KDIGO CLINICAL PRACTICE GUIDELINE ON THE MANAGEMENT OF BLOOD PRESSURE IN CHRONIC KIDNEY DISEASE

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PUBLIC REVIEW DRAFT

JANUARY 2020

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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**
Level 1 "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.
Level 2 "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
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
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.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				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
	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.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Creatinine	mg/dl	88.4	μmol/l

Note: Conventional unit x conversion factor = SI unit

ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	> 300	> 30	> 300	Severely increased**

ACR = albumin:creatinine ratio; AER = albumin excretion rate; CKD = chronic kidney disease
*Relative to young adult level
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [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 Table 1 in Chapter 1. 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 parts of the definition. The values are often inconsistent between clinics and providers performing the measurements. In additional, it does not bear 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 is not part of the definition.
Ambulatory blood pressure monitoring (ABPM)	Blood pressure obtained on a frequent intermittent basis (i.e., 15-30 minutes per 24 hours) 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 parts 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
ACEi	Angiotensin-converting enzyme inhibitor(s)
ACR	Albumin:creatinine ratio
AOBP	Automated office blood pressure
AKI	Acute kidney injury
ARB	Angiotensin II-receptor blocker
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
CV	Cardiovascular
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBPM	Home blood pressure monitoring
HF	Heart failure
HR	Hazard ratio
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major adverse cardiovascular events
MAP	Mean arterial pressure
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PCR	Protein:creatinine ratio
p.o.	Oral
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RR	Relative risk
SBP	Systolic blood pressure
SCr	Serum creatinine
SGLT2i	Sodium-glucose co-transporter 2 inhibitor(s)
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study Group
UK	United Kingdom
US	United States

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. 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.

Note: This draft version of the KDIGO Clinical Practice Guideline on Blood Pressure in Chronic Kidney Disease is *not final*. Please do not quote or reproduce any part of this document.

FOREWORD

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 two existing guidelines on the Management of Blood Pressure in CKD and Glomerulonephritis, respectively. In addition, KDIGO has convened a group of experts to develop guideline recommendations related to Diabetes Management in CKD.

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

The KDIGO Controversies Conference on Blood Pressure in CKD assembled a global panel of multidisciplinary clinical and scientific expertise to identify key issues relevant to the updating of the 2012 KDIGO BP guideline. The objective of this conference was to assess the current state of knowledge related to the optimal means for measuring BP; management of hypertension in CKD patients with and without diabetes (including older adults), as well as the pediatric and kidney transplant subpopulations. The 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 is now available for public review as well, and the Work Group will critically review the public input, and revise 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, 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 direct linkage of the evidence to the recommendation statement. In addition, he introduced a new concept to the format called Practice Points, which is a new form of guidance in addition to recommendations. Where 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, 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, rich in guidance, while still 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.

In summary, we are confident that this guideline will prove useful to clinicians around the world treating people with high blood pressure and kidney disease and 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 evidence and the recommendations themselves.

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	Recommendations will be provided when
• No systematic review was conducted	• Systematic review was conducted
• There is insufficient evidence	• Ample evidence is available
• Evidence was inconclusive (less evidence than required)	• Evidence shows a clear preference for one action over the alternatives
• The alternative option is illogical	• Consensus statements are supported with evidence and explicit discussion of the balance of benefits and harms, values and preferences will be necessary
• The guidance does not imply action for the physician	• Application of guidance requires explicit discussion of values and preferences or on resource
• Consensus statements providing guidance and guidance in the absence of evidence may consider benefits and harms but will not be explicitly discussed	• Guidance is always actionable
• Guidance does not require an explicit discussion of values and preferences or of resource considerations, although is implied that these were considered	• The guidance is more useful displayed as or requires additional explanation in text
• The guidance may be more useful as a table/figure/algorithm	

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.

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 should be 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:

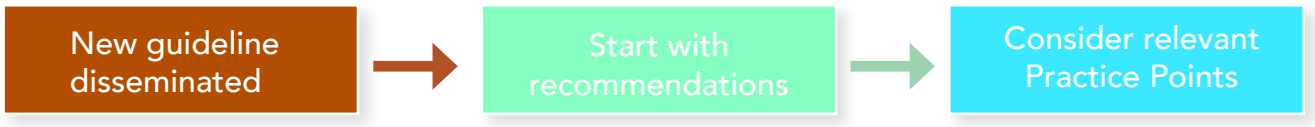
1. Balance of benefits and harms,
2. Quality of evidence,
3. Values and preferences,
4. Resource use and costs, and
5. Considerations for implementation.

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 quality 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.



What happened to the old “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 rigour (better link 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 that metformin be used as the first-line treatment for hyperglycemia in patients with T2D who have eGFR ≥ 30 ml/min/1.73m^2 (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
- The quality of evidence: to form this recommendation was based on clinical recommendations extracted from RCTs, systematic reviews performed in the general population, and outcomes from observational studies were considered.
- Resources and other costs: least expensive, widely available, affordable.
- Considerations for implementation: dose adjustments are required, no safety data for patients with eGFR < 30 ml/min/1.73m2 and must be switched off when this level is reached.

Practice Point 1. Treat kidney transplant recipients with T2D and eGFR ≥ 30 ml/min/1.73m^2 with metformin according to recommendations for patients with T2D and CKD

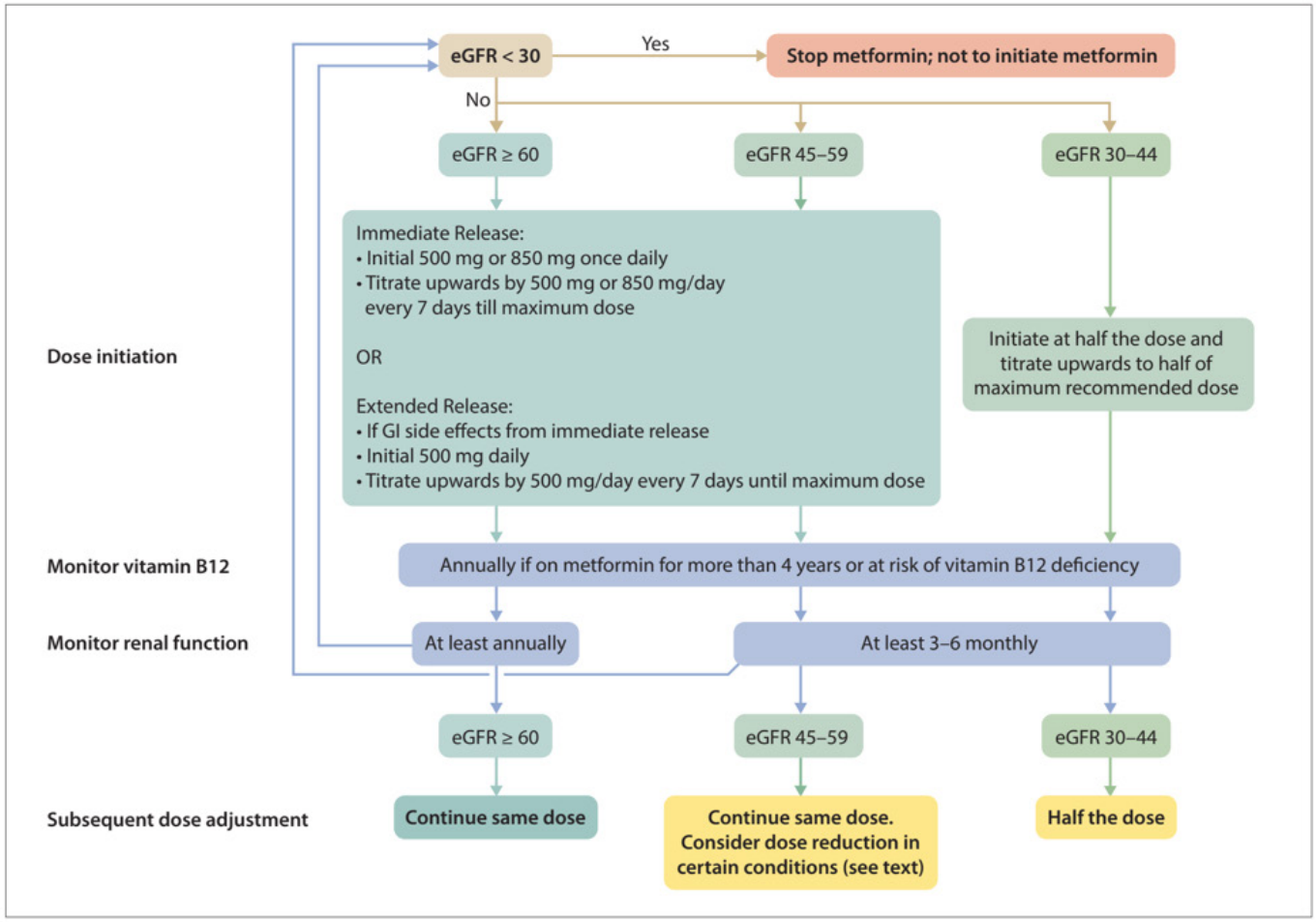
Why was this formatted as a Practice Point?

- Less robust data than recommendation; no systematic review was done.
- Few studies found, most data 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 should be based on the eGFR, same approach for CKD group.

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/1.73m²



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 done.
- An Algorithm was a clear visual presentation of the approach to monitoring; one can imagine trying to describe this algorithm in a series of statements, but the graphic is more useful to the reader.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guideline on the 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 treatment, antihypertensive therapies in non-dialysis CKD including special populations such as kidney transplant recipients and children. In addition, this guideline also 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 literature systematic review. Another aim is to propose research recommendations for areas where there are gaps in knowledge. The guideline targets to a broad audience of clinicians treating high blood pressure and CKD while being mindful of policy and resource implications. Development of this guideline update followed an explicit process of evidence review and appraisal. 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 also presented.

Keywords: chronic kidney disease; glomerular diseases; blood pressure; blood pressure measurement; blood pressure monitoring; lifestyle; blood pressure targets; antihypertensive agents; RAAS; ACEi; ARB; kidney transplant recipients; pediatrics; children; KDIGO; guideline; systematic review; evidence-based

INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

The original and only KDIGO Management of Blood Pressure (BP) in Chronic Kidney Disease (CKD) guideline in the non-dialysis CKD population was published in 2012. Since then, completion of the SPRINT trial and the revision of BP guidelines by many guideline task forces around the world have prompted the re-examination of KDIGO Guideline on BP. Upon invitation by the KDIGO Executive Committee, a Work Group consisting 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 constantly 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 non-dialysis CKD (CKD ND) population, 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 re-organized. The section on pharmacological agents in the original chapter on "Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients" has been significantly streamlined. The lifestyle chapter, Chapter 2, now focuses on dietary sodium restriction and physical activities. The use of renin-angiotensin-aldosterone inhibitors (RAASi) 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 combined into the current Chapter 3 which covers both subgroups, with the literature on diabetic and non-diabetic patients 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 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 two major areas that warrant particular attention in this guideline update because of new evidence and interests emerged since the publication of the original guideline. These two areas are (i) BP measurement (Chapter 1) and (ii) BP targets within the domain of BP management in CKD ND patients (Chapter 3). These two issues are closely related to each other as the systolic BP target of <120 mm Hg recommended in Chapter

3 is contingent upon proper BP measurement technique following recommended rigorous procedures.

This lower systolic BP target is largely based on its cardioprotective, survival, and potential cognitive benefits. There are no new data supporting the kidney-protective benefits of targeting systolic BP <120 mm Hg. The overall evidence for kidney protection at this low systolic BP level is almost non-existent, but 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 systolic BP 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, those with advanced CKD (G4 and G5), those with significant proteinuria, those with very low diastolic blood pressure, those at extreme ages (younger or older), and those with "white-coat"hypertension. As such, randomized trials 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 ND, the target is SBP <120 mm Hg. For kidney transplant recipients (Chapter 4), the target SBP is <130 mm Hg and target diastolic BP is <80 mm Hg. For children with CKD (Chapter 5), a mean arterial pressure (MAP) less than or equal to the 50th percentile for age, sex, and height is the primary target.

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

The Co-Chairs would like to recognize all the efforts from 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 CKD and high blood pressure and we hope this updated guideline will succeed in doing so for the global nephrology community.

Alfred K. Cheung, MD
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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 patients group uner consideration. For most patients with CKD ND, the target is SBP <120 mm Hg. For kidney transplant recipients (Chapter 4), the target SBP remains <130 mm Hg and target diastolic BP is <80 mm Hg. For children with CKD (Chapter 5), mean arterial pressure (MAP) is the primary target. Since these targets vary according to patient group, we have avoided the term 'hypertension' when referring to treatment decisions, as the term "hypertension" requires a single numerical definition

CHAPTER 1. BLOOD PRESSURE MEASUREMENT

Recommendation 1.1. We recommend standardized office BP in preference to routine office BP for the diagnosis and 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.

Practice Point 1.2. Automated office BP (AOBP) 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 be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the diagnosis and management of high BP *(2B)*.

CHAPTER 2. LIFESTYLE TREATMENT FOR LOWERING BLOOD PRESSURE IN NON-DIALYSIS CKD PATIENTS

2.1. Sodium intake

Recommendation 2.1.1. We suggest targeting salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) among CKD patients with high BP *(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 DASH-type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism because of the potential for hyperkalemia.

2.2. Physical activity

Recommendation 2.2.1. We suggest that patients with high BP and CKD 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 NON-DIALYSIS CKD PATIENTS WITH AND WITHOUT DIABETES

3.1. Blood pressure targets

Recommendation 3.1.1. We suggest that adults with CKD and high BP be treated with a target systolic blood pressure (SBP) of less than 120 mm Hg 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 due to autonomic neuropathy.

3.2. Treatment with RAAS inhibitors (RAASi) and other antihypertensives

Recommendation 3.2.1. We suggest starting RAASi (ACEi or ARB) for people with concomitant CKD without diabetes, albuminuria (≥3 mg/mmol, G1-G4, A2, A3), and high BP *(2C)*.

Recommendation 3.2.2. We recommend RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, albuminuria (≥3 mg/mmol), normal or low GFR (G1-G4, A2, A3), and high BP *(1B)*.

Practice Point 3.2.1. RAASi (ACEi or ARB) should be administered using maximally recommended doses to achieve the benefits described because the proven benefits were achieved in trials using this dose.

Recommendation 3.2.3. We suggest RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, eGFR <60 ml/min/1.73 m^2, normal albuminuria, and high BP *(2C)*.

Practice Point 3.2.2. Monitor for changes in blood pressure, serum creatinine, and serum potassium within two to four weeks of initiation or increase in the dose of an ACEi or ARB.

Practice Point 3.2.3. Reduce the dose or discontinue ACEi or ARB in the setting of symptomatic hypotension, uncontrolled hyperkalemia despite medical treatment, or while preparing for imminent kidney replacement therapy.

Practice Point 3.2.4. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

3.3. Role of dual therapy with RAAS inhibition

Recommendation 3.3.1. We recommend not treating with any combination of ACEi, ARB, and direct renin inhibitor 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 that is <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, BP should be treated to lower 24-hour mean arterial pressure (MAP) by ABPM to less than or equal to the 50th percentile for age, sex, and height *(2C)*.

Practice Point 5.1. We suggest monitoring BP once a year with ABPM, and monitoring every three to six months with standardized auscultatory office BP.

Practice Point 5.2. 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 risk of hyperkalemia and have adverse fetal risks for pregnant women.

CHAPTER 1. BLOOD PRESSURE MEASUREMENT

Background

This chapter makes recommendations on how to measure blood pressure (BP) among adults aged ≥18 years with chronic kidney disease (CKD).

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

Throughout this chapter, standardized office BP refers to measurements obtained according to recommended preparation procedures (Table 1). In contrast, routine office BP refers to measurements obtained without following these recommended preparation procedures.

*Table 1. Checklist for standardized office blood pressure measurement**

1 Properly prepare the patient	1 Have the patient relax, sitting in a chair (feet on floor, back supported) for > 5 min 2 The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement 3 Ensure patient has emptied his/her bladder 4 Neither the patient nor the observer should talk during the rest period or during the measurement 5 Remove all clothing covering the location of cuff placement 6 Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria
2 Use proper technique for BP measurements	1 Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically 2 Support the patient's arm (eg, resting on a desk) 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) 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 5 Either the stethoscope diaphragm or bell may be used for auscultatory readings
3 Take the proper measurements needed for diagnosis and treatment of elevated BP	1 At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings 2 Separate repeated measurements by 1–2 min 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 4 For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds
4 Properly document accurate BP readings	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 2 Note the time of most recent BP medication taken before measurements
5 Average the readings	Use an average of ≥ 2 readings obtained on ≥ 2 occasions to estimate the individual's level of BP
6 Provide BP readings to patient	Provide patients with the SBP/DBP readings

*From Whelton *et al*.; 2017 ACC/AHA High Blood Pressure Guideline
BP = blood pressure, DBP = diastolic blood pressure; SBP = systolic blood pressure

Once the appropriate preparations have been made, standardized office BP can be measured preferably by an automated oscillometric device (see Practice Point 1.1.). It can also be measured manually, after the appropriate preparations, using an auscultatory method with either a mercury or aneroid sphygmomanometer. However, aneroid devices require frequent calibration: every six months for wall-mounted and every two to four weeks for handheld devices. Oscillometric devices generally require less frequent calibration (e.g., every 1 to 2 years, based on manufacturers' recommendations) than aneroid devices.[1]

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.

Recommendation 1.1. We recommend standardized office BP in preference to routine office BP for the diagnosis and 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 to harms

This recommendation relies heavily on the importance of standardized office BP measurement protocols that are consistent with large clinical trials with clinically important outcomes that have been used to define BP targets. Standardized office BP measurements allow for extrapolation of the clinical trial findings to clinical practice, and avoids overtreatment or undertreatment of high BP if non-standardized measurements are used. The negative aspects of standardized office BP measurement include the increased burden on patient, provider, staff time, and clinic space.

Quality of evidence

There is moderate quality evidence that routine office BP is generally higher than standardized office BP, regardless of whether manual or oscillometric devices are used. There

is strong evidence that the relationship between routine office BP and standardized office BP is highly variable among individuals.

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 randomized controlled trials (RCTs) far outweighs the additional burden and costs for providers, staff and patients.

Routine office BP measurements are generally higher than standardized office BP measurements.[2, 3] 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 the minority of persons where 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.[2, 3] It is therefore not possible to convert a routine office BP into a standardized office BP using a correction factor in an individual person. 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 will take longer to perform than routine office BP, given the need to follow proper preparatory procedures (Table 1). 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 allow 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 completed.

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 stage.

Rationale

This chapter is an addition to the 2012 KDIGO BP guideline. This recommendation places a relatively higher value on consistency with BP measurement methods used in prior

BP-lowering trials 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),[4, 5] European Society of Cardiology (ESC)[6]).

Practice Point 1.1. An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement.

Oscillometric BP devices may be preferred over manual BP devices, as the former minimizes potential sources of inaccuracies in BP measurement that can occur with manual BP measurement such as hearing impairment, improper deflation rate, or terminal-digit bias.[7]

RCTs and prospective cohort studies used standardized office BP measured with either oscillometric (in newer studies) or manual devices (in older studies) (Table 2). 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 two types of devices (Table S4[8-10]). 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.

*Table 2. Blood pressure measurement method and device for selected RCTs and prospective observational studies**

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

* From Drawz and Ix, JASN 2017 - adapted with modifications

† ONTARGET was published in 2008 (NEJM 2008, 358: 1547-1559). The BP measurement approach used in the trial was subsequently published in the 2012 article cited above

‡ de Galan *et al*., JASN 2009
§ Peralta *et al*., Circulation 2016
CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; SCr = serum creatinine; T2D = Type 2 diabetes

The negative aspects of oscillometric BP devices are the potentially higher cost of the device than manual device, requirement for 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.[11-13] Providers working in areas where oscillometric BP devices are not available may use a manual BP device but proper calibration of latter BP devices is required as noted in the Background above.

Regardless of the type of BP device used, proper preparation and BP measurement techniques (Table 1) are paramount.

Practice Point 1.2. Automated office BP (AOBP) may be the preferred method of standardized office BP measurement.

Proper preparation prior to BP measurement is rarely followed in clinical practice. In the opinion of the Work Group, AOBP may increase the likelihood of adherence to proper preparation, 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. Notably, AOBP was the BP measurement method used in several large trials, including SPRINT, ONTARGET, and ACCORD (Table 2).

The AOBP devices also allow for unattended BP measurements, which discourages talking during the BP measurement process. Unattended BP measurement may also reduce the likelihood of "white-coat" hypertension, although well-conducted studies have not shown large differences in attended versus unattended standardized office BP measurements.[14] From a practical standpoint, unattended BP measurement may have the added advantage of 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 estimate 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. Although oscillometric devices

may be less accurate for estimating diastolic BP (DBP), the population with atrial fibrillation is, on average, older and the emphasis in older adults has been on SBP.[15]

Recommendation 1.2. We suggest that out-of-office BP measurements be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the diagnosis and 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 1). In the judgment of the Work Group, the potential benefits of additional information obtained from out-of-office BP measurements outweighs the additional costs and increased patient burden that making these measurements impose. We suggest using an initial ABPM to supplement office BP and HBPM for ongoing management of BP. 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, one week of daily HBPM prior to each office visit may be useful to complement standardized office BP for clinical management decisions.

Figure 1. Blood pressure patterns informed by out-of-office blood pressure measurements in addition to standardized office blood pressure measurement

This is a weak recommendation since there are no large outcome trials comparing the effects of lower versus higher BP goals on clinical outcomes in adults used out-of-office measurements to guide the BP intervention. 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 "white-coat" effect (Figure 1). Further, observational studies indicate a stronger association of out-of-office BP measurements with cardiovascular (CV) and kidney outcomes than office BP measurements in the general population and CKD.[16-18]

Masked hypertension and masked uncontrolled hypertension are present among 9% to 30% of adults without high BP based on office measurements, and is associated with higher risk for cardiovascular disease (CVD) and kidney outcomes compared with sustained normotension. "White-coat" hypertension and "white-coat" effect are present among 15% to 30% of adults with high BP based on office measurements. In a recent meta-analysis, "white-coat" hypertension was associated with a modest increased risk for CVD, compared to sustained normotension.[16] However, this risk was substantially lower than the risk for participants with sustained hypertension.[18] Additionally, "white-coat" effect was not associated with increased risk for CVD when compared to people with sustained normotension.[16]

The prevalence of "white-coat" hypertension, masked hypertension, "white-coat" effect, and masked uncontrolled hypertension is each high among patients with CKD.[19-21] Identification of "white-coat" hypertension and masked hypertension for patients not taking antihypertensive medication and "white-coat" effect and masked uncontrolled hypertension for patients taking antihypertensive medication may have potential treatment implications (see Rationale). 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 "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 the evidence

There are systematic reviews in the general population showing out-of-office BP is associated with CVD risk independent of office BP. Although there are no systematic reviews in populations of 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. Therefore, there is no reason to suspect that findings in the general population would not also apply to patients with CKD. The systematic reviews and meta-analyses of general population studies were rated as moderate quality evidence because of the inherent limitations of observational studies but upgraded from low because of the strength of associations of out-of-office BP measurements with critically important outcomes.

Values and preferences

This recommendation places a relatively higher value on providing complementary information to standardized office BP that may affect clinical decisions. The recommendation places a relatively lower value on potential lack of device availability, costs, and patient burden. In the opinion of the Work Group, most but not all patients and providers will value the information provided by ABPM and HBPM. The Work Group recognizes that some patients will find ABPM and HBPM to be uncomfortable and 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 diagnosis of high BP in the general population.[22, 23] In contrast, the cost-effectiveness of HBPM for diagnosis of high BP is unclear.[22, 23] Persons with limited financial resources or 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 stage.

Rationale

This recommendation places a high value on informing an individual's overall BP profile and identifying persons with high CVD risks related to high BP. ABPM is cost-effective and cost-saving for diagnosis of high BP across all age groups and in both men and women. 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, "white-coat" effect, and masked uncontrolled hypertension has potential treatment implications. Antihypertensive medication initiation and intensification may be considered for patients with masked hypertension and masked uncontrolled hypertension, respectively, while those with "white-coat" hypertension and "white-coat" effect may choose to defer initiation and defer intensification of antihypertensive medication, respectively. 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.

RESEARCH RECOMMENDATIONS

There are several areas in which more research is needed 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 shorter interval period 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, "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 CVD.
- Assess the cost-effectiveness of ABPM and HBPM, separately, for identifying "white-coat" hypertension, masked hypertension, "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 "white-coat" effect, treatment of masked hypertension, and intensifying treatment for masked uncontrolled hypertension.

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CHAPTER 2. LIFESTYLE TREATMENT FOR LOWERING BLOOD PRESSURE IN NON-DIALYSIS CKD PATIENTS

2.1. Sodium intake

Recommendation 2.1.1. We suggest targeting salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) among CKD patients with high BP *(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 CVD endpoints in CKD patients. The recommendation is weak because of the low quality evidence supporting the benefits of low sodium intake specifically in hypertensive CKD population; yet, many well-informed patients would agree to follow the guidance.

Key information

Balance of benefits and harms

In most populations worldwide, estimated sodium intake is much higher than the proposed target of sodium intake <90 mmol (<2 g) per day for the general population. Recent meta-analyses of RCTs in non-CKD populations demonstrate a graded benefit in both BP and CVD 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.[24] Indeed, achieved mean sodium intake typically was in the 3-3.5 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.

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 where 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. Nonetheless, although there is

still controversy about the risk:benefit ratio of potassium intake and clinical outcomes, observational studies often found that a higher potassium intake may be associated with a lower risk for death, CV disease, and death. However, at advanced stages of CKD, a high potassium intake may be associated with higher risk.[25-27] 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 the safety and efficacy of their use in CKD become available. (see Practice Point 2.1.2.).

Quality of the evidence

The Cochrane systematic reviews updated for this guideline found moderate quality evidence demonstrating that dietary sodium reduction results in short-term reductions in BP in CKD populations.[28, 29] This was evident for both SBP and DBP in non-diabetic CKD (moderate) (Table S5[30-39]), populations with Type 1 diabetes (T1D) and CKD (Table S6[40-44]), Type 2 diabetes (T2D) and CKD (low) (Table S7[45-50]), and populations with diabetes and severely increased albuminuria (low) (Table S8 and S9[44, 47, 49, 50]). 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.[24]

There is also moderate strength of evidence from systematic reviews that sodium reduction reduces CVD in the general population.[24] The systematic review conducted for this guideline found no RCT data evaluating the effects of dietary sodium reduction on clinical outcomes including kidney failure (ESKD), CVD, 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 II receptor blockers (ARB), and the kidney and CV benefits of these medications may be enhanced if accompanied by a low-sodium diet.[51]

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 suggesting 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 CVD 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 <90 mmol of sodium per day; thus, effects on important clinical outcomes are uncertain, but 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 are often 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 recognized that, while feasible, following a low sodium diet is challenging in many Western food environments. However, this recommendation may benefit not only individual patients, but may also influence public-health interventions and policy makers to consider targeting reductions of sodium in the food supply. While 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 from the general population. While 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 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.[24] CKD populations also have high risk of CVD and may therefore have a greater absolute risk reduction of such events with dietary sodium reduction, if the relative benefits in the general population is indeed applicable to CKD. Finally, ARBs are commonly used in CKD patients, and *post hoc* analyses of RCTs demonstrate that a low sodium intake may enhance the effects these medications on kidney and CV outcomes.[51]

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 targets that modify the <90 mmol (<2 g) daily target for body weight in children would be reasonable.[52]

The Work Group considered the specific target of sodium intake of <90 mmol (<2 g) 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.[24, 52, 53] Therefore, this guideline was created in the absence of data suggesting superiority or inferiority of other targets in CKD populations, and for concordance across guidelines from various organizations that might facilitate policy decisions, Work Group members agree a target <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 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-pharmacological intervention to lower BP in CKD populations. Relatively lower value was placed on the challenges in following a low sodium diet in many current Western food environment. This recommendation is weak 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.

While there is a lack of RCT data on use of potassium-containing salt substitutes in CKD populations, Work Group members were concerned about the risk of hyperkalemia that these salt substitutes may pose to persons with advanced CKD, as well as observational data suggesting higher dietary potassium intake may be associated with increased risk of CV and kidney outcomes in CKD populations,[26, 27] although there is evidence to the contrary in people at high CV risk.[54, 55] Therefore, the 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 DASH-type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism because of the potential for hyperkalemia.

2.2. Physical activity

Recommendation 2.2.1. We suggest that patients with high BP and CKD 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 improves quality of life, lowers BP, 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 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 the 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 recognized a higher prevalence of comorbidity and frailty in CKD compared to the general population, and was 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 the 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 one study conducted over 12 months that physical activity may improve SBP and DBP, and low quality evidence from the same study that physical activity may improve eGFR over 12 months.[56] These findings, however, were inconsistent with other studies suggesting little or no differences. The updated Cochrane systematic review finds that physical activity decreases weight and improves the mental components of quality of life in CKD.[57] Evaluating 282 patients from seven studies, the systematic review found very low quality evidence evaluating the association of physical activity with increased adverse events, an important topic given the high burden of comorbidity and frailty in CKD populations (Table S10[56, 58-64]). Observational data also show a dose-response relationship between greater levels of physical activity and lower risk of mortality in CKD patients.[65] Thus, the Work Group was uncertain whether physical activity increases or decreases adverse events. 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 to 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 non-pharmacological 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 CVD 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 available data on critical outcomes were not available, and those for other health benefits and risks were 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 the 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 was 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 and 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 is 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 risks and benefits of physical activity interventions. The available data are of low quality or very low quality evidence. Nonetheless, the available data from short-term studies suggest that physical activity interventions may lower BP, and appears to 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 CVD 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 CVD 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 evidence currently available to directly support it.

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)[66] and the recently released AHA/ACC lifestyle guidelines for primary prevention of CVD.[5] 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 Management of Diabetes and CKD guideline Work Group. 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 the individual patient's comorbidities and exercise tolerance allow it. For others, the degree of physical activity should be individualized according to their cognitive, cardiovascular, and physical tolerance.

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.

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 a heart healthy diet pattern have been demonstrated in randomized trials to lower BP in the general population. These lifestyle interventions may 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 blood pressure 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 endpoints of critical importance for CKD populations.
- Conduct RCTs evaluating sodium reduction interventions for clinical endpoints including kidney failure (ESKD), CVD, and mortality.
- There are inconsistencies in the relationship of dietary sodium intake with health outcomes in persons with diabetes.[26, 27, 67] Additional research is required to investigate the consistency of effects of dietary sodium changes on health benefits and harms across different causes and severity of CKD.
- It is unknown if there is a minimum dietary sodium level in CKD below which health risks are increased; yet, 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 urine specimens,[56] and potential increased risk of adverse health outcomes at the low-sodium intake range when assessed by this method.[68] Additional research is required both in 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 sodium bicarbonate supplementation versus placebo have not observed changes in BP.[69, 70] These findings raise the possibility that the anion(s) 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(s).
- 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, but not all, observational data in CKD populations demonstrate that higher potassium intake is associated with higher risk of CKD progression and CVD. 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.[71] Whether results are similar 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 may have the greatest or least BP benefit from physical activity interventions, and also those that may be at greater risk for harm. Identification of these factors and algorithms to tailor physical activity intensity and supervision to different CKD patients are 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 NON-DIALYSIS CKD PATIENTS WITH AND WITHOUT DIABETES

3.1. Blood pressure targets

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

This recommendation assumes that standardized office BP measurement has been taken according to Recommendation 1.1. The recommendation is weak because adjusting BP-lowering therapy to achieve this target SBP causes potential benefits and harms that may vary with co-morbidities, severity of CKD, existing treatment burden, and the presence of "white-coat" or masked hypertension. The statement is also weak because it is based primarily on a (prespecified) subgroup from one RCT, albeit a very high-quality trial. 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

There is evidence that targeting SBP to <120 mm Hg, when measured under standardized conditions, causes reductions in CV events and all-cause mortality in CKD (Table S11[72-74]). In most patients, 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 patients would weigh these benefits and harms is lacking. These benefits extend to patients with and without CKD. Still, the certainty that the benefits outweighs the harms becomes less with the following scenarios:

- CKD G4 and G5: With lower GFR, there is less certainty around the benefit of lower BP target and potential risk of harm.
- Diabetes: The benefits of intensive BP-lowering are less certain among patients with concomitant diabetes and CKD.
- Individuals with SBP 120-129 mm Hg: Observational data suggest that individuals with SBP 120-129 mm Hg are at higher CV risk than those with SBP <120 mm Hg.[75] Lowering the SBP from 120 to 129 mm Hg to <120 mm Hg may therefore be beneficial. 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 pharmacological or non-pharmacological means is tentative.
- Patients with very low baseline diastolic BP (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.

- Older age: The ratio of benefits to harms of intensive BP reduction in people at the upper spectrum of age (e.g., >85 years old) are less certain.
- 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 very low absolute risks of CV disease and all-cause death, are less certain. This includes younger patients with primary glomerulonephritis, as the evidence is less certain in this population.
- "White coat" hypertension: If office BP, even when measured under standardized conditions, is substantially higher than daytime ambulatory or home BP, the risks of additional BP-lowering treatment to achieve office BP <120 mm Hg are likely to be higher with less certainty of benefits.

The importance of standardized BP measurement when applying this guideline cannot be overemphasized. Routine, non-standardized office BP measurements often overestimate BP, compared to measurements under standardized conditions (see Chapter 1). Importantly, the extent to which routine measurements overestimate 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.

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,[76] the African American Study of Kidney Disease and Hypertension (AASK) trial,[77] and the Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) trial,[78] 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,[79] the Secondary Prevention of Small Subcortical Strokes (SPS3) trial,[80] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[73] and the Systolic Blood Pressure Intervention Trial (SPRINT)[74] used CV events as the primary outcomes and had relatively few kidney events. 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 CVD, and with no difference in proportional risk reductions across groups defined according to higher or lower baseline SBP.[81-85] The meta-analysis of 21 RCTs by Xie *et al*.[85] concluded that the absolute benefits of SBP-lowering were greater and the numbers-to-treat smaller in trials where all enrolled patients had vascular disease, diabetes, or kidney disease; however, it did not report on the benefits in patients with diabetes and/or kidney disease without co-existing vascular disease. 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-reduction 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 the elderly and to those with frailty.[72, 86] The benefits of targeting SBP <120 mm Hg in SPRINT, in a pre-specified analysis, included a significant reduction in the combined endpoint of probable dementia and mild cognitive impairment, with no interaction with baseline CKD.[87] Secondary analyses further suggest that beneficial effect of intensive BP-lowering on the incidence of mild cognitive impairment *per se* may extend to those with CKD[86] and those who were 80 years or older.[88]

A recent meta-analysis of 74 RCTs with broader inclusion criteria than those discussed above[82, 84, 85] concluded that the effect of BP-lowering differed by baseline BP with no clear effect on death or CVD in participants with no prior coronary heart disease (CHD) and SBP <140 mm Hg at baseline.[89] This finding has been used by some guideline groups, such as the UK National Institute for Health and Care Excellence (NICE), 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 in which BP measurement technique was less precisely specified reduces the reliability of the conclusions.

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.[90] 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 among patients with CKD than in those without CKD.[84]

SPRINT intentionally included a CKD subgroup *a priori* and examined SBP target of <120 mm Hg, as recommended in the present guideline, versus <140 mm Hg. In the primary analysis of the entire cohort, SPRINT demonstrated benefits for the primary CV outcome [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/1.73 m^2 with urine protein <1 g/g.[72, 74] Indeed, in the subgroup with CKD, the CV benefit missed significance while the mortality benefit was significant. That said, SPRINT was not powered for subgroup analyses, even more so since it ended early because of the substantial CVD and mortality benefit. Nevertheless, it is the largest trial testing two BP targets in CKD with approximately 2600 CKD patients. Three other trials comparing different BP targets generated far too few CV events or death outcomes (MDRD, AASK, REIN2). A meta-analysis by Malhotra *et al*. examining death as outcome exclusively in the CKD subgroups of the large hypertension treatment RCTs also found a benefit of lower target BP.[91]

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 lower treatment target ≤140/90 mm Hg.[92] 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. 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 (≥65 years) and provided long-term CV and safety outcomes.[93] SPRINT met 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 were 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 CVD 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 CVD outcome or all-cause death [HR 0.66 (95% CI 0.49, 0.90)].[74] 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

old 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)].[88]

Adults with diabetes and CKD

Among patients with concomitant diabetes and CKD, the benefits of intensive BP-lowering are less certain than those with non-diabetic CKD. All previous studies in diabetes with and without CKD have favored more instead of less intensive BP reduction (UKPDS-38,[94] SHEP,[79] Syst-Eur,[95] ABCD,[96] HOT[97]). 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.[84] 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 with respect to the presence or absence of diabetes.[91] 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.[98]

Two major caveats should be noted regarding these meta-analyses in diabetes. First, these meta-analyses differ substantially in their respective inclusion criteria. Second, none of the trials conducted prior to ACCORD and SPRINT examined SBP target as low as <120 mm Hg.

The ACCORD trial that enrolled exclusively diabetic patients did not show a difference in the pre-specified primary endpoint of composite CV events between the intensive SBP target (<120 mm Hg) and standard SBP target (<140 mm Hg), but did demonstrate a significant reduction in stroke [HR 0.59 (95% CI 0.39, 0.89)], a pre-specified secondary outcome, with intensive SBP-lowering.[73] However, ACCORD included few patients with CKD, since patients with serum creatinine (SCr) >1.5 mg/dl (132 μmol/l) were excluded and those with CKD were mostly proteinuric with well-preserved eGFR.[99] 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 of CKD with the benefit of intensive BP-lowering on the reduction in stroke risk.

In contrast to ACCORD, SPRINT included a substantial number of participants with CKD. Although SPRINT specifically excluded patients with diabetes, 42% of the cohort had prediabetes, defined as baseline fasting serum glucose >100 mg/dl, at baseline. A *post hoc* analysis of SPRINT comparing participants with and without pre-diabetes found that the CV

and survival benefits of intensive SBP reduction (<120 mm Hg) were similar in the two subgroups.[100]

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 benefits of intensive BP-lowering therapy in the presence or absence of diabetes.[101] ACCORD was not only a BP trial and 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 statin. The trial of glycemic control was terminated early because of higher CV and all-cause mortality with intensive glycemic control.[73] These adverse effects of intensive glycemic control were also demonstrated in the CKD subgroup of ACCORD.[99] The ACCORD BP trial reported no statistical interaction between glycemic control and BP control on pre-specified primary and secondary CV outcomes. However, a more detailed combined analysis of data from ACCORD and SPRINT found that the 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.[102, 103] 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.[102] 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.[104]

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/1.73 m^2 who were not assigned to intensive glycemic control.[105] Collectively, these aforementioned *post hoc* analyses support the notion that intensive BP control improves clinical outcomes even in diabetic CKD patients, but glycemic control modulates the effects of intensive BP control on CV outcomes.

Low diastolic blood pressure

Numerous observational studies, including those that examine data from RCTs in a *post hoc* observational manner, have suggested a J-shaped curve with very low DBPs being associated with an increased risk of CV events, particularly MI among patients with pre-existing coronary artery disease. The validity of these observations is supported by biological plausibility, since low DBP in the setting of coronary stenosis could lead to impaired subendocardial blood flow during diastole. However, this association is heavily confounded, since 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 quartile at baseline with a mean DBP of 61 ± 5 mm Hg.[106] 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-aldosterone system (RAAS) and sodium-glucose cotransporter-2 (SGLT-2) 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 auto-regulation[107].
ii. Urinary excretion of various tubular biomarkers during intensive SBP treatment in SPRINT was not indicative of tubular damage.[108, 109]
iii. Albuminuria 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.[110]

Nonetheless, the overall rate of decline of eGFR was higher rather than lower on intensive treatment in SPRINT in both CKD[72] and non-CKD subgroups,[111] ACCORD,[73]and SPS3.[112] In both ACCORD and SPRINT, participants assigned to intensive BP target also developed more incident CKD on follow-up than standard BP target.[111, 113] There was no difference in the rate of doubling of SCr 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 six months was small (0.47 vs. 0.32 ml/min/1.73 m^2/year in the intensive and standard arms, respectively). If this slope persisted long-term, it would take 20 years to cause a 3 ml/min/1.73 m^2 difference in eGFR between intensive and standard SBP treatment. Taking both 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,[76] AASK,[114] and REIN-2.[78] During the trial phase while 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), rather than

SBP or DBP. The lower target was a MAP of <92 mm Hg (equivalent to 125/75 mm Hg, 140/68 mm Hg, 160/58 mm Hg or many other combinations of SBPs and DBPs), while the higher target was a MAP of <107 mm Hg (equivalent to 140/90 mm Hg, 125/98 mm Hg, or many other combinations of SBPs and DBPs). Further, the MAP targets varied in MDRD, depending on the age of the patients.[115]

A meta-analysis in 2011, conducted by the ERT of the KDIGO 2012 guideline on BP found only these three studies (MDRD, AASK, and REIN-2) that were pertinent to the discussion of whether a lower BP target reduced the risk of progression to ESKD in the presence of proteinuria. They concluded that the evidence was inconclusive.[116] Similarly, the current ERT review found no effect modification according the presence of proteinuria (Table S12[76-78, 114, 117]). 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)[76, 118] and long-term post-treatment follow-up from MDRD[117] and AASK.[114]. 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 SCr and >50% reduction in eGFR or ESKD), with effect modification by baseline proteinuria.[119] Intensive BP control reduced the risk of kidney failure only among those with baseline proteinuria (defined as protein:creatinine ratio (PCR) >0.22 mg/mg). The MDRD and AASK studies were major contributors of this evidence base. However, there was a concern about risk of bias in these trials partly due to a lack of independent end-point adjudication.

The REIN-2 study compared a higher DBP target of <90 mm Hg with a lower target of <130/80 mm Hg by adding felodipine to baseline ramipril therapy in patients with non-diabetic proteinuric CKD.[78] REIN-2 found no benefit of intensified BP control. 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 (59/2362) and standard (58/2371) SBP groups. SPRINT excluded patients with proteinuria >1 g/d and baseline median albumin:creatinine ratio (ACR) was only 13 mg/g in the CKD subgroup. ESKD events were rare in SPRINT with a total of only 16/9361. No reliable conclusions can therefore be reached on the effects of SBP target <120 mm Hg on progression to kidney failure in patients with CKD from ACCORD or SPRINT (Table S11[72-74]).

Previous guidelines, including the KDIGO 2012 BP guideline, recommended more aggressive BP-lowering for patients with albuminuria than those without albuminuria.[120] These

recommendations were based largely on the subgroup findings of the MDRD,[76] AASK[77] as described above and, in the pediatric population, the ESCAPE trial[121] (see Chapter 5). 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 five RCTs examining the effects of intensive versus less intensive BP control on mortality in patients with CKD without diabetes (Table S13[72, 74, 76, 78, 114, 117, 122]). Over a mean follow-up of 3.23 years of the 9351 participants in these five 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, 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.[123, 124] The mortality rates were low in these studies, and the conclusions can only be interpreted as hypothesis-generating.

When studies in CKD patients without diabetes are combined with CKD patients with diabetes, the effect of intensive BP-lowering on all-cause mortality was attenuated. In eight studies with 11,411 participants and a mean of three years follow-up, intensive BP targets compared with higher BP targets resulted in 10 fewer deaths per 1000 patients, but the 95% CI indicated 21 fewer to 2 more deaths per 1000 (Table S13[72, 73, 76-78, 96, 114, 117, 122, 125-127]).

A recent meta-analysis of 18 trials comprising 15,294 patients with CKD (defined as an eGFR <60 ml/min/1.73 m^2) 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.[91] This meta-analysis included RCTs that compared a range of target BPs, but also included trials comparing antihypertensive agents with placebo or no treatment.

Evidence of the effects of SBP target of <120 mm Hg versus <140 mm Hg in patients with CKD without diabetes is available only from SPRINT.[72] There were 53 deaths per 1000 participants in the standard BP control arm and 39 deaths per 1000 participants in the intensive BP control arm, resulting in a statistically significant difference of 14 fewer per 1000 participants (95% CI 24, 1 fewer deaths per 1000 participants) (Table S11[72, 74]). This difference is also evident when the CKD subgroups in both ACCORD (comprising of all diabetic patients) and SPRINT (comprising of no diabetic patients) are combined. There were 53 deaths per 1000 participants on standard BP targets and 40 deaths per 1000 participants on intensive BP targets, resulting in 13 fewer deaths per 1000 participants (95% CI 23, 1 fewer deaths per 1000 participants) over a mean 3 years and 5 months of follow-up (Table S11[72-74]).

Adverse effects

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 ≥75 years or even ≥80 years in age at baseline, of which approximately 44% and 50% respectively had eGFR <60 ml/min/1.73 m^2, the risk profile for clinical adverse events with intensive BP-lowering was also quite favorable.[86, 88] There were no differences in serious adverse events and injurious falls between the intensive and standard BP arms.

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 control arms, although most of these were AKI Stage 1 and showed full recovery.[128] 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,[129] there was a significant interaction between baseline eGFR and SBP-lowering, such that patients with a baseline eGFR <45 ml/min/1.73 m^2, had an increased risk of AKI in the intensive BP arm but no reduction in the primary CV outcome. 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 two other *post hoc* analyses of SPRINT, the respective risks of AKI were marginally increased with the intensive target BP in people ≥75 years old [HR 1.41 (95% CI 0.98, 2.04)] and increased in people ≥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 or kidney failure 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 (Table S11[72-74]).[86, 88]

Polypharmacy

Most participants in ACCORD and SPRINT were taking one or two BP-lowering therapies before randomization. The benefits of intensive SBP-lowering are less certain among patients who require four 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.[130] 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. In contrast, in another study using the SPRINT database and more advanced statistical techniques (avoiding confounding by indication), adding a new antihypertensive drug class led to significant reduction in SBP and in major CV event rates but no differences in serious adverse events. These incremental effects appeared to be consistent regardless of the level of baseline drug use.[131] Nonetheless, polypharmacy also adds to treatment burden and is often associated with reduced adherence, which may be attenuated by the use of single pill combination agents.

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 more tenuous. 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 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 (Table S11[72-74]).

The kidney-protective effects of BP-lowering in CKD are primarily derived from MDRD and AASK trials. The evidence is considered to be low quality due to study limitations, and serious inconsistency. The effects were seen only in the proteinuric subgroups and, in the case of AASK, the effects were seen only during the long-term post-trial follow-up (Table S13[72, 73, 76-78, 96, 114, 117, 122, 125-127]), (Table S12[76-78, 114, 117]). The short-term negative effects of intensive SBP-lowering on eGFR changes in SPRINT did not provide support to the evidence of kidney-protection.

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 kidney-protective 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 value on higher pill burden, more clinic visits, electrolyte abnormalities, hypotension, syncope, injurious falls, and AKI that may be caused by targeting a SBP <120 mm Hg. However, intensive SBP-targeting in CKD patients did not cause more serious adverse event, orthostatic hypotension, syncope, or injurious fall 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.

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 did 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.[132] Nonetheless, it is possible that there will be difficulties in implementing these recommendations in countries in which resources are more limited; in those settings, it is probably more important to ensure that all eligible patients have at least reasonable BP control 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 is predictive of long-term adverse clinical outcomes, no adequately-powered trial based on home BP targets has been performed. 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 "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 rationales, and 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 the 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 (those who would have been eligible for SPRINT) and less certain in others (e.g., people with diabetes, advanced CKD with eGFR <20 ml/min/1.73 m^2, and older adults aged >85 years).

Rationale

This recommendation replaces the KDIGO 2012 recommendation on BP management in CKD.[120] 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 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 non-diabetic CKD 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 similar to, albeit slightly higher than, the lower BP goal in SPRINT.

The KDIGO 2012 guideline reversed previous recommendations 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 arm. Since then, SPRINT and further analyses of ACCORD, together with combined analyses of these two trials, have supported the conclusion that intensive BP-lowering therapy might well confer similar benefits among CKD patients with diabetes as in non-diabetic patients. However, the quality of evidence for BP target among CKD patients with concomitant CKD and diabetes is low, especially among those with CKD G3 to G5.

The recommendation of SBP <120 mm Hg is weak (in the dichotomous classification of strong and weak), 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 (strong or weak, depending on the strength of evidence) for lower SBP (<120 mm Hg) targets in specified subgroups. This more complex alternative was eventually rejected, on the basis that it would probably cause 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 rationales 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 inclusion criteria. However, wide pulse pressure that 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.[133, 134] 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 SBP and a DBP target in the intensive BP arm, which is equivalent to 125/75 mm Hg or 116/80 mm Hg. As discussed earlier, these studies suggest that this intensive MAP target may provide kidney-protective 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 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 2018 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 ESC/ESH (target 130-139 mm Hg), by NICE (target 120-139 mm Hg), or Hypertension Canada (target <140mm Hg).[4, 6, 135, 136] 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; reliance on routine office BP to adjust BP-lowering therapy is unjustifiable.

The ACC/AHA guideline provides a table of equivalent BPs, allowing translation between standardized office, home, daytime ambulatory, night-time ambulatory, and measurements. These equivalents were established using an outcomes-based approach that determines the BP threshold with each measurement technique that is associated with similar long-term outcomes in study populations.[137] However, differences in BP values obtained using different measurement techniques vary greatly among individual persons and even within a given individual over time. Thus, the KDIGO Work Group (see Chapter 1) found no evidence, in an individual patient, that one can reliably estimate the BP that would be obtained under standardized office conditions from measurements taken in any other setting and decided that the best evidence-based approach is to use standardized office BP for management.

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 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, in this situation, the risks of BP-lowering therapy may outweigh the benefits.

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 due to autonomic neuropathy.

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

RESEARCH RECOMMENDATIONS

- Information is needed on how patient values and preferences influence decisions relating 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); and (iii) with very low GFR (<20 ml/min/1.73 m^2. ACCORD included only small numbers of patients with CKD, most of whom qualified for the trial as a result of albuminuria, and is therefore uninformative for patients with CKD G3 to G5. On the other hand, SPRINT explicitly excluded patients with diabetes.
- While 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 and concomitant T2D. 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, as well as acute and chronic changes in kidney function require further examination.

3.2. Treatment with RAAS inhibitors (RAASi) and other antihypertensives

Background

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 evidence review included an assessment of subgroups based on the amount of albuminuria A1 to A3 (ACR <3 mg/mmol, 3 to 30 mg/mmol, >30 mg/mmol). The outcomes evaluated, where available, include all-cause mortality; CV events, including MI, stroke, HF; kidney outcomes, including kidney failure (ESKD), doubling of SCr; as well as adverse effects including AKI, and hyperkalemia.

Recommendation 3.2.1. We suggest starting RAASi (ACEi or ARB) for people with concomitant CKD without diabetes, albuminuria (≥3 mg/mmol, G1-G4, A2, A3), and high BP *(2C)*.

This recommendation is weak based on evidence from RCTs of sufficient duration to evaluate kidney protection. There is very limited evidence to guide decisions on treatment of people with low GFR with no albuminuria (G3 to G4, A1). There was insufficient data to assess the impact of RAASi by albuminuria subgroups.

Key information

Balance of benefits and harms

Overall, the HOPE study,[138] the largest RAASi study, found in a prespecified subgroup analysis of those with CKD (eGFR <65 ml/min/1.73m^2, estimated by the Cockcroft Gault formula; N= 3394; mean follow-up 4.5 years, approximately one-third patients had diabetes) that angiotensin-converting enzyme inhibitor (ACEi) versus placebo reduced the risk for all-cause mortality by 20% (95% CI 0.67, 0.96), MI by 26% (95% CI 0.61, 0.91), and stroke by 31% (95% CI 0.49, 0.90).[139]

In smaller studies in patients without diabetes and non-dialysis CKD identified by the ERT systematic review, ACEi were compared to placebo, no treatment, or standard of care. There were a non-significant reduction of all-cause mortality by 28% (95% CI 0.34, 1.53) based on data from four studies with 686 participants,[140-143] CV mortality by 68% (95% CI 0.07, 1.51) based on data from one study with 102 participants,[142] CV events by 68% (95% CI 0.07, 1.56) based on data from 817 patients in five studies with mean follow-up of 28 months.[140-144] For ESKD, there was a non-significant 51% reduction (95% CI 0.12, 1.97) based on data from 387 patients in three studies with mean follow-up of 28 months,[141, 143, 144] and a reduction of greater than 50% loss of eGFR by 64% (95% CI 0.12, 1.11) based on data from 233 patients in two studies with a mean follow-up of 18 months (Table S14[142, 144]).

In studies of ARB compared to placebo or standard of care in patients without diabetes and non-dialysis CKD, there were only two RCTs. (Table S15) For all-cause mortality, there was no difference between the arms in either study during mean 24 months of follow-up.[145, 146] However, there was a 28% reduction in CV events (95% CI 0.53, 0.98) based on data from 71 patients in one study with a mean follow-up of 36 months.[145]

There is sparse evidence for other agents to be used as initial therapy in people with CKD and high BP. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study CKD subgroup analysis, 5662 patients with and without diabetes were assessed and coronary heart disease was more frequent then kidney failure and neither lisinopril or chlorthalidone were more effective in preventing either type of event.[147] For mineralocorticoid receptor antagonist (MRA), there were four RCTs with a total of 1426 participants mainly from HF trials, not hypertension trials, with defined CKD subgroups.[147] With that caveat and relatively few events for the individual outcomes,[148-150] for the combined outcome of CV events and mortality, there was a 29% risk reduction (95% CI 0.48, 0.87) based on data from 978 participants in two studies with a mean follow-up of 31 months (Table S16[150, 151]).

In older high-risk patients with hypertension and reduced eGFR (<60 ml/min/1.73 m^2) from ALLHAT, the 6-year risk for a CV event was considerably higher than that for ESKD, neither the calcium channel blocker (CCB) amlodipine nor the ACEi lisinopril was superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone was superior to both for preventing HF, independent of level of kidney function.[147, 152] Previously the ALLHAT authors reported that there were no differences in ESKD among the drugs.[152]

Similarly, beta blockers (Table S17[153, 154]) and CCBs (Table S18[155-158]) made little or no difference compared to placebo or RAASi for the critical and important outcomes. For direct-renin inhibitors (DRI), there was only one study versus RAASi with no events in either arm (Table S19[159]). There were no relevant studies for diuretics in patients with CKD without diabetes.

A network meta-analysis by Xie *et al*., including 119 RCTs (n=64,768) examining the benefits of treating with RAASi compared to placebo or active therapy in patients with CKD for kidney and CV outcomes, resulted in improved precision with narrower credible intervals.[160] Both ACEi and ARBs reduced the risk of kidney failure; by 39% and 30%, respectively; compared to placebo with high certainty, and 35% and 25%, respectively, against active controls with moderate certainty. Both agents reduced major CV events compared to placebo (18% for ACEi and 24% for ARB, respectively), but only ACEi reduced the odds of all-cause death compared to active controls.

When balancing resource use and costs, the risks and benefits of RAASi therapy should be weighed when treating patients with CKD who do not have a strong indication for ACEi or ARB therapy, such as G3 to G4, A1.

Quality of the evidence

The overall quality of the evidence comparing ACEi or ARB with placebo and standard of care in patients with CKD and albuminuria without diabetes is low. The quality of the evidence was downgraded because of study limitations (inadequate reporting of sequence generation and allocation concealment). Some outcomes, such as all-cause mortality, CV mortality, and ≥50% GFR loss were downgraded to low because of serious imprecision (wide CIs indicating appreciable benefit and harm) (Table S14[140-144]). For trials that compared ARB with placebo and standard of care, the quality of the evidence was low, as only small studies with few events and study limitations reported critical and important outcomes (Table S15[145, 146]).

The quality of evidence for other antihypertensive therapies in this population was lower as it has only been examined in a limited number of RCTs for MRA (Table S16[148-151, 161]), beta-blockers (Table S17[153, 154]), CCB (Table S18[155-158]), DRI (Table S19[159]), and diuretics in the CKD subgroup of ALLHAT.[162]

Values and preferences

In the opinion of the Work Group, most well-informed patients would place greater emphasis on preventing CV outcomes in addition to preventing CKD progression. In addition to the higher prevalence of CVD, its presence plays a significant role on the quality of life and prognosis of patients with CKD.[163]

Resource use and costs

The risks and benefits of RAASi therapy should be weighed when treating patients with CKD who do not have a strong indication for ACEi or ARB therapy, such as G1/2, A2 and G3 to G4, A1.

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 a weak recommendation for all or nearly all well-informed patients with CKD not on dialysis without diabetes because the desirable benefits for kidney and CV protection outweigh the potential adverse risks associated with therapy. We feel that patients put a large value on the benefits (reducing CVD and kidney disease progression) and are

willing to tolerate the potential harms of therapy with RAASi, particularly hyperkalemia and AKI. These side effects may lead to higher costs from additional visits and lab testing.

Recommendation 3.2.2. We recommend RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, albuminuria (≥3 mg/mmol), normal or low GFR (G1-G4, A2, A3), and high BP *(1B)*.

This is a strong recommendation, based on evidence from RCTs of sufficient duration to evaluate kidney protection. 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, that are often transient. Where data are available, analyses by albuminuria subgroup are provided.

Key information

Balance of benefits and harms

The two main studies demonstrating kidney benefit from RAASi independently from BP control were the IDNT[164] and RENAAL[165] studies. These studies demonstrated that RAASi therapy improved the composite outcome of death, dialysis, and doubling of SCr in patients with diabetes, low GFR, and overt nephropathy (G3 to G4, A3). Further, the RENAAL study demonstrated that remaining on RAASi therapy significantly delayed the onset of dialysis by a mean of six months in patients who doubled their SCr during the study. In the IDNT study, hyperkalemia necessitating a stop in therapy occurred in 2% of patients with RAASi versus 0.5% of patients without. Overall serious adverse events were actually lower in the RAASi group than in control group. Therefore, in this group in particular (G3 to G4, A3), there is strong evidence supporting the treatment with RAASi because of their kidney-protective effects.

Data for people with G1, G2, A2 with diabetes comes from the Micro-HOPE study where people with diabetes, moderately increased albuminuria, and higher CV risk had improved CV outcomes with ACEi therapy compared to placebo.[138] For the combined outcome of MI, stroke, CV death, there was a relative risk reduction of 28.6% (95% CI 0.6, 0.9), based on 1140 patients from the Micro-HOPE study with a mean follow-up of 4.5 years. Kidney benefit in this group is largely limited to reducing progression from moderately increased albuminuria to severely increased albuminuria. There are limited data for people with diabetes and G1, G2, A3.

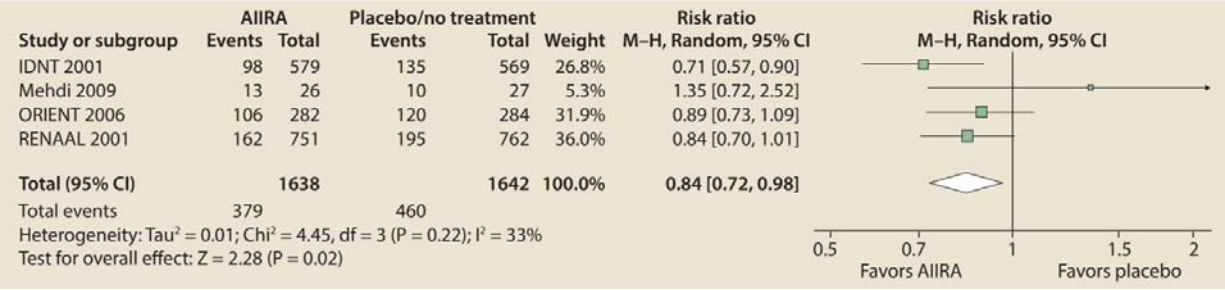
Overall, we found that, compared to placebo or standard of care, ACEi did not reduce the risk for all-cause mortality, based on data from 7516 patients in 23 studies with a mean follow-up of 32 months (Table 20[138, 165-186]). The absolute difference was 9 fewer events per 1000 (95% CI 28 fewer, 15 more) and was not statistically significant. For kidney benefit, the

risk of doubling of SCr was reduced by 32% (95% CI 0.47, 1.00) based on 6780 patients from nine studies with a mean follow-up of 27 months and an absolute difference of 14 fewer events per 1000 (95% CI 23 fewer, no difference).[138, 169, 175, 177, 178, 182, 184, 185, 187]

For progression from moderately increased albuminuria to severely increased albuminuria, the risk was reduced by 55% (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).[138, 168, 170, 172, 175, 184, 185, 188-196]

Compared to placebo or standard of care, ARBs did not show a difference in all-cause mortality, CV mortality, MI, HF, stroke, or CV benefit, but did show a kidney benefit with a reduction of doubling of SCr of 16% (95% CI 0.72, 0.98) based on 3280 patients from four studies with a mean follow-up of 34 months (Table S21[164, 165, 197, 198]). No difference on adverse events was noted. (Figure 2.)

Figure 2. Adverse events with ARB compared to placebo/standard of care in adults with diabetes and CKD



There were no differences between ACEi and ARB for the outcomes of all-cause mortality, CV mortality, MI, stroke, HF, and kidney function in the albuminuric and non-albuminuric diabetic subpopulations (Table S22[180, 199-202]).

There is little evidence to support the use of other agents as the initial therapy in diabetic patients with albuminuria. For MRA compared to placebo, there were three studies (Table S23[198, 203, 204]) with no beneficial effect on all-cause mortality, MI, and stroke. There were too few events to determine the effect on doubling of SCr and other kidney outcomes. Similarly, for beta blockers (Table S24[205-212]) and CCBs (Table S25[172, 193, 213-222]) compared to ACEi or ARB, there was no evidence of benefit in clinical outcomes. For example, in AASK with a mean follow-up of 4.1 years, metoprolol was not significantly different from either ramipril or amlodipine for CV events, but was inferior to ramipril for kidney clinical outcomes.[77]

The importance of diuretic therapy for lowering BP is demonstrated by the ADVANCE study comparing treatment with an ACEi plus diuretic combination (perindopril plus

indapamide) to usual care without a thiazide-type diuretic in 11,140 people with diabetes over a mean of 4.3 years (Table S26[223]). There were no differences in any study outcomes. However, in a *post hoc* analysis of 4526 patients with CKD G1 or G2 with albuminuria, and all patients with CKD G3 to G5,[224] the combination of perindopril and indapamide reduced all-cause mortality by 17% (95% CI 0.78, 0.88), CV mortality by 21% (95% CI 0.63, 0.99)[223] and the main kidney outcome (doubling of SCr, kidney replacement therapy, onset of severely increased albuminuria, or kidney death) by 19% (95% CI 0.65, 1.00),[223] although there was no significant effect on major coronary events and stroke. These improvements in clinical outcomes were associated with a fall in BP of 5.3/2.1 mm Hg in patients with CKD G1 or G2, and 4.5/1.8 mm Hg in patients with CKD G3 to G5. There was no effect modification by the presence of baseline albuminuria. It should be noted that at baseline of the ADVANCE study, 49% of the placebo group were already treated with RAASi, which further increased to 73% at the end of the study. This suggests that much of the benefit seen in ADVANCE might have been due to the addition of the diuretic and greater BP-lowering in the active treatment group.

Quality of the evidence

The ERT updated a Cochrane systematic review on antihypertensive therapies in patients with diabetes and CKD.[225] The overall quality of the evidence was rated as moderate, as the studies examining the use of RAASi therapy exhibited study limitations with unclear allocation concealment for critical and important outcomes. The quality of the evidence was lower for CV outcomes because of the fewer events and reporting of these outcomes in trials (Table S20-S29).

The best evidence for kidney-protective effects of RAASi therapy independent of BP control in patients with diabetic G3 to G4, A3 comes from the IDNT and RENAAL studies. For CV outcomes, the Micro-HOPE study provides the best evidence. There is insufficient evidence to recommend that patients with diabetes, but without high BP or CV risk factors should be treated with RAASi. One meta-analysis[226] found a reduction of all-cause mortality, CV mortality, and major CV events in people with diabetes in 32,827 patients treated with ACEi, but this was not found in 23,867 patients treated with ARBs. Most of the studies were in patients with high BP. Yet, another meta-analysis comparing RAASi to other antihypertensives in people with diabetes did not find CV outcome improvement.[227] There was also no improvement in kidney failure outcomes. These meta-analyses included patients with diabetes G1, G2, A1 to A3, and G3, G4, A1 to A3, respectively. It is likely that including the low risk and high-risk groups together led to the lack of clinical significance. While it is tempting to extrapolate the beneficial effects of RAASi to all people with diabetes, in the absence of high BP, CV risk, and lower GFR (G3 to G4 with A2/3), the evidence is only weak at best. For the treatment with RAASi, there is therefore a gradation of evidence from strong (G3 to G4 A3) to weak (G1/2 A2, G3 to G4 A2) for people with diabetes and albuminuria.

In the ADVANCE study, the quality of evidence is low according to GRADE.[228] The quality of the evidence was downgraded due to serious risk of bias, with unclear blinding and imprecision as it is only study with CKD subgroups, when the results were negative in the entire cohort. (Table S26).

Values and preferences

In the opinion of the Work Group, this recommendation for people with diabetes and CKD places higher value on the ability of RAASi to prevent CV and CKD events, such as doubling of SCr and dialysis. It places less value on the risks of hyperkalemia and AKI.

Resource use and costs

The costs of the RAASi medications are probably low in most countries. However, adding RAASi to all patients with diabetes and albuminuria will require more lab testing and visits to the health care providers, especially in those with low GFR. It will also likely lead to more incidences of hyperkalemia and AKI, hence the associated costs of managing and monitoring these occurrences.

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

Practice Point 3.2.1. RAASi (ACEi or ARB) should be administered using maximally recommended doses to achieve the benefits described because the proven benefits were achieved in trials using this dose.

Recommendation 3.2.3. We suggest RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, eGFR <60 ml/min/1.73 m^2, normal albuminuria, and high BP *(2C)*.

This recommendation is based on evidence from RCTs of sufficient duration to evaluate kidney protection. This recommendation places a relatively higher value on preventing progression of CKD and a relatively lower value on the risks of AKI or hyperkalemia. Where data were available, analyses by albuminuria were made.

Key information

Balance of benefits and harms

Very few studies reported on the effects of RAASi on clinical outcomes in CKD patients with normal albuminuria (defined as <30 mg/g per day). Importantly, no improvements in clinical outcomes were noted[180, 229] for ACEi versus placebo (Table S20), ARB versus placebo (Table S21), DRI versus RAASi (Table S27), DRI in combination with RAASi versus RAASi therapy alone (Table S28), and ACEi versus ARB (Table S22). For MRA (Table S23) or beta blockers (Table S24), no studies have included diabetic CKD subgroups with normal albuminuria. For CCB versus other therapies, there was no difference in eGFR outcomes according to the presence of albuminuria or proteinuria, and no other outcomes could be assessed due to limited reporting (Table S25, Table S29).

The HOPE study found in a prespecified subgroup analysis of patients with diabetes, that the effect of ramipril on the combined primary outcome was independent of history of moderately increased albuminuria and diabetes.[138] Also, for people with diabetes, 67% did not have moderately increased albuminuria and the risk for MI, stroke, or CV death was 15.3% for patients on placebo and 12.6% for patients on ramipril resulting in an absolute risk reduction of 2.7%.[230] Thus, those with diabetes and CKD benefited on CV outcomes from ramipril versus placebo even in the absence of elevated albuminuria.

The risks and benefits of RAASi therapy should be weighed when treating patients with and without diabetes who do not have a strong indication for ACEi or ARB therapy such as G3 to G4, A1.

Quality of the evidence

These meta-analyses included patients with diabetes G1, G2, A1 to A3, and G3, G4, A1 to A3. It is likely that heterogeneity among these groups led to the lack of clinical significance. While it is tempting to extrapolate these findings to all people with diabetes for the use of RAASi in the absence of high BP, higher CV risk, and lower GFR (G3, G4 with A2, A3), the quality of the evidence is low.

Values and preferences

In the opinion of the Work Group, this recommendation places higher value on preventing CV outcomes in patients with kidney disease and on preventing CKD progression to hard kidney endpoints, including doubling of SCr and dialysis.

Resource use and costs

BP-lowering in patients with diabetes has been demonstrated to be highly cost-effective and even cost saving (UKPDS).[231, 232] Adding RAASi to all patients with diabetes and CKD

will lead to more hyperkalemia and AKI events, the need for more lab testing, and visits to the health care providers.

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 weak recommendation for patients with CKD and diabetes with low eGFR (<60 ml/min/1.73 m^2) and normal albuminuria. We feel that patients would put a large value on the benefits of BP reduction, and are willing to tolerate the potential harms, particularly hyperkalemia. These side effects may lead to higher costs from additional visits and lab testing. The panel was less confident of its applicability to patients with G3 to G4 A1.

Practice Point 3.2.2. Monitor for changes in blood pressure, serum creatinine, and serum potassium within two to four weeks of initiation or increase in the dose of an ACEi or ARB.

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 pressure and not unexpectedly, a decrease in the GFR and a rise in the SCr. In addition, RAAS blockade inhibits the action of aldosterone with a greater propensity for hyperkalemia. An increase in SCr level, if it occurs, will typically happen during the first two weeks of treatment initiation, and should stabilize within two to four weeks in the setting of normal sodium and fluid intake.[233] Therefore, patients should be monitored for symptomatic hypotension, hyperkalemia and excessive rise in SCr within two to four weeks after initiating or change in the dose of the drug, depending on resource availability and patient preferences.

Practice Point 3.2.3. Reduce the dose or discontinue ACEi or ARB in the setting of symptomatic hypotension, uncontrolled hyperkalemia despite medical treatment, or while preparing for imminent kidney replacement therapy.

The dose of ACEi or ARBs should only be reduced or discontinued as a last resort in patients with hyperkalemia, after other measures have failed to achieve a normal serum potassium level. Similar efforts should be made to discontinue other concurrent BP medication before attempting to reduce the dose of ACEi or ARBs in patients who experience symptomatic hypotension.

When these drugs are used in patients with eGFR <30 ml/min/1.73 m^2, close monitoring of serum potassium is required. Withholding these drugs solely on the basis of the level of kidney function will unnecessarily deprive many patients of the CV benefits that they otherwise would have received, particularly when measures could be undertaken to mitigate the risk of hyperkalemia. However, in patients with advanced CKD who are experiencing uremic symptoms or dangerously high serum potassium levels, it is reasonable to discontinue ACEi and ARB temporarily to allow time for kidney replacement therapy preparation.

Practice Point 3.2.4. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

The steroidal MRA spironolactone and eplerenone have, in small and short-term studies, been found to reduce BP in resistant hypertension[234, 235] (defined as uncontrolled hypertension on three antihypertensive agents including a diuretic) and to lower albuminuria in diabetes patients with elevated urinary albumin excretion.[161] There are no long-term data from RCTs on clinical benefits. In addition, side effects, particularly hyperkalemia and decline in kidney function,[236] are a concern when added to background therapy with an ACEi or ARB or diuretic, particularly among patients with eGFR <45 ml/min/1.73 m^2.[237] Thus, blocking aldosterone may be particularly useful in patients with resistant hypertension without a history of high potassium, and GFR>45, and should not be used with eGFR <45 ml/min/1.73 m^2 and high risk of elevated potassium. Whether newer non-steroidal MRA may provide benefit in diabetes and CKD with less side effects is an area of ongoing research.[237, 238]

RESEARCH RECOMMENDATIONS

- Patients with CKD G3 to G4, A1 with or without diabetes have not been adequately studied. Future studies should examine if RAASi therapies 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 without diabetes. In the ALLHAT study, a subgroup analysis of patients with CKD (eGFR <60 ml/min/1.73 m^2) found a trend to less progression to ESKD or worsening kidney function with amlodipine or lisinopril, compared to chlorthalidone.[147] It would be helpful to clarify the role of diuretics, at least in early CKD.

3.3. Role of dual therapy with RAASi

Background

RAASi have been shown to both lower BP and to 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 where therapy with ACEi or ARB has shown improvement of kidney and CV outcomes. However, recent analyses and reviews are casting doubt on the role of RAASi for CKD patients without diabetes and without albuminuria.[239] In addition, the role of dual therapy with ACEi, ARB, and/or aliskiren, compared to monotherapy with ACEi or ARB, appears to be associated with more adverse effects, including hyperkalemia and AKI, that may outweigh any potential CV or kidney benefit.

Recommendation 3.3.1. We recommend not treating with any combination of ACEi, ARB, and direct renin inhibitor 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 protection. There is growing evidence that dual RAAS blockade with an ACEi and an ARB, or with a combination of one of these drugs with a DRI, does not lead to long-term benefit and is associated with 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.

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 in nine RCTs of 17,750 participants. Two of these studies did not include participants with diabetes.[160] For all-cause mortality, there was no benefit from dual blockade versus monotherapy in seven studies of 16,862 patients with mean follow-up of 3.4 years. There was no difference in progression to ESKD based on seven studies of 16,507 patients with a mean follow-up of 40 months, and no improvement of CV events.[160]

In studies of patients with CKD with and without diabetes, dual blockade (see Figure 3) compared to monotherapy was associated with an 9% higher risk of all-cause mortality (95% CI 1.00, 1.20) based on data from 10,615 patients in four studies with a mean follow-up of 31 months,[240] PRONEDI 2013,[241] VA-Nephron-D,[242] ONTARGET[243] (Table S30). For CV mortality, MI, and stroke, there was also no statistically significant difference.

In contrast, in patients with CKD with or without diabetes (see Figure 4), there was evidence that dual therapy increase the incidence of AKI by 40% (95% CI 1.26, 2.04), compared to monotherapy, based on data from 6139 patients in two studies with a mean follow-up of 39 months: VA-NEPHRON-D,[242] ONTARGET[243] (Table S30).

Combining data for patients who have both diabetes and CKD from three large outcome trials, there was no benefit in all-cause mortality with 9% fewer events with monotherapy compared to dual therapy (95% CI 0.84, 1.01) based on data from 10,486 patients with a mean follow-up of 52 months (PRONEDI 2013,[241] VA-NEPHRON-D,[242] ONTARGET 2011[243]). There was a marginally reduction of 20% [RR 0.80 (95% CI 0.65, 1.00)] in doubling SCr by dual therapy, compared to monotherapy, during the study of 10,486 patients from three studies with a mean follow-up of 42 months (PRONEDI 2013,[241] VA-NEPHRON-D,[242] ONTARGET 2011[243]). However, the lower confidence interval reaches the null indicating there may be little or no difference. This beneficial effect was more pronounced in patients with baseline moderately increased albuminuria, compared to those without baseline moderately increased albuminuria. However, there was a 38% greater risk (95% CI 0.49, 0.79) for AKI based on data from 10,381 patients in two studies with a follow-up of 40 months (VA-NEPHRON-D,[242] ONTARGET 2011[243]). This was present in patients with moderately increased albuminuria compared to patients without (Table S30).

Figure 3. All-cause mortality with monotherapy compared to dual RAASi therapy for patients with CKD with or without diabetes.

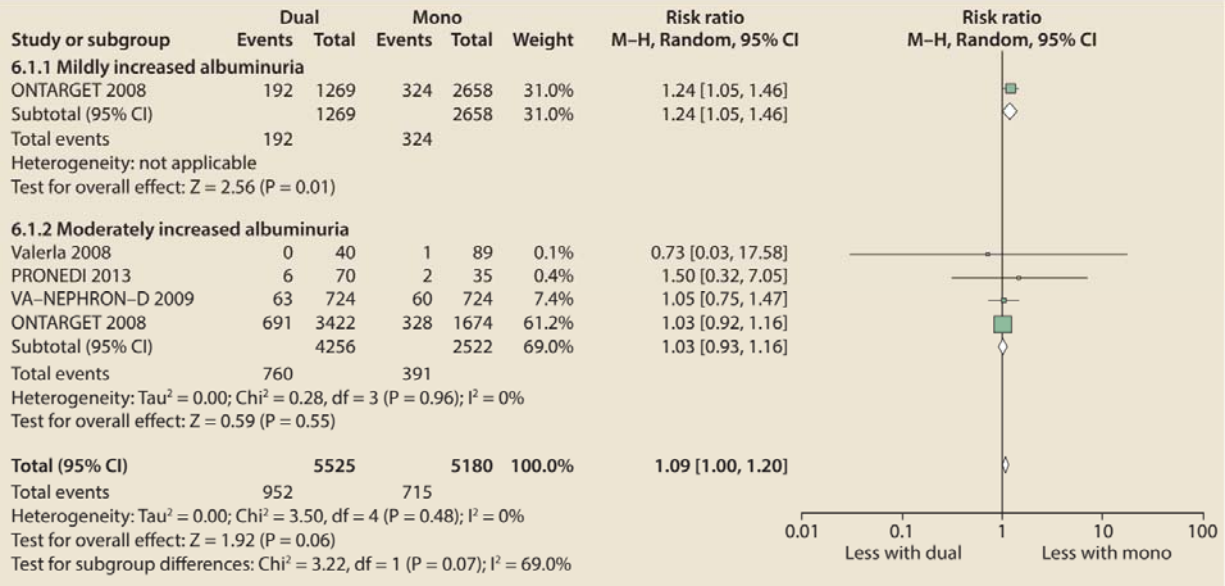
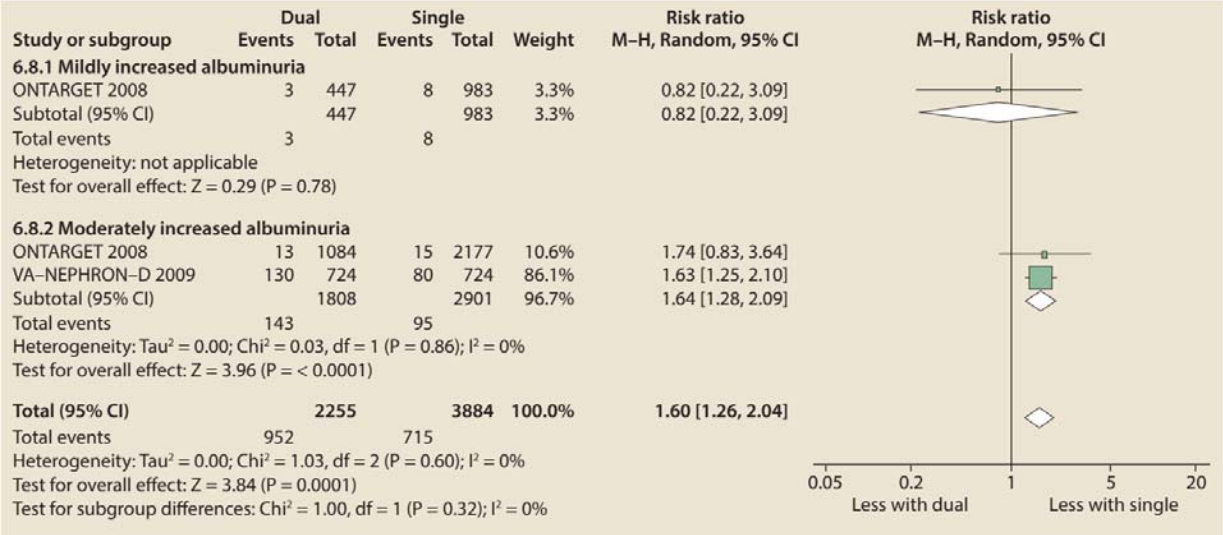


Figure 4. AKI with monotherapy compared to dual RAASi therapy for patients with CKD with or without diabetes



There are four studies in patients with CKD and diabetes that compared dual RAAS blockade with either an ACEi, an ARB, or aliskiren, a DRI. ONTARGET compared dual ACEi and ARB therapy with ACEi or ARB alone in a subgroup of 9023 patients with diabetes and additional CV risk factor, the majority without CKD. Over a mean follow-up of 54 months, there were no differences in the primary (CV) or secondary (kidney) outcomes between the two arms. There was, however, an increased risk of adverse events including hyperkalemia and AKI with dual therapy. The number of CKD patients in this study was 2943. In 1297 patients with eGFR <60 ml/min/1.73 m^2 without albuminuria (33.8% had diabetes), there was also no improvement with dual therapy compared to monotherapy.

The VA-NEPHRON-D trial compared losartan and lisinopril to lisinopril and placebo in 1448 patients with T2D and CKD.[242] The baseline eGFR was 53.7 ml/min/1.73 m^2 (± 16.2) in the monotherapy arm and 53.6 (± 15.5) in the dual therapy arm, mean ACR was 862 mg/g across both groups. Over 90% of the participants were on RAASi at baseline. This trial was stopped early after only a mean of 26.4 months of follow-up due to increased incidences of hyperkalemia (9.9% vs. 4.4%) and the high rate of AKI (12.2 vs. 6.7 per 100 patient-years) in the dual therapy group with no differences in primary (kidney) or secondary (CV) outcomes between the two arms.

Similarly, the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE)[244] compared ACEi or ARB plus aliskiren with ACEi or ARB alone in 8561 patients with T2D and CKD. The baseline eGFR was 57 ml/min/1.73 m^2 (± 21.9) in the aliskiren-treated group and 57 ml/min/1.73 m^2 (± 23) in the control group, and geometric ACR mean was 206 mg/g (IQR 57, 866) mg/g in the aliskiren group and 208 mg/g (IQR 58, 912) in the control group. This trial was stopped early after 2.7 years for increased incidence of hyperkalemia with dual therapy without differences in the co-primary outcomes of major CV or kidney outcomes between the two arms. There were also no differences in progression to

kidney failure or progression from normal albuminuria to moderately increased albuminuria, although there was a 24% increased regression from severely increased albuminuria to normal albuminuria with dual therapy. Hyperkalemia in ALTITUDE and in AVOID[245] (a small pilot trial to ALTITUDE) was more common with dual therapy [HR 1.30 (95% CI 1.26, 1.34)] based on data from 9153 patients in these two studies (ALTITUDE 2009,[244] AVOID 2008[245]) (Table S28).

The ORIENT study, a smaller trial with 566 subjects with T2D, CKD, and ACR of 1700 mg/g compared kidney outcomes with an ACEi plus olmesartan to an ACEi and placebo.[197]. Over a mean follow-up of 38.4 months, there was a reduction in albuminuria with dual therapy, but there were no differences in kidney or CV outcomes. Dual therapy also caused an increased discontinuation rate for hyperkalemia (9.2% versus 5.3%).

In adults without diabetes and with early CKD stage G1 to G3, one study has evaluated the role of dual therapy with ACEi and ARB compared to monotherapy with ACEi or ARB.[246] No differences in CV or kidney outcomes were noted, although the Ferrari study evaluated only 20 participants over 7.5 months.

Quality of the evidence

The overall quality of the evidence was moderate. The network meta-analysis that compared dual RAASi with mono RAASi exhibited moderate quality of the evidence because of concerns regarding inconsistency for all-cause mortality and CV events, serious imprecision for ESKD due to wide CIs that indicated appreciable benefits and harms (Table S31).[160] The ERT's review (including Cochrane reviews that were updated[225, 247]) found moderate quality of the evidence for studies that compared dual with mono RAASi because of study limitations, with unclear reporting for Cochrane risk of bias[248] domains, random sequence generation and allocation concealment (Table S30).[197, 239-241, 243, 246] The ERT updated a Cochrane review protocol on the addition of aliskiren to RAASi therapy with mono RAASi.[249] The quality of the evidence was moderate for most outcomes (Table S28[244, 245, 250-253]). For CV mortality, ESKD, moderately increased albuminuria, and doubling of SCr, the quality of the evidence was downgraded because of serious imprecision due to only one study reporting these outcomes, and all-cause mortality was downgraded due to wide confidence intervals that indicate appreciable benefit and harms. Finally, for the serious adverse events outcomes, 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. While 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 lab tests, office and emergency visits, additional short-term therapies, and adjustment in diet.

Resource use and costs

Resource utilization and costs decrease, instead of increase, by not instituting dual RAASi therapy, compared to monotherapy.

Considerations for implementation

There is unfortunately no data on safety or kidney efficacy of dual therapy in patients with nephrotic syndrome. As more blockade of the RAAS leads to lowered proteinuria, nephrologists might try dual therapy or high-dose RAASi just to lower proteinuria in selected patients, recognizing the risks of hyperkalemia and AKI.[254] 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. Dual therapy with an ACEi and an ARB should be discouraged for patients with CKD with or without diabetes, with or without albuminuria.

Rationale

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

Addition of a MRA to ACEi or ARB

Limited data have shown that the addition of a MRA, such as spironolactone or eplerenone, for kidney protection in patients with diabetes and nephropathy on an ACEi or ARB resulted in a reduction of albuminuria but higher risk of hyperkalemia. No adequately-powered study examining GFR and kidney failure outcomes has been completed.[255] Finerenone, a newer agent in this class, is currently being tested in two large outcome trials against placebo in patients with diabetes and kidney disease on an ACEi or ARB, with either kidney or CV outcomes as primary (FIGARO and FIDELIO trials). Results are expected in the next two years.

RESEARCH RECOMMENDATIONS

- The benefits of dual versus monotherapy on major kidney outcomes in people with CKD and high-grade proteinuria (e.g., for example >2-3 g/d), have not been well

studied. Future trials should examine such subgroups and try to curtail risks of hyperkalemia and AKI.

- Conduct studies examining the combination of RAAS blockade with endothelin blockade, SGLT-2 inhibition, or GLP-1 receptor activation and other therapies for potential kidney benefits.
- In the era of personalized medicine, research should be directed to identify individuals who will benefit or experienced harm from each of these therapies.

CHAPTER 4. BLOOD PRESSURE MANAGEMENT IN KIDNEY TRANSPLANT RECIPIENTS (CKD G1T-G5T)

Background

This chapter makes recommendations for BP management in adult (≥18 years) kidney transplant recipients (CKD G1T-G5T). The evidence review for this chapter included an update of a previous Cochrane review[256] in addition to a new search of the Cochrane Kidney and Transplant Specialized Register for all RCTs trials.

The term "high BP" is used throughout the document to BP above the target. For kidney transplant recipients (Chapter 4), the target SBP is <130 mm Hg and target DBP is <80 mm Hg.

Practice Point 4.1. Treat adult kidney transplant recipients with high BP to a target BP that is <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 2012 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease.[257] The target is also consistent with the recommended target of <130/80 mm Hg as defined in the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients.[258] Although 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, the Work Group judged that a target of <130 mm Hg systolic remained a reasonable goal and is consistent with the recently published ACC/AHA BP guidelines.[4] 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.[259-261] 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. There has only been one trial report of intensified BP control in kidney transplant recipients. This was conference abstract outlining a trial protocol and baseline characteristics of pediatric kidney transplant recipients randomized to either conventional BP targets (MAP between 50th & 99th percentiles) versus intensified BP control (MAP <50th percentile).[262] Further, evidence from the SPRINT trial showed that patients in the intensive arm had modestly higher rates of eGFR decline within the three-year duration of the trial,[263] AKI (albeit mild in intensity),[128] and incident CKD,[111] 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. 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.

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 any potential 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

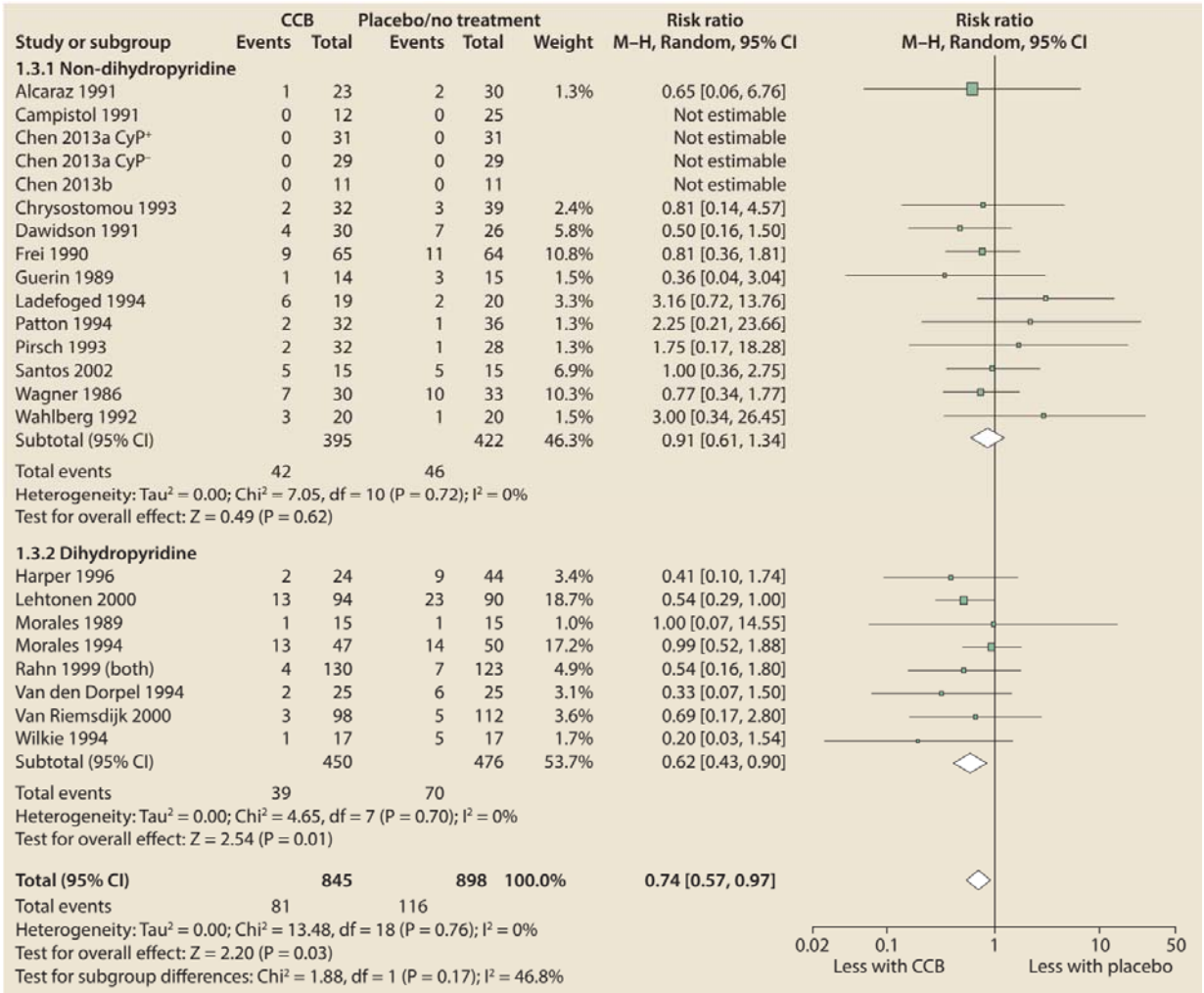
This recommendation relies heavily on the importance of preventing graft loss to kidney transplant recipients and clinicians.[264, 265] The evidence review has found that CCB use, compared to placebo (Table S32), caused a mean 26% reduction in graft loss [RR 0.74 (95% CI 0.57, 0.97)] (Figure 5). This evidence is derived from a meta-analysis of 20 RCTs involving 1747 patients.[266-285] These 20 trials, however, evaluated both dihydropyridine (e.g., amlodipine, nifedipine) CCBs and non-dihydropyridine (e.g., diltiazem, verapamil) CCBs. From a pharmacological 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)], compared to placebo (Figure 5). This evidence was derived from eight RCTs involving 926 participants followed for a mean of 25 months (21, 23-25, 28, 30, 31, 34). In contrast, the non-dihydropyridine CCB group had a non-significant reduction in graft loss [RR 0.91 (95% CI 0.61, 1.34)], compared to placebo (Figure 5). The evidence review has also found that ARB use, compared to placebo (Table S33), caused a 65% reduction in graft loss [RR 0.35 (95% CI 0.15, 0.84)]. This evidence was derived from three RCTs involving 786 participants followed for a mean of 37 months.[286-288]

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, caused a lower SCr concentration [mean difference 16.01 µmol/l lower (95% CI 7.05, 24.97 lower)] and a higher GFR [mean difference 5.27 ml/min higher (95% CI 2.79, 7.74 higher)] compared to placebo, over a mean follow-up of 16 months (Table 32[273, 276, 277, 280, 282, 289-293]).

The tradeoff or harms with these interventions include well-known adverse events for both dihydropyridine CCB (e.g., edema[294]) and ARB (e.g., anemia, acute decline in kidney function, hyperkalemia[295]).

The evidence review found that ACEi, alpha-blockers, beta-blockers and MRAs, compared to placebo/no treatment, had no significant effect on mortality, graft loss or CV events (Table S34[291, 296-308], Table S35[309], Table S36[310], Table S37[311]).

Figure 5. CCB vs placebo/no treatment for the outcome of graft loss



Quality of evidence

The ERT updated a Cochrane systematic review[256] and evaluated the quality of the evidence based on RCTs only. The evidence for the use of an ARB or CCB compared to placebo/no treatment is considered low quality because of a significant 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 amongst 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 Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) group was established to determine which outcomes to measure in transplant trials.[264] 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 three consensus conferences in which patients and caregivers participated.[264, 265] Kidney allograft survival was unequivocally the dominant priority for patients/caregivers and health professionals.[264, 265] From the patient's perspective, there was a prevailing dread of dialysis and they focused on well-being and avoiding dialysis.[264] Preventing graft loss was the top priority, even over death, as the patients were more concerned with quality rather than quantity of life.[264]

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/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[312] and the relatively low cost of CCB or ARB, it is likely that the initiation of a CCB or ARB would be cost-effective. However, a formal economic analysis evaluating different antihypertensive agents in the kidney transplantation setting has not been performed.[313]

Considerations for implementation

High BP can be difficult to control in kidney transplant recipients and most patients will require more than one antihypertensive agent.[259-261] 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. Females trying to conceive or who are pregnant should be treated with a CCB, which is generally safe during

pregnancy and lactation. In patients with proteinuria and high BP, ARB should be considered first given the known proteinuria-lowering effects of these medications.[256] In the early post-transplant period, ARBs should be avoided until kidney transplant function stabilizes as the acute effect of an ARB on GFR can be mistaken for 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 profile, availability and low cost.

This recommendation is strong because, in the judgment of the Work Group, the potential prevention of transplant failure far outweighs any 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 small proportion would not. Finally, the Work Group judged that the majority, if not all clinicians, would be comfortable in starting a CCB or ARB due to the familiarity with these agents and their well-known safety profile.

RESEARCH RECOMMENDATIONS

- Adequately powered RCT evaluating CV and kidney effects of targeting SBP <120 mm Hg vs. <130 mm Hg SBP among patients with kidney transplants.
- Adequately powered RCT evaluating CV and kidney effects of ARB vs. 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, BP should be treated to lower 24-hour mean arterial pressure (MAP) by ABPM to less than or equal to the 50th percentile for age, sex, and height *(2C)*.

This recommendation is weak 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 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 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 to 99th percentile of normal children) (Table S38[121, 314-317])This study showed a probable benefit in slowing kidney disease progression and no higher numbers 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/1.73 m^2, and those with PCR >1.5 g/g 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.[318] This is based on a subgroup analysis of the ESCAPE data which suggested that those children with a PCR <0.5 g/g 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. On the other hand, there are potential CV end-organ benefits, such as less left ventricular hypertrophy.[319]

The single RCT of BP control and kidney failure outcomes in the pediatric CKD population utilized 24-hour MAP as the BP target.[121] 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 BPs.[320] Targeting BP control by ABPM is also recommended by the American Academy of Pediatrics (AAP).[316] However, in clinics that do not have the capacity to provide ABPM, performance of standardized, protocol-driven manual BP measurement using an aneroid sphygmomanometer may provide similar prognostic information as ABPM.[321, 322] In the clinic, the use of auscultatory BP is preferred, since normative BP data in children are obtained using this technique, and there are significant differences between values obtained by oscillometric and auscultatory measurements.[323] However, RCT data targeting oscillometric BP measurements obtained in the clinic setting in children are lacking.[324]

Quality of the 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 (Table S38[121]). 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 the Chronic Kidney Disease in Children Study (CKiD) suggest that MAP targets <90th percentile are beneficial for children with either glomerular and non-glomerular causes of CKD, and lower MAP <50th percentile may have an additional benefit.[325] Therefore, a range of targets, including the 50th to 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 all well-informed patients or caregivers. Published patient-reported outcome data from the Standardized Outcomes in Nephrology (SONG)-Kids study reported that both children with kidney disease and caregivers rated kidney function as an important outcome, while BP control was also rated as an important outcome by caregivers.[326] 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 will be more inclined not to follow this recommendation and to choose a target MAP of <90th percentile instead.

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. However, to our knowledge, no trial data are available on clinic-based auscultatory BP targets. Observational data from the CKiD study showed that the highest risk of CKD progression was observed for those with auscultatory clinic systolic BP ≥90th percentile, and achieved office BP between the 50th to 75th percentiles appeared to offer the greatest protection against CKD progression in this cohort.[327]

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/races. However, compared to other forms of kidney diseases, children with proteinuria may derive more clinical benefits from intensive BP-lowering.[121]

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 came from the ESCAPE trial in which children with baseline CKD with eGFR 20 to 80 ml/min/1.73 m^2 and 24-hour average ambulatory MAP >95th percentile were randomized to <50th percentile versus 50th to 90th percentile of MAP in the normogram of healthy children. Both arms received ramipril. The primary endpoint (the composite of 50% GFR decline and ESKD) favored the intensive BP arm [HR 0.65 (95% CI 0.44, 0.94)].[121]

Existing guidelines from other organizations include the 2016 European Society of Hypertension 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. Observational data on standardized auscultatory office monitoring suggests achieved office SBP and DBP of 50th to 75th percentile offers protection against kidney function decline, compared to office SBP and DBP >90th percentile in children with CKD.

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 in normogram of healthy children, as measured using by 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. This guideline also recommends that children and adolescents with CKD, hypertension, and proteinuria should be treated with an ACEi or ARB, largely based on observational data.[325] 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 include that the prior KDIGO guideline made a recommendation for the initiation of antihypertensive medication when the MAP is consistently above the 90th percentile for gender, age, and height, whereas in the current guideline, all children with CKD and BP 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. 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.[328, 329] There was no difference in effects between losartan and enalapril.[330, 331]

Practice Point 5.1. We suggest monitoring BP once a year with ABPM, and monitoring every three to six months with standardized auscultatory office BP.

Practice Point 5.2. 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 risk of hyperkalemia and have adverse fetal risks for pregnant women.

RESEARCH RECOMMENDATIONS

- Develop normative reference values for ABPM in pediatric populations that include various 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 as outcome.

METHODS FOR GUIDELINE DEVELOPMENT

AIM

This an update of the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (CKD) published in 2012.[120] 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.[332]

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.[333, 334] This guideline has been conducted and reported in accordance with the AGREE II reporting checklist.[335] The processes undertaken for the development of the KDIGO 2020 Clinical Practice Guideline for the Management of Blood Pressure in CKD are described below.

- Appointing Work Group members and the Evidence Review Team (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 pre-defined 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 rationales
- Public review in January 2020
- Guideline update
- Finalizing and publishing the guideline.

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, dietetics, 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 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 met for a one-day meeting in Houston, Texas, USA in February 2018 to discuss the previous guideline, the findings from the KDIGO Controversies Conference on Blood Pressure in Chronic Kidney Disease,[332] and finalize the guideline development process. Guideline topics from the previous guideline and new guideline topics were linked with appropriate clinical questions to underpin 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[120] and the KDIGO Controversies Conference on Blood Pressure in CKD.[332] 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 Population, Intervention, Comparator, Outcome (a list of critical and important outcomes was compiled after voting from the Work Group (Table 3)), and Method (PICOM) format. 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.[120] Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in the Table 4. All evidence reviews were conducted in accordance to the Cochrane Handbook,[336] and guideline development adhered to the standards of GRADE (Grades of Recommendation, Assessment, Development and Evaluation).[337]

Table 3. Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Cardiovascular mortality • ESKD • Cardiovascular events (MI, stroke, HF) • Dementia or cognitive impairment
Important outcomes	• Doubling SCr • AKI • Falls • Fatigue • Body weight • Blood pressure
Non-important outcomes	• eGFR/creatinine clearance • Proteinuria

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

Table 4. Clinical questions and systematic review topics in PICOM format

Guideline chapter	Blood pressure measurement
Clinical question	In patients with CKD, what is the diagnostic accuracy of BP measurement techniques compared to standardized auscultatory office-based BP?
Population	Patients with CKD (CKD G1-G5 ND, 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
Clinical question	In the general population, what is the diagnostic accuracy of BP measurement techniques (oscillometric office and home BP, ambulatory BP) compared to standardized auscultatory office-based BP in diagnosing high BP?
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
Clinical question	In the general population, what is the association between differing approaches to measuring BP including in the clinic (standardized vs. non-standardized), at home and ambulatory with classification of BP and long-term outcomes?
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
Guideline topic	Lifestyle treatment for lowering blood pressure in CKD non-dialysis patients
Clinical question	In adults with non-diabetic CKD, does reducing protein intake compared to usual protein intake improve clinically relevant outcomes and decrease harms?

Population	Adults with CKD (CKD G1-G5 ND) with and without diabetes
Intervention	Low protein diet
Comparator	Usual protein diet
Outcomes	Outcomes listed in Table 3
Study design	RCTs
Cochrane review	Hahn D, et al. Low protein diets for non-diabetic adults with chronic kidney disease (Review). Cochrane Database of Systematic Reviews. 2018:10; CD001892
Clinical question	In adults with CKD without diabetes, does reducing dietary salt intake compared to usual salt intake improve clinically relevant outcomes and decrease adverse effect?
Population	Adults with CKD (CKD G1-G5 ND) without diabetes
Intervention	Low salt diet
Comparator	Normal salt diet
Outcomes	Outcomes listed in Table 3 Additional outcomes – sodium excretion, SCr, BP
Study design	RCTs
Cochrane systematic review	McMahon EJ, et al. Altered dietary salt intake for people with chronic kidney disease (Review). Cochrane Database of Systematic Reviews. 2015:2; CD010070
Clinical question	In adults with diabetes and CKD, does reducing dietary salt intake compared to usual dietary salt intake improve clinically relevant outcomes and decrease harms?
Population	Adults with CKD (CKD G1-G5 ND) and diabetes (T1D and T2D)
Intervention	Low salt diet
Comparator	Usual salt diet
Outcomes	Outcomes listed in Table 3 Additional outcomes – body mass index
Study design	RCTs
Cochrane review	No relevant Cochrane Kidney and Transplant review
Clinical question	What are the benefits and harms of dietary interventions/patterns among adults with CKD, including people with

	ESKD, treated with kidney transplantation?
Population	Adults with CKD (CKD G1-G5 ND)
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 Table 3 Additional outcomes – BP
Study design	RCTs
Cochrane systematic review	Palmer SC, et al. Dietary interventions for adults with chronic kidney disease. Cochrane Database of Systematic Reviews. 2017:4; CD011998
Clinical question	In adults with CKD and hypertension, does exercise improve clinically relevant outcomes and decrease harms?
Population	Adults with CKD (CKD G1-G5 ND) and high blood pressure
Intervention	Any exercise intervention greater than eight weeks duration (to examine the effects of regular ongoing physical exercise training)
Comparator	Standard of care
Outcomes	Outcomes listed in Table 3 Additional outcomes – fat mass, BP, quality of life
Study design	RCTs
Cochrane systematic review	Heiwe S and Jacobson SH. Exercise training for adults with chronic kidney disease (Review). Cochrane Database of Systematic Reviews. 2011:10; CD00323
Guideline chapter	Blood pressure management in CKD non-dialysis with and without diabetes
Clinical question	In patients with CKD does lower (intensive) BP targets compared to standard BP targets improve clinical efficacy outcomes and reduce adverse effects?
Population	Adults with CKD (CKD G1-G5 ND) 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 Table 3
Study design	RCTs

Cochrane systematic review	None relevant
Clinical question	In patients with CKD does renin-angiotensin-aldosterone system (RAAS) inhibition compared to placebo/no treatment or standard of care improve clinical efficacy outcomes and reduce adverse effects?
Population	Adults with CKD (CKD G1-G5 ND) 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 Table 3
Study design	RCTs
Cochrane systematic reviews	Strippoli GFM, et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database of Systematic Reviews. 2006:4; CD006257 Sharma P, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. Cochrane Database of Systematic Reviews. 2011:10; CD007751
Clinical question	In patients with CKD does non-RAAS inhibition compared to placebo or RAAS inhibition improve clinical efficacy outcomes and reduce adverse effects?
Population	Adults with CKD (CKD G1-G5 ND) and with and without diabetes (T1D and T2D)
Intervention	Non-RAAS inhibition (alpha blockers, beta-blockers, CCB, DRI, diuretics)
Comparator	Placebo or RAASi
Outcomes	Critical and important harms listed in Table 3
Study design	RCTs
Cochrane systematic reviews	None relevant
Clinical question	In patients with CKD does dual-RAAS inhibition compared to mono-RAAS inhibition improve clinical efficacy outcomes and reduce adverse effects?
Population	Adults with CKD (CKD G1-G5 ND) and with and without diabetes (T1D and T2D)
Intervention	Dual RAAS inhibition

Comparator	Mono RAAS inhibition
Outcomes	Critical and important harms listed in Table 3
Study design	RCTs
Cochrane systematic reviews	Strippoli GFM, et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database of Systematic Reviews. 2006:4; CD006257 Sharma P, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease
Clinical question	In patients with CKD and chronic hyperkalemia, do potassium binders compared to placebo or standard of care improve clinically relevant outcomes, and decrease harms?
Population	Adults with CKD (CKD G1-G5 ND) with chronic hyperkalemia
Intervention	Potassium binders
Comparator	Placebo/standard of care
Outcomes	Critical and important harms listed in Table 3 Additional outcomes reported – hospitalization, hypokalemia, SBP, and DBP
Study design	RCTs
Cochrane systematic reviews	Natale P, et al. 2018. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease (Protocol). Cochrane Database of Systematic Reviews. 2018:11:CD013165
Guideline chapter	Blood pressure management in kidney transplant recipients
Clinical question	In transplant recipients, does reducing protein intake compared to usual protein intake improve clinically relevant outcomes and decrease harms?
Population	Kidney transplant recipients
Intervention	Low protein diet
Comparator	Usual protein diet
Outcomes	Outcomes listed in Table 3
Study design	RCTs
Cochrane review	None relevant

Clinical question	In transplant recipients, does reducing dietary salt intake compared to usual salt intake improve clinically relevant outcomes and decrease adverse effect?
Population	Kidney transplant recipients
Intervention	Low salt diet
Comparator	Normal salt diet
Outcomes	Outcomes listed in Table 3 Additional outcomes – sodium excretion, SCr, BP
Study design	RCTs
Cochrane systematic review	None relevant
Clinical question	What are the benefits and harms of dietary interventions/patterns among transplant recipients, including people with ESKD, treated with kidney transplantation?
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 Table 3 Additional outcomes – BP
Study design	RCTs
Cochrane systematic review	Palmer SC, et al. Dietary interventions for adults with chronic kidney disease. Cochrane Database of Systematic Reviews. 2017:4; CD011998
Clinical question	In transplant recipients and hypertension, does exercise improve clinically relevant outcomes and decrease harms?
Population	Kidney transplant recipients and high BP
Intervention	Any exercise intervention greater than eight weeks duration (to examine the effects of regular ongoing physical exercise training)
Comparator	Standard of care
Outcomes	Outcomes listed in Table 3 Additional outcomes – body mass index, BP, quality of life

Study design	RCTs
Cochrane systematic review	Heiwe S and Jacobson SH. Exercise training for adults with chronic kidney disease (Review). Cochrane Database of Systematic Reviews. 2011:10; CD00323
Clinical question	In transplant recipients does lower (intensive) BP target compared to standard BP targets improve clinical efficacy outcomes and reduce adverse effects?
Population	Adult and children kidney transplant recipients
Intervention	Lower BP target
Comparator	Standard BP target
Outcomes	Critical and important outcomes listed in Table 3
Study design	RCTs
Cochrane systematic review	None relevant
Clinical question	In transplant recipients what antihypertensive agents improve efficacy outcomes and reduce adverse effects?
Population	Adult and children kidney transplant recipients
Intervention	RAAS inhibition (ACEi, ARB, aldosterone antagonists), and non-RAAS inhibition (alpha-blockers, beta-blockers, CCB, diuretics, DRI)
Comparator	Placebo or standard of care
Outcomes	Critical and important outcomes listed in Table 3 Other outcomes reported: BP
Study design	RCTs
Cochrane systematic review	Cross NB, et al. Antihypertensive treatment for kidney transplant recipients. Cochrane Database of Systematic Reviews. 2009:3; CD003598
Clinical question	In transplant recipients with chronic hyperkalemia, do potassium binders compared to placebo or standard of care improve clinically relevant outcomes, and decrease harms?
Population	Kidney transplant recipients with chronic hyperkalemia
Intervention	Potassium binders
Comparator	Placebo/standard of care

Outcomes	Critical and important harms listed in Table 3
Study design	RCTs
Cochrane systematic reviews	Natale P, et al. 2018. Potassium binders for chronic hyperkalemia in people with chronic kidney disease (Protocol). Cochrane Database of Systematic Reviews. 2018:11:CD013165
Guideline chapter	Blood pressure management in children with CKD
Clinical question	In children with CKD does a lower BP target compared to a higher BP target improve efficacy outcomes and reduce adverse effects?
Population	Children with CKD
Intervention	Lower BP target
Comparator	Standard BP target
Outcomes	Critical and important outcomes listed in Table 3
Study design	RCTs
Cochrane systematic review	None relevant
Clinical question	In children with CKD what antihypertensive agents compared to standard of care improve efficacy outcomes and reduce adverse effects?
Population	Adults with CKD (CKD G1-G5 ND and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	RAAS inhibition (ACEi, ARB, aldosterone antagonists), and non-RAAS inhibition (alpha-blockers, beta-blockers, CCB, diuretics, DRI)
Comparator	Placebo or standard of care
Outcomes	Critical and important outcomes listed in Table 3 Additional outcomes: BP, SCr
Study design	RCTs
Cochrane systematic reviews	Bagga A, et al. Antihypertensive agents for children with chronic kidney disease (Protocol). Cochrane Database of Systematic Reviews. 2014:1; CD010911

Literature searches and article selection

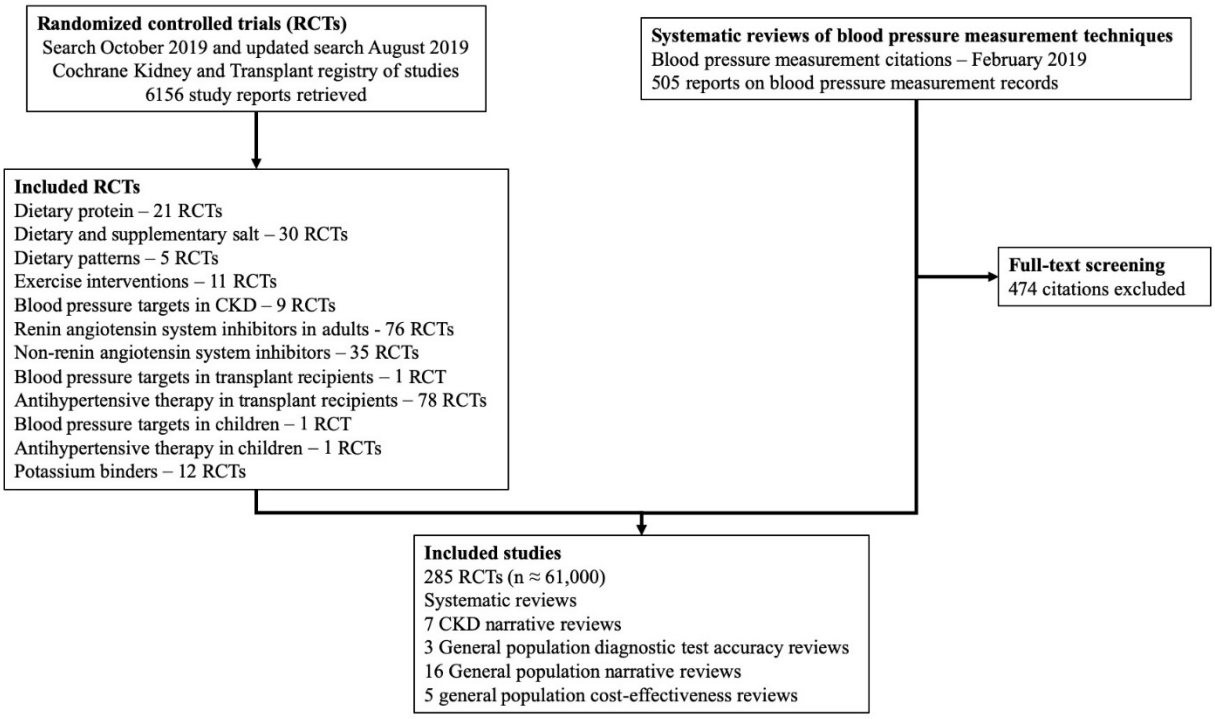
Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including clinicaltrials.gov and International Clinical Trials Register search portal.

For review topics that matched to 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 only included RCTs and not linked to any an existing Cochrane systematic review. For clinical questions that included other study types, for example, systematic reviews on non-CKD populations, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in the Data Supplement, Appendix Table S1.

The titles and abstracts resulting from the searches were screened by two members of the ERT 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 6661 citations were screened. Of these, 285 RCTs, 31 reviews were included in the evidence review (Figure 6).

Figure 6. Search yield and study flow diagram



Data extraction

Data extraction was performed independently by two members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner was 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 abstraction 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:[248]

- 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 a risk of bias?

For some topics where 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.[338] For systematic reviews of diagnostic test accuracy studies, the QUADAS-2 tool was used to assess study limitations.[339] All critical appraisal was conducted independently by two members of the ERT, 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, cardiovascular mortality, ESKD, cardiovascular events (MI, stroke, HF), dementia or cognitive impairment, doubling SCr, AKI, falls, fatigue, body weight, and BP) results were expressed as relative risk (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 effects model for dichotomous outcomes and 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.[336]

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 $P < 0.05$ was used to denote statistical heterogeneity and with an I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[336] We used conventions of interpretation as defined by Higgins et al. 2003.[340]

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 versus standard error of the effect size) when a sufficient number of studies were available (i.e., more than ten studies).[336] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity – Subgroup analysis was undertaken to explore whether 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: stage of CKD, primary kidney disease, elderly age/presence of co-morbidities, presence of proteinuria or albuminuria, diabetes, number of antihypertensives, lifestyle behaviors / health behaviors. The test of subgroup differences used the I^2 statistic and a P-value of 0.1 (noting that this is a weak test).[336]

Sensitivity analysis - The following sensitivity analyses were considered:

- 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 versus other), and country the study was conducted in.

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

Grading the quality of the evidence and 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.[337, 341] The GRADE approach 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 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 one study) all indicating concerns about the precision of the results.[341] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 5). For

observational studies and other study types, it is possible for the quality of the evidence to be upgraded from low quality of the evidence according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence see Table 6.

For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from low quality of the evidence according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence see Table 16.

Table 5. Classification for quality of the of the evidence

Grade	**Quality of evidence**	**Meaning**
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
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.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 6. GRADE system for grading quality of evidence

Study design	Staring 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) +2 very large effect size (e.g., 0.2)
	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	

Summary of findings tables

Summary of findings tables were developed to include a description of the population and the intervention and comparator. In addition, summary of findings 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 are also provided in the summary of findings table. The summary of findings tables were generated using MAGICapp, an online software application designed to support guideline development, and are available in the Data Supplement.

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, United States of America, January 2019) and by email communication. The final draft was sent for external public review, reviewers provided open-ended responses. Based on feedback, it 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 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 7). 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 the evidence, patient preferences and values, resources and other considerations (Table 8).

Table 7. KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "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.
Level 2 "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 8. 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 provided.
Quality of the evidence	A higher quality of the evidence, the more likely a strong recommendation is provided. However, there are exceptions where 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 in the judgment of the Work Group where 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.

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.

The overall quality of the evidence – The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account relative importance for each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C, or D) (Table 5).

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 judgements on the preferences and values of patients. Formal qualitative evidence synthesis on patient priorities and preferences were not undertaken.

Resources and other considerations – Healthcare and non-health care resources, including all inputs in the treatment management pathway,[342] were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs, non-healthcare resources (such as 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, for example, 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 supplement recommendations for which a larger quality 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 may also be based on limited evidence. For example, practice points were provided on monitoring, dosing adjustments for the stage of CKD, and use of therapies in specific subgroup populations. 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 or weak) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by key information (benefits and harms, quality of the evidence, values and preferences, resource use and costs), rationale, and consideration for implementation. Each recommendation is linked to relevant summary of findings 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 hand searching of journals were not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature and formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, whilst resource implications were considered in formulation of recommendations, not all topics had formal economic evaluations undertaken.

KDIGO CLINICAL PRACTICE GUIDELINE ON BLOOD PRESSURE IN CKD

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