 ERT members who independently assessed retrieved abstracts, and if necessary, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

A total of 6863 citations were screened. Of these, 290 RCTs, 35 reviews, and 14 observational studies were included in the evidence review ([Figure 8](#)).

**Data extraction.** Data extraction was performed independently by 2 members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner were included. The ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

**Critical appraisal of studies.** The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items<sup>383</sup>:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?

- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

For some topics, for which there were no RCTs in the CKD population, the ERT conducted reviews of existing systematic reviews. AMSTAR 2 was used to critically appraise systematic reviews.<sup>385</sup> For systematic reviews of diagnostic test accuracy studies, the QUADAS-2 tool was used to assess study limitations.<sup>386</sup> All critical appraisal was conducted independently by 2 ERT members, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

**Evidence synthesis and meta-analysis.** *Measures of treatment effect.* Dichotomous outcomes (all-cause mortality, CV mortality, kidney failure, CV events [MI, stroke, HF], dementia or cognitive impairment, doubling serum creatinine, AKI, falls, fatigue, body weight, and BP) results were expressed as RR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment, such as body weight, the mean difference (MD) with 95% CI was used.

*Data synthesis.* Data were pooled using the Mantel-Haenszel random-effects model for dichotomous outcomes, and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.<sup>383</sup>

*Assessment of heterogeneity.* Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and  $\chi^2$  tests. A *P* value of <0.05 was used to denote statistical heterogeneity, and an *I*<sup>2</sup> was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.<sup>384</sup> We used conventions of interpretation as defined by Higgins *et al.* (2003).<sup>387</sup>

*Assessment of publication bias.* We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).<sup>383</sup> Other reasons for the asymmetry of funnel plots were considered.

*Subgroup analysis and investigation of heterogeneity.* Subgroup analysis was undertaken to explore whether there were clinical differences between the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: severity of CKD, primary kidney disease, elderly age/presence of comorbidities, presence of proteinuria or albuminuria, diabetes, number of antihypertensives, lifestyle behaviors/health behaviors. The test of subgroup differences used the *I*<sup>2</sup> statistic and a *P* value of 0.1 (noting that this is a weak test).<sup>383</sup>

*Sensitivity analysis.* The following sensitivity analyses were considered:

**Table 2 | Clinical questions and systematic review topics in the PICOM format**

Guideline Chapter 1	Blood pressure measurement
<b>Clinical question</b>	<b>In patients with CKD, what is the diagnostic accuracy of various BP measurement techniques compared to standardized auscultatory office-based BP?</b>
Population	Patients with CKD (CKD G1–G5 without kidney transplant, and kidney transplant recipients)
Index test	Oscillometric (office-based) BP (unattended or attended), ambulatory BP, home oscillometric monitors
Reference standard	Auscultatory office-based BP monitoring
Outcomes	Sensitivity, specificity, negative predictive value, positive predictive value
Study design	Systematic reviews
SoF table	<a href="#">Supplementary Table S41</a>
<b>Clinical question</b>	<b>In the general population, what is the diagnostic accuracy of various BP measurement techniques (oscillometric office and home BP, ambulatory BP) compared to standardized auscultatory office-based BP in diagnosing high BP?</b>
Population	General population
Index test	Oscillometric (office-based) BP (unattended or attended), ambulatory BP, home oscillometric monitors
Reference standard	Auscultatory office-based BP monitoring
Outcomes	Sensitivity, specificity, negative predictive value, positive predictive value
Study design	Systematic reviews
SoF table	<a href="#">Supplementary Tables S4, S42, and S43</a>
<b>Clinical question</b>	<b>In the general population, what is the association among various approaches to measuring BP including in the clinic (standardized vs. non-standardized), at home, and ambulatory with classification of BP and long-term outcomes?</b>
Population	General population
Index test	Oscillometric (office-based) BP (unattended or attended), ambulatory BP, home oscillometric monitors
Reference standard	Auscultatory office-based BP monitoring
Outcomes	Cost-effectiveness
Study design	Systematic reviews
SoF table	<a href="#">Supplementary Tables S43 and S44</a>
Guideline Chapter 2	Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis
<b>Clinical question</b>	<b>In adults with CKD without diabetes, does reducing protein intake compared to usual protein intake improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) without diabetes
Intervention	Low-protein diet
Comparator	Usual-protein diet
Outcomes	Outcomes listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	Hahn D, <i>et al.</i> Low protein diets for non-diabetic adults with chronic kidney disease (Review). <i>Cochrane Database of Systematic Reviews</i> . 2020;10:CD001892. <sup>37B</sup>
SoF table	<a href="#">Supplementary Tables S49 and S50</a>
<b>Clinical question</b>	<b>In adults with CKD without diabetes, does reducing dietary salt intake compared to usual dietary salt intake improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) without diabetes
Intervention	Low-salt diet
Comparator	Usual salt diet
Outcomes	Outcomes listed in <a href="#">Table 1</a>
Study design	Additional outcomes—sodium excretion, serum creatinine, BP
Cochrane review	RCTs McMahon EJ, <i>et al.</i> Altered dietary salt intake for people with chronic kidney disease (Review). <i>Cochrane Database of Systematic Reviews</i> . 2015;2: CD010070. <sup>47</sup>
SoF table	<a href="#">Supplementary Table S5</a>
<b>Clinical question</b>	<b>In adults with CKD and diabetes, does reducing dietary salt intake compared to usual dietary salt intake improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and diabetes (T1D and T2D)
Intervention	Low-salt diet
Comparator	Usual salt diet
Outcomes	Outcomes listed in <a href="#">Table 1</a>
Study design	Additional outcomes—body mass index
Cochrane review	RCTs No relevant Cochrane Kidney and Transplant review
SoF table	<a href="#">Supplementary Tables S6–S9, S45, and S46</a>
<b>Clinical question</b>	<b>What are the benefits and harms of dietary interventions/patterns among adults with CKD, including people with kidney failure treated with kidney transplantation?</b>
Population	Adults with CKD (CKD G1–G5 including kidney transplant recipient)
Intervention	Dietary modifications (including dietary advice or lifestyle management)

**Table 2 |** (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline Chapter 2	Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis
Comparator	Standard of care (including lifestyle advice) or any other dietary pattern
Outcomes	Outcomes listed in <a href="#">Table 1</a> Additional outcomes—BP
Study design	RCTs
Cochrane review	Palmer SC, <i>et al.</i> Dietary interventions for adults with chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2017;4:CD011998. <sup>379</sup>
SoF table	<a href="#">Supplementary Tables S51–S53 and S90</a>
<b>Clinical question</b>	<b>In adults with CKD and hypertension, does exercise improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and high BP
Intervention	Any exercise intervention greater than 8 weeks' duration (to examine the effects of regular ongoing physical exercise training)
Comparator	Standard of care
Outcomes	Outcomes listed in <a href="#">Table 1</a> Additional outcomes—fat mass, BP, quality of life
Study design	RCTs
Cochrane review	Heiwe S and Jacobson SH. Exercise training for adults with chronic kidney disease (Review). <i>Cochrane Database of Systematic Reviews</i> . 2011;10:CD00323. <sup>380</sup>
SoF table	<a href="#">Supplementary Tables S10, S47, and S48</a>
Guideline Chapter 3	Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis
<b>Clinical question</b>	<b>In patients with CKD, does lower (intensive) BP targets compared to standard BP targets improve clinical efficacy outcomes and reduce adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and with or without diabetes (T1D and T2D)
Intervention	Lower BP target (<140/80 mm Hg, <130/80 mm Hg, <120 mm Hg, MAP <92 mm Hg target)
Comparator	Standard BP target (including MAP target 102–107 mm Hg)
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	None relevant
SoF table	<a href="#">Supplementary Tables S11–S14, S54–S59, and S75–S78</a>
<b>Clinical question</b>	<b>In patients with CKD, does RAS inhibition compared to placebo/no treatment or standard of care improve clinical efficacy outcomes and reduce adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and with and without diabetes (T1D and T2D)
Intervention	ACEi, ARB, aldosterone antagonists
Comparator	Placebo/standard of care
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	Strippoli GFM, <i>et al.</i> Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2006;4:CD006257. <sup>259</sup> Sharma P, <i>et al.</i> Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2011;10:CD007751. <sup>281</sup> Chung EYM, Ruospo M, Natale P, <i>et al.</i> Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2020;10:CD007004. <sup>193</sup>
SoF table	<a href="#">Supplementary Tables S15–S17, S21–S24, and S60–S62</a>
<b>Clinical question</b>	<b>In patients with CKD, does non-RAS inhibition compared to placebo or RAS inhibition improve clinical efficacy outcomes and reduce adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and with and without diabetes (T1D and T2D)
Intervention	Non-RAS inhibition (alpha-blockers, beta-blockers, CCBs, DRIs, diuretics)
Comparator	Placebo or RASi
Outcomes	Critical and important harms listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	None relevant
SoF table	<a href="#">Supplementary Tables S18–S20, S25–S30, S63–S72, S79, and S81–S87</a>
<b>Clinical question</b>	<b>In patients with CKD, does dual-RAS inhibition compared to mono-RAS inhibition improve clinical efficacy outcomes and reduce adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) and with and without diabetes (T1D and T2D)
Intervention	Dual RAS inhibition
Comparator	Mono RAS inhibition
Outcomes	Critical and important harms listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	Strippoli GFM, <i>et al.</i> Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2006;4:CD006257. <sup>259</sup> Sharma P, <i>et al.</i> Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2011;10:CD007751. <sup>281</sup>

(Continued on following page)

**Table 2 |** (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline Chapter 3	Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis
SoF table	<a href="#">Supplementary Tables S31, S32, and S80</a>
<b>Clinical question</b>	<b>In patients with CKD and chronic hyperkalemia, do potassium binders compared to placebo or standard of care improve clinically relevant outcomes, and decrease adverse effects?</b>
Population	Adults with CKD (CKD G1–G5 without kidney transplant) with chronic hyperkalemia
Intervention	Potassium binders
Comparator	Placebo/standard of care
Outcomes	Critical and important harms listed in <a href="#">Table 1</a> Additional outcomes reported—hospitalization, hypokalemia, SBP, and DBP
Study design	RCTs
Cochrane review	Natale P, <i>et al.</i> 2020. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2020;6:CD013165. <sup>381</sup>
SoF table	<a href="#">Supplementary Tables S73, S74, and S88</a>
Guideline Chapter 4	Blood pressure management in kidney transplant recipients
<b>Clinical question</b>	<b>In kidney transplant recipients, does reducing protein intake compared to usual protein intake improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Kidney transplant recipients
Intervention	Low-protein diet
Comparator	Usual protein diet
Outcomes	Outcomes listed in <a href="#">Table 1</a>
Study design	RCTs
Cochrane review	None relevant
SoF table	None
<b>Clinical question</b>	<b>In kidney transplant recipients, does reducing dietary salt intake compared to usual salt intake improve clinically relevant outcomes and decrease adverse effect?</b>
Population	Kidney transplant recipients
Intervention	Low-salt diet
Comparator	Usual salt diet
Outcomes	Outcomes listed in <a href="#">Table 1</a> Additional outcomes—sodium excretion, serum creatinine, BP
Study design	RCTs
Cochrane review	None relevant
SoF table	<a href="#">Supplementary Table S89</a>
<b>Clinical question</b>	<b>What are the benefits and harms of dietary interventions/patterns among kidney transplant recipients?</b>
Population	Kidney transplant recipients
Intervention	Dietary modifications (including dietary advice or lifestyle management)
Comparator	Standard of care (including lifestyle advice) or any other dietary pattern
Outcomes	Outcomes listed in <a href="#">Table 1</a> Additional outcomes—BP
Study design	RCTs
Cochrane review	Palmer SC, <i>et al.</i> Dietary interventions for adults with chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2017;4:CD011998. <sup>379</sup>
SoF table	<a href="#">Supplementary Table S90</a>
<b>Clinical question</b>	<b>In kidney transplant recipients and high BP, does exercise improve clinically relevant outcomes and decrease adverse effects?</b>
Population	Kidney transplant recipients and high BP
Intervention	Any exercise intervention greater than 8 weeks' duration (to examine the effects of regular ongoing physical exercise training)
Comparator	Standard of care
Outcomes	Outcomes listed in <a href="#">Table 1</a> Additional outcomes—body mass index, BP, quality of life
Study design	RCTs
Cochrane review	Heiwe S and Jacobson SH. Exercise training for adults with chronic kidney disease (Review). <i>Cochrane Database of Systematic Reviews</i> . 2011;10:CD00323. <sup>380</sup>
SoF table	<a href="#">Supplementary Table S91</a>
<b>Clinical question</b>	<b>In kidney transplant recipients does lower (intensive) BP target compared to standard BP targets improve clinical efficacy outcomes and reduce adverse effects?</b>
Population	Kidney transplant recipients, adult and children
Intervention	Lower BP target
Comparator	Standard BP target
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a>
Study design	RCTs

**Table 2 |** (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline Chapter 4		Blood pressure management in kidney transplant recipients
Cochrane review	None relevant	
SoF table	None	
<b>Clinical question</b>	<b>In kidney transplant recipients, what antihypertensive agents improve efficacy outcomes and reduce adverse effects?</b>	
Population	Kidney transplant recipients, adult and children	
Intervention	RAS inhibition (ACEi, ARB, aldosterone antagonists), and non-RAS inhibition (alpha-blockers, beta-blockers, CCBs, diuretics, DRI)	
Comparator	Placebo or standard of care	
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a> Other outcomes reported: BP	
Study design	RCTs	
Cochrane review	Cross NB, <i>et al.</i> Antihypertensive treatment for kidney transplant recipients. <i>Cochrane Database of Systematic Reviews</i> . 2009;3:CD003598. <sup>296</sup>	
SoF table	<a href="#">Supplementary Tables S33–S39 and S92–S106</a>	
<b>Clinical question</b>	<b>In kidney transplant recipients with chronic hyperkalemia, do potassium binders compared to placebo or standard of care improve clinically relevant outcomes and decrease adverse effects?</b>	
Population	Kidney transplant recipients with chronic hyperkalemia	
Intervention	Potassium binders	
Comparator	Placebo/standard of care	
Outcomes	Critical and important harms listed in <a href="#">Table 1</a>	
Study design	RCTs	
Cochrane review	Natale P, <i>et al.</i> 2020. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. <i>Cochrane Database of Systematic Reviews</i> . 2020;6:CD013165. <sup>381</sup>	
SoF table	None	
Guideline Chapter 5		Blood pressure management in children with CKD
<b>Clinical question</b>	<b>In children with CKD, does a lower BP target compared to a higher BP target improve efficacy outcomes and reduce adverse effects?</b>	
Population	Children with CKD	
Intervention	Lower BP target	
Comparator	Standard BP target	
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a>	
Study design	RCTs	
Cochrane review	None relevant	
SoF table	<a href="#">Supplementary Table S40</a>	
<b>Clinical question</b>	<b>In children with CKD, what antihypertensive agents compared to standard of care improve efficacy outcomes and reduce adverse effects?</b>	
Population	Children with CKD (CKD G1–G5 without kidney transplant and kidney transplant recipients) and diabetes (T1D and T2D)	
Intervention	RAS inhibition (ACEi, ARB, aldosterone antagonists), and non-RAS inhibition (alpha-blockers, beta-blockers, CCBs, diuretics, DRI)	
Comparator	Placebo or standard of care	
Outcomes	Critical and important outcomes listed in <a href="#">Table 1</a> Additional outcomes: BP, serum creatinine	
Study design	RCTs	
Cochrane review	Bagga A, <i>et al.</i> Antihypertensive agents for children with chronic kidney disease (Protocol). <i>Cochrane Database of Systematic Reviews</i> . 2014;1:CD010911. <sup>382</sup>	
SoF table	<a href="#">Supplementary Table S107</a>	

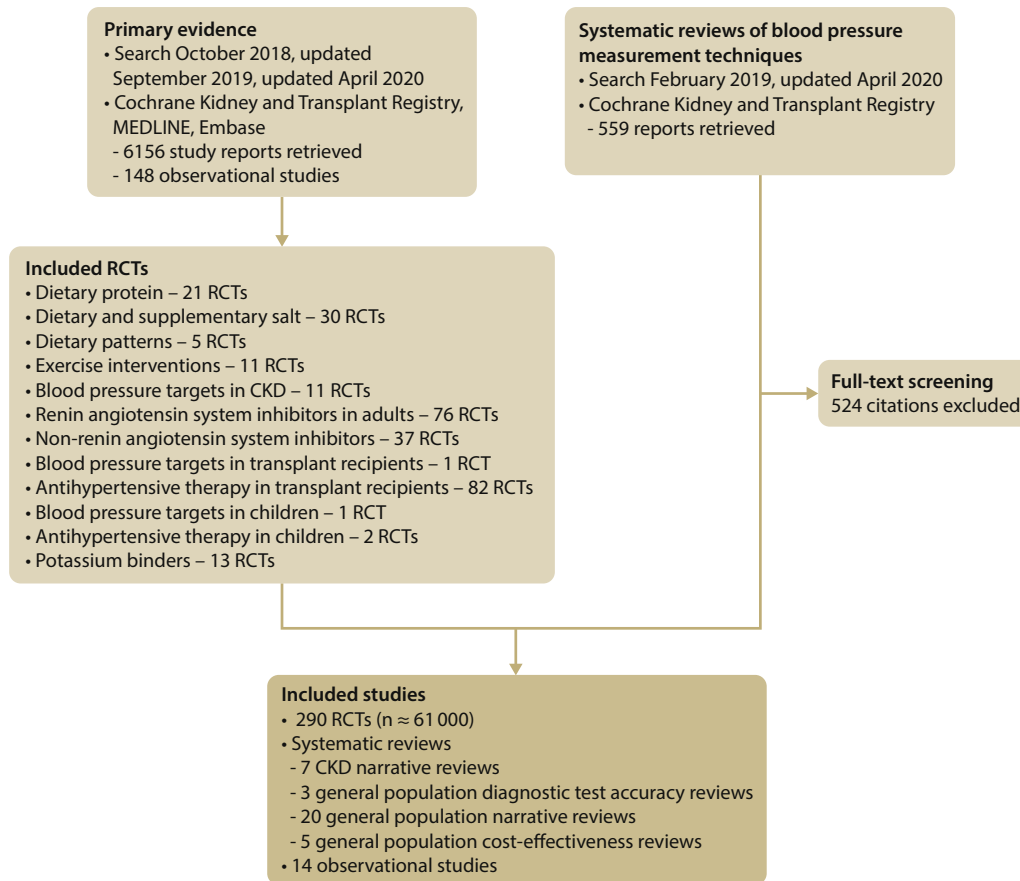
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; DRI, direct renin inhibitor; MAP, mean arterial pressure; RAS(i), renin-angiotensin system (inhibitor); RCT, randomized controlled trial; SBP, systolic blood pressure; SoF, summary of findings; T1D, type 1 diabetes; T2D, type 2 diabetes.

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis taking account of the risk of bias, as specified
- Repeating the analysis, excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis, excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

**Grading the quality of the evidence and the strength of a guideline recommendation.** GRADING the quality of the evidence for each outcome across studies. The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach,<sup>384,388</sup> which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. For observational studies, the initial quality of the evidence is low. The quality of the evidence is lowered in the event of study limitations; important inconsistencies in results across





**Figure 8 | Search yield and study flow diagram.** CKD, chronic kidney disease; RCT, randomized controlled trial.

**Table 3 | Classification for certainty and quality of the evidence**

Grade	Quality of evidence	Meaning
<b>A</b>	High	We are confident that the true effect is close to the estimate of the effect.
<b>B</b>	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
<b>C</b>	Low	The true effect may be substantially different from the estimate of the effect.
<b>D</b>	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size, low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.<sup>388</sup> The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from a rating of low quality, according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence, see Table 4.

**Summary of findings (SoF) tables.** The SoF tables were developed to include a description of the population and the intervention and comparator. In addition, the SoF tables included results from the

data synthesis as relative and absolute effect estimates. The grading of the quality of the evidence for each critical and important outcome is also provided in the SoF table. The SoF tables were generated using MAGICapp, an online software application designed to support guideline development, and they are available in the [Data Supplement Appendix C and Appendix D \(https://kdigo.org/guidelines/blood-pressure-in-ckd/\)](https://kdigo.org/guidelines/blood-pressure-in-ckd/).

**Developing the recommendations.** The recommendations were drafted by the Work Group Co-Chairs and Work Group members. Recommendations were revised in a multistep process during a face-to-face meeting (New Orleans, LA, USA, January 2019) and by e-mail communication. The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by Work Group Co-Chairs and members. All Work Group members provided feedback on initial and final drafts of the recommendation statement and guideline text and approved the final version of the guideline. The ERT also provided a descriptive

**Table 4 | GRADE system for grading quality of evidence**

Study design	Starting grade of the quality of the evidence	Step 2—Lower grade	Step 3—Raise grade for observational studies
RCTs	High	Study limitations: –1, serious –2, very serious	Strength of association: +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: –1, serious –2, very serious	Evidence of a dose–response gradient
Observational studies	Low	Indirectness: –1, serious –2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: –1, serious –2, very serious  Publication bias: –1, serious –2, very serious	

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

**Table 5 | KDIGO nomenclature and description for grading recommendations**

Grade	Implications		
	Patients	Clinicians	Policy
<b>Level 1 ‘Strong’</b> “We recommend”	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
<b>Level 2 ‘Weak’</b> “We suggest”	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

**Table 6 | Determinants of the strength of recommendation**

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, where possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resources and other considerations	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

summary of the evidence quality in support of the recommendations.

**Grading the strength of the recommendations.** The strength of a recommendation is graded as strong or weak (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall quality of evidence, patient preferences and values, resources, and other considerations (Table 6).

**Balance of benefits and harms.** The Work Group and ERT determined the anticipated net health benefit on the basis of

expected benefits and harms across all critical and important outcomes from the underlying evidence review. In addition to the evidence review, the ERT assisted Work Group members in evaluating the balance of benefits and harms arising from key individual studies.

**The overall quality of evidence.** The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded A, B, C, or D (Table 3).

*Patient preferences and values.* No patients or caregivers were involved in the Work Group. The Work Group, from their experience in managing BP in patients with CKD and their understanding of the best available scientific literature, made judgments on the preferences and values of patients. Formal qualitative evidence synthesis on patient priorities and preferences was not undertaken.

*Resources and other considerations.* Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,<sup>389</sup> were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs, non-healthcare resources (e.g., transportation and social services), informal caregiver resources (e.g., time of family and caregivers), and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics. However, the ERT conducted searches for systematic reviews of cost-effectiveness studies in support of selected topics, such as BP measurement techniques.

### Practice points

In addition to graded recommendations, KDIGO guidelines now include “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. These were used when no formal systematic evidence review was undertaken, or there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on

limited evidence. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

### Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1 or weak, level 2) and the quality of evidence (A, B, C, D). The recommendation statements are followed by a short remark, Key information (Balance of benefits and harms, Quality of evidence, Values and preferences, Resource use and costs, Considerations for implementation), and a rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale supported each practice point.

### Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. For a select number of clinical questions in this guideline, the ERT undertook a comprehensive evidence review beyond RCTs. However, these reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

## Biographic and disclosure information



**Alfred K. Cheung, MD (Work Group Co-Chair)**, is Dialysis Research Foundation Presidential Endowed Chair, Professor of Internal Medicine, Chief of the Division of Nephrology & Hypertension, Executive Director of the Dialysis Program, and Vice-chair for Research in the Department of Internal Medicine at

the University of Utah, Salt Lake City, UT, USA.

His research has focused on CKD, hemodialysis, vascular access, and hypertension. He has served on various committees in the American Society of Nephrology, the US National Kidney Foundation, the US Food & Drug Administration, the US Centers for Medicare & Medicaid Services, and as a councilor at the International Society of Nephrology. He has also been a chartered member or *ad hoc* member of grant review committees for the US National Institutes of Health (NIH) and other research funding organizations. He was interim Co-Editor-in-chief of the *Journal of American Society of Nephrology*.

He co-chaired the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines on “Cardiovascular Disease in Dialysis Patients.” Of particular relevance to this task, he was a member of the Steering Committee and the Principal Investigator of the Utah Clinical Center Network in the Systolic Blood Pressure Intervention Trial (SPRINT) sponsored by the NIH.

*Consultancy: Amgen, Bard, Boehringer Ingelheim, Calliditas, Tricida, and UpToDate*

*Grant/research support: National Institutes of Health for SPRINT\**

*\*Monies paid to institution.*



**Johannes F.E. Mann, MD (Work Group Co-Chair)**, is a professor of medicine at the University of Erlangen-Nürnberg, Erlangen, Germany, and head of the KfH Kidney Centre, Munich, Germany. He is also an international scholar at the Population Health Research Institute, McMaster University, Hamilton, Canada. He is board-certified in internal

medicine, nephrology, intensive care, and pharmacology. His work focused initially on the physiology of the RAS in experimental animals and later on the role of this system in the diseases of the kidney and the heart. From there, his

interest moved to the treatment of progressive kidney diseases. The latter included steering, adjudication, and data safety monitoring board memberships in outcome trials, namely AIPRI, HOPE, MICRO-HOPE, HOPE-TOO, RENAL-ONTARGET, RENAL-TRANSCEND, ASCEND, DIABHYCAR, ORIGIN, LEADER, SONAR, SOUL, FLOW, DAPA-CKD.

His scientific work includes about 270 original papers.

*Consultancy: AstraZeneca, Bayer, Boehringer Ingelheim, Fresenius Medical Care, Novo Nordisk, and Vifor Fresenius Medical Care Renal Pharma*

*Grant/research support: Boehringer Ingelheim, Canadian Institutes Health Research, European Union, Idorsia, Novo Nordisk, Sandoz, and Sanofi*

*Speaker bureaus: AstraZeneca, B. Braun, Fresenius Medical Care, Novartis, Novo Nordisk, and Roche*



**Tara I. Chang, MD, MS**, is an associate professor of medicine, division chief, and director of clinical research in the Division of Nephrology at Stanford University School of Medicine in Palo Alto, CA, USA. She received her medical degree at the University of Michigan before completing her internal medicine residency at the University of California, San Francisco, CA, USA, and her nephrology

fellowship at Stanford. Dr. Chang maintains an active clinical research program that focuses on improving cardiovascular outcomes among patients with CKD. Dr. Chang's research projects involve clinical epidemiology and clinical trials. She recently served as a US national leader for the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) trial. Dr. Chang is a member of the KDIGO Executive Committee and is actively involved with the American Society of Nephrology and the US National Kidney Foundation. Her other responsibilities include serving as an associate editor for the *American Heart Journal*, and as a member of the editorial boards of *Kidney360*, the *Clinical Journal of the American Society of Nephrology*, and the *Journal of Human Hypertension*.

*Consultancy: Bayer, Gilead, Janssen Research and Development, Novo Nordisk, Tricida, and Vascular Dynamics*

*Advisory boards: AstraZeneca and Fresenius Medical Care Renal Therapies Group*

*Grant/research support: AstraZeneca and Satellite Healthcare*



**William C. Cushman, MD, FAHA, FACP**, is the medical director of the Department of Preventive Medicine, and a professor of preventive medicine, medicine, and physiology at the University of Tennessee Health Science Center (UTHSC) in Memphis, TN, USA. He was trained at the University of Mississippi School of Medicine in Jackson, Mississippi, USA.

After serving on the faculty there and as staff at the Department of Veterans Affairs (VA) Medical Center, he moved to the UTHSC and the VA in Memphis, Tennessee. He retired from the VA in 2020 to assume his current position at UTHSC.

Dr. Cushman is recognized for his expertise in hypertension. He was a VA champion for the 2014 and 2020 US VA/DoD Hypertension Clinical Practice Guideline committees, and was on the leadership committees for the Joint National Committee (JNC) 7 and JNC 8 US hypertension guidelines. He has participated in the leadership for many National Heart, Lung and Blood Institute, VA, and industry-sponsored clinical trials in hypertension and diabetes. He has authored more than 300 journal article and book chapter publications and has received several awards, including the 2010 VA Clinical Science Research and Development Barnwell Award, the 2017 Inter-American Society of Hypertension Lifetime Achievement Award, and the 2018 American Heart Association's Council on Hypertension Irvine Page-Alva Bradley Lifetime Achievement Award.

*Grant/research support: National Institutes of Health\* and Eli Lilly\**

*\*Monies paid to institution.*



**Susan L. Furth, MD, PhD**, is Vice-chair of the Department of Pediatrics, associate Chair for Academic Affairs, and professor of pediatrics and epidemiology at the University of Pennsylvania, Philadelphia, PA, USA. She is chief of the nephrology division at Children's Hospital of Philadelphia, Philadelphia, PA, USA. She is the

principal investigator of the Chronic Kidney Disease in Children (CKiD) Study, the largest multicenter prospective cohort study of children with CKD ever conducted in North America, now in its 16th year. She also leads the Pediatric Center of Excellence in Nephrology at the Children's Hospital of Philadelphia. She has authored over 250 publications, and in 2020, she was awarded the Maureen Andrew Mentor Award by the Society for Pediatric Research.

*Grant/research support: National Institutes of Health\**

*\*Monies paid to institution.*



**Fan Fan Hou, MD, PhD**, is a nephrologist and professor of medicine at the Southern Medical University in Guangzhou, China. She is an academician of the Chinese Academy of Sciences and a member of the Third World Academy of Sciences. Dr. Hou received her nephrology training at the Brigham and Women's Hospital and

Harvard Medical School in Boston, MA, USA. She assumed her current position as chief of nephrology at Nanfang Hospital, Southern Medical University, Guangzhou, China in 1999. Dr. Hou has been serving as Chair of the National Clinical Research Center for Kidney Disease since 2013. She is currently a councilor of the International Society of Nephrology and an Executive Committee member of KDIGO.

Dr. Hou is a clinician–scientist with an interest in kidney disease, specifically the intervention of CKD and mechanisms underlying CKD progression. She had served as a steering committee member of international clinical trials, including ALBUM, SONAR, DAPA-CKD, and principal investigator of several national trials such as ESBARI, ROAD, and CSPPT-CKD. Dr. Hou has published hundreds of papers in peer-reviewed journals such as the *New England Journal of Medicine*, the *Journal of the American Medical Association*, *Nature Medicine*, the *Journal of the American Society of Nephrology*, and *Kidney International*.

*Consultancy: AstraZeneca*



**Joachim H. Ix, MD, MAS**, received his medical degree from the University of Chicago, Pritzker School of Medicine, IL, USA. He trained in internal medicine and nephrology and subsequently joined the faculty at University of California San Francisco, CA, USA. He was recruited to University of California

San Diego, CA, USA, in 2007 and has served as chief of the Division of Nephrology-Hypertension at University of California San Diego since 2013. Dr. Ix's research interests broadly focus on the overlap between kidney disease and vascular disease. His work has primarily utilized epidemiologic methods and clinical trials to understand disease patterns that overlap between kidney and vascular disease, and to test novel therapies to improve vascular disease in the kidney patient. He is particularly interested in the effects of blood pressure control on kidney disease and its complications and is a principal investigator of an NIH award focused on this topic. He also served as the San Diego Site principal investigator and a member of the CKD working group within the SPRINT trial. Dr. Ix has co-authored over 370 peer-reviewed scientific papers, has previously served as an associate editor for the *Journal of the American Society of Nephrology* and *Circulation*.

In 2020, he received the Shaul G. Massry Award from the US National Kidney Foundation.

*Consultancy: AstraZeneca and Sanifit*

*Grants/research support: Baxter International\* and National Institutes of Diabetes and Digestive and Kidney Diseases\**

*Travel expenses: American Society of Nephrology and Institute of Medicine*

*\*Monies paid to institution.*



**Gregory A. Knoll, MD, MSc, FRCPC**, is head of the Division of Nephrology at the Ottawa Hospital and a professor of medicine at the University of Ottawa, Canada. He currently holds the University of Ottawa Chair in Clinical Transplantation Research and is a senior scientist with the Clinical Epidemiology Program of the Ottawa

Hospital Research Institute. He completed his nephrology fellowship at the University of Ottawa, followed by a kidney transplant fellowship at the University of Alabama at Birmingham, USA. Following this training, he took further graduate work and received a master's degree in epidemiology. For over 15 years, he was the medical director of kidney transplantation at the Ottawa Hospital. He assumed his current position as head of the nephrology division in 2016. He is a past president of the Canadian Society of Transplantation. Dr. Knoll is involved in ongoing studies related to cardiac screening in kidney transplant candidates, systematic reviews on immunosuppressive strategies, and measuring quality in transplantation. He was the lead author on the Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. He also served as the Co-Chair of the KDIGO Clinical Practice Guideline on Evaluation and Management of Candidates for Kidney Transplantation.

*Grant/research support: Canadian Institutes of Health Research\**

*\*Monies paid to institution.*



**Paul Muntner, PhD, MHS, FASH, FAHA**, is associate dean for research and a professor of epidemiology at the University of Alabama at Birmingham (UAB), AL, USA. Additionally, he is the co-director of the UAB Pharmacoepidemiology and Economics Research Unit. He earned a master's degree in biostatistics and a doctorate in epidemiology from the Johns Hopkins University, Baltimore, MD, USA. Since 2015, Dr. Muntner has served as the director for the UAB American Heart Association Strategically Focused Research Network hypertension center. He is the principal investigator on grants from the US National Heart, Lung, and Blood Institute. From 2015 to 2018, he was Vice-chair of the Statistics Committee for the American Heart Association and

chaired the 2019 American Heart Association Scientific Statement on blood pressure measurement. His research has focused on the prevention and treatment of cardiovascular disease and its risk factors. Dr. Muntner has an extensive bibliography in clinical and population hypertension, including over 500 peer-reviewed journal articles.

*Consultancy: Amgen*

*Grant/research support: Amgen and National Institutes of Health*



**Roberto Pecoits-Filho, MD, PhD, FASN, FACP**, is a senior research scientist at Arbor Research Collaborative for Health in Ann Arbor, MI, USA, and a professor of medicine at the Pontifical Catholic University of Paraná in Curitiba, Brazil. As a clinician, he has broad activities in internal medicine and nephrology based at the university-affiliated hospitals, where he was chief

of the Department of Internal Medicine between 2010 and 2016, and the director of the residency program in nephrology from 2013 to 2016. Dr. Pecoits-Filho is the principal investigator for CKDOPPS, a multinational study on practice patterns and outcomes in CKD, and acts as a scientific leader for clinical trials in nephrology with George Clinical, Sydney, Australia.

Dr. Pecoits-Filho received his medical degree and trained in internal medicine and nephrology in Curitiba, Brazil, before completing a research nephrology fellowship at the University of Missouri, Columbia, MO, USA, and a PhD from the University of Sao Paulo, Brazil. He was a visiting scholar for extended periods at the Karolinska Institute in Sweden and the George Institute in Australia. He has participated as a principal investigator, regional leader, and on steering committees in multinational clinical trials. Dr. Pecoits-Filho served as a member of the Executive Committee of the ISN (2017–2019), the SONG Initiative (2017–present), and KDIGO (2016–2018).

*Consultancy: Akebia, AstraZeneca, Fresenius Medical Care, and Novo Nordisk*

*Grant/research support: Fresenius Medical Care\**

*Speaker bureaus: AstraZeneca and Novo Nordisk*

*\*Monies paid to institution.*



**Mark J. Sarnak, MD, MS**, is chief of the Division of Nephrology at Tufts Medical Center and the Gerald J. and Dorothy R. Friedman Professor of Medicine at Tufts University School of Medicine, Boston, MA, USA. Dr. Sarnak's primary research interest is in cardiovascular disease in CKD. He has also focused on cognitive function, novel biomarkers, and hypertension in CKD. Dr. Sarnak's research is funded by the NIH.

He is a previous recipient of the Shaul Massry Award from the US National Kidney Foundation.

Dr. Sarnak has a long record of national and international leadership positions in nephrology. He was Co-Chair and lead author of a review commissioned by the Kidney Council of the American Heart Association, "CKD as a Risk Factor for Cardiovascular Disease." He chaired the subgroup covering CKD patients without diabetes on the previous KDIGO Blood Pressure Guideline. He chaired the Kidney Disease Outcomes Quality Initiative Commentary on the KDIGO Clinical Practice Guideline for Lipid Management in CKD, and most recently, he co-chaired the KDIGO Controversies Conference on Coronary Artery and Valvular Disease in CKD.

Dr. Sarnak is a previous recipient of a K24 Midcareer Career Award in Patient-Oriented Research and has mentored more than 20 research fellows and 9 junior faculty members. He has published more than 350 articles, including more than 85 peer-reviewed, non-review articles, with his mentee as the first author. His mentees now include professors of medicine and chiefs of divisions of nephrology at other institutions.

*Consultancy: Akebia\*, Bayer, and Cardurion Pharmaceuticals*

*Grant/research support: National Institutes of Health\**

*\*Monies paid to institution.*



**Sheldon W. Tobe, MD, FRCP, FACP, FAHA, MScCH (HPTE)**, received his medical degree in 1985 from the University of Calgary, Alberta, Canada. Dr. Tobe trained in internal medicine and nephrology at the University of Toronto, Ottawa, Canada. He is a professor of medicine at both

the University of Toronto and the Northern Ontario School of Medicine and the Nephrology Postgraduate Fellowship Director at the University of Toronto. Dr. Tobe was previously the director of the nephrology division at Sunnybrook Research Institute. His clinical activities focus on hemodialysis and patients with CKD and hypertension. His main research interests are implementation science for the dissemination of cardiovascular-focused clinical practice guidelines. Dr. Tobe was Chair of the Canadian Hypertension Education Program from 2005 to 2012 and is a Co-Chair of the Canadian Cardiovascular Harmonized National Guidelines Endeavor (C-CHANGE). He also chairs the diabetes subgroup of Hypertension Canada's clinical practice guidelines. Dr. Tobe serves on the Board of Directors of the American Society of Hypertension Specialists Program. Dr. Tobe has had continuous peer-reviewed funding for 25 years. Dr. Tobe has received many teaching awards and other career distinctions, has published over 150 peer-reviewed articles, and has led and participated in peer-reviewed, investigator-initiated, and multi-centered international research collaborations.

*Consultancy: AstraZeneca*

*Grant/research support: Bayer\**

*Speaker bureaus: AstraZeneca and Janssen*

*\*Monies paid to institution.*



**Charles R.V. Tomson, MA, BM, Bch, DM, FRCP**, received his undergraduate training at Cambridge and Oxford, UK, and underwent clinical training in Nottingham, Newcastle upon Tyne, and Leicester, UK, before taking up consultant posts at St Barts, London (1991–1993), Bristol (1993–2014), and Newcastle upon Tyne

(2014–2018). He has authored or coauthored 36 book chapters and over 250 journal articles on a wide range of topics including hypertension, CKD, and cardiovascular complications of kidney disease. His involvement in guideline development started with the third edition of the Renal Association Clinical Practice Guidelines. He was a member of the group that produced the KDIGO 2012 Management of Blood Pressure in CKD guideline. He was a Health Foundation Quality Improvement Fellow at the Institute for Healthcare Improvement in Boston from 2003 to 2004, a placement that led to a keen interest in the translation of evidence into reliable practice and in shared decision-making. He was Chair of the UK Renal Registry (2006–2010), president of the Renal Association (2010–2012), and is a current trustee of Kidney Research UK. He retired from clinical practice in 2018 but returned during the COVID-19 pandemic.

*Travel: Attendance at a London Hatter Institute meeting organized by The Lancet and University College London with arm's length funding from pharmaceutical companies.*

#### KDIGO Chairs



**Michel Jadoul, MD**, received his medical degree in 1983 at the Université Catholique de Louvain (UCLouvain) in Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as Chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc since 2003 and is currently a full clinical

professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include  $\beta$ 2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has coauthored over 260 scientific papers, most of them published in major nephrology journals. He is

currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS; 2001–present). In 2008, he received the international distinguished medal from the US National Kidney Foundation. He was previously a member of the KDIGO Executive Committee (2010–2015) and the ERA-EDTA Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

*Consultancy: Astellas\*, AstraZeneca\*, Merck Sharp & Dohme\*, Mundipharma\*, and Vifor Fresenius Medical Care Renal Pharma\**

*Expert testimony: Vifor Fresenius Medical Care Renal Pharma\**

*Grants / research support: Amgen\*, Janssen-Cilag\*, Otsuka\*, and Roche\**

*Speaker bureaus: Amgen\*, Menarini\*, Merck Sharp & Dohme\*, Mundipharma, and Vifor Fresenius Medical Care Renal Pharma\**

*Travel: Amgen\* and Sanofi\**

*\*Monies paid to institution.*



**Wolfgang C. Winkelmayer, MD, MPH, ScD**, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medicine in Houston, TX, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Austria, and later earned a Master of Public Health in healthcare management (1999) and a Doctor of

Science in health policy (2001) from Harvard University, Cambridge, MA, USA. He then spent 8 years on the faculty of Brigham and Women's Hospital and Harvard Medical School, where he established himself as a prolific investigator and leader in the discipline of comparative-effectiveness research as it pertains to patients with kidney disease. From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, CA, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, Texas. Dr. Winkelmayer has authored over 300 peer-reviewed publications, and he has a particular interest in medical publishing. He currently serves as associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He also volunteers his

time toward important initiatives of the American Society of Nephrology (e.g., Public Policy Board), and he joined KDIGO volunteer leadership as an executive committee member in 2015 and has served as its Co-Chair since 2016.

*Consultancy: Akebia, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Relypsa, and Vifor Fresenius Medical Care Renal Pharma*

#### Methods Chair



**Marcello Tonelli, MD, SM, MSc, FRCPC**, is senior associate dean (clinical research) at the Cumming School of Medicine in Calgary, Alberta, Canada. He is associate vice president (health research) at the University of Calgary. He received his medical degree from the University of Western Ontario, Canada, a Master of Science in epidemiology from Harvard University, Cambridge,

MA, USA, and a Master of Science in health policy from Imperial College London, UK. He is a nephrologist and professor at the University of Calgary.

Dr. Tonelli has served in the past as president of the Canadian Society of Nephrology, councilor of the ISN, and a member of the KDIGO Executive Committee. Dr. Tonelli is Chair emeritus of the Canadian Task Force for Preventive Health Care, a national panel of experts that makes recommendations about preventive health services to Canada's 36,000 family physicians.

A unique aspect of Dr. Tonelli's research program includes partnering with regional, provincial, and national decision makers to ensure that the findings will be used to produce rational health policy.

*Speaker bureaus: B. Braun\**

*\*Monies donated to charity.*

#### Evidence Review Team



**Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Director**, is an internationally recognized clinician and scientist and holds the position of vice president and executive dean of the College of Medicine & Public Health at Flinders University, Adelaide, South Australia. Professor Craig has made a significant contribution to the clinical research landscape in the prevention, identification, management, and treatment of CKD, particularly in relation to children and in indigenous communities.

He has led the formation of state, national, and international networks to conduct high-quality, relevant trials in children. He has been instrumental in the development and implementation of best-practice methods and guidelines

He has led the formation of state, national, and international networks to conduct high-quality, relevant trials in children. He has been instrumental in the development and implementation of best-practice methods and guidelines



relating to CKD in Australia and globally. Professor Craig's many current advisory roles include member of the National Health and Medical Research Council's (NHMRC) Health Translation Advisory Committee, the Pharmaceutical Benefits Advisory Committee, Medical Services Advisory Committee, and Commonwealth Department of Health Life Savings Drug Program.

He is a past member of the World Health Organization expert review panel for global strategy and plan of action on public health, innovation and intellectual property; a past chairman of the Steering Group of the Cochrane Collaboration; and a past member of the Expert Advisory Group for the Structural Review of NHMRC's Grant Program.

*Dr. Craig declared no competing interests.*

**Suetonia C. Palmer, MBChB, FRACP, PhD, Evidence Review Team Co-Director**, is an academic nephrologist at the University of Otago at Christchurch in New Zealand. She studied medicine at the University of Otago, graduating in 1995. She became a fellow of the Royal Australasian College of Physicians in Nephrology in 2005. She later completed a PhD in 2010 on the link between kidney function and heart health and a 2-year postdoctoral fellowship in Boston, MA, USA, at the Brigham and Women's Hospital.

Dr. Palmer began as an author with the Cochrane Renal Group in 2004 during her training to become a nephrologist. Through systematic reviews, she discovered a passion for understanding more about the amount and quality of evidence that are required to make good clinical decisions in nephrology. She is actively engaged in the conduct of systematic reviews of interventions (the treatments we use), prognosis (whether risk factors for disease link to important outcomes), and trial quality (how good is the evidence on which to base our decisions).

Dr. Palmer enjoys training others in systematic review and meta-analysis using an evidence-based approach to research. She has strong collaborative links with researchers in Italy, Australia, Europe, and North America with an increasing research output, including recent publications in key internal medicine and nephrology journals.

*Dr. Palmer declared no competing interests.*

**Giovanni F.M. Strippoli, MD, MPH, M Med (Clin Epi), PhD, Evidence Review Team Co-Director**, has made significant contributions to clinical research in CKD, with particular focus on prevention of kidney disease, and management of kidney failure, including hemodialysis, peritoneal dialysis, and kidney transplantation. He has contributed strongly to the development of policy in the area of kidney disease management through an international network designing and conducting epidemiologic studies in the field, including systematic reviews, RCTs, and cohort studies, among others. Professor Strippoli has been an active contributor in his positions as chairman, deputy chairman, and council in nephrology societies including the ISN and the

Italian Society of Nephrology, as well as editorial positions in nephrology and general medicine scientific journals.

*Dr. Strippoli declared no competing interests.*



**Martin Howell, PhD, Assistant Project Director**, is a senior research fellow in health economics in the Sydney School of Public Health (University of Sydney), NSW, Australia. Since 2009, Martin has been responsible for evidence review and synthesis and the development of over 20 clinical practice guidelines for the Kidney Health Australia—Caring

for Australasians with Renal Impairment (KHA-CARI) guidelines group. His research focuses on applied health economics, predominantly in the areas of assessment of preferences using discrete choice methods and economic evaluations. His PhD project involved the application of a type of choice experiment known as a Best Worst Scaling survey to elicit preferences of recipients of kidney transplants for outcomes after transplantation. This methodology has since been applied to address a diverse range of health-related issues. He is currently leading the economic evaluations of 9 active clinical trials. He is an author on 57 publications (first author on 10). These publications show the broad application of his research from clinical trials to translation of clinical evidence to clinical practice guidelines and patient-centered care.

*Dr. Howell declared no competing interests.*



**David J. Tunnicliffe, PhD, Evidence Review Project Team Leader and Project Manager**, is a research fellow at the University of Sydney, School of Public Health, and the Centre for Kidney Research at the Children's Hospital at Westmead, NSW, Australia. He was awarded his PhD in 2018 at the University of Sydney. David has a research

interest in meta-research and the utilization of living evidence in the management of CKD, and teaching epidemiology, which he performs through the Masters (Medicine) Clinical Epidemiology program, as a unit coordinator of introductions to systematic reviews.

As part of Cochrane Kidney and Transplant, David has served as the evidence review project team leader and project manager for the 2021 update of the KDIGO 2012 Clinical Practice Guideline for the Management of Blood Pressure in CKD, providing methodological expertise on evidence synthesis and guideline development. His role was key in coordinating the formation of key clinical questions to guide literature searching and leading data extraction, critical appraisal, meta-analysis, and evidence grading.

*Dr. Tunnicliffe declared no competing interests.*

**Fiona Russell, PhD, Cochrane Kidney and Transplant, Managing Editor**, has more than 20 years' experience at media organizations such as News Corp and Fairfax Media in a variety of editorial positions including reporter, sub-editor, deputy editor, and production editor. Two years as an information technology supervisor led to an ongoing technological change management role at both companies, developing new system procedures and workflows, and providing training solutions for new and existing staff.

During her editorial career, Dr. Russell also gained a bachelor's degree in journalism, international relations, and literary studies, a graduate degree in cognitive science, and a PhD in comparative cognition research. She has been the managing editor of *Cochrane Kidney and Transplant* since October 2015.

*Grants/grants pending: National Health and Medical Research Council of Australia*

**Gail Y. Higgins, BA, Grad Ed, Grad Dip LibSc, Information Specialist**, completed a bachelor's degree in arts, a graduate diploma in education from the University of Sydney, NSW, Australia, and a graduate diploma in Library Science from Kuring-gai College of Advanced Education. Following a number of years as a teacher-librarian, she changed tack and spent 3 years with the NSW TAFE Information Systems Division. After that, she joined the University of Sydney Library and worked as a pharmacy librarian and then as an internet training librarian. She has worked as an information specialist for the Cochrane Haematological Malignancies Group in Cologne, Germany, and the Cochrane Cancer Network in Oxford, UK. In 2007 and 2008, she completed a secondment with the World Health Organization in Geneva, Switzerland, on the International Clinical Trials Registry Platform (ICTRP) project.

*Ms. Higgins declared no competing interests.*

**Tess E. Cooper, MPH, MSc (Evidence-based Health Care), Research Associate**, has completed an MSc in evidence-based health care, a Master of Public Health, and a bachelor's degree in population health and marketing. Ms. Cooper is the in-house systematic reviewer for the Cochrane Kidney and Transplant Review Group, based at the University of Sydney, NSW, Australia. In addition, she works with several other Cochrane Review groups, including the Pain; Palliative and Supportive Care; Ear, Nose, and Throat (ENT); and Skin groups, based in the United Kingdom. She has research experience in evidence-based health care, long-term cohort studies, chronic disease prevention, and is a current PhD candidate researching kidney transplant patients.

*Grants/grants pending: Australian Government PhD scholarship*

**Nicole Evangelidis, MPH, MPhil, Research Associate**, is a public health researcher at the Centre for Kidney Research at the University of Sydney, NSW, Australia. She has experience in chronic disease prevention, patient-centered research, and the development of core outcome sets. She is interested in diet and lifestyle changes for the prevention of chronic disease. She undertook key aspects of the evidence review for the KDIGO guideline, including data extraction, synthesis, and preparation of evidence summaries.

*Ms. Evangelidis declared no competing interests.*

**Brydee Cashmore, MPH, Research Associate**, has a Master of Public Health from the University of Sydney, NSW, Australia, as well as a bachelor's degree in science, a double major in physiology and human nutrition, a graduate diploma in science in psychology, and a postgraduate diploma in science in human nutrition from Massey University, New Zealand. She is a researcher at the Centre for Kidney Research at the University of Sydney, where she undertakes evidence review and synthesis for Cochrane Kidney and Transplant and the KHA-CARI Guideline group. She was involved across all of the KDIGO Clinical Practice Guideline on the Management of Blood Pressure in CKD subtopics and undertook key aspects of the evidence review, including data extraction, evidence synthesis, and the writing and preparation of evidence summaries in MAGICapp.

*Ms. Cashmore declared no competing interests.*

**Rabia Khalid, MND, Research Associate**, graduated from the University of Sydney, NSW, Australia, in 2016 with a Master of Nutrition and Dietetics. Since then, she has been working as an accredited practicing dietitian in the community. In 2017, she started her additional role as a researcher at the Centre for Kidney Research, where her role has ranged from helping with guideline development to assisting with and coordinating clinical trials. Her passion lies in increasing the availability of evidence-based knowledge for the general public.

*Ms. Khalid declared no competing interests.*

**Claris Teng, BPsych (Hons), Research Associate**, is a PhD candidate at the University of Sydney, NSW, Australia. Her thesis title is "Perspectives and preferences of people with dementia and their caregivers about long-term care: establishing a person-centered framework for decision-making." As a research associate, Ms. Teng undertook key aspects of the evidence review for the KDIGO Clinical Practice Guideline on the Management of Blood Pressure in CKD, including data extraction, synthesis, and preparation of evidence summaries.

*Ms. Teng declared no competing interests.*

# Acknowledgments

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