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

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Additional information in the form of supplementary materials can be found online at http://www.kidney.org/clinical_practice_guidelines/bp.php
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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Patients</th>
<th>Implications</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
<td>Most patients should receive the recommended course of action.</td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td>Level 2</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
<td>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.</td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
</tr>
</tbody>
</table>

*The additional category ‘Not Graded’ was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

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.

STAGES OF CHRONIC KIDNEY DISEASE

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Description</th>
<th>GFR (ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5*</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; GFR, glomerular filtration rate.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

<table>
<thead>
<tr>
<th>CKD categories</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>CKD of any stage (1–5), with or without a kidney transplant, including both non-dialysis dependent CKD (CKD 1–5 ND) and dialysis-dependent CKD (CKD 5D)</td>
</tr>
<tr>
<td>CKD ND</td>
<td>Non-dialysis-dependent CKD of any stage (1–5), with or without a kidney transplant (i.e., CKD excluding CKD 5D)</td>
</tr>
<tr>
<td>CKD T</td>
<td>Non-dialysis-dependent CKD of any stage (1–5) with a kidney transplant</td>
</tr>
</tbody>
</table>

Specific CKD Stages

| CKD 1, 2, 3, 4 | Specific stages of CKD, CKD ND, or CKD T |
| CKD 3–4, etc. | Range of specific stages (e.g., both CKD 3 and CKD 4) |
| CKD SD | Dialysis-dependent CKD 5 |
| CKD HD | Hemodialysis-dependent CKD 5 |
| CKD SPD | Peritoneal dialysis-dependent CKD 5 |

CONVERSION FACTORS OF METRIC UNITS TO SI UNITS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metric units</th>
<th>Conversion factor</th>
<th>SI units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea nitrogen</td>
<td>mg/ml</td>
<td>0.357</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Creatinine (serum)</td>
<td>mg/dl</td>
<td>88.4</td>
<td>μmol/l</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>ml/min</td>
<td>0.01667</td>
<td>ml/s</td>
</tr>
</tbody>
</table>

Note: Metric unit × conversion factor = SI unit.
Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASK</td>
<td>African American Study of Kidney Disease and Hypertension</td>
</tr>
<tr>
<td>ABCD</td>
<td>Appropriate Blood Pressure Control in Diabetes</td>
</tr>
<tr>
<td>ABPM</td>
<td>Ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>ACCF</td>
<td>American College of Cardiology Foundation</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin/creatinine ratio</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation</td>
</tr>
<tr>
<td>AER</td>
<td>Albumin excretion rate</td>
</tr>
<tr>
<td>AGREE</td>
<td>Appraisal of Guidelines for Research and Evaluation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin-receptor blocker</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CASE J</td>
<td>Candesartan Antihypertensive Survival Evaluation in Japan</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>CKD Epidemiology Collaboration</td>
</tr>
<tr>
<td>CKD ND</td>
<td>Non-dialysis-dependent CKD of any stage</td>
</tr>
<tr>
<td>CKD T</td>
<td>Non-dialysis-dependent CKD of any stage with a kidney transplant</td>
</tr>
<tr>
<td>CKD 5D</td>
<td>Dialysis-dependent CKD 5</td>
</tr>
<tr>
<td>CKD-D</td>
<td>Chronic Kidney Disease in Children</td>
</tr>
<tr>
<td>CNI</td>
<td>Calcineurin inhibitor</td>
</tr>
<tr>
<td>COGS</td>
<td>Conference on Guideline Standardization</td>
</tr>
<tr>
<td>COX-2</td>
<td>Cyclooxygenase-2</td>
</tr>
<tr>
<td>CPG</td>
<td>Clinical practice guideline</td>
</tr>
<tr>
<td>CRIC</td>
<td>Chronic Renal Insufficiency Cohort</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study</td>
</tr>
<tr>
<td>DRI</td>
<td>Direct renin inhibitor</td>
</tr>
<tr>
<td>EDC</td>
<td>Pittsburgh Epidemiology of Diabetes Complications Study</td>
</tr>
<tr>
<td>ERT</td>
<td>Evidence review team</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients</td>
</tr>
<tr>
<td>EUROPA</td>
<td>European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>HOT</td>
<td>Hypertension Optimal Treatment</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan Diabetic Nephropathy Trial</td>
</tr>
<tr>
<td>INVEST</td>
<td>International Verapamil SR Trandolapril study</td>
</tr>
<tr>
<td>JATOS</td>
<td>Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients</td>
</tr>
<tr>
<td>JNC</td>
<td>Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>KEEP</td>
<td>Kidney Early Evaluation Program</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention trial</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NKF</td>
<td>National Kidney Foundation</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial</td>
</tr>
<tr>
<td>PCR</td>
<td>Protein/creatinine ratio</td>
</tr>
<tr>
<td>PEACE</td>
<td>Prevention of Events with Angiotensin-Converting Enzyme Inhibitor Therapy</td>
</tr>
<tr>
<td>PREVEND IT</td>
<td>Prevention of Renal and Vascular Endstage Disease Intervention Trial</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril Protection Against Recurrent Stroke Study</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>REIN-2</td>
<td>Ramipril Efficacy in Nephropathy 2</td>
</tr>
<tr>
<td>RENAL</td>
<td>Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SECRET</td>
<td>Study on Evaluation of Candesartan Cilexetil after Renal Transplantation</td>
</tr>
<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Program</td>
</tr>
<tr>
<td>SPRINT</td>
<td>Systolic Blood Pressure Intervention Trial</td>
</tr>
<tr>
<td>STONE</td>
<td>Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>Shanghai Trial of Nifedipine in the Elderly</td>
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<tr>
<td>TRANSCEND</td>
<td>Systolic Hypertension in Europe</td>
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<tr>
<td>VALISH</td>
<td>Valsartan in Elderly Isolated Systolic Hypertension</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE
This Clinical Practice Guideline document is based upon systematic literature searches last conducted in January 2011, supplemented with additional evidence through February 2012. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

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 as a result of 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 or 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’ Biographic and Disclosure Information section, and is kept on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO.
It is our hope that this document will serve several useful purposes. Our primary goal is to improve patient care. We hope to accomplish this, in the short term, by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice. By providing comprehensive evidence-based recommendations, this guideline will also help define areas where evidence is lacking and research is needed. Helping to define a research agenda is an often neglected, but very important, function of clinical practice guideline development.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and the strength of recommendations. In all, there were no recommendations in this guideline for which the overall quality of evidence was graded ‘A,’ whereas 4 (23.5%) were graded ‘B,’ 3 (17.7%) were graded ‘C,’ and 10 (58.8%) were graded ‘D.’ Although there are reasons other than quality of evidence that underpin a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 8 (47.1%) recommendations graded ‘1’ and 9 (52.9%) graded ‘2.’ There were no recommendations graded ‘1A,’ 4 (23.5%) were ‘1B,’ 2 (11.8%) were ‘1C,’ and 2 (11.8%) were ‘1D.’ There were no recommendations graded ‘2A’ or ‘2B,’ 1 (5.9%) was ‘2C,’ and 8 (47.1%) were ‘2D.’ There were 4 (19.1%) statements that were not graded.

Some argue that recommendations should not be made when evidence is weak. However, clinicians still need to make decisions in their daily practice, and they often ask, ‘What do the experts do in this setting?’ We opted to give guidance, rather than remain silent. These recommendations are often rated with a low strength of recommendation and a low quality of evidence, or were not graded. It is important for the users of this guideline to be cognizant of this (see Notice). In every case these recommendations are meant to be a place for clinicians to start, not stop, their inquiries into specific management questions pertinent to the patients they see in daily practice.

We wish to thank Dr Gavin Becker who co-chaired the Work Group with David Wheeler, along with all of the Work Group members who volunteered countless hours of their time developing this guideline. We also thank the Evidence Review Team members and staff of the National Kidney Foundation who made this project possible. Finally, we owe a special debt of gratitude to the many KDIGO Board members and individuals who volunteered time reviewing the guideline, and making very helpful suggestions.

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Abstract

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease aims to provide guidance on blood pressure management and treatment for all non-dialysis-dependent CKD patients and kidney transplant recipients. Guideline development followed an explicit process of evidence review and appraisal. Treatment approaches are addressed in each chapter and guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. Ongoing areas of controversies and limitations of the evidence are discussed and additional suggestions are also provided for future research.

**Keywords:** blood pressure; chronic kidney disease; clinical practice guideline; evidence-based recommendation; KDIGO; systematic review

**CITATION**

Chapter 2: Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients

GENERAL STRATEGIES
2.1: Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. (Not Graded)
2.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (Not Graded)

LIFESTYLE MODIFICATION
2.3: Encourage lifestyle modification in patients with CKD to lower BP and improve long-term cardiovascular and other outcomes:
   2.3.1: We recommend achieving or maintaining a healthy weight (BMI 20 to 25). (1D)
   2.3.2: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated. (1C)
   2.3.3: We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week. (1D)
   2.3.4: We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. (2D)

Chapter 3: Blood pressure management in CKD ND patients without diabetes mellitus

3.1: We recommend that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)
3.2: We suggest that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2D)
3.3: We suggest that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2C)
3.4: We suggest that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. (2D)
3.5: We recommend that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.
Chapter 4: Blood pressure management in CKD ND patients with diabetes mellitus

4.1: We recommend that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)

4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2D)

4.3: We suggest that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). (2D)

4.4: We recommend that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

Chapter 5: Blood pressure management in kidney transplant recipients (CKD T)

5.1: We suggest that adult kidney transplant recipients whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)

5.2: In adult kidney transplant recipients, choose a BP-lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co-morbid conditions. (Not Graded)

Chapter 6: Blood pressure management in children with CKD ND

6.1: We recommend that in children with CKD ND, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (1C)

6.2: We suggest that in children with CKD ND (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (2D)

6.3: We suggest that an ARB or ACE-I be used in children with CKD ND in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (2D)

Chapter 7: Blood pressure management in elderly persons with CKD ND

7.1: Tailor BP treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. (Not Graded)
Chapter 1: Introduction


There is a strong association between chronic kidney disease (CKD) and an elevated blood pressure (BP) whereby each can cause or aggravate the other. BP control is fundamental to the care of patients with CKD and is relevant at all stages of CKD regardless of the underlying cause. Clinical practice guidelines (CPGs) have been published on this topic by many authoritative bodies over the past decade, the most comprehensive being the National Kidney Foundation’s (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease, which was based on evidence collected up to 2001 (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm). The Kidney Disease: Improving Global Outcomes (KDIGO) Board believed that it would be clinically useful to update this CPG to incorporate the evidence gathered since then. KDIGO therefore commissioned an evidence review to include the recent literature and assembled a Work Group with the mandate of writing an updated guideline relevant to an international audience. This KDIGO Guideline, entitled “Management of Blood Pressure in Chronic Kidney Disease,” is the result of these efforts.

Scope of this guideline

This Guideline has been developed to provide advice on the management of BP in patients with non-dialysis-dependent CKD (CKD ND) (see Reference Keys).

BP. We have avoided using the term ‘hypertension’ in our title because this implies that there is a BP value above or below which morbidity or mortality changes in a stepwise fashion, hence suggesting that it is possible to set a universal BP target. In reality, it proved difficult to define precise targets appropriate for all CKD subpopulations, consistent with the notion that the ‘ideal’ BP may differ between patients, once other factors are considered. These factors include specific features of CKD such as the severity of albuminuria or proteinuria, the presence of other risk factors for cardiovascular disease (CVD) and co-morbidities. Another reason for our choice of terminology is that agents introduced primarily to treat high BP may have actions that may not be directly linked to BP-lowering (e.g., the anti-albuminuric effects of angiotensin-convertase enzyme inhibitors [ACE-Is] and angiotensin-receptor blockers [ARBs]).

Definition of CKD. The Work Group defined CKD according to the standard KDOQI classification system\(^2\) as endorsed by KDIGO.\(^3\)

Populations of interest. The populations covered in this guideline are:
- Adults with CKD ND without diabetes mellitus
- Adults with CKD ND with diabetes mellitus
- Adults with CKD ND who have received a kidney transplant (CKD T)
- Children with CKD ND
- Elderly with CKD ND

The scope of this guideline did not include BP management in patients with dialysis-dependent CKD 5 (CKD 5D) since this has been the topic of a recent KDIGO consensus conference\(^4\) and has been covered by two recent systematic reviews.\(^5,6\) There are other groups of patients with CKD for whom specific recommendations might be welcome, but who are not represented in sufficient numbers in randomized controlled trials (RCTs) to constitute a sufficiently robust evidence base. The evidence review team (ERT) was asked to present the evidence separately for adults with CKD and diabetes, since these individuals constitute the single largest subgroup of CKD patients in the world.

The separation of the evidence base according to diabetes status meant that there were two separate datasets for the Work Group to review. Although the two sets of recommendations had much in common, the Work Group decided that they differed sufficiently in detail to warrant two separate chapters. Adults who received a kidney transplant, children, and the elderly were also thought to deserve dedicated chapters, although the evidence base for each of these subpopulations is rather small.

The Work Group was unable to identify sufficient evidence to make recommendations according to severity (stage) of CKD, although common sense dictates that pharmacological management should differ at least between mild CKD (patients with normal glomerular filtration rate [GFR]) and advanced CKD (patients with low GFR). However, the Work Group did consider the modification of drug dosages and risks related to the various classes of BP-lowering agents in the context of CKD in Chapter 2.

Clearly there are many other populations that could have been considered. CKD patients with glomerulonephritis are the subject of a recent KDIGO Guideline,\(^7\) so they were not considered separately here. Although management of BP in the pregnant CKD patient is an important issue, there is insufficient evidence in this subgroup to allow recommendations to be made.\(^8\) Furthermore, the Work Group did not consider the management of BP in patients with acute kidney injury.
Interventions. Interventions primarily aiming at modifying BP include advice on lifestyle and administration of pharmacological agents that reduce BP. The efficacies of both strategies have been widely studied in the general population with high BP. The pharmacology of anti-hypertensive agents was detailed in the 2004 KDOQI guideline.5

Of the available RCTs that met our inclusion criteria, most involved agents interfering with the renin-angiotensin-aldosterone system (RAAS). Accordingly, these agents may be over-represented in this Guideline, and if so, it is because of the availability of the evidence rather than a deliberate focus by the Work Group.

Evidence for interventions

Because CKD is common and BP levels are often elevated in CKD populations, the management of BP in CKD patients could have an enormous global impact. Given that the focus of the Guideline is on management and the comparative effectiveness of various interventions, the preferred and most robust evidence is derived from large-scale RCTs which assessed hard clinical outcomes. The ERT was asked to include RCTs with a minimum of 50 patients in each arm and interventions included pharmacological agents (alone or in combination), lifestyle modifications, and trials assessing various levels of BP control. Outcomes of interest were mortality, cardiovascular events and changes in kidney function including urine albumin or protein excretion.

Reduction in BP, particularly when achieved using agents that interfere with the RAAS, can lead to acute reductions in kidney function and albuminuria; thus the minimal duration of follow-up in RCTs required for their inclusion in the evidence review was set at 1 year for kidney function, cardiovascular outcomes, and mortality and 3 months for urine albumin or protein levels. Because there were so few trials assessing lifestyle modifications, BP reduction was included as an outcome, with the minimum follow-up period set at 6 weeks.

The approach to the evidence review is described in detail in Methods for Guideline Development. The ERT conducted a systematic review of RCTs involving individuals with CKD. This was supplemented with published systematic reviews and meta-analyses (which often included smaller RCTs). Work Group members further supplemented this yield with selected RCTs that included individuals at increased risk of CVD but who were not specifically chosen on the basis of having CKD. The Work Group also helped identify RCTs that included CKD subgroups. To a lesser extent, the Work Group made reference to observational evidence from large population studies where evidence from RCTs was perceived to be insufficient.

Not all questions of interest have been the subject of RCTs; some issues do not lend themselves to be studied in this manner. To facilitate further discussion on major issues relevant to management of BP in CKD patients (for which there is some evidence but ongoing controversy remains), the Work Group included a chapter on Future Directions and Controversies (Chapter 8). For other issues widely accepted in practice, but not supported by evidence from RCTs, the Work Group wrote ungraded recommendations reflecting the consensus of its members. These ungraded statements are explained in detail in the accompanying narrative.

The Work Group did not wish to provide advice on specific treatment questions for which there was no supporting evidence. By highlighting these gaps in knowledge, we aim to promote further research.

During the preparation of this Guideline, the Work Group was aware that other international organizations were writing new or updating old guidelines that were potentially relevant to the management of BP in CKD patients. The Work Group kept in contact with these other organizations and sought to achieve consistency with their recommendations as much as possible.

Measurement of BP

The Work Group recognized that many reviews on the methodology of BP measurement have been published9,10 and that this topic was covered in detail in the 2004 KDOQI Guideline.1 Previous publications have highlighted inconsistencies between conventional office (or clinic) BP measurements and other methods, such as self-measurement of BP at home or ambulatory blood pressure monitoring (ABPM).11–13 Many recommendations regarding when and how to use ABPM in hypertensive patients not known to have CKD have also been published. Although few studies have assessed the value of ABPM CKD patients, the small, short-term studies that do exist reflect the inconsistency between office BP measurements and other BP measurements and also suggest that ABPM gives a better indication of overall BP and kidney prognosis than office BP measurements.11–13 Despite this, to date there has only been one large RCT of BP control in CKD patients (all of whom were children) in which ABPM was used as the method for BP assessment.14 We therefore cannot provide evidence-based recommendations regarding the use of ABPM to evaluate BP in CKD patients but existing evidence is reviewed in Chapter 8.

Since office BP measurements are used in almost all RCTs of interventions that modify BP in CKD, this Guideline can only make recommendations about BP assessed by this method. Because office readings are known to vary from day to day, management decisions should be based on repeated measurements,15 as emphasized in this guideline by the use of the term ‘consistently’ (e.g., Recommendation 4.1 … maintain a BP that is consistently ≤140 mm Hg systolic …). The term is used simply to imply that the BP has been measured more than once and that there was meaningful agreement between the measurements.

The Work Group also discussed whether to consider pulse pressure and/or pulse wave velocity, measures of arterial compliance that may provide important prognostic information in CKD patients. However, there is a paucity of data from RCTs showing that any particular intervention reliably
alters these measures and subsequently influences mortality or morbidity. Thus the Work Group was not able to make any evidence-based recommendations relating to these measurements. However, these issues are of interest for the future of BP assessment in CKD patients and are discussed in further detail in Chapter 8.

**Albuminuria and proteinuria**

Some BP-lowering agents are particular effective at reducing albuminuria or proteinuria, suggesting that BP management should differ depending on the amount of albumin or protein in the urine.16–19 Accordingly, as in the KDOQI 2004 Guidelines and the majority of other CPGs addressing BP control in patients with CKD or diabetes, the Work Group has attempted to stratify treatment effects according to urinary albumin excretion. Based on a recent KDOQI Controversies Conference and data from the CKD Prognosis Consortium, the Work Group used three categories (levels) of albuminuria.20 Wherever possible, the Work Group modified its recommendations to fit these categories, although since not all RCTs use this classification system, consistency was not achievable. The three categories of urinary albumin excretion are as follows: >300 mg per 24 h (or ‘macroalbuminuria’), 30 to 300 mg per 24 h (or ‘microalbuminuria’), and <30 mg per 24 h (Table 1). When other measures (such as assessment of proteinuria, ratios of urinary albumin or urinary protein to urine creatinine, or protein reagent strip readings) were used in RCTs, these measures were translated to albumin excretion rates (AERs) per 24 h, recognizing that these converted values are approximations at best. Recommendations and suggestions for interventions based on albumin levels expressed in milligrams per 24 h can also be converted (Table 1).

**BP thresholds and targets**

Perhaps the most important questions for health care professionals are first, at what BP level should BP-lowering strategies be introduced in CKD patients (i.e., what is the BP treatment threshold?), and second, what BP levels should be aimed for (i.e., what is the BP treatment target?). Although the evidence base for the BP treatment threshold differs from the evidence base for the BP target, we could not find a robust justification to recommend different BP levels for these two parameters. Doing so might also lead to confusion, since we would be recommending two different BP levels possibly with two evidence ratings and would not be able to provide coherent advice for managing patients between the recommended threshold and target BPs.

Studies that have not specifically targeted CKD patients demonstrate that BP is a continuous risk factor for CVD outcomes.21 BP targets could differ depending on the presence of other CVD risk factors in each patient. This approach contrasts with the ‘one size fits all’ philosophy that has previously been endorsed. There are far less data in CKD patients to inform the best approach. In RCTs involving CKD patients who are randomized to different BP targets, the achieved differences between groups are usually less than the targeted differences. Intention-to-treat analyses allow conclusions to be drawn based on target BP levels rather than achieved BP levels. The Work Group generally followed this convention and based recommendations on target levels BP levels rather than those achieved in the RCTs. It also considered the evidence derived from RCTs in which patients were not randomized to BP targets but achieved BPs were reported. The logic for using target BP levels in RCTs rather than the achieved BP levels observed as the basis for setting guideline targets has been questioned;22 this concern is one reason for our conservative approach to BP target setting in this Guideline.

**Outcomes**

The major outcomes relevant to BP control in CKD patients are kidney disease progression and cardiovascular events (including stroke).

**Kidney outcomes.** Although it is possible for a diagnosis of CKD to be made in an individual with a normal GFR and AER and even a normal BP (for example on the basis of an imaging study, as in early adult polycystic kidney disease), most patients recruited into RCTs addressing BP and its management in CKD have a reduced GFR or persistently elevated albumin excretion. Entry criteria for RCTs involving
CKD patients are usually based on these parameters, changes in which may form the basis for kidney end points. 

**Kidney function.** Changes in kidney function are important outcomes in clinical trials assessing the effects of various BP-management regimens in CKD patients. Although the most important events are the requirement for renal replacement therapy or death due to kidney failure, many studies have used surrogates such as changes in GFR or the percentage of patients in whom the serum creatinine (Scr) level doubles. Such numerical end points may be particularly relevant in trials that include patients with early-stage CKD, among whom kidney failure and death are uncommon events. One problem with the assessment of such surrogates is that the therapeutic agent used to modify BP may also directly alter kidney function. For example, ACE-Is are known to reduce GFR through a vasodilator effect on the efferent arteriole. This effect may be beneficial in the early stages of CKD when a reduced intra-glomerular pressure is protective, but might be detrimental at a later stage when kidney function is severely compromised and dialysis may be imminent, at which time GFR may increase if ACE-Is are withdrawn. Thus, a drug may modify GFR via a mechanism that does not directly involve changes in systemic BP and the impact of this effect on the patient may vary according to CKD stage. The Work Group bore such considerations in mind when assessing the evidence and viewed consistency in the change of GFR outcomes across various CKD stages as a strong indicator of the benefits of a particular agent on kidney function.

**Albuminuria.** The level of albuminuria in CKD predicts not only the prognosis with respect to kidney function but also morbidity and mortality from CVD events including stroke. Urinary albumin excretion is influenced by BP and by many of the agents used to reduce BP, particularly ACE-Is and ARBs.

The concept of using albuminuria as a surrogate marker for CKD progression and CVD outcomes is widely accepted, with the reduction of urine albumin levels often being regarded as a target for therapy. This would mean that treatment would be escalated to reduce albuminuria to a preferred level, regardless of BP. Treating to an albumin target usually involves an escalation of RAAS blockade, which can be achieved by restricting dietary salt intake, increasing doses of an ACE-I or an ARB, combining the two classes of medication, or by adding a thiazide diuretic, an aldosterone-receptor blocker or a direct renin inhibitor (DRI).

While a strong case has been made for targeting a reduction of albuminuria, particularly with agents that interfere with the RAAS, there have been no large studies in CKD patients reporting long term differences in GFR or CVD outcomes where reduction in urinary albumin levels (regardless of BP) was the primary objective. There is also uncertainty as to whether the dose of a particular agent that is required to achieve BP control is necessarily the same as the dose required for albuminuria reduction. The Work Group thus decided that it was premature to recommend an albuminuria reduction target strategy for all cases of CKD but felt this deserved further discussion in Chapter 8.

**Cardiovascular outcomes.** Recognition that premature CVD is a major cause of death in CKD has led to CVD risk management becoming a recognized component of the care of the CKD patient. In planning appropriate interventions, one strategy is simply to extrapolate data from CVD outcomes trials in the general population. This approach has been challenged because the benefits of interventions predicted in observational studies are not always observed in RCTs involving CKD patients. In CKD-ND patients, unlike CKD patients on dialysis (CKD 5D), a higher BP is generally associated with a higher CVD risk, making BP-lowering an attractive goal in an effort to reduce cardiovascular morbidity and mortality.

Although no RCTs assessing BP lowering agents have been specifically designed or powered to assess cardiovascular event rates as the primary outcome in any group of CKD patients, several studies assessing cardiovascular outcomes have included CKD patients and this information was considered in making the recommendations.

**Intended Users of this Guideline**

This Guideline is primarily aimed at health care professionals caring for individuals with CKD, including nephrologists, nurses, and pharmacists, as well as at physicians involved in the care of patients with diabetes and primary care providers. The Guideline is not aimed at health care administrators, policy makers, or regulators, although the explanatory text might be of value to these groups and assist in enhancing implementation and adherence to BP-lowering strategies. The Guideline is also not designed to be used in the development of clinical performance measures. Some of the difficulties in implementation and in auditing BP target achievement are discussed in Chapter 8.

**DISCLAIMER**

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Chapter 2: Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients


INTRODUCTION
This section outlines lifestyle and pharmacological methods to reduce BP in patients with non-dialysis-dependent CKD (CKD ND). Because these strategies were covered in detail in the 2004 KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm),1 we concentrate on issues relating to BP control in CKD patients that have arisen since 2004. Additional information that may be of help to the clinician (although not specifically relevant to CKD patients) can be found in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf).9

GENERAL STRATEGIES
It is generally accepted that a stepwise combination of lifestyle modifications and drug therapy should be used to lower BP in CKD patients, with escalation of efforts depending on factors such as the severity of the BP elevation, the co-morbidities present and the age of the patient.

2.1: Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. (Not Graded)

RATIONALE
We recognize that individual decision making is required regarding BP targets and agents with the risks and benefit being taken into consideration; however, since there is little evidence from RCTs to guide these decisions, this recommendation has not been graded.

The potential benefits of lower BP include a decreased risk of both CVD and progression of CKD. To assess the likely benefit in a given patient, the clinician needs to consider such issues as the prior rate of CKD progression, the expected course of the specific disease, the level of urinary albumin excretion and the presence or absence of other risks of CVD. Potential adverse effects generic to treatment used to lower BP include decreases in cerebral perfusion (contributing to dizziness, confusion and falls) and acute deterioration in kidney function.

It is widely acknowledged that achievement of a reduction in BP can be difficult in CKD patients, particularly in the elderly, those with co-morbidities, and those with diabetes mellitus.1,9,30 Increased conduit-artery stiffness, resulting in high pulse pressure (with high systolic and low diastolic pressures) is common in CKD patients, the elderly and patients with diabetes.31–36 Arterial stiffening is associated with an increased risk of CVD independent of other recognized risk factors.37–39 With a high pulse pressure, efforts to reduce systolic BP in older patients and those with coronary artery disease (CAD) can result in lowering diastolic BP to levels well below diastolic targets, which may be associated with greater morbidity or mortality.40,41 A J-shaped relationship between achieved BP and outcome has been observed in the elderly and in patients with vascular disease, possibly suggesting that BP can be reduced too far in these patients.40,42,43 Discussion of this issue is further elaborated in Chapters 7 and 8. Unfortunately, in CKD patients, the available evidence proved to be insufficient to allow the Work Group to define the lowest BP targets (see Chapter 8).

Similarly, when considering the choice of BP-lowering agents, decision making should be tailored to the individual patient. For instance, ACE-Is and ARBs are potentially harmful in the presence of significant renovascular disease or volume depletion, or when used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors (as outlined later in this chapter). The presence of diabetic retinopathy in a CKD patient may also influence BP target and choice of agent as outlined in Chapter 4.

Based on these considerations, the Work Group concluded that it is good clinical practice to assess the risks and benefits of BP-lowering treatment in an individual patient and to tailor therapy accordingly.

2.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (Not Graded)

RATIONALE
Patients with CKD, particularly the elderly31 and diabetic patients with autonomic neuropathy, are prone to orthostatic hypotension,44,45 which may be exacerbated by volume depletion. Many CKD patients will require combinations of drugs to control BP including vasodilators, which can cause or exacerbate postural hypotension. This can lead to postural dizziness, reduced adherence and in extreme cases, syncope.
or falls with consequent injury. Accordingly, it is sensible to regularly check for symptoms of postural dizziness and to compare lying, sitting and standing BP in CKD patients, particularly before and after altering the treatment regimen.

**LIFESTYLE MODIFICATION**

The impact of lifestyle-related factors on BP and the risk of cardiovascular and other diseases have been well documented. A number of observational studies in the general population have linked factors such as salt intake, weight and body mass index (BMI), exercise frequency, and alcohol intake with BP level. RCTs addressing many of these factors have been undertaken, the results of which have led the authors of BP guidelines for the general population (e.g., JNC 7) to make specific recommendations about the management of lifestyle as a key component of BP management.

Individuals with CKD generally have higher BP levels than people with normal kidney function and their BP may be particularly sensitive to some factors related to lifestyle. For example, high salt intake may potentially have a greater impact on BP in patients with CKD than in those without CKD since CKD may reduce the ability to excrete the salt load in the urine. CKD patients may also be more sensitive to harms related to lifestyle interventions; for instance, an individual with tubular disease with salt wasting from the kidney could be at increased risk of hypovolemia if salt intake is restricted. Furthermore, some potential lifestyle interventions, such as increased physical exercise, may be difficult for patients with CKD owing to reduced energy levels.

Lifestyle modification offers the potential to lower BP in a simple, inexpensive, effective fashion while also improving a range of other outcomes (e.g., changes in lipid levels resulting from diet and exercise and liver function through moderation of alcohol intake). Because lifestyle changes are applicable to the general population and are potentially implementable at low expense worldwide, the Work Group felt many were sufficiently important to warrant an evidence grade of level 1, with the strength of the evidence varying in accordance to their potential to do harm in CKD patients.

2.3: **Encourage lifestyle modification in patients with CKD to lower BP and improve long-term cardiovascular and other outcomes:**

2.3.1: We recommend achieving or maintaining a healthy weight (BMI 20 to 25). (*ID*)

**RATIONALE**

- Weight reduction lowers BP in the general population.
- Observational studies show that weight-loss strategies reduce BP in CKD patients.
- Weight-reduction strategies may result in other health benefits to CKD patients including reduction in urine albumin or protein levels, improved lipid profile and increased insulin sensitivity.

The prevalence of obesity is very high in Western countries and is increasing rapidly in developed and developing countries around the world. A strong relationship exists between body weight (usually defined as BMI) and BP levels in the general population. Compared with a person of normal weight, individuals who are overweight or obese tend to have higher BP levels, abnormalities in a range of other cardiovascular parameters (e.g., dyslipidemia), and an increased risk of cardiovascular events.

**Weight and BP.** A weight-reducing diet has been clearly demonstrated to lower BP in overweight individuals in the general population. A systematic review published in 2006 identified 14 trials assessing the effects of dietary modification on BP in the general population, all but two of which assessed the effects of weight reduction in overweight persons. Many of the 14 trials also included other modifications to diet (e.g., increased fruit and vegetable intake and salt reduction) and lifestyle (e.g., increased exercise). Trials were 8 to 52 weeks in duration and mostly included participants with elevated BP levels. The quality of the trials was generally suboptimal. Overall, dietary modification reduced systolic BP by 6.0 mm Hg (95% confidence interval [CI] 3.4–8.6) and diastolic BP by 4.8 mm Hg (95% CI 2.7–6.9). High levels of heterogeneity in the trial results were observed.

The available data regarding the effects of weight loss in CKD patients has been systematically reviewed by Navaneethan et al. Only two randomized trials were identified but 11 observational studies were also included. A range of surgical and non-surgical weight-loss interventions were assessed. All interventions, when taken together, resulted in significant reduction in weight among CKD patients. This was associated with a reduction in urinary protein excretion (described in two studies) but no overall effect on the GFR, possibly due to the short term nature of the studies. Effects on BP were not reported in the RCTs, whereas the observational studies reported consistently large, significant reductions in BP compared to baseline with both non-surgical weight loss (weighted mean difference, 22.6 mm Hg; 95% CI 19.1–26.2; *P* < 0.0001) as well as surgical weight loss (weighted mean difference, 22.6 mm Hg; 95% CI 19.1–26.2; *P* < 0.0001). Thus, weight loss likely improves BP in patients with CKD, although high-quality RCTs are needed to confirm this finding.

**Body weight and outcomes.** In the general population, overweight and obesity have been clearly shown to be associated with an increased risk of cardiovascular events and death. A J-curve relationship has been described in many reports, revealing an increased risk in underweight individuals (e.g., those with a BMI <18.5) as well. RCTs have demonstrated that weight loss reduces the incidence of diabetes, but any beneficial effects on cardiovascular outcomes or survival remain to be proven. Indeed, a number of RCTs involving use of pharmacological agents to induce weight loss have been stopped early owing to unintended and unanticipated adverse
effects of the agent being assessed (e.g., rimonabant and sibutramine).56,57

The data are less clear for patients with CKD. Obesity has been proposed as a possible potentiator of CKD progression; however, reliable data remain sparse. Many observational studies have suggested that among patients with advanced CKD who are dialysis-dependent, and particularly hemodialysis-dependent, clinical outcomes might actually be better for overweight individuals than for non-overweight individuals.58,59 Other studies have reported conflicting results.60 It is possible that these observations are due to reverse causality, with the results driven by underlying malnutrition or inflammation in the lower-weight patients and they may also reflect differences in the proportions of muscle and fat in patients with CKD compared with people without CKD. These data should therefore be interpreted with caution.

For overweight individuals, the method used to reduce body weight may be important within the context of CKD. Popular and widely recommended weight-loss diets are commonly high in potassium and protein and may therefore increase risks of hyperkalemia and CKD progression in patients with CKD. As the potential benefits and harms have not been specifically addressed in the CKD population, the use of these diets is not recommended.

Overall, the available data suggest that achieving or maintaining a body weight in the healthy range will lead to improved BP levels and better long-term CKD outcomes. This is particularly clear for individuals with CKD stages 1–2. Caution should be exercised in patients with more advanced CKD, because malnutrition may be associated with adverse outcomes. Since a high weight may be protective in CKD 5D patients, there could be risks associated with encouraging weight loss in those with advanced CKD. Hence, Recommendation 2.3.1 was graded 1D.

2.3.2: We recommend lowering salt intake to <90 mmol (≤2 g) per day of sodium (corresponding to 5.0 g of sodium chloride), unless contraindicated. (1C)

RATIONALE
- Lowering salt intake reduces BP in the general population.
- In CKD patients with reduced GFR, salt retention is associated with an increase in BP.

A relationship between average daily salt intake and BP levels has long been recognized, leading to calls from the World Health Organization (WHO) for salt intake to be restricted to improve BP levels (http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf).61 Restricting salt intake clearly lowers BP by a moderate amount, as demonstrated in a systematic review of seven trials,53 most of which assessed the impact of restricting salt intake to 4 to 6 g (70–100 mmol). Overall, BP levels were reduced as compared to baseline levels: systolic BP by 4.7 mm Hg (95% CI 2.2–7.2) and diastolic BP by 2.5 mm Hg (95% CI 1.8–3.3). Moderate heterogeneity was observed in the effects on systolic BP, but this was corrected when one outlier trial was excluded. Other systematic reviews including a different group of trials have suggested similar but somewhat smaller benefits.62

Altering in salt handling are likely to be a significant contributor to elevated BP levels in patients with CKD. Although no large scale long term RCTs of salt restriction in CKD patients were found, there is no reason to believe that BP reductions should not also be observed. Reducing salt intake could have a greater capacity to lower BP in patients with CKD who have salt and water retention and this intervention should be routinly discussed with such individuals. A low-sodium diet has been shown to further reduce BP and urine albumin or protein levels in the short term in patients on ARBs63–66 and may be a consideration for those with high BP who have a poor response to ACE-Is or ARBs.

Some forms of CKD may be associated with salt wasting from the kidney. Affected individuals may be at higher than usual risk of volume depletion and electrolyte disturbances potentiated by salt restriction. Volume and electrolyte status should thus be carefully monitored in patients with CKD undergoing salt restriction. Recent studies suggesting that low urinary sodium excretion (hence perhaps low dietary sodium intake) associates with higher mortality in diabetes have yet to be confirmed by others or explained.67,68

Since salt restriction is an inexpensive and important contributor to lowering BP in the generally population worldwide, this intervention was deemed a level 1 recommendation. But since the evidence base for CKD patients included only small, short-term RCTs involving special circumstances, Recommendation 2.3.2 was graded 1C.

2.3.3: We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week. (1D)

RATIONALE

Increased physical exercise has been linked to a broad range of positive health outcomes through a wide variety of mechanisms. A clear inverse relationship between exercise and average daily BP has been demonstrated by a large volume of previous epidemiological data in the general population, although exercise may lead to modest and acute physiological increases in BP during the time of the activity.

The effects of exercise on BP in the context of RCTs have been systematically reviewed in the general population.53 Most of the 21 RCTs included in the review examined the efficacy of 3 to 5 weekly sessions of aerobic exercise lasting 30 to 60 minutes. Overall, the exercise group had an average reduction in systolic BP of 6.1 mm Hg from baseline (95% CI 2.1–10.1) and in diastolic BP of 3.0 mm Hg (95% CI 1.1–4.9). The effects were slightly reduced when one outlier trial was excluded from the analysis (to average reductions of 4.6 and 2.6 mm Hg, respectively), but moderate heterogeneity among the results remained.
No RCTs in the CKD population were found. A post hoc observational analysis of the Modification of Diet in Renal Disease (MDRD) study population did not identify a clear relationship between level of physical activity at baseline and the subsequent risk of death, although trends toward better outcomes for active individuals were observed. Two larger studies from the US Renal Data System found that CKD 5D patients who are sedentary have a higher risk of death than those who are active. All of these studies are observational and more data are required.

The benefits of exercise on BP and on general health appear likely to be similar in the CKD and the general population, with no strong rationale for different recommendations. On this basis, Recommendation 2.3.3 was graded 1D.

2.3.4: We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. (2D)

RATIONALE
Alcohol has been shown to produce both acute and chronic increases in BP, suggesting that restricting alcohol intake would lower BP. In a systematic review of four trials, restricting alcohol intake in the general population resulted in a 3.8 mm Hg reduction (95% CI 1.4–6.1) in systolic BP and a 3.2 mm Hg reduction (95% CI 1.4–5.0) in diastolic BP, with no evidence of heterogeneity among the results. No data specific to CKD patients were found, but the effects are expected to be similar.

Most data suggest that up to two standard drinks per day for a man and 1 standard drink per day for a woman are likely to be safe. The definition of a standard drink varies from 8 to 19.7 g of alcohol in different countries (see http://whqlibdoc.who.int/hq/2000/who_msd_msb_00.4.pdf). 10 g of alcohol is equivalent to 30 ml of spirits, 100 ml of wine, 285 ml of full-strength beer, and 425 ml of light beer. The benefits of alcohol moderation on BP and on general health appear likely to be similar in the CKD and the general population, with no strong rationale for different recommendations. On this basis, Recommendation 2.3.4 was graded 2D.

OTHER INTERVENTIONS
Cigarette smoking. Cigarette smoking and exposure to environmental tobacco smoke are clearly among the most potent modifiable risk factors for CVD in the general population and in patients with CKD. Although it does not have a clear, direct impact on long-term BP, the avoidance of exposure to cigarette smoke is a critical aspect of cardiovascular risk reduction but as yet there are no RCTs in the CKD population.

Dietary supplementation. The effects of potassium supplementation on BP have been assessed in a number of studies. These have produced conflicting results, with some but not all indicating a benefit. CKD patients often have reduced capacity for potassium excretion, particularly as the GFR falls, such that the risk of hyperkalemia may be increased. In the absence of specific studies demonstrating a benefit in CKD patients, we cannot recommend potassium supplementation to reduce BP in patients with CKD.

The evidence base for magnesium supplementation is similar, with some but not all studies suggesting a benefit with respect to BP. Although hypermagnesemia is not a common problem in CKD patients, magnesium supplementation cannot be recommended without specific data demonstrating its safety and efficacy.

Fish-oil supplementation has been shown to produce small but significant reductions in BP in a number of RCTs and systematic reviews. The mechanisms of these effects remain uncertain, however and the safety of fish oil has not been clearly demonstrated in CKD patients. Although some data supporting the use of fish oil exists for patients with IgA nephropathy, it is premature to recommend this treatment for BP lowering in the CKD population.

BP-LOWERING AGENTS
RCTs involving both CKD and non-CKD populations in which a target BP has been set at the levels recommended in this Guideline clearly show that most patients will require two or more antihypertensive agents to achieve these targets. Surveys of BP control in CKD patients indicate that three or more agents are frequently needed. With the exception of ARBs or ACE-Is in CKD patients with high levels of urinary albumin or protein excretion, there is no strong evidence to support the preferential use of any particular agent(s) in controlling BP in CKD; nor are there data to guide the clinician in the choice of second- and third-line medications. Since the 2004 KDOQI Guideline was published, there has been an increasing trend towards tailoring antihypertensive therapy to the individual patient, taking into account issues such as the presence or absence of high urine albumin excretion, co-morbidities, concomitant medications, adverse effects, and availability of the agents. Ultimately, the choice of agents is less important than the actual reduction in BP achieved, since BP reduction is the major measurable outcome in the individual patient.

Other information of value in deciding on the optimal BP lowering regimen include data on drug half-life and dose adjustments in CKD stage 5D, which may be of help in guiding the use of BP lowering drugs in advanced CKD.

The optimal timing of administration of medication has not been studied in CKD patients. CKD patients who do not have the normal decrease in BP during sleep (non-dippers and reverse dippers) have worse cardiovascular and kidney outcomes when compared to dippers. Whether the recently reported strategy of evening dosing to produce nocturnal dipping will improve outcomes in CKD patients, as has been described in individuals with essential hypertension, remains to be established.

The ERT was not asked to search for evidence of the effectiveness of established anti-hypertensive agents in lowering BP in patients with CKD, since it is generally believed that all such drugs are effective, although the sensitivity in individual patients may vary, as may be the side
effects. Instead, the ERT focused on two issues. Firstly, studies that compared different BP targets were identified. In these studies, only the BP targets were randomized; the protocols varied with respect to the sequence of drugs and escalation of dose. Secondly the ERT searched for studies that included a comparison of different combinations of anti-hypertensive agents. In these studies, only the choice of first-line drug was randomized, with study protocols varying with respect to drug dose, use of concomitant agents and BP thresholds for drug titration (Table 5, see Methods for Guideline Development).

The KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm) contains details of clinical pharmacology and practical guidance on the use of the various agents to lower BP in CKD patients. Information on CKD- and CVD-related indications, side effects, dosages and contraindications relevant to all commonly used anti-hypertensive agents as well as strategies to improve adherence and warnings regarding the hazards of certain combinations are also noted therein. The Work Group believed that there was insufficient new evidence to warrant rewriting the clear guidance provided in the KDOQI Guideline. However, at the request of the KDIGO Board, the Work Group summarize specific aspects of the use of antihypertensive agents in CKD patients. We outline the information that can be drawn from the known pharmacology of agents or observations in non-CKD patients, emphasizing the difficulty in extrapolating to CKD patients, especially those with advanced CKD.

Given that the prescribed drug regimen commonly involves many medications, it is reasonable to use strategies that might maximize the likelihood of adherence, including the use of cheaper drugs, convenient frequency of dosing and reduction in pill numbers. This can be achieved by prescribing once-daily medication and combination pills (which are simpler to take and in some circumstances may be less expensive than the individual agents) when possible.

**Renin-angiotensin-aldosterone system blockers**

Because of its pivotal role in regulation of BP, the RAAS system is an obvious target for BP-lowering medications. Although other agents, particularly beta-blockers, interfere with the RAAS pathway, the main RAAS inhibitors are ACE-Is, ARBs, aldosterone antagonists, and DRIs.

**ACE-Is and ARBs.** ACE-Is block the conversion of angiotensin I to angiotensin II and the degradation of bradykinin. It seems likely that the accumulation of bradykinin leads to persistent dry cough, a recognized side effect which occurs in 5 to 20% of patients on ACE-Is. Angioneurotic edema can occur with both ACE-Is and ARBs, although the relative frequencies and the mechanism are not clear. ARBs act by competitively antagonizing the interaction between angiotensin II and angiotensin receptors and were first introduced as an alternative to ACE-Is in patients who had an ACE-I induced cough.

ACE-Is and ARBs are valuable BP-reducing agents in CKD patients, are indicated if urinary albumin excretion is elevated and are safe to combine with most other BP-reducing agents. Clinically significant hyperkalemia and reductions in GFR can occur in patients receiving ACE-Is or ARBs, particularly in those who have renal-artery stenosis or reduced intravascular volume, or when these agents are used together with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. The use of these drugs in women of child-bearing age should be balanced with the risk of pregnancy since they are potentially teratogenic (see Chapter 6).

The sequential marketing of ACE-Is first (captopril in 1977) and ARBs later (losartan in 1995) has influenced the design of RCTs involving these drug classes. The first large-scale RCT of RAAS blockade in diabetes involved patients with type 1 disease given captopril. By the time ARBs were introduced, the benefits of ACE-Is (in CKD patients with type 1 diabetes) were well established. Thus RCTs involving ARBs generally targeted individuals with type 2 diabetes. This has led to some bias in the evidence base underpinning recommendations for using ACE-Is or ARBs in the treatment of BP. There is no substantive evidence to suggest that ACE-Is and ARBs differ in their ability to reduce BP in patients with essential hypertension. In most health care settings, ACE-Is are less expensive than ARBs, which may influence the choice between an ACE-I or ARB.

The most prominent BP-related effects of the blockade of angiotensin II by ACE-Is or ARBs are as follows:

- Generalized arterial vasodilatation, resulting in lower BP.
- Vasodilatation of the efferent and afferent glomerular arterioles, particularly the efferent, resulting in decreased intra-glomerular pressure and hence reduction in both GFR and urine albumin excretion. This is believed to result in some degree of long-term renoprotection, at least in patients with albuminuria. On initiation of therapy a reversible reduction in GFR of up to 30% (accordingly a 30% increase in SCr concentration) has been regarded as reasonably attributable to this physiological mechanism. Greater reductions may indicate underlying renal artery stenosis. It has been suggested that in advanced CKD, cessation of RAAS blockade may allow an increase in GFR of sufficient magnitude to delay end-stage kidney failure. This concept is further discussed in Chapter 8.
- Reduction in adrenal secretion of aldosterone. In about 50% of subjects prescribed ACE-Is or ARBs, aldosterone production is restored to at least pre-treatment levels over a period of months (a phenomenon termed aldosterone breakthrough). This may explain the efficacy of aldosterone antagonists in patients already taking an ACE-I or ARB.

ACE-Is and ARBs may have other effects, including inhibition of fibrosis and enhancement of vascular and cardiac remodelling. Discussion of these effects, which may...
be of relevance to renoprotection, is beyond the scope of this Guideline.

**Dose considerations in CKD patients.** Most available ACE-Is have active moieties that are largely excreted in the urine. Fosinopril and trandolapril are partially (in general, approximately 50%) excreted by the liver, such that the blood levels are less influenced by kidney failure than levels of other ACE-Is which are predominantly excreted by the kidneys. Since ACE-Is are generally titrated to achieve optimal clinical effect, the mode of excretion is not regarded as a major factor in dosing.\textsuperscript{76} If hyperkalemia occurs in CKD patients taking a renal excreted ACE-I, possible interventions include dietary advice, reducing the dose, switching to fosinopril or trandolapril, or adding a potassium-losing diuretic.

All ARBs are substantially excreted by the liver, with the proportion of drug elimination ranging from 40% (in the case of candesartan) to >95% (in the case of irbesartan and telmisartan). As with ACE-Is, the dose in ARBs is usually adjusted according to clinical effect rather than kidney function.\textsuperscript{76}

ACE-Is and ARBs should be used with caution or even avoided in certain CKD subgroups, particularly in patients with bilateral renal-artery stenosis or with intravascular fluid depletion, because of the risk of a large reduction in GFR. The normal capacity of the kidney to auto-regulate GFR in the face of fluctuations in BP is impaired in CKD and further compromised by the use of ACE-Is or ARBs. Hypotension (e.g., as a result of hypovolemia or sepsis) may cause an acute decline in GFR in patients with CKD taking ACE-Is or ARBs.\textsuperscript{90} Several case series have reported a high risk of acute kidney injury in diabetic patients on an ACE-I or ARB during sepsis\textsuperscript{91–93} and when they are used in combination with NSAIDs\textsuperscript{94} or diuretics.\textsuperscript{95} Reducing the dose or holding off on using ACE-Is or ARBs until recovery is sensible in patients who develop inter-current illnesses that lead to dehydration as a result of diarrhea, vomiting, or high fever.

**Indications for ACE-Is and ARBs.** In this guideline, ACE-Is and ARBs are recommended for specific groups of CKD patients with increased urinary albumin excretion in which context use of these agents may be associated with better kidney\textsuperscript{96} and cardiovascular outcomes.\textsuperscript{97} In non-CKD patients, these drugs are indicated for the treatment of heart failure and for use soon after myocardial infarction, stroke, and in patients with high cardiovascular risk.\textsuperscript{98–100}

The Oregon Health Resources Commission reported in 2005 on the use of ACE-Is in essential hypertension. No differences were found among various ACE-Is in terms of the BP-lowering effect and serious complications which were independent of gender, age, or African-American heritage.\textsuperscript{99} In 2006, the Commission reviewed the evidence for the use of ARBs.\textsuperscript{100} It reported that there were no data to suggest that any particular ARB was superior to another in the context of a variety of clinical scenarios, including essential hypertension and high cardiovascular risk; nor was there evidence of any ARB being associated with a higher risk of serious complications or differences in efficacy or side effects regardless of age, race, or gender. In reviewing studies specifically involving patients with CKD, no important differences in the effect of ARBs on BP or side effects were found.

Accordingly, ACE-Is or ARBs might be considered for use in patients with CKD who have heart failure, recent myocardial infarction, a history of stroke, or a high cardiovascular risk. However, it is not possible to make any recommendations for CKD patients in particular, since the data are largely from studies of non-CKD patients. In addition, because CKD patients are at higher risk of side effects, particularly hyperkalemia and reduction in GFR, the use of ACE-Is or ARBs may not have the same risk-to-benefit ratio in CKD patients as in non-CKD populations.

**Drug combinations.** The antihypertensive and antialbuminuric effects of ACE-Is and ARBs are complemented by dietary sodium restriction or administration of diuretics.\textsuperscript{63,65,66} ACE-Is and ARBs are therefore valuable adjuncts to diuretics for the treatment of high BP and vice versa. Co-administration of beta-blockers and calcium-channel blockers with ACE-Is or ARBs is also acceptable. One recent post hoc analysis of a large trial involving hypertensive individuals demonstrated that a combination of an ACE-I (benazepril) and calcium antagonist (amlodipine) was superior to the same ACE-I used with a diuretic (hydrochlorothiazide) in slowing CKD progression.\textsuperscript{101}

Patients given NSAIDs, COX-2 antagonists or potassium-sparing diuretics can develop hyperkalemia if these drugs are used in combination with ACE-Is or ARBs. The combination of ACE-Is and/or ARBs with aldosterone-blocking antagonists is an area of current controversy that is covered in more detail below and in Chapter 8.

**Aldosterone antagonists.** The aldosterone antagonist spironolactone has been in use as a BP-lowering agent since the late 1950s. Prescribed as a diuretic in the treatment of edema and resistant hypertension, it fell into disuse with the advent of more powerful diuretics and antihypertensives. With the high doses initially used (up to 300 mg/day), spironolactone use was associated with side effects, particularly those due to its estrogen-like activity (gynecomastia and menstrual disturbances). Recognition that BP-lowering could be achieved with much lower doses of spironolactone (12.5–50 mg/day) has led to renewed interest in aldosterone antagonists over the past decade.\textsuperscript{102–105} As a result, eplerenone, a mineralocorticoid-receptor blocker without estrogen-like effects, has been developed. In CKD, the major emphasis has been on using aldosterone antagonists to reduce urine albumin levels and as an adjunct to other antihypertensive agents in treating resistant hypertension. Aldosterone antagonists are of proven benefit in non-CKD patients with heart failure, including heart failure after myocardial infarction. Because of the risk of hyperkalemia and reduction in GFR, they should be used with caution in CKD patients.

**Dose considerations in CKD patients.** Impaired renal excretion of native drug or active metabolites of spironolactone and eplerenone and an increased risk of hyperkalemia
may limit their use in patients with CKD. Plasma potassium levels and kidney function should be monitored closely during the introduction of aldosterone antagonists and during intercurrent illnesses, particularly those associated with a risk of GFR reduction, as occurs with dehydration.

**Indications for aldosterone antagonists.** In patients without CKD, aldosterone antagonists are recommended for the treatment of severe cardiac failure that is resistant to other therapies and for use after acute myocardial infarction complicated by cardiac failure. These agents also have a place in the management of essential hypertension that is resistant to other therapies. It is unclear whether this information can be extrapolated to CKD patients, particularly those with advanced CKD in whom the risks associated with the use of aldosterone antagonists, particularly of hyperkalemia, may be increased.

In patients with CKD, aldosterone antagonists have been shown to decrease urine albumin excretion when added to ACE-I or ARB therapy. In the largest relevant RCT available involving CKD patients with elevated urine albumin levels and type 2 diabetes, 177 patients received eplerenone (either 50 or 100 mg daily) and 91 patients received placebo.\(^{106}\) The addition of eplerenone to enalapril (20 mg/day) resulted in a reduction in AERs of 40 to 50% by 12 weeks in the eplerenone groups, but by <10% in the placebo group. The greater reduction in AER in the CKD patients receiving an aldosterone antagonist in addition to an ACE-I or ARB is consistent with the findings of many smaller trials.\(^{103,107,108}\)

Small reductions in GFR and systolic BP have also been reported. Hyperkalemia is a risk, but may have been mitigated by the concurrent use of a thiazide diuretic according to the smaller studies. Thiazide diuretics, however, were not used in the larger RCT cited above and the risk of hyperkalemia was similar among participants receiving enalapril alone and those receiving the combination of eplerenone and enalapril in that trial.\(^{106}\) It is premature to draw a definite conclusion as to whether aldosterone antagonists—through their anti-albuminuric, anti-hypertensive, or anti-fibrotic effects—reduce the rate of decline in kidney function in the long term. This is an area for future research.\(^{109,110}\)

**Drug combinations.** Aldosterone antagonists are potassium-sparing diuretics and thus may be combined with thiazide or loop diuretics that enhance potassium loss in the urine. Great care should be exercised when aldosterone antagonists are combined with ACE-Is, ARBs, or other potassium-sparing diuretics. There is little information regarding the combination of aldosterone antagonists with NSAIDs or COX-2 inhibitors, but as with ACE-Is and ARBs, caution is warranted. Both spironolactone and eplerenone interact with cytochrome P-450, but definitive information regarding any effect on calcineurin inhibitors (CNIs) is not available. Caution is also advised when aldosterone antagonists are combined with other cytochrome P-450–metabolized agents such as verapamil.

**Direct renin inhibitors.** The first clinically available DRI, aliskiren, was approved by the US Food and Drug Administration (FDA) in 2007. It binds to renin, preventing the conversion of angiotensin I to angiotensin II. Data relevant to DRIs were not available at the time of publication of the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease in 2004.\(^{1}\)

**Dose considerations in CKD patients.** The usual dose of aliskiren is 150 to 300 mg given once daily. The dose is not modified according to kidney function. It has been reported that cyclosporine administration increases the half-life of aliskiren in healthy subjects.\(^{111}\)

**Indications for DRIs.** Although approved by the US FDA only for the treatment of hypertension, it is uncertain whether the indications for DRIs will eventually be similar to those of ACE-Is and ARBs.

There has been one large study of aliskiren in CKD patients, in which the drug was used in combination with the ARB losartan in patients who also had type 2 diabetes with nephropathy.\(^{112}\) A total of 599 patients were randomized to losartan, 100 mg daily, either alone (control group) or plus aliskiren—150 mg daily for 3 months and then 300 mg daily for 3 months. The addition of the 300 mg dose of aliskiren reduced the urinary albumin/creatinine ratio (ACR) by 20% as compared with the use of losartan alone. There were only small differences in BP between the two groups, and no differences between the rates of adverse or serious adverse events. Given the limited data available, the place of DRIs in the management of BP in CKD has yet to be determined. Indeed another trial involving the use of DRI combined with losartan in patients with diabetes and CKD has recently been terminated early due to an increased risk of adverse events and no evidence of benefit in the combination therapy group.

Early termination of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial casts doubt on the future use of DRIs in combination with ACE-Is or ARBs,\(^{113}\) and very recently the US FDA has counselled against this combination.\(^{114}\)

**Diuretics**

Salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema. Thus, diuretics potentially have an important role in the control of hypertension in this clinical setting. The pharmacology of diuretics and indications for their use have recently been reviewed.\(^{115}\) Given that most CKD patients will require multiple drugs to control elevated BP, thiazides have a role, especially since their only major drawback is a propensity to induce or aggravate hyperglycemia and other features of the metabolic syndrome.\(^{116}\)

**Thiazides.** Of the currently available antihypertensive agents, thiazides and thiazide-like diuretics are most often used and have been assessed in many RCTs involving CKD patients, either as the primary investigational agent or as an add-on therapy. Their side-effect profile is well known and their pharmacology has recently been extensively reviewed.\(^{115}\)
as has their role in treating hypertension.\textsuperscript{115,117,118} Although salt and water excretion may initially account for their antihypertensive effect, why they lower BP over the long term is less well understood and may involve direct or indirect vasodilator actions.\textsuperscript{115,119} The metabolic side effects (hyperglycemia, hyperuricemia, visceral adiposity) are also not completely understood\textsuperscript{119} but should be considered in patients at risk of metabolic syndrome.

There are 2 broad groups of thiazide-type diuretics: thiazides whose names end in ‘thiazide,’ and thiazide-like agents such as chlorothalidone and indapamide. In recent years, the thiazide diuretics have been used in low doses in treatment of hypertension (hydrochlorothiazide 12.5 to 25 mg, bendroflumethiazide 2.5 mg daily). The valid comparison is thus of low dose thiazide versus thiazide-like diuretic. These regimens have been compared in the recent UK National Institute for Health and Clinical Excellence (NICE) guidelines on primary hypertension.\textsuperscript{117} There was limited evidence of any differences in BP control, clinical outcomes or cost-effectiveness. NICE recommended that in newly treated primary hypertensives, the thiazide-like diuretics were preferable to the thiazides, based on the larger volume of evidence for efficacy. The relevance of these observations to CKD patients is unclear.

**Dose considerations in CKD patients.** Although thiazides are excreted by the kidney, no dose adjustment is recommended in patients with reduced GFR. As the GFR falls below about 30–50 ml/min/1.73 m\textsuperscript{2}, the ability of thiazides to overcome fluid retention is diminished, although their antihypertensive benefit may be preserved, at least according to small, short-term studies in humans.\textsuperscript{120} Most clinicians switch to a loop diuretic in patients with CKD 4, particularly if the BP is becoming resistant to therapy or edema becomes a problem.

**Drug combinations.** Thiazides are often one of the first 2 or 3 drugs used for BP lowering in CKD, particularly if there is edema or if ACE-I or ARBs have already been prescribed. Thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACE-I and ARBs\textsuperscript{63,66} and may also reduce the risk of hyperkalemia. The inclusion of thiazides in fixed-dose combinations with other antihypertensives is convenient for patients and may improve compliance.\textsuperscript{83}

**Loop diuretics.** Furosemide (also called frusemide), bumetanide, torsemide and ethacrynic acid are the most commonly used loop diuretics, with wide dose ranges and differing pharmacodynamics. In primary hypertension they are effective in the short term\textsuperscript{121} but less so than thiazides in the long term.\textsuperscript{115} Loop diuretics are particularly useful when treating edema and high BP in CKD 4–5 patients in addition or as an alternative to thiazide diuretics.

**Potassium-sparing diuretics.** Triamterene and amiloride are usually avoided in patients with CKD because of the risk of hyperkalemia. They are less effective in reducing extracellular fluid volume than thiazides or loop diuretics. Aldosterone antagonists such as spironolactone and eplerenone are discussed separately, above.

**Beta-blockers**

Beta-blockers are one of the most extensively investigated class of agents, having been used to treat hypertension and CVD for over 40 years. Although all beta-blockers are effective at reducing BP, other issues may influence whether they are appropriate in a given patient and which specific drug is chosen, since beta-blockers vary widely in their pharmacology.\textsuperscript{122,124} Specific attention should be paid to beta-blocker accumulation in patients with advanced CKD and to ensuring that the beta-blocker usage is appropriate in targeting a patient’s co-morbidities.

**Dose considerations in CKD patients.** In patients with CKD, the accumulation of beta-blockers or active metabolites could exacerbate concentration-dependent side effects such as bradycardic arrhythmias.\textsuperscript{123} Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol, or metoprolol.\textsuperscript{123}

**Indications for beta-blockers.** A consensus report based on evidence reviewed by the Pharmaceutical Subcommittee of the Oregon Health Resources Commission in 2008 gave an update of the indications for use of beta-blockers in non-CKD patients.\textsuperscript{125} The subcommittee concluded that although no particular beta-blocker had been shown to be more effective in reducing BP or alleviating angina than another, in cases of mild-to-moderate heart failure, bisoprolol, carvedilol, and metoprolol succinate reduced mortality and in cases of severe heart failure, carvedilol and metoprolol succinate reduced mortality. After a recent myocardial infarction, acebutolol, carvedilol, metoprolol tartrate, propranolol and timolol all reduced mortality. A recent systematic review and meta-analysis of beta-blockers in CKD\textsuperscript{126} endorsed the use of beta-blockers in CKD patients with heart failure but did not provide any definitive specific advice on the their efficacy in preventing mortality, cardiovascular outcomes or renal disease progression in CKD patients without heart failure.

**Drug combinations.** Beta-blockers have often been combined with diuretics in RCTs and clinical practice.\textsuperscript{124,127} There are no theoretical reasons why beta-blockers should not be combined with ACE-I or ARBs.\textsuperscript{128} The combination of atenolol or bisoprolol (which accumulate in CKD patients) with bradycardia-inducing drugs such as non-dihydropyridine calcium-channel blockers is not recommended. The combination of lipophilic beta-blockers (which cross the blood-brain barrier) with other centrally acting drugs such as clonidine may lead to drowsiness or confusion, particularly in the elderly. Again, the relevance of these data to patients with CKD remains uncertain.

**Calcium-channel blockers**

Calcium-channel blockers are valuable BP-lowering agents in CKD patients, but this class of drugs is very heterogeneous in several respects and the choice of the type of agent used should take into account these differences as well as co-morbidities and other medications the patient is taking.
The major subclasses are the dihydropyridines (e.g., amlodipine, nifedipine and lercanidipine), the non-dihydropyridine benzothiazepines (e.g., diltiazem) and the phenylalkylamines (e.g., verapamil). Dihydropyridines tend to be more selective for vascular smooth muscle (vasodilatation) with less action on the myocardium. Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic in patients with CKD. Dizziness, headache and redness in the face are also common side effects. Non-dihydropyridines have direct effects on the myocardium, including the sinoatrial and atrioventricular nodes and reduce the heart rate and cardiac-muscle contraction.

Calcium-channel blockers also vary in their effects on glomerular arterioles, reflecting differential blockage of T-channel receptors (on the afferent and efferent arteriole) versus L-channel receptors (predominantly on the afferent arteriole). T-channel blockade leads to a reduction in intraglomerular pressure, and accordingly a fall in urine albumin levels, while an increase in the urine albumin level can occur with blockage of L-channel receptors. In general, dihydropyridine calcium-channel blockers act on L-channel receptors, hence have the effect of increasing urine albumin excretion, whereas non-dihydropyridines tend not to be associated with this side effect. Later generation dihydropyridines (e.g., manipine, cilnidipine) are less prone to increasing albumin excretion and may even reduce it.

**Dose considerations in CKD patients.** Most calcium-channel blockers do not accumulate in patients with impaired kidney function, with the exception of nicardipine and nimodipine. Accumulation of these agents may also be due to reduced blood flow to the liver in the elderly. Caution is thus advised when using these two agents in elderly patients with CKD.

**Indications for calcium-channel blockers.** Calcium-channel blockers are widely used in the treatment of hypertension, angina, and supra-ventricular tachycardia. The Oregon Health Resources Commission report on calcium-channel blockers in 2005 concluded that there was no clear evidence to differentiate the antihypertensive effects of one calcium-channel blocker from another (inadequate evidence for to differentiate the antihypertensive effects of one calcium-channel blockers in 2005 concluded that there was no clear evidence for). Non-dihydropyridines have direct effects on the myocardium, including the sinoatrial and atrioventricular nodes and reduce the heart rate and cardiac-muscle contraction.

Fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD, such that avoiding other vasodilators may be sensible. The combination of non-dihydropyridines such as verapamil and diltiazem with beta-blockers can lead to severe bradycardia, particularly in patients with advanced CKD if drugs such as atenolol and bisoprolol (that accumulate in CKD) are used.

Calcium-channel blockers, particularly non-dihydropyridines, interfere with the metabolism and excretion of the CNIs, cyclosporine and tacrolimus, as well as the mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus (Table 2). This is relevant to the treatment of high BP in kidney-transplant recipients, but also in patients with immune-mediated CKD requiring immunosuppression. When such patients are prescribed non-dihydropyridine calcium-channel blockers, careful monitoring of CNIs and mTOR inhibitors blood levels is required if drugs or dosages are changed. Some clinicians use non-dihydropyridine calcium-channel blockers to increase CNI or mTOR inhibitor blood levels and thus reduce cost, particularly in kidney-transplant patients.

**Centrally acting alpha-adrenergic agonists**
Centrally acting alpha-agonists cause vasodilatation by reducing sympathetic outflow from the brain. The main agents in use are methyldopa, clonidine, and moxonidine. Moxonidine was not widely available in 2004 and thus was not reviewed for the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease. The use of this drug in essential hypertension was extensively reviewed by Fenton et al. in 2006. Dosing of centrally acting alpha-antagonists is limited by side effects, but since they interact minimally with other antihypertensives or immunosuppressants, they are valuable as adjunct therapy for resistant hypertension in CKD patients.

**Dose considerations in CKD patients.** Doses of methyldopa or clonidine are not generally reduced in patients with impaired kidney function. Moxonidine is extensively excreted by the kidney and accordingly it has been recommended that the dosage (usually 200 to 400 mg daily) should be reduced in the presence of a low GFR. On the other hand, an RCT of moxonidine, 300 mg daily, or the calcium-channel blocker nitrendipine, 20 mg daily, added to an ACE-I or ARB plus loop diuretic in 177 hypertensive CKD patients (GFR by the Cockcroft-Gault equation, <30 ml/min/1.73 m²) indicated that adverse events occurred in similar proportions of patients treated with moxonidine (50 of 89 [56.2%]) and nitrendipine (46 of 82, [56.1%]), as did those adverse events possibly due to the study drug (moxonidine 28%, nitrendipine 32%), suggesting that although side effects are common, moxonidine can be used in advanced CKD.

![Table 2 - Selected calcium-channel blockers](image-url)

<table>
<thead>
<tr>
<th>Class</th>
<th>Accumulate in renal failure</th>
<th>Increase CNI levels</th>
<th>Increase sirolimus levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>D</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>B</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Felodipine</td>
<td>D</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>Isradipine</td>
<td>D</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>D</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>D</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>—</td>
<td>Y</td>
<td>—</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>D</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

B, non-dihydropyridine benzothiazepine; CNI, calcineurin inhibitor; D, Dihydropyridine; N, No; P, phenylalkylamine; Y, Yes; —, no data.
severe adverse events associated with moxonidine in this RCT were gastrointestinal symptoms, dizziness, headache and tiredness; all of which occurred in between 10 to 15% of the patients receiving moxonidine.

**Indications for centrally acting alpha-agonists.** Since alpha-agonists do not interact with other commonly used antihypertensive agents, they are valuable as adjunctive therapy for high BP in CKD patients already taking other antihypertensive medications. Because of the side-effect profile, however, caution is advised when using alpha-agonists in the elderly, in patients with advanced CKD and in those taking sedating drugs.

In one large study of non-CKD patients with advanced heart failure, high-dose moxonidine use was associated with increased mortality.\(^1\) How this relates to patients with CKD is unclear. Avoidance is probably wise if overt heart failure is present. Since clonidine can slow pulse rate, this drug should be avoided if bradycardia or heart block is present.

**Drug combinations.** Combination of alpha-agonists with thiazides is probably advantageous to reduce vasodilatation-induced fluid retention. Combination with other antihypertensive drugs is usually trouble-free, but caution is advised if the agents have similar side effects. Interactions are not common between alpha-agonists and CNIs or mTOR inhibitors.

**Alpha-blockers**
Alpha-adrenergic blockers selectively act to reduce BP by causing peripheral vasodilatation. Prazosin, doxazosin, and terazosin are the alpha-blockers most commonly used in treatment of hypertension. Alpha-blockers are an adjunctive treatment for elevated BP in CKD patients whom ACE-Is, ARBs, diuretics, calcium-channel blockers, and beta-blockers have failed or are not tolerated. Alpha-blockers may also be advantageous if symptoms of prostatic hypertrophy are present.

**Dose considerations in CKD patients.** Alpha-blockers do not require dose modification in cases of kidney failure, since they are excreted via the liver.\(^1\) **Indications for alpha-blockers.** Alpha-blockers reduce the symptoms of benign prostatic hyperplasia, which may be a co-morbidity to consider in older men with CKD. In general, alpha-blockers are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia and headache. They should be commenced at a low dosage to avoid a first-dose hypotensive reaction.

**Drug combinations.** There are few data available about alpha-blocker combinations with other BP lowering drugs. Vasodilatation can lead to peripheral edema, so diuretics are commonly combined with alpha-blockers, although the efficacy of this maneuver has not been studied. Alternatively, a non-selective beta-blocker can be used.

**Direct vasodilators**
Hydralazine and minoxidil both act by directly causing vascular smooth-muscle relaxation and hence vasodilatation. There have been no important changes to our understanding of these drugs since the publication of the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease* in 2004.\(^1\)

**Dose considerations in CKD patients.** Hydralazine and minoxidil do not require dose adjustment in patients with impaired kidney function.\(^1\)

**Indications for direct vasodilators.** Hydralazine has little value in the management of chronically elevated BP in CKD, although it is sometimes used as a parenteral hypotensive agent. Minoxidil is generally used in patients with very resistant hypertension and thus may be helpful in patients with CKD. However, its side effects (e.g., severe fluid retention, headache, tachycardia, hirsutism, and pericardial effusion) limit its use to the most resistant cases.

**Drug combinations.** Because of the side effects of fluid retention and tachycardia, direct vasodilators (especially minoxidil) are usually combined with a beta-blocker and loop diuretic.

**RESEARCH RECOMMENDATIONS**
- Salt restriction appears to be a very promising method of reducing BP and the risk of progressive kidney disease and cardiovascular events. Therefore, large scale RCTs assessing the impact of this intervention on these patient-level outcomes are required. Patients with CKD should be included in these trials, given the potential for differences in the risks and benefits of reduced salt intake in these individuals.
- RCTs should be undertaken to evaluate the benefit of weight loss at different stages of CKD.
- RCTs should be undertaken in CKD with and without elevated albumin excretion levels comparing various combinations of RAAS blocking drugs.

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**Chapter 3: Blood pressure management in CKD ND patients without diabetes mellitus**


**INTRODUCTION**

This chapter addresses the management of BP in adult CKD patients (specifically non-dialysis-dependent CKD [CKD ND]) without diabetes mellitus. There is overlap with BP management in the elderly (defined as persons >65 years of age or as persons with CKD and aging-related co-morbid conditions). In the elderly in particular and to a lesser extent in younger CKD patients, these co-morbid conditions may require modifications in the approach to BP management.

In this chapter we consider two primary adverse outcomes related to high BP: progression of kidney disease and development of CVD. The data are sufficient to provide recommendations on BP targets for ACE-Is or ARBs, although there is evidence of heterogeneity in both areas according to the urine albumin level. We therefore divided the target populations on the basis of urine albumin level.

We did not find sufficient data to suggest any differences according to CKD stage, so our recommendations are not stage-specific. It is not possible to recommend specific regimens or BP targets for all the various causes of CKD. Although there are strong observational data, there is no evidence from RCTs to indicate that the treatment approach should differ substantially for the patient with glomerular disease and high urine albumin levels compared to the patient with severe renovascular disease. Although we would have preferred to give a target range (lowest to highest) for BP rather than a single target for highest acceptable BP, there are insufficient data based on RCTs to recommend a target for lowest BP level. The recommendations and suggestions in this chapter therefore emphasize an approach based on highest acceptable BP and severity of albuminuria, but the interventions should be implemented cautiously and with subsequent surveillance for adverse effects.

We also recognize that BP agents other than those recommended or suggested below, such as diuretics, may be necessary for BP control, especially as CKD progresses and volume retention becomes more of an issue. However, few RCTs addressing hard cardiovascular or kidney outcomes have randomized patients to a diuretic versus another agent on top of an ACE-I or ARB. Therefore, in contrast to the 2004 KDOQI guideline, we do not provide a guideline statement regarding diuretic use as a preferred second-line agent. The use of diuretics and other BP agents are discussed in more detail below and in Chapter 2.

3.1: We recommend that non-diabetic adults with CKD ND and urine albumin excretion < 30 mg per 24 hours (or equivalent*) whose office BP is consistently > 140 mm Hg systolic or > 90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic. (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- High BP is a risk factor for CVD and development and progression of CKD.
- Lowering BP in the general population reduces cardiovascular risk.
- Lowering BP in CKD patients reduces the rate of CKD progression.
- CKD is a major risk factor for CVD.

Most recent BP guidelines have suggested a target BP of < 140/90 mm Hg for all individuals who are not at high risk for CVD. This is based on several lines of evidence, including observational data suggesting that high BP is a risk factor for CVD, observational data suggesting that high BP is a risk factor for development and progression of CKD, RCTs of BP agents in the general population showing a benefit of a lower target BP, and RCTs in the general population demonstrating that the treatment of BP reduces CVD outcomes.

Several previous guidelines for kidney disease have recommended a BP target of < 130/80 mm Hg for all patients with CKD, irrespective of the level of urine protein. These recommendations are primarily based on observational data in the general population showing that the presence of CKD, irrespective of the level of urine protein, is associated with high risk of CVD. In addition, data from the MDRD study, which randomized patients to a mean arterial pressure (MAP) of < 92 mm Hg (equivalent to 125/75 mm Hg) versus 107 mm Hg (equivalent to 140/90 mm Hg) showed that tight BP control reduced progression of kidney disease in patients with > 1 g of urine protein per 24 hours.
Since the publication of previous guidelines, several events have resulted in more caution about advocating a BP target of \( \leq 130/80 \text{ mm Hg} \) in CKD patients without albuminuria. RCTs in CKD populations have shown that data from the general population cannot necessarily be extrapolated to the CKD population.\(^{26,27}\) Moreover, particularly in RCTs related to anemia, the RCT findings may be inconsistent with observational data.\(^{154,155}\) Guideline agencies\(^{156,157}\) are now requiring more rigorous data, in particular from RCTs, as a basis for recommendations. Several manuscripts have recently emphasized that tight BP control may have adverse effects,\(^{22,158}\) particularly in the elderly and those with CAD and low diastolic BP.\(^{40}\) Furthermore, less tight control (i.e., control involving the use of fewer drugs) may improve adherence and reduce costs of treatment, a benefit particularly relevant in resource-poor environments.

Finally, several recent RCTs have not shown a benefit of lower BP targets in patients without proteinuria. For instance, the African American Study of Kidney Disease and Hypertension (AASK) randomized participants to treatment to a MAP of either \( \leq 92 \text{ mm Hg} \) or \( 102 \text{ to } 107 \text{ mm Hg}.\)\(^{140}\) During the long-term follow-up of participants, there was a benefit associated with the lower BP target among patients with a urine protein/creatinine ratio (PCR) of \( > 220 \text{ mg/g} \) (\( > 22 \text{ mg/mmol} \)), but not among those with a PCR \( \leq 220 \text{ mg/g} \) (\( \leq 22 \text{ mg/mmol} \)). In fact, in some analyses, there was a trend toward worse outcomes in those targeted to low BP when the urine PCR was \( \leq 220 \text{ mg/g} \) (\( \leq 22 \text{ mg/mmol} \)). Similarly, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,\(^{159}\) no benefit was found with regard to the primary composite outcome with a systolic BP target \( < 120 \text{ mm Hg} \) versus a target of \( < 140 \text{ mm Hg} \).

We therefore propose that targets currently recommended in the general population be extrapolated to those with CKD who do not have elevated urinary albumin or protein levels. Results of subgroup analyses of CKD patients included in RCTs assessing target BPs are consistent with the primary results of these trials\(^{160}\) (Supplementary Table 1 online). This move towards a more conservative target is consistent with other guidelines.\(^{161}\) We have graded this recommendation as 1B, given that this BP target is currently considered the standard of care for the general population.

### 3.2: We suggest that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent\(^*\)) whose office BP is consistently \( > 130 \text{ mm Hg systolic or } > 80 \text{ mm Hg diastolic} \) be treated with BP-lowering drugs to maintain a BP that is consistently \( \leq 130 \text{ mm Hg systolic and } \leq 80 \text{ mm Hg diastolic}. \)\(^{2D}\)

\*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

### RATIONALE
- Urine albumin level of 30 to 300 mg per 24 hours (microalbuminuria) is a risk factor for CVD and CKD progression.
- RCTs suggest that a BP \( \leq 130/80 \text{ mm Hg} \) may reduce progression of CKD.

Patients with microalbuminuria are at high risk for progression of CKD as well as development of CVD.\(^{18,153,162–165}\) RCT data suggest that BP control is particularly important in CKD patients with high urine albumin levels.

Short-term follow-up data from the MDRD study\(^{142}\) showed an interaction of BP target with level of urine protein, with a definitive benefit for kidney outcomes in patients with \( > 1 \text{ g} \) of urine protein per 24 hours and GFR of 25–55 m/min per 1.73 m\(^2\) (in MDRD Study A), with a trend toward a benefit with lower protein levels. Long-term follow-up showed a benefit of a low target BP and no interaction with the urine protein level, suggesting that the benefit may extend to all protein levels. In subgroup analyses, the benefit was statistically significant in those with urine protein excretion of \( > 0.3 \text{ g} \) per 24 hours\(^{166}\) (H Tighiouart, personal communication). However, there may have been insufficient statistical power to detect the interaction; hence, the risk reduction may have been greater in those with higher urine protein levels. Long-term follow-up data from the MDRD study also showed a benefit with regard to kidney outcomes with a lower target BP in specific groups, such as patients with polycystic kidney disease and non-glomerular diseases, that frequently have low urine albumin levels. Long-term follow-up in the AASK study demonstrated a benefit of lower target BPs in patients with a PCR \( > 220 \text{ mg/g} \) (\( > 22 \text{ mg/mmol} \)).\(^{140}\) It is unclear whether this PCR cutoff can be translated into an albumin-level cutoff, as this conversion is likely to be dependent on the type of kidney disease, and the ratio of glomerular albuminuria to tubular proteinuria. In the Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) study,\(^{14}\) a lower BP target was of benefit in reducing the risk of kidney outcomes, particularly in children with higher urine protein levels (\( P=0.06 \) for interaction of treatment target with urine protein level).

There have been no BP target trials involving CKD patients focused on hard CVD outcomes. Subgroup analyses from the Hypertension Optimal Treatment (HOT) trial\(^{167}\) did not show a benefit for CVD outcomes in association with a lower diastolic BP target in CKD patients, although the statistical power to detect a difference was limited (\( n=470 \) for those with a creatinine level \( > 1.5 \text{ mg/dl} \) [133 \text{ mmol/l}]). Furthermore, albuminuria data were not available.

Because patients with CKD and microalbuminuria are at high risk, and given that the evidence does not support using different BP targets in non-diabetics and diabetics (see Chapter 4), the Work Group suggests
a BP target of ≤130/80 mm Hg. This ensures consistency among recommendations between persons with diabetes and those without diabetes and facilitates implementation into clinical practice.

3.3: We suggest that non-diabetic adults with CKD ND and urine albumin excretion > 300 mg per 24 hours (or equivalent*) whose office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. (2C)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE
- Albuminuria is a major risk factor for CVD and CKD progression.
- RCTs show that BP ≤130/80 mm Hg may reduce progression of CKD in patients with urine albumin excretion > 300 mg per 24 hours (‘macroalbuminuria’).

Patients with macroalbuminuria are at very high risk for both progression of CKD and development of CVD. Observational data suggest that hypertension is a risk factor for CVD and progression of CKD in patients with macroalbuminuria. As noted above, short-term follow-up data from the MDRD study showed an interaction of BP target with the level of urine protein, with a definitive benefit in patients with a urine protein level > 1 g per 24 hours (in Study A) and a trend toward a benefit with lower protein levels; long-term follow-up data showed a benefit of a lower target BP. In subgroup analyses, a benefit was noted in patients with urine protein excretion > 0.3 g per 24 hours (H. Tighiouart, personal communication). Long-term follow-up data from AASK also showed a benefit of a lower target BP in patients with PCR > 220 mg/g (>22 mg/mmol). and the ESCAPE trial showed a benefit in the entire population with a borderline interaction of treatment target and urine protein level.

In summary, we believe there is sufficient evidence to suggest a BP target of ≤130/80 mm Hg for kidney protection in those with macroalbuminuria. We have graded this suggestion 2C, for the following reasons. The reported benefits in the AASK and the MDRD study are based on post hoc and subgroup analyses. Furthermore, in both the MDRD study and AASK, MAP was targeted rather than systolic and diastolic BP, and a specific MAP may translate into different systolic and diastolic BP, depending on the individual patient. Additionally, in the MDRD study, a higher MAP was targeted in patients over the age of 60 years. The Ramipril Efficacy in Nephropathy 2 (REIN-2) study did not show a benefit of tight BP control, although admittedly this was a short-term study with relatively few outcomes and it is unclear whether the use of a dihydropyridine calcium-channel blocker (felodipine) in the low-target arm may have confounded the results (See Supplementary Tables 2–4 online). We also do not believe that this recommendation should in any way hinder trials from randomizing patients with CKD and urine protein excretion < 1 g per 24 hours to various BP targets, as there is sufficient equipoise and uncertainty to endorse these trials. One such trial that will evaluate this question is Systolic Blood Pressure Intervention Trial (SPRINT) which is funded by National Institutes of Health (NIH). It will evaluate cardiovascular and kidney outcomes in patients randomized to a systolic BP of < 140 mm Hg versus < 120 mm Hg. There is a CKD component for patients with GFR 20-60 ml/min/1.73 m². Patients with diabetes and those with 24-hour urine protein excretion of > 1 g per 24 hours are excluded from this study.

3.4: We suggest that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. (2D)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE
- Urine albumin excretion of 30 to 300 mg per 24 hours (microalbuminuria) is a risk factor for CVD and CKD progression.
- ACE-Is and ARBs have been shown to reduce urine albumin levels.
- RCTs suggest that ACE-Is or ARBs may help reduce progression of CKD and possibly CVD in patients with urine albumin excretion of 30 to 300 mg per 24 hours.

As mentioned above, patients with microalbuminuria are at high risk for both progression of CKD and development of CVD. Here, we describe the trial data which either focused on kidney disease or CVD outcomes. Some trials focused on both.

Kidney disease. In AASK, a study of patients with a PCR < 220 mg/g (<22 mg/mmol), the ACE-I ramipril decreased the urine protein level. It remains to be determined whether this translates into a clinically important benefit. In post hoc analyses of the Heart Outcomes Prevention Evaluation (HOPE), which was an RCT involving patients with diabetes or vascular disease and at least one other CVD risk factor, ramipril prevented progression of proteinuria or development of new-onset microalbuminuria, independent of diabetes status. In a post hoc analysis of Candesartan...
Antihypertensive Survival Evaluation in Japan (CASE J), which was an RCT comparing the ARB candesartan with the calcium-channel blocker amlodipine,\textsuperscript{178} candesartan reduced progression of CKD 4 (see Supplementary Table 5 online). In subgroup analyses of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSEND), an RCT that included patients with vascular disease or diabetes, in patients with microalbuminuria (defined as an ACR > 3.4 mg/mmol [> 34 mg/g]), the ARB telmisartan decreased the risk of the composite kidney outcome (doubling of SCR level, dialysis, or death) in comparison with placebo.\textsuperscript{179} There was an interaction whereby telmisartan benefited patients with microalbuminuria but was associated with harm in those without microalbuminuria (P = 0.006 for interaction). Finally, in patients with diabetes, ACE-I s and ARBs have been shown to prevent the development of macroalbuminuria in subjects with microalbuminuria,\textsuperscript{180,181} and we have not found evidence of substantive differences between diabetics and non-diabetics with respect to either BP target or agent.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large RCT examining the effects of the ACE-I lisinopril, the thiazide chlorthalidone, and the dihydropyridine calcium-channel blocker amlodipine in individuals > 55 years of age with hypertension and at least one other CVD risk factor. Lisinopril did not show a benefit for doubling of creatinine or kidney failure when compared with chlorthalidone in the entire cohort or among patients with CKD at baseline\textsuperscript{175} (see Supplementary Table 6 online). ALLHAT, however, did not permit the use of an ACE-I with a diuretic—a combination that is frequently required in clinical practice to achieve adequate BP control.\textsuperscript{182–184} In addition, the diuretic arm in ALLHAT achieved better BP control making comparison of agents more difficult to interpret. Unfortunately, albuminuria or proteinuria status was not measured in the enrolled subjects, but assuming that ALLHAT was consistent with other trials of high-risk individuals recruited from the general population (e.g., HOPE or TRANSEND), the median level of proteinuria was most likely below the microalbuminuria cutoff.

**CVD.** There have been few RCTs of BP agents that have focused on CVD outcomes in CKD patients without diabetes mellitus (Supplementary Tables 7–32 online). Most of the data are taken from subgroup analyses of patients with CKD from general population studies (Supplementary Tables 1, 5–6, 33–36 online). HOPE showed a benefit for CVD outcomes in patients randomized to ramipril.\textsuperscript{185} This benefit extended to those with a creatinine level > 1.4 mg/dl (124 mmol/l) or a creatinine clearance < 65 ml/min (1.1 ml/sec) in non-diabetic individuals,\textsuperscript{173} as well as those with microalbuminuria.\textsuperscript{185} In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which included patients with a history of cerebrovascular disease, the ACE-I perindopril, as compared with placebo, decreased the rate of recurrent stroke in those with CKD.\textsuperscript{186} Although the level of urine albumin was not specified in PROGRESS, it seems reasonable to assume that CVD protection would extend to those with microalbuminuria. In patients with stable coronary disease in the Prevention of Events with Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) trial, the ACE-I trandolapril, as compared with placebo, reduced mortality in those with a GFR < 60 ml/min/1.73 m\textsuperscript{2}, although trandolapril did not have a benefit in those with a GFR ≥ 60 ml/min/1.73 m\textsuperscript{2}.\textsuperscript{187} However, the effect of trandolapril therapy on outcomes was not significantly modified by the level of albuminuria.\textsuperscript{188} In the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), there was no modification of benefit by level of kidney function, and perindopril (versus placebo) decreased the risk of the primary composite end point of cardiovascular death, non-fatal myocardial infarction, or resuscitated cardiac arrest in patients with a GFR < 75 ml/min/1.73 m\textsuperscript{2} as well as those with a GFR > 75 ml/min/1.73 m\textsuperscript{2}.\textsuperscript{189} ALLHAT, however, did not show a benefit of lisinopril over chlorthalidone with respect to CVD outcomes in the subgroup of patients with CKD.\textsuperscript{176}

The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) included CKD patients with urine albumin levels of 15 mg to 300 mg per 24 hours. Patients were randomized to the ACE-I fosinopril or placebo. Fosinopril decreased albumin excretion by 26% and showed a trend toward reducing the risk of CVD outcomes (hazard ratio [HR] versus placebo 0.60; 95% CI 0.33–1.10).\textsuperscript{190} Similarly, in the CASE J trial, candesartan reduced the rate of CVD outcomes, as compared with amlodipine, in CKD 4 patients\textsuperscript{178} (Supplementary Table 5 online).

The Work Group suggests ACE-I s or ARBs as the preferred class of BP-modifying agent in CKD patients with microalbuminuria. This recommendation is based on observational data and subgroup and post hoc analyses, hence the grade of 2D.

### 3.5: We recommend that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion > 300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Urine albumin excretion > 300 mg per 24 hours (‘macroalbuminuria’) is a risk factor for CVD and for CKD progression.
- In RCTs involving patients with CKD and urine albumin excretion > 300 mg per 24 hours, ARBs or ACE-I s reduce
the risks of ‘hard’ outcomes such as the doubling of SCr level, kidney failure, or death.

Patients with macroalbuminuria are at very high risk for both progression of CKD and development of CVD.\textsuperscript{18,162,163}

\textit{Kidney disease.} Several trials have demonstrated a benefit, in patients with macroalbuminuria, of ACE-Is or ARBs over either placebo or other agents, in reducing the risk of macroalbuminuria, doubling of creatinine levels, and development of kidney failure (See Supplementary Tables 7–12 online).

These trials include RCTs in patients with CKD of various causes, primarily glomerulonephritis,\textsuperscript{191} African-Americans with hypertension,\textsuperscript{177} and patients with advanced CKD (a GFR of 20–70 ml/min/1.73 m\(^2\)).\textsuperscript{192} A meta-analysis of individual patient data from 11 RCTs compared antihypertensive regimens including ACE-Is to regimens without ACE-Is in 1860 patients with predominantly non-diabetic CKD. In adjusted analyses, ACE-Is were associated with a HR of 0.69 for kidney failure (95\% CI 0.51–0.94) and 0.70 for the combined outcome of doubling of the baseline SCr concentration or kidney failure (95\% CI 0.55–0.88). Patients with greater urinary protein excretion at baseline benefited more from ACE-I therapy \(P = 0.03\) for kidney failure and \(P = 0.001\) for the combined outcome.\textsuperscript{141}

The Work Group did not find heterogeneity with regard to the benefit of ACE-Is according to CKD stage; therefore, the guideline statements are not divided on this basis. Furthermore, few RCTs with hard CVD or kidney-disease outcomes randomized patients to a diuretic or another agent in addition to an ACE-I or ARB; therefore, we have not included any guideline statements to support this practice. In fact, one RCT in individuals predominantly without CKD showed that the risk of doubling of the creatinine level was higher with an ACE-I-hydrochlorothiazide combination than with ACE-I-amlodipine.\textsuperscript{101} The clinical importance of this end point remains to be determined,\textsuperscript{193} as it may reflect a reversible hemodynamic effect. Finally, there is only limited quality evidence evaluating either differences in ACE-I versus ARB, or comparison of ACE-I plus ARB versus either ACE-I or ARB with regard to hard clinical outcomes (Supplementary Tables 13–15 online).

\textit{CVD.} Only a few RCTs of BP agents have focused on CVD outcomes in subjects with CKD (Supplementary Tables 7–32 online); therefore, most of the data are from subgroup analyses of CKD patients from general population studies. Several analyses have shown a benefit of ACE-Is or ARBs over placebo or another agent, and although most of these studies were performed in patients with urine albumin levels below the macroalbuminuria cutoff, there is no obvious reason why the benefit would not extend to individuals with macroalbuminuria (Supplementary Tables 7–12 online).

In summary, the data in support of the use of ACE-Is or ARBs are reasonably strong for preventing progression of CKD and less so for CVD protection. Notably, they show no harm of either class of drugs with regard to CVD. Taken together, the data on both drug classes support a grade 1B recommendation for ACE-Is or ARBs as a preferred agent in CKD patients with albumin excretion > 300 mg per 24 hours or its equivalent.

\textbf{RESEARCH RECOMMENDATIONS}

- Large RCTs of BP targets are needed in CKD patients without diabetes (stratified by GFR and albuminuria) that are powered for clinical outcomes including kidney failure, CVD events and mortality.
- Large RCTs of BP agents are needed in CKD patients without diabetes (stratified by GFR and albuminuria) that are powered for clinical outcomes including kidney failure, CVD events and mortality.
- Subgroup analyses in new, large-scale RCTs as described above by specific causes of CKD are needed.
- Studies are needed to examine how intermediate outcomes for CKD and CVD (i.e., doubling of creatinine level, change in urine protein level, and development or regression of left ventricular hypertrophy) track with clinical outcomes to assess their validity as prognostic tools and possible surrogate outcomes going forward.
- Development of prediction tools for clinical outcomes in patients with CKD and testing in clinical trials for exploration of treatment heterogeneity are encouraged.
- Development of prediction tools for the adverse outcomes of ACE-Is and ARBs is encouraged.
- Cost-effectiveness analyses of lower BP targets in CKD patients without diabetes as stratified by GFR and albuminuria should be conducted.

\textbf{DISCLAIMER}

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\textbf{SUPPLEMENTARY MATERIAL}

\textit{Supplementary Table 1.} General population RCTs comparing BP targets in CKD subgroups.

\textit{Supplementary Table 2.} Evidence profile of RCTs examining the effect of blood pressure target in patients with CKD without DM.
Supplementary Table 3. RCTs examining the effect of blood pressure targets in patients with CKD without DM [categorical outcomes].

Supplementary Table 4. RCTs examining the effect of blood pressure targets in patients with CKD without DM [continuous outcomes].

Supplementary Table 5. General population RCTs comparing ARB versus CCB in CKD subgroups with and without DM.

Supplementary Table 6. General population RCTs comparing ACEI or ARB versus control (active or placebo) in CKD subgroups with and without DM.

Supplementary Table 7. Evidence profile of RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM [categorical outcomes].

Supplementary Table 8. RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM [continuous outcomes].

Supplementary Table 9. Evidence profile of RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM [categorical outcomes].

Supplementary Table 10. Evidence profile of RCTs examining the effect of ACEI or ARB versus CCB in patients with CKD without DM.

Supplementary Table 11. RCTs examining the effect of ACEI or ARB versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 12. Evidence profile of RCTs examining the effect of ACEI versus ARB in patients with CKD without DM [continuous outcomes].

Supplementary Table 13. RCTs examining the effect of ACEI versus ARB versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 14. Evidence profile of RCTs examining the effect of high versus low dose ACEI in patients with CKD without DM [continuous outcomes].

Supplementary Table 15. RCTs examining the effect of high versus low dose ACEI versus placebo in CKD with DM [categorical outcomes].

Supplementary Table 16. Evidence profile of RCTs examining the effect of high versus low dose ACEI in patients with CKD with DM [continuous outcomes].

Supplementary Table 17. RCTs examining the effect of high dose ACEI versus low dose ACEI in patients with CKD with DM [categorical outcomes].

Supplementary Table 18. Evidence profile of RCTs examining the effect of high versus low dose ARB in patients with CKD with DM.

Supplementary Table 19. Evidence profile of RCTs examining the effect of high versus low dose ARB in patients with CKD with DM.

Supplementary Table 20. RCTs examining the effect of high dose ARB versus low dose ARB in patient with CKD without DM [categorical outcomes].

Supplementary Table 21. RCTs examining the effect of high dose ARB versus low dose ARB in patient with CKD without DM [continuous outcomes].

Supplementary Table 22. RCTs examining the effect of ACEI versus β-blocker in patients with CKD without DM [categorical outcomes].

Supplementary Table 23. RCTs examining the effect of ACEI versus β-blocker in patients with CKD without DM [continuous outcomes].

Supplementary Table 24. RCTs examining the effect of ACEI + CCB versus ACEI in patients with CKD without DM [categorical outcomes].

Supplementary Table 25. RCTs examining the effect of ACEI + CCB versus ACEI in patients with CKD without DM [continuous outcomes].

Supplementary Table 26. RCTs examining the effect of ACEI + CCB versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 27. RCTs examining the effect of ACEI + CCB versus CCB in patients with CKD without DM [continuous outcomes].

Supplementary Table 28. RCTs examining the effect of CCB versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 29. RCTs examining the effect of CCB versus CCB in patients with CKD without DM [continuous outcomes].

Supplementary Table 30. RCTs examining the effect of β-blocker versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 31. RCTs examining the effect of β-blocker versus CCB in patients with CKD without DM [continuous outcomes].

Supplementary Table 32. RCTs examining the effect of central-acting agent versus CCB in patients with CKD without DM [categorical outcomes].

Supplementary Table 33. General population RCTs comparing ACEI + diuretic versus placebo in CKD with DM subgroups [categorical outcomes].

Supplementary Table 34. General population RCTs comparing ACEI + diuretic versus placebo in CKD with DM subgroups [continuous outcomes].

Supplementary Table 35. General population RCTs comparing ARB or (ACE + ARB) versus ACE in CKD subgroups with and without DM.

Supplementary Table 36. General population RCTs comparing CCB versus active control in CKD subgroups with and without DM.

Supplementary material is linked to the online version of the paper at http://www.kdlgo.org/clinical_practice_guidelines/bp.php
Chapter 4: Blood pressure management in CKD ND patients with diabetes mellitus


INTRODUCTION

This chapter addresses the management of BP in adult CKD patients (specifically non-dialysis-dependent CKD [CKD ND]) with diabetes mellitus. Previous guidelines1,30 have used the term ‘diabetic nephropathy’ or ‘diabetic kidney disease.’ This Work Group decided to use the term ‘diabetes with CKD’ in recognition of the fact that many patients who have co-existing diabetes and CKD do not undergo kidney biopsy and may have other forms of kidney damage with or without the changes that characterize diabetes. Examples of alternative pathologies include nephroangiosclerosis, atheromatous embolism, atherosclerotic renal artery disease, or glomerulonephritis. In addition, there is evidence that the classic histological features of diabetic nephropathy can on occasion be found in patients who do not have a high urine albumin level.194-196 Also, progressive loss of excretory kidney function has been observed in the absence of progression from microalbuminuria to overt proteinuria in some patients with diabetes.197

Observational studies in the general population provide strong evidence of a linear relationship between BP and risk of cardiovascular events.21 A large number of RCTs have also shown that drugs that reduce BP also reduce the risk of subsequent cardiovascular events.198 The benefits of BP reduction observed in clinical trials involving high-risk patients have also been shown to be consistent across a range of baseline BP levels in recent, large meta-analyses.198,199 In addition, baseline BP levels have been shown to be a powerful determinant of the subsequent risk of kidney failure in large population-based studies from around the world.148,200

Diabetes increases the risk of CVD by a factor of two to three at every level of systolic BP,201 and this risk is further potentiated by the presence of CKD. In addition, type 2 diabetes is a leading cause of CKD, accounting for 30 to 50% of new cases of kidney failure in the industrialized world.202 Microalbuminuria is one of the earliest detectable manifestations of kidney disease in patients with diabetes, with a prevalence of 25% after 10 years of diabetes and an annual rate of progression to overt nephropathy of approximately 3%.203,204 The risk of incident and progressive microalbuminuria is highly associated with BP levels.204 Progression of retinopathy is also closely associated with high BP.205-208 It is therefore important that the clinician is provided with clear, evidence-based recommendations on the use of BP-lowering drugs in the management of patients with diabetes and CKD.

This management should also include interventions for multiple risk factors, which have been shown to improve outcomes in patients with diabetes.209-211

The Work Group recognizes that the benefits of BP reduction in patients with diabetes and CKD may include reductions of the risks of progressive loss of kidney function, CVD and progression of diabetic retinopathy. We also took into account the fact that the effects of BP reduction may differ among outcomes; for instance, a lower achieved BP may be associated with an increased risk of one outcome but a reduced risk of another.

These recommendations are not stratified by CKD stage as there are remarkably few studies in which the effect of BP-lowering therapy has been reported according to CKD stage. The Work Group could find no evidence that the balance of benefits and harms of BP-lowering therapy, or specific types of therapy, varied with the GFR—other than the known risks of hyperkalemia, particularly with agents that directly interfere with renin-angiotensin-aldosterone system (see Chapter 2).

4.1: We recommend that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- RCTs that have examined various BP targets or compared active treatment with placebo, along with observation studies, have been consistent in suggesting that lowering BP so that it is consistently <140/90 mm Hg will prevent major cardiovascular events. Lowering BP to these levels is also likely to reduce the risk of progressive CKD.
- The evidence for the benefit of further lowering of the BP target is mixed, with modest cardiovascular benefits in patients with diabetes partly offset by increases in the risk of serious adverse effects in trials, and inconsistency in results among observational studies using clinical trial datasets.
Recommendation 4.1 applies to diabetic patients with CKD, defined as a GFR <60 ml/min/1.73 m², and normal albumin excretion (normoalbuminuria) prior to the use of BP-lowering drugs such as ACE-Is or ARBs. Several studies have shown that this is not a rare occurrence in patients with type 2 diabetes.\(^{195,196,212-217}\) For example, in the National Health and Nutrition Examination Survey (NHANES), 36% of adults with type 2 diabetes and a GFR <60 ml/min/1.73 m² had normal urine albumin levels.\(^{195}\) A population-based study in Japan found 262 of 3297 people (7.9%) with type 2 diabetes and a GFR <60 ml/min/1.73 m² had a normal AER. The diabetic patients with CKD but a normal AER were older and included a higher proportion of women and patients with hypertension, hyperlipidemia, and CVD but fewer smokers, compared with the diabetic patients with a normal AER and preserved GFR.\(^{217}\)

A long-term follow-up study of participants with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that 24% of those who developed a GFR <60 ml/min/1.73 m² had an AER <30 mg per 24 hours at all previous evaluations,\(^{218}\) indicating that normoalbuminuric CKD is also an important entity in type 1 diabetes.

**RCTs.** The Work Group could not identify any RCTs in which patients with CKD and normoalbuminuric diabetes had been randomized to various BP targets. Several trials have been completed in broader populations with diabetes, some of whom had CKD at study entry. These are summarized here.

In the United Kingdom Prospective Diabetes Study (UKPDS) 38,\(^{219}\) patients with diabetes, a minority of whom also had nephropathy, were randomized to BP <150/85 mm Hg or <180/105 mm Hg. Tighter BP control was associated with a reduction in risk of diabetes-related death, stroke, and progression of retinopathy.

The HOT study\(^{220}\) recruited 18,790 adults with diastolic BP between 100 and 115 mm Hg and randomized them to one of three diastolic BP targets: ≤90, ≤85, and ≤80 mm Hg. Among the 1501 subjects with diabetes (a relatively small proportion, suggesting under-representation of diabetics), the risk of major cardiovascular events in the group targeted to a diastolic BP ≤80 mm Hg was half that of the group targeted to 90 mm Hg. Baseline data on cardiovascular risk factors were not provided for the diabetic subgroup, leading some commentators to speculate whether this result was due to imbalance between the groups rather than to a genuine treatment effect. No data were given on urinary albumin excretion in the diabetic subgroup.

The Appropriate Blood Pressure Control in Diabetes (ABCD) study was a 5-year prospective RCT comparing intensive and moderate BP control in patients with diabetes.\(^{221}\) The hypertensive arm comprised diabetic patients with a diastolic BP >90 mm Hg randomized to a diastolic BP target of 75 mm Hg or 80 to 89 mm Hg. Patients assigned to the lower BP target were also randomized to receive either nisoldipine or enalapril. This arm of the trial was terminated early because of a significantly higher incidence of myocardial infarction (a prespecified secondary end point) in the nisoldipine group.\(^{222}\) At 5 years of follow-up, there was no difference in the rate of prespecified kidney outcomes or cardiovascular outcomes between the group targeted to 75 mm Hg and the group targeted to 80 to 89 mm Hg but a significantly lower incidence of death in the 75 mm Hg group.\(^{183}\)

The normotensive arm in the ABCD study comprised diabetic patients (around 30% of whom had CKD, as defined on the basis of albumin excretion) with a baseline BP <140/90 mm Hg who were randomized to placebo or active treatment (and in that group, further randomized to either enalapril or nisoldipine) titrated to reduce the diastolic BP to 10 mm Hg below baseline.\(^{223}\) As compared with less-intensive treatment, intensive treatment (to the lower BP target) was not associated with any difference in the change in creatinine clearance over the study period but was associated with lower risks of progression from normoalbuminuria to microalbuminuria and from microalbuminuria to overt proteinuria, as well as a reduced risk of stroke and of progression of retinopathy. The inclusion criteria for the normotensive arm of ABCD prevents reliable extrapolation of this finding to patients whose baseline BP is >140/90 mm Hg.

The ACCORD study\(^{159}\) randomized 4733 patients with diabetes and high cardiovascular risk to a systolic BP target <140 mm Hg or <120 mm Hg. A total of 39% of patients had an elevated urinary AER. There was no difference between the two groups in the primary composite end point (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). However, the lower systolic BP target was associated with a significant reduction in the risk of stroke (62 events with <140 mm Hg target vs. 36 events with <120 mm Hg target, \(P=0.01\)), a pre-specified secondary end point, but also with a significant increase in rate of serious adverse events (30 events vs. 77 events, respectively; \(P<0.001\)).\(^{224}\)

As compared with the group targeted to <140 mm Hg, the group targeted to <120 mm Hg had higher rates of hyperkalemia and elevations in SCr level. The mean GFR was significantly lower in the intensive-therapy (lower-target) group than in the standard-therapy group at the final visit was significantly lower with intensive therapy, intensive treatment (to the lower BP target) was not associated with any difference in the change in creatinine clearance over the study period but was associated with lower risks of progression from normoalbuminuria to microalbuminuria and from microalbuminuria to overt proteinuria, as well as a reduced risk of stroke and of progression of retinopathy. The inclusion criteria for the normotensive arm of ABCD prevents reliable extrapolation of this finding to patients whose baseline BP is >140/90 mm Hg.

The ACCORD study\(^{159}\) randomized 4733 patients with diabetes and high cardiovascular risk to a systolic BP target <140 mm Hg or <120 mm Hg. A total of 39% of patients had an elevated urinary AER. There was no difference between the two groups in the primary composite end point (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). However, the lower systolic BP target was associated with a significant reduction in the risk of stroke (62 events with <140 mm Hg target vs. 36 events with <120 mm Hg target, \(P=0.01\)), a pre-specified secondary end point, but also with a significant increase in rate of serious adverse events (30 events vs. 77 events, respectively; \(P<0.001\)).\(^{224}\)

As compared with the group targeted to <140 mm Hg, the group targeted to <120 mm Hg had higher rates of hyperkalemia and elevations in SCr level. The mean GFR was significantly lower in the intensive-therapy (lower-target) group than in the standard-therapy group at the last visit. There were significantly more instances of a single GFR measurement <30 ml/min/1.73 m² in the intensive-therapy group than in the standard-therapy group (99 events vs. 52 events, respectively; \(P<0.001\)), but the proportion of participants with more than one GFR reading <30 ml/min/1.73 m² was similar in the two groups (38% vs. 32%, respectively; \(P=0.46\)). The frequency of macroalbuminuria at the final visit was significantly lower with intensive therapy than with standard therapy, and there was no between-group difference in the frequency of kidney failure or initiation of dialysis (in 58 patients vs. 59 patients, \(P=0.93\)).\(^{159}\)

The ACCORD trial also showed that intensive glycemic control and combination lipid-lowering treatment, but not
intensive BP control, was associated with a reduction in the rate of progression of retinopathy.\textsuperscript{224}

**Observational studies.** There have been several large observational studies of patients with diabetes, CKD, or both, most of which found a lower risk of cardiovascular or kidney outcomes in people with lower BP.\textsuperscript{148,225} These studies have been cited by many previous guidelines and used to support a BP target of <130/80 mm Hg for patients with CKD or diabetes. However, none of these studies prove causality and it is equally possible that higher BP, whether occurring before initiation of BP-lowering treatment or after, is simply a marker for more severe disease, which in turn has a poorer prognosis.\textsuperscript{22}

Among patients screened for the Multiple Risk Factor Intervention (MRFIT) trial, there was a strong, graded, positive relationship between baseline BP and subsequent risk of kidney failure; the association was weaker among older men, blacks, and men with diabetes.\textsuperscript{148} In the diabetic subgroup of MRFIT participants,\textsuperscript{201} the risk of cardiovascular death increased to a greater degree with increasing risk factors, including systolic BP, than in the non-diabetic subgroup.

A strong association between baseline BP and subsequent risk of kidney failure was also demonstrated in an Okinawan study.\textsuperscript{226} After adjustment for age and BMI, there was a significant, positive association between systolic BP and the risk of diabetic kidney failure, with a relationship also demonstrated for diastolic BP in women only.

The Pittsburg Epidemiology of Diabetes Complications (EDC) study\textsuperscript{227} reported on 589 patients with childhood-onset diabetes. A graded association between baseline BP and subsequent risk of major events was found.

Data from the Cardiovascular Health Study and the Atherosclerosis Risk In Communities study\textsuperscript{158} showed that among participants with CKD, there was a J-shaped relationship between systolic BP and risk of stroke, with a higher risk of stroke with a systolic BP <120 mm Hg; this relationship was not seen in those without CKD.

**Post hoc analyses of RCTs.** Post hoc analyses of several large RCTs have indicated various relationships between achieved BP and outcomes.

A post hoc analysis of achieved BP and outcome in the Irbesartan Diabetic Nephropathy Trial (IDNT)\textsuperscript{228} indicated that systolic BP <120 mm Hg was associated with an increased (rather than decreased) risk of cardiovascular events.

A post hoc analysis of UKPDS 36,\textsuperscript{229} irrespective of treatment allocation, revealed a significant association between higher systolic BP and higher risk of clinical complications over a systolic BP range of 115 to 170 mm Hg.

The International Verapamil SR Trandolapril (INVEST) study recruited patients with hypertension and CAD and compared the effects of verapamil and atenolol. Trandolapril, hydrochlorothiazide, or both were added to achieve either a BP <140/90 mm Hg or a BP of <130/85 mm Hg in patients with diabetes or kidney impairment.\textsuperscript{230} In an analysis of achieved BP among participants with diabetes (irrespective of their randomized treatment assignments), those who achieved tight BP control (i.e., a systolic BP <130 mm Hg) had similar rates of cardiovascular outcomes, and higher rates of death, than those with usual BP control (i.e., systolic BP, 130 to 140 mm Hg). Both groups had better outcomes than did a third group with poor BP control (i.e., systolic BP >140 mm Hg). The increased risk of mortality in the tight-control group persisted during an extended follow-up period.\textsuperscript{231}

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)\textsuperscript{232} collaborative group showed that the addition of perindopril plus indapamide to current therapy used in patients with type 2 diabetes and high cardiovascular risk reduced the rate of major or microvascular events.\textsuperscript{232} In a secondary analysis, kidney events (mostly measures of appearance or worsening of urinary AER) were less frequent with a lower achieved BP at the follow-up visit.\textsuperscript{233} The absolute risk reductions for cardiovascular and kidney end points associated with active treatment (irrespective of BP) were greater among patients with CKD 3–5 than among patients with CKD 1–2.\textsuperscript{234}

**Interpretation.** The Work Group believed that the data for reducing usual systolic BP to ≤140 mm Hg and diastolic BP to ≤90 mm Hg were strong, on the basis of the data presented above, as well as the clear relationship between BP levels and the risk of cardiovascular and kidney outcomes consistently noted in observational studies in both the general population\textsuperscript{21,198,199} and in patients with diabetes with a systolic BP >140 mm Hg and a diastolic BP >90 mm Hg.\textsuperscript{229,233} Further support is provided by reports from a number of clinical trials or trial subgroups demonstrating that BP-lowering therapy prevents cardiovascular and kidney events in patients with diabetes, most of whom had BP levels >140/90 mm Hg at trial entry.\textsuperscript{183,219,221,223,232} There are few data for individuals with diabetes and CKD, but those that are available have reported broadly consistent findings.\textsuperscript{234}

The Work Group does not believe that the evidence is sufficiently strong to support a lower target BP level for all patients with diabetes and CKD. Some support for lower BP targets is provided by the ACCORD and ABCD trials population. However in ACCORD, these benefits must be balanced against the increased risk of adverse events. As a result, it was felt that the risk-to-benefit ratio is likely to be unfavorable for at least some groups of individuals with diabetes and CKD. These include patients with diabetes and non-albuminuric CKD, who may be likely to have additional co-morbidities; the elderly, who are prone to falls; patients with marked systolic hypertension; and those with severe autonomic neuropathy. Such patients may have been under-represented in the RCTs and observational studies.

A target BP of ≤140 systolic and ≤90 mm Hg diastolic may appear to require less aggressive therapy than the targets recommended in some other guidelines for patients with diabetes. However, whether this is true depends on how targets are interpreted by clinicians. There is extensive evidence from routine clinical practice that many patients do not achieve the targets set in guidelines; instead, achieved
values often have a normal distribution around the target. This distribution of values is the reason for the wording we have chosen for the recommendation statements: that BP be “consistently” below a given level. For instance, to account for random fluctuations in resting office BP over time, the intervention threshold needs to be significantly < 130 mm Hg to achieve a systolic BP consistently < 130 mm Hg.

The Work Group, therefore, is confident that most individuals with diabetes and CKD should have their usual BP lowered to be consistently ≤ 140/90 mm Hg (hence the grade of 1B for recommendation 4.1), and that targets lower than ≤ 140/90 mm Hg could be considered on an individual basis for patients believed to be more likely to benefit than to be harmed by the treatment (e.g., patients not already on several BP-lowering agents, younger individuals, or persons at high risk of stroke).

Overall, the evidence supporting the statement that systolic BP should be lowered to ≤ 140 mm Hg is at least level B. However, the evidence supporting the implication that systolic BP needs to be lowered further, for instance to ≤ 130 mm Hg, is weaker. This grading should not, therefore, be taken to imply that no further research is required on the question of lower BP targets in this group.

Comparison with current guidelines. Recommendation 4.1 is consistent with recommendations made by numerous international and national guidelines for the general population, all of which agree on a treatment goal of ≤ 140/90 mm Hg on the grounds that BP-lowering drugs reduce the risk of all-cause and cardiovascular mortality in people whose BP is > 140/90 mm Hg. There is no reason to expect that patients with diabetes and CKD are less likely to have a benefit. Although there is observational evidence that the risk of CVD is higher among diabetic patients than non-diabetic patients at any given BP, these findings do not, in the absence of RCT evidence, support a recommendation that BP should be lowered further than is recommended in diabetic patients.

The Work Group is aware that this recommendation appears more conservative than the recommendations of some other international and national guidelines that recommend a BP target ≤ 130/80 mm Hg for patients with diabetes and CKD. However, there is insufficient high-quality evidence from RCTs to support a lower target for patients with diabetes and CKD (which we defined as a GFR < 60 ml/min/1.73 m²) who do not have an increased urinary AER. All other guidelines have relied on observational evidence to support a lower systolic BP threshold for patients with diabetes. The Work Group did not consider the evidence from the HOT trials and ABCD trials strong enough to justify a recommendation to lower the target diastolic BP to ≤ 80 mm Hg.

The Work Group analyzed the evidence base for the existing guidelines carefully to ensure that the apparent departure from accepted wisdom was justified. Few existing guidelines specify how patients with normoalbuminuric CKD and diabetes should be treated with BP-lowering drugs, with the majority advising a BP target of ≤ 130/80 mm Hg for all patients with diabetes, irrespective of GFR or albuminuria. Although the grades (and grading system) of these recommendations vary, all supporting statements acknowledge that the evidence is largely observational. For instance, many guidelines refer back to JNC 7, which qualified the recommendation with the caveat, ‘although available data are somewhat sparse to justify the low target level of 130/80 mm Hg …’. The JNC 7 goes on to cite the American Diabetes Association guidelines and the supporting literature analysis, which rely on the HOT findings for justification of the 80 mm Hg diastolic BP target and on Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (Syst-Eur) trial (both studies of the general population) for the 140 mm Hg systolic BP target. Finally, the JNC 7 states that ‘Epidemiological studies indicate that there is a benefit to reducing systolic BP still further to 130 mm Hg or below’, citing two references, UKPDS 36 and a study from Allegheny County that contains no data on BP.

We have not made recommendations about the choice of the BP-lowering drug to be used in patients with CKD and diabetes who do not have elevated rates of urinary albumin excretion. Although there is some evidence that inhibitors of the renin-angiotensin system might prevent an increase in urinary AER, particularly in the presence of higher BP, and might also reduce cardiovascular risk, such studies have not been performed in patients with reduced GFR but normal urinary albumin excretion. In such patients, the balance of risks and benefits of the use of ACE-Is or ARBs may well differ from the balance of their use for primary prevention of diabetic kidney disease.

Considerations. Most interpretations of the observational evidence predict that achieved BPs below a target of ≤ 140/90 mm Hg in patients with CKD and diabetes would be associated with additional benefit in the prevention of both progressive kidney disease and cardiovascular events. However, no RCTs have demonstrated such a benefit. It remains possible that clinical harm could be done, at least in some subgroups, by attempting to reach lower BPs. Achieving lower BPs would require multiple drug treatments in the majority of patients with CKD and diabetes, particularly those with high pulse pressures. This has implications both for adherence and for the cost of treatment, of which the latter is particularly important in resource-poor settings.

4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion > 30 mg per 24 hours (or equivalent*) whose office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. (2D)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.
**RATIONALE**

- Observational studies show that the level of urine albumin predicts the risk of adverse cardiovascular and kidney outcomes.
- BP lowering reduces the rate of urinary albumin excretion, which may in turn lead to a reduced risk of both kidney and cardiovascular events, although this has not been shown in RCTs.

**RCTs.** The Work Group found only one RCT, from the Steno Diabetes Centre in Copenhagen (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria [Steno-2 study]) in which diabetic patients with high urine albumin were selected and randomized to two BP targets. In the Steno-2 study, 160 adults with microalbuminuria and type 2 diabetes were randomized to intensive multifactorial intervention or to conventional therapy. The intensive-care arm received ACE-I or ARB irrespective of BP and had a BP target that was initially 140/85 mm Hg but was reduced to 130/80 mm Hg during the study, as compared to <160/95 mm Hg which was subsequently reduced to <135/85 mm Hg in the conventional arm. However, intensive intervention also included dietary advice, exercise, lipid-lowering treatment, help with smoking cessation, vitamin supplementation, aspirin, and intensified glycemic control. This intensive therapy was shown to be associated with a reduced risk of CVD, nephropathy, retinopathy, and autonomic neuropathy. The improvements seen in the intensive-therapy group were mostly in BP and the lipid profile, with only minor differences between the two groups in glycemic control and no differences in smoking, exercise measures, or body weight.

**Observational evidence.** There is strong observational evidence of an association between higher BP and an increased risk of worsening kidney function. Diabetic patients with microalbuminuria are at increased risk of both CVD and progressive kidney disease as compared to diabetic patients with normal albumin excretion. Reduction of the rate of urinary albumin excretion during treatment is associated with a better kidney and cardiovascular prognosis. However, these associations do not prove causation, and it remains possible, albeit highly unlikely, that patients in whom the rate of urine albumin excretion declines, either spontaneously or in response to treatment, have intrinsically less severe disease than those in whom no remission occurs. RCTs examining the effects of targeting certain levels of urine albumin on clinically relevant end points are needed before it can be concluded that treatment to reduce the rate of urinary albumin excretion will improve prognosis.

The Work Group therefore felt that benefits of targeting lower BP levels were likely to be greater for individuals with micro- or macroalbuminuria, so a target BP of ≤130/80 mm Hg is suggested; however, stronger evidence is required in this population, hence the grade of 2D.

### 4.3: We suggest that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). (2D)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Patients with diabetes and microalbuminuria are at increased risk of kidney failure and cardiovascular events.
- ACE-Is and ARBs reduce the level of urine albumin in patients with diabetes and microalbuminuria at baseline, but data regarding the effects on kidney failure or cardiovascular outcomes are limited.

Microalbuminuria is much more common than frank proteinuria or albuminuria in patients with diabetes, but it is also associated with an increased risk of kidney and cardiovascular events. Several trials have shown a benefit of ACE-Is or ARBs over placebo in patients with microalbuminuria, irrespective of pre-treatment BP (See Supplementary Tables 37–42 online). All of these trials studied the effects of treatment on surrogate outcomes, most commonly the transition to overt proteinuria; none demonstrate conclusively that these improvements are associated with a reduction in hard end points in this population, although this may be the result of low event rates, inadequate statistical power, and short follow-up times. The Work Group believes that ACE-Is and ARBs should be the preferred classes of BP-lowering agent used in patients with diabetes and microalbuminuria, although the relatively weak available evidence is reflected in the poor grade assigned to this guideline statement (2D).

We have not made statements about prevention of microalbuminuria as this topic will be addressed in the forthcoming KDOQI Diabetes guideline update.

### 4.4: We recommend that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Patients with diabetes and high levels of urine albumin are at a particularly high risk of adverse cardiovascular and kidney outcomes.
- There is strong evidence from RCTs conducted in patients with diabetes and CKD demonstrating that ACE-Is and ARBs protect against kidney failure and increases in albumin levels.

Individuals with elevated levels of urinary albumin or protein and diabetes have some of the highest rates of cardiovascular events and kidney failure of any group with CKD. For
example, in IDNT and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, the annual risk of the kidney and cardiovascular end points all approached 10%. 182,184,259–261

**RCTs.** Several RCTs have provided high-quality evidence, both in type 1 diabetes269 and type 2 diabetes,182,184 that ARBs and ACE-Is reduce the risk of kidney outcomes,270 as compared to placebo or a dihydropyridine calcium-channel blocker,184 although no clear effect on cardiovascular outcomes has been established (possibly due to inadequate power) (see Supplementary Tables 37–42 online). However, applicability of study findings to the entire CKD and diabetes population is somewhat limited, because major studies have excluded patients with clinically significant CVD. There is high-quality evidence from trials of high-risk individuals from the general population showing that ARBs and ACE-Is improve cardiovascular outcomes,185,271–276 including in patients with diabetes.277,278 But these studies did not focus on patients with clinically significant albuminuria. In contrast, there was no benefit of ACE-Is as compared to diuretic therapy in the CKD and diabetic subgroups in ALLHAT,279 although, again, few of the study patients were likely to have had frank albuminuria. Moreover, ALLHAT showed clear BP differences in favor of diuretic therapy over ACE-Is, making the comparison between the two groups somewhat difficult. As the RCT data in this population is strong and consistent, the level of evidence is high (see Supplementary Table 37 online). The decision on the grade of this recommendation statement (1B) was made by a majority vote. The minority of Work Group members supported an evidence grade of A.

The choice between an ACE-I and an ARB in CKD patients is controversial. In general, the evidence for kidney outcomes that supports the use of ACE-Is is older and applies largely to type 1 diabetes, whereas the evidence supporting the use of ARB comes from more recent trials in type 2 diabetes. For cardiovascular protection in patients with diabetes, the evidence largely points to ACE-Is. The available data are consistent, suggesting the effects of both classes of agents are likely to be similar. Cost and availability may be an important consideration in some countries. However, extrapolations within and between drug classes must be made with care: within-class effects on hard outcomes may differ substantially and may depend on the dose, making extrapolation to other drug classes problematic. A 2004 meta-analysis concluded that there was insufficient evidence on the relative effects of ACE-Is versus ARBs on survival.280 We were unable to find trials directly comparing ACE-Is and ARBs in patients with diabetes and albuminuria. No clear difference between the effects of the two classes of drugs was found in the large Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial involving people at high cardiovascular risk, including subgroups with diabetes or CKD.281,282 However, this study was not powered to make this comparison, so a real difference remains possible.

The data are even more scarce regarding the effects of other drug classes on outcomes in patients with diabetes and proteinuria. In IDNT, patients with proteinuria were randomized to irbesartan, amlodipine, or placebo. Amlodipine did not significantly affect the risk of kidney or cardiovascular events as compared to placebo and was clearly inferior to irbesartan for the prevention of kidney outcomes.184 Aldosterone antagonists can reduce the risk of proteinuria in non-diabetic CKD patients109,283 and in patients with diabetic nephropathy,108 but adequately powered studies are lacking.

In the opinion of the Work Group, ACE-Is and ARBs are likely to be similarly effective in improving outcomes in patients with diabetes and proteinuria. Practitioners should therefore base prescribing decisions on the evidence available for each class, the risk of side effects, and cost considerations.

**RESEARCH RECOMMENDATIONS**

- Prospective RCTs of a risk-based approach to the reduction of cardiovascular risk and kidney end points are encouraged.
- Studies comparing various BP intervention thresholds and targets among patients with diabetes, with or without an increased urinary AER, and with or without a reduced GFR are needed.
- Studies in which drug dose is titrated on the basis of the urine albumin level (or change in GFR) are needed.
- Studies on the effects of non-dihydropyridine calcium-channel blockers on long-term outcomes are needed.
- Prospective studies of add-on therapy (consisting of thiazides, aldosterone antagonists, or DRIs) and reduction of sodium chloride intake on the effects of ACE-Is or ARBs in patients with diabetes and CKD are encouraged.
- Prospective studies of the combination of ACE-Is and ARBs in patients with diabetes and CKD are encouraged.
- Prospective studies of different target BP levels stratified by GFR are encouraged.

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SUPPLEMENTARY MATERIAL

**Supplementary Table 37.** Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM.

**Supplementary Table 38.** RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM [categorical outcomes].

**Supplementary Table 39.** RCTs examining the effect of ACEI or ARB vs. placebo in patient with CKD and DM [continuous outcomes].

**Supplementary Table 40.** Evidence profile of RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM.

**Supplementary Table 41.** RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [categorical outcomes].

**Supplementary Table 42.** RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [continuous outcomes].

**Supplementary Table 43.** Evidence profile of RCTs examining the effect of ACEI vs. ARB in patients with Type 2 DKD.

**Supplementary Table 44.** RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [categorical outcomes].

**Supplementary Table 45.** RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes].

**Supplementary Table 46.** Evidence profile of RCTs examining the effect of ARB vs. ARB in patients with CKD and DM.

**Supplementary Table 47.** RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes].

**Supplementary Table 48.** RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [continuous outcomes].

**Supplementary Table 49.** RCTs examining the effect of DRI + ARB vs. placebo + ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes].

**Supplementary Table 50.** RCTs examining the effect of dihydropyridine CCB vs. placebo in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes].

**Supplementary Table 51.** RCTs examining the effect of aldosterone antagonist + ACEI vs. placebo + ACEI in patients with CKD and Type 2 DM [continuous outcomes].

**Supplementary Table 52.** RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [categorical outcomes].

**Supplementary Table 53.** RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [continuous outcomes].

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php
Chapter 5: Blood pressure management in kidney transplant recipients (CKD T)


INTRODUCTION
This chapter addresses the management of BP in adults with non-dialysis-dependent CKD who have received a kidney transplant (CKD T). There is insufficient evidence to make recommendations specific to children with a kidney transplant.

5.1: We suggest that adult kidney transplant recipients whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)

RATIONALE
In adult kidney transplant recipients we consider two primary outcomes from the standpoint of BP: graft function and CVD. High BP is well recognized as an important risk factor for both decline in graft function and development of CVD. Increased levels of both systolic and diastolic BP are associated with worse graft survival over a 7-year period after transplantation, and maintaining a systolic BP <140 mm Hg at 3 years after transplantation is associated with improved graft survival and reduced cardiovascular mortality at 10 years. Similarly, high BP is associated with an increased risk of graft loss and all-cause mortality.

Although no RCT defines BP targets in adult kidney transplant recipients for clinically important end points such as graft survival, cardiovascular events, or all-cause mortality, our suggestion is that the BP target should not deviate from the recommended target of ≤130/80 mm Hg as defined in the recent KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, since there have been no recent data to contradict this recommendation. Although the European Best Practice Guidelines for Renal Transplantation 2002 recommended a target BP ≤125/75 mm Hg in proteinuric patients, there is no evidence to differentiate BP target based on albumin excretion in renal transplant recipients. Because adult CKD T patients are at high risk for both graft loss and development of CVD, we favor a target of ≤130/80 mm Hg rather than a target of ≤140/90 mm Hg. We recognize that this recommendation is based on observational data and have therefore given it a grade of 2D.

5.2: In adult kidney transplant recipients, choose a BP-lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co-morbid conditions. (Not Graded)

RATIONALE
BP-lowering agents are prescribed in 70 to 90% of kidney transplant recipients, according to both registry reports and RCTs. There are many considerations in choosing anti-hypertensive drugs for use in adult kidney transplant recipients. These include side effects that are also seen in the general population, side effects particular to kidney transplant patients (e.g., increased propensity to hyperkalemia or anemia with ACE-Is or ARBs), level of urine albumin, degree of hemodynamic stability and the associated potential to alter graft perfusion (especially in a period soon after transplantation), co-morbid conditions that may indicate or preclude certain agents, interactions with immunosuppressive medications or other medications unique to patients with kidney transplant patients, and long-term impact on graft function, CVD, and all-cause mortality. Because of these considerations and the absence of large trials with clinically important outcomes, there is marked variability in the prescription of cardioprotective medications after transplantation.

Short-term RCTs (of duration ≤2 years) suggest a beneficial effect of calcium-channel blockers, as compared with either placebo or ACE-Is, with regard to level of kidney function. In addition, a recent meta-analysis of RCTs indicated that the use of calcium-channel blockers, versus placebo or no treatment (plus additional agents in either arm, as needed) was associated with a 25% lower rate of graft loss (relative risk [RR] 0.75; 95% CI 0.57-0.99) and higher GFR (by 4.5 ml/min; 95% CI 2.2-6.7). These findings prompted the Canadian Society of Transplantation and Canadian Society of Nephrology to question the recommendation from the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients to use any class of antihypertensive agent after kidney transplantation.

Most transplantation centers prefer to use dihydropyridine calcium-channel blockers for initial therapy after transplantation, since these agents dilate afferent arterioles and counteract the vasoconstrictive effect of CNIs (Supplementary Tables 54-59 online). However, non-dihydropyridines might interfere with the metabolism and excretion of...
the CNIs cyclosporine and tacrolimus, as well as the mTOR inhibitors sirolimus and everolimus. When renal transplant recipients are prescribed non-dihydropyridine calcium-channel blockers, careful monitoring of CNIs and mTOR inhibitors blood levels is required if drugs or dosages are changed.

ACE-Is and ARBs are known to have acute hemodynamic effects, resulting in an increase in SCr level, and are therefore frequently avoided within the first 3 to 4 months after transplantation, when acute rejection is a strong possibility, and an increase in creatinine level can be difficult to interpret.\textsuperscript{298,304,305} Side effects of ACE-Is and ARBs when used soon after transplantation include increased creatinine levels, hyperkalemia, and anemia. One study showed that although 44% of patients were receiving ACE-Is or ARBs at the time of transplantation, the proportion dropped to 12% at 1 month and subsequently increased to 24% at 6 months.\textsuperscript{294}

In the longer term, especially in kidney-transplant patients with persistent albuminuria, ARBs and ACE-Is should be considered. Two analyses of registry data have been published, with one showing a benefit and the other no benefit with the use of ACE-Is or ARBs for graft and patient survival.\textsuperscript{306,307} Small trials have examined various agents to lower BP in kidney-transplant patients. One examined losartan, captopril, and amlodipine and noted no change in BP or kidney function between baseline and end of follow-up. ACE-Is and ARBs did, however, reduce the risk of proteinuria, as compared with a calcium-channel blocker\textsuperscript{308} (Supplementary Table 60 online).

The Study on Evaluation of Candesartan Cilexetil after Renal Transplantation (SECRET) was an RCT of candesartan versus placebo.\textsuperscript{309} The primary outcome was all-cause mortality, cardiovascular morbidity, or graft failure. Enrollment of 700 patients was planned, but unfortunately, the study was terminated prematurely due to lower-than-expected event rates after enrollment of 502 participants because only 26 events took place in the 20 months of follow-up (with no difference in frequency between the two arms), whereas 210 events had been predicted over 3 years. Although there was slightly better BP control in the active group versus the control group (mean BP, 131/80 mm Hg vs. 137/83 mm Hg, respectively), the relatively tight BP control in both arms might have contributed to the low event rate. The protein excretion rate decreased in the ARB arm and increased in the placebo arm, but this difference may have been influenced by the different achieved BP levels (Supplementary Tables 61–62 online).

A large Canadian RCT of ramipril versus placebo is ongoing.\textsuperscript{310} It will enroll 528 kidney-transplant patients who underwent transplantation >6 months previously, have protein excretion of >0.2 g per 24 hours, and have a GFR 20–55 ml/min/1.73 m\textsuperscript{2}. Outcomes will include doubling of SCr level, kidney failure, and death.

Because no large studies with clinically important outcomes have been completed, we have chosen to follow the recommendations of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients\textsuperscript{292} and to provide an ungraded statement.

**RESEARCH RECOMMENDATIONS**

RCTs are needed to determine:

- The optimal target BP for adult patients with kidney transplants with a focus on clinically important outcomes such as graft survival, CVD, and mortality.
- The effects of ACE-Is and ARBs versus placebo, ACE-Is and ARBs versus calcium-channel blockers, and calcium-channel blockers versus placebo regarding long-term graft survival, CVD, and patient survival.

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**SUPPLEMENTARY MATERIAL**

*Supplementary Table 54.* Evidence profile of RCTs examining the effect of ACEI or ARB vs. CCB in transplant recipients without DM.

*Supplementary Table 55.* RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM (categorical outcomes).

*Supplementary Table 56.* RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients without DM (continuous outcomes).

*Supplementary Table 57.* Evidence profile of RCTs examining the effect of CCB vs. placebo in transplant recipients without DM.

*Supplementary Table 58.* RCTs examining the effect of CCB vs. placebo in transplant recipients (categorical outcome).

*Supplementary Table 59.* RCTs examining the effect of CCB vs. placebo in hypertensive transplant recipients without DM (continuous outcome).

*Supplementary Table 60.* RCTs examining the effect of ARB vs. placebo in transplant recipients without DM (categorical outcome).

*Supplementary Table 61.* RCTs examining the effect of ARB vs. placebo in transplant recipients without DM (continuous outcome).

*Supplementary Table 62.* RCTs examining the effect of ARB vs. placebo in transplant recipients without DM (continuous outcome).

Supplementary material is linked to the online version of the paper at http://www.kidigo.org/clinical_practice_guidelines/bp.php
INTRODUCTION
This chapter addresses the management of BP in children (defined as 18 years or younger, although chronological age does not necessarily parallel biological or social development). Children with non-dialysis-dependent CKD (CKD ND) differ from adults in the etiologies of CKD, definition of hypertension, and CKD associated co-morbidities. As cardiovascular end points such as myocardial infarction, stroke, or cardiovascular death are rare, effects of high BP and its treatment on kidney outcomes (e.g., lowering of GFR, initiation of dialysis, or transplantation) and target-organ damage are relevant end points in studies of children with CKD, although in the longer-term, CVD has a more important role.

Elevated BP and high BP are common in children with CKD, but RCTs of various treatment agents or targets are scarce. Observational studies and registry data demonstrate that more than half of children with CKD have high BP based upon a casual BP reading. Observational data also suggest that hypertensive children with CKD progress to kidney failure significantly faster than normotensive children with CKD. In studies of young adults with kidney failure whose kidney disease began in childhood, the risk of cardiovascular death is extremely high. Sudden cardiac death is the main cause of cardiac death in these individuals.

In light of the high prevalence and substantial morbidity associated with elevated BP in children with CKD, we systematically reviewed the existing literature and previously published guideline statements regarding the management of elevated BP in this vulnerable population. As RCTs are considered to provide the strongest evidence for CPGs, we reviewed RCTs with kidney and cardiovascular outcomes in which children with CKD was the study population. We supplemented this limited RCT evidence with information obtained from case series, cohort studies, and previous guideline statements on BP in healthy children and children with CKD. We further described the evidence base in detail in the narrative following each recommendation statement.

The strict evidence-based approach of formulating recommendations may have resulted in statements that do not include some commonly accepted treatment practices in children. The rationale for this approach is that we do not wish to provide guideline recommendations and discourage research in areas where evidence is weak. The research recommendations listed at the end of the chapter illustrate areas where more evidence is needed.

BACKGROUND
Definitions. For this Guideline, the age range for children is defined as from birth through 18 years. The preferred method of BP measurement in children is auscultation, and reference tables for BP percentiles for age, sex, and height can be accessed at the National Heart, Lung, and Blood Institute’s Fourth Report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents at http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

Throughout this guideline when we refer to thresholds or targets for BP therapy, we are referring to manual, auscultatory measurements of both systolic and diastolic BP unless otherwise specified. Correct BP measurement requires a cuff that is appropriate to the size of the child’s upper arm and elevated BP must be confirmed on repeated visits. In deciding on treatment, unless severe hypertension is present, an individual’s BP level should be determined as an average of multiple BP measurements taken over weeks to months. Current recommendations suggest that measurements obtained by oscillometric devices that exceed the 90th percentile for age, sex, and height should be repeated by auscultation. Detailed descriptions of appropriate BP measurement techniques in children and the strengths and limitations of various BP measurement methods in children with CKD have been detailed previously in the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease, Guideline 13: Special Considerations in Children.

Although there is insufficient trial evidence to recommend the use of ABPM in this Guideline, by virtue of frequent measurement and recording, ABPM allows the practitioner to compute the mean BP during the day, night, and over 24 hours, as well as to assess the time in which BP exceeds the upper limit of the normal range (i.e., the BP load). A number of reviews and guidelines suggest that in children with CKD, ABPM is a particularly useful tool to assess BP patterns. In children, ABPM can be particularly useful, as a significant number of patients have masked hypertension and would not be recognized as having hypertension based on the outpatient measurements only. A few studies using ABPM in patients with CKD suggest that it may give a better measure of overall BP and better indicate risk for kidney disease progression than office BP measurement. In fact, the only large RCT of BP control in children with CKD used ABPM as the method for BP assessment. Further research may elucidate
that future guidelines for therapy should be based on ABPM, rather than office based measures that are commonly used today. We have not recommended ABPM targets in this Guideline as ABPM is currently expensive and not readily available as routine clinical care in many settings.

6.1: We recommend that in children with CKD ND, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (1C)

RATIONALE

CVD has long been recognized as a substantial cause of late morbidity and mortality in individuals with onset of CKD during childhood.324 The majority of children with CKD are hypertensive,312 and a substantial proportion show evidence of target-organ damage associated with both masked and confirmed hypertension in a dose-dependent fashion.325 However, few RCTs directly comparing thresholds for initiation of BP treatment (vs. no treatment) or targets of BP treatment to prevent or reverse target-organ damage have ever been performed in children with CKD.

Observational studies of healthy children suggest that persistent elevations in BP are associated with significant late sequelae. In cross-sectional studies, elevated BP is associated with evidence of target-organ damage, including left ventricular hypertrophy and increased carotid intimal- medial thickness.326 In longitudinal analysis from the Bogalusa Heart Study, high systolic or diastolic BP was associated with an increased risk of developing kidney failure during long-term follow-up,327 and high childhood BP was an independent predictor of increased ankle-brachial pulse wave velocity in young adults.328 Persistently elevated BP in the young has been associated with decreased measures of carotid artery elasticity.329

In healthy children, in the absence of long-term data linking specific BP levels with adverse cardiovascular or kidney events, hypertension is defined as average systolic BP above the 90th percentile for sex, age, and height on three or more occasions.319 In healthy children, the goal of anti-hypertensive treatment is reduction of the BP to below the 95th percentile, unless concurrent conditions are present. CKD is considered such a concurrent condition. In children with CKD, according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents, the BP should be lowered to below the 90th percentile (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).319 The rationale for this approach is similar to the recommended treatment of hypertension in adults with additional cardiovascular risk factors or co-morbid conditions.

A number of expert panels have reviewed the existing literature and made similar recommendations. The National High Blood Pressure Education Program Working Group on High BP in Children and Adolescents has recommended initiating pharmacologic therapy for BP above the 90th percentile if a compelling indication such as CKD is present.319 In 2004, the NKF KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease3 recommended that the target BP in children with CKD should be lower than the 90th percentile for normal values adjusted for age, sex, and height or <130/80 mm Hg, whichever is lower. Similarly, the Cardiovascular Risk Reduction in High-Risk Pediatric Patients report330 listed children with CKD or kidney failure as a pediatric population at high risk for CVD, for which a target BP below the 90th percentile for age, sex, and height is suggested. According to that consensus statement, CKD is considered a coronary heart disease equivalent for which the treatment recommendations are similar to those in secondary prevention guidelines for adults with established coronary disease.

Among children with CKD, observational data have shown that those with hypertension (i.e., BP above the 95th percentile) have a more rapid decline in estimated GFR than those without hypertension.313,331 In a study by the European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood, children with a systolic BP >120 mm Hg had a significantly faster decline in GFR.332

In children who have received a kidney transplant, hypertension is a strong predictor of accelerated GFR decline333 and graft loss.334,335 Preliminary data from the ongoing observational Chronic Kidney Disease in Children (CKiD) study show that, among 425 children with repeated measures of GFR, having systolic BP above the 90th percentile for age, sex, and height is associated with faster progression of CKD as compared with lower BP.336 In this cohort, the annualized percent change in GFR among those with systolic BP above the 90th percentile was −7.5 ml/min/1.73 m² (95% CI −16.6–0.1), compared to −3.8 (95% CI −11.8–3.8) in those with systolic BP between the 50th and 90th percentiles and −2.5 (95% CI −8.9–3.9) in those with systolic BP below the 50th percentile. In the ESCAPE trial (described in detail in the next section), the kidney survival rate was 66% during follow-up among those with systolic BP below the 90th percentile but only 41% among those with systolic BP above the 90th percentile (P = 0.0002). In ESCAPE, a diastolic BP below the 90th percentile was associated with a kidney survival rate of 67%, compared to 28% among those with diastolic BP above the 90th percentile (P < 0.0001) (F. Schaefer and E. Wuhl, personal communication). On the basis of the RCT evidence, observational data, and other guidelines, the Work Group graded this recommendation as 1C. The quality of evidence was graded as C because the RCT evidence is limited to inferred evidence from one trial.

6.2: We suggest that in children with CKD ND (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (2D)
RATIONALE

The evidence for this recommendation comes largely from the ESCAPE trial,\(^{14}\) which showed a benefit in slowing CKD progression by targeting 24-hour MAP by ABPM to less than the 50th percentile for age, height and sex. Secondary analysis of the data suggested the effect was stronger in proteinuric children with CKD.\(^{14}\) (See Supplementary Tables 63–64 online). Based largely on the ESCAPE results, the European Society of Hypertension guidelines recently recommended that in children with CKD, BP targets should be below the 50th percentile in the presence of proteinuria and below the 75th percentile in the absence of proteinuria.\(^{337}\) In the European Society of Hypertension guidelines, the rationale for choosing the 75th percentile as a threshold in children with CKD without proteinuria is based on a re-analysis of ESCAPE results, examining kidney outcomes according to achieved 24-hour mean BP level. Since the 75th percentile was not an original targeted intervention in the ESCAPE trial, and the trial was not powered to detect differences by levels of proteinuria in recruited subjects, we have not made a separate specific recommendation distinguishing between the presence and absence of proteinuria for target BP levels for children with CKD, but this is an important area for future study.

Our guideline includes a statement of caution in aggressively pursuing low BP targets in children with CKD. We recognize that children are particularly susceptible to intercurrent illnesses, gastroenteritis and dehydration, and aggressive use of BP lowering medications in polyuric and dehydrated patients can lead to hypotension and alterations in renal perfusion. Clinicians who prescribe anti-hypertensive medications, particularly ACE-Is and ARBs in children need to be aware of the risk of drug toxicity in children susceptible to intravascular dehydration. Clinicians should consider discontinuing the drugs in the presence of acute diarrhea.\(^{338}\)

Additionally we recognize that reaching a target of less than the 50th percentile BP may be quite difficult in some children with CKD. The risks of polypharmacy have to be weighed against the potential benefits of achieving lowered BP.

In the ESCAPE trial,\(^{14}\) 468 hypertensive children with a 24-hour MAP above the 95th percentile for age, sex, and height, and a GFR (based on the Schwartz formula) of 15–80 ml/min/1.73 m\(^2\), received ramipril at a fixed dose of 6 mg/m\(^2\)/day and were randomized to target a 24-hour MAP, measured by means of ABPM, of either between the 50th and 90th percentile or below the 50th percentile. Additional anti-hypertensive agents, except for other antagonists of the RAAS, were added at the discretion of the local provider to achieve the target BP.

In this study—the largest prospective RCT of BP therapy in children with CKD to date—fixed-dose ramipril and a lower therapeutic BP target (MAP below the 50th percentile for age, sex, and height by ABPM delayed the progression to kidney failure. There were no differences in the frequency or types of adverse events between the intensified and conventional BP target arms in the trial. In subsequent stratified analyses, the effects were more pronounced in children with glomerulopathy and kidney hypodysplasia or dysplasia. There was no evidence of improved outcomes in individuals with hereditary nephropathies or other congenital causes of kidney disease other than aplasia or dysplasia, although there were relatively few individuals in these subgroups. Additionally, in stratified analyses, the efficacy of the intensified BP control intervention was most marked in children with a urine PCR of > 150 mg/g (> 15 mg/mmol) (see supplement of Wuhl et al.\(^{14}\)).

Data presented at the American Society of Nephrology 2010 annual meeting from the observational CKiD study\(^{356}\) also shows slower progression of decline in kidney function in individuals with auscultatory manual BP below the 50th percentile for age, sex, and height as compared to individuals with BP between the 50th and 90th percentile and those with BP above the 90th percentile. BS in this study is measured according to a standard protocol at annual study visits with an aneroid device.

BP targets in children with CKD should be individualized on the basis of susceptibility to hypotension. Many causes of childhood CKD include diagnoses associated with salt and water losses in the urine. As such, the risk of hypotension associated with aggressive BP control should temper the ramping-up of BP-lowering medication to reach a low BP target.

6.3: We suggest that an ARB or ACE-I be used in children with CKD ND in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (2D)

RATIONALE

This recommendation is based on published experience with these agents in children with hypertension, showing the drugs to be safe and effective in lowering BP and to confer a benefit for slowing CKD and reducing urine protein levels in adults with CKD. However in teenage girls, pregnancy testing and the use of birth control prior to and during ACE-I/ARB therapy need to be considered. Additionally, as mentioned above, discontinuing these agents during episodes of diarrheal illness and dehydration should be considered.\(^{338}\)

ACE-Is or ARBs should be the preferred choice in treating proteinuric CKD (see Chapters 3 and 4). Multiple studies in adults with CKD have shown renoprotection with the use of ACE-Is or ARBs. RAAS antagonists preserve kidney function not only by lowering BP but also by means of anti-proteinuric, anti-fibrotic, and anti-inflammatory properties. In the ESCAPE trial described above, on the basis of previous research in adults, the children in both arms of the intervention received a fixed, maximum dose of the ACE-I ramipril.\(^{32}\) Further BP lowering was achieved through the addition of other medications at the discretion of the local provider.

Others have recommended ACE-Is or ARBs as first-line agents in treating children with CKD and high BP,\(^{339}\) particularly in those with proteinuria.\(^{340}\) The recently released European Society of Hypertension guidelines\(^{337}\) assert that “it is reasonable to recommend agents blocking
the renin–angiotensin system as first choice in proteinuric, and also in non-proteinuric patients with CKD. However, limited direct evidence from clinical trials is available with which to assess the efficacy of RAS in children with CKD. In healthy children with hypertension, a number of clinical trials have examined the safety and efficacy of ACE-Is.

Small, uncontrolled studies have shown stable kidney function in children with CKD treated with ACE-Is or ARBs. Kidney dysfunction that is hemodynamic in origin has been more commonly associated with the use of ACE-Is and ARBs than with other anti-hypertensive agents. Additionally, since elevations in serum potassium levels have also been observed, counselling about potassium intake and addition of thiazide or loop diuretics are sometimes advised.

Although analysis of registry data from the ItalKid Project database failed to show clear evidence of ACE-I efficacy in slowing the progression of CKD, other observational evidence shows that ACE-Is are associated with lower urine protein levels and that BP control in childhood CKD is superior with anti-hypertensive regimens containing an ACE-I or ARB. In a small trial, an ARB was more effective at lowering urine protein levels than a calcium-channel blocker. The only study to date that has compared ACE-Is and ARBs in children found that urine protein levels were similarly reduced with the ACE-I enalapril and the ARB losartan.

As in adults, ARBs may be more tolerable than ACE-Is in children, with fewer adverse events such as cough, angio-neurotic edema, and hyperkalemia—but this has not been systematically studied in large trials. Combination therapy with ACE-Is and ARBs may be used for additive anti-proteinuric and renoprotective effects, but this approach has rarely been studied in children. Small randomized trials of combinations of ACE-Is and ARBs in children with CKD demonstrate significant reductions in urine protein levels as compared to the use of only one of the drug classes. However, further study of long-term outcomes and safety data are necessary.

Use of ACE-Is and ARBs should be individualized on the basis of susceptibility to hypotension and of the risk of pregnancy in young women of child-bearing age. ACE-Is and ARBs are labelled by the US FDA as pregnancy category C for the first 3 months of pregnancy and category D for the last 6 months (the second and third trimesters). Pregnancy category C means that a risk may exist but its magnitude is unknown because of a lack of trustworthy studies in pregnant women, and animal studies either have shown risk in pregnancy or have not been performed. Pregnancy category D means that there have been studies in pregnant women showing that the drug is associated with some risk for the fetus, but the benefit of the drug may still outweigh that risk for some patients.

Monitoring for hyperkalemia may be considered in high-risk children as kidney function declines. In the ESCAPE trial, individuals with CKD receiving a high-dose ACE-I had an increase in mean (± standard deviation [SD]) serum potassium levels from 4.31 ± 0.52 mmol/l to 4.71 ± 0.57 mmol/l. The upper limit of the normal range for children (5.6 mmol/l) was exceeded in 3.3% of tests. In all but 5 patients, medical management through adjustment of diet, addition of a diuretic, or prescription of potassium-exchange resins resulted in persistent normalization of serum potassium levels while the child remained on ACE-I therapy.

ACE-Is and ARBs have similar hemodynamic effects in the kidney which leads to decrease in GFR. It has been stated that increases of the SCr level by up to 30% should be expected and tolerated after initiating therapy with ACE-Is or ARBs in adults with chronic kidney failure, but children have not been prospectively studied in this regard.

Few direct comparisons of classes of anti-hypertensive agents have been performed in children with CKD. Extensive reviews of different drugs and classes of anti-hypertensive agents in children with CKD have recently been published. There is no clear evidence that one second-line BP agent is superior to the other in children. In the ESCAPE trial, calcium-channel blockers were used as first-choice anti-hypertensive co-medication (in 38% of patients), followed by diuretics (in 36%) and beta-blockers (in 26%), without differences between the randomization groups. Other guidelines suggest diuretics or calcium-channel blockers as the most suitable second-line agents.

LIMITATIONS

In children with CKD, there is a dearth of RCTs; in fact, the recommendations in this chapter are largely based on a single trial, ESCAPE, which limits the quality of the evidence and the strength of the recommendations. The ESCAPE trial was performed in a predominantly Caucasian population. Therefore, the generalization of these findings to other populations is uncertain.

RESEARCH RECOMMENDATIONS

- Further RCTs are needed to replicate the findings from ESCAPE and to examine the safety and efficacy of intensified BP control on slowing CKD progression and incidence of CVD in children with CKD.
- Studies addressing BP targets and comparing home BP monitoring via oscillometric devices, ABPM, and clinic-based BP monitoring are needed, as are robust ABPM reference measures in populations of various races and ethnicities.
- Long-term observational studies of the onset of target-organ damage in children with CKD are necessary to obtain evidence on which to base thresholds for BP treatment and targets rather than relying on population-based percentiles. Large, long-term randomized trials addressing targets and comparing various agents to prevent target-organ damage are also necessary to improve knowledge of the advantages and disadvantages of specific doses and classes of anti-hypertensive agents in this population.
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SUPPLEMENTARY MATERIAL
Supplementary Table 63. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [categorical outcome].
Supplementary Table 64. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [continuous outcome].
Supplementary material is linked to the online version of the paper at http://www.kidigo.org/clinical_practice_guidelines/bp.php
Chapter 7: Blood pressure management in elderly persons with CKD ND


INTRODUCTION

This chapter specifically addresses the BP management of older patients with CKD that is non-dialysis-dependent (i.e., CKD ND), many of whom have accumulated co-morbidities associated with aging, including vascular disease, osteoporosis, and general frailty. The term ‘elderly’ is used for persons ≥65 years of age,354 whereas ‘very elderly’ is reserved for persons >80 years of age, consistent with the terminology used in the literature reviewed in this chapter.43,149,355,356 In using these definitions, we recognize that chronological age is used as a surrogate for biological age, although this relationship is highly variable.

The elderly comprise the most rapidly growing proportion of the population in most parts of the world.357 From 30 to 40 years of age, the GFR generally (but not invariably) declines, and in the older person, tubular and endocrine dysfunction in the kidney are common.358,359 Combine this with the increased prevalence of type 2 diabetes mellitus and high BP among older persons, it is not surprising that the elderly constitute the most rapidly growing population of CKD patients.

In population health surveys, a large proportion of the elderly have a reduced GFR. In the United States, NHANES 1999–2004 data showed that 37.8% of subjects >70 years had a GFR of <60 ml/min/1.73 m² (measured using the MDRD equation); this prevalence had increased from 27.8% in the NHANES 1988–1994 data.360,361 Nearly 50% of United States veterans aged >85 years fulfilled the definition for CKD.362 Similarly in China,363 Australia,364 and Japan,365 a high prevalence of CKD has been found in older populations. With greater access to health care among the elderly, this group is the fastest-growing population requiring dialysis, with 25% and 21.3% of dialysis patients in the United States and Australia, respectively, being ≥75 years of age366,367 and between 31 and 36% of patients receiving renal replacement therapy in different regions of the United Kingdom being ≥65 years of age.368

7.1: Tailor BP treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. (Not Graded)

RATIONALE

The relationships between CKD and BP in the elderly in the United States have recently been reviewed in detail.369 Among NHANES III (1988–1994) subjects aged ≥60 years of age, either treated or not treated for a high BP, there was a J-shaped relationship between BP and CKD prevalence. Thus, persons with a systolic BP of 120 to 159 mm Hg or a diastolic BP of 80 to 99 mm Hg had the lowest CKD prevalence, with a higher prevalence associated with a systolic BP <120 mm Hg or diastolic BP <80 mm Hg and a systolic BP ≥160 mm Hg or a diastolic BP ≥100 mm Hg.361 Analyses of data from the Kidney Early Evaluation Program (KEEP), as well as NHANES, indicate that with increasing age, there is an increase in the prevalence and severity of CKD, confirming the strong relationship between BP and CKD in the elderly.370,371

Despite these findings, there is little evidence on which to base recommendations for BP management in elderly patients with CKD. Systematic assessment of the evidence base underpinning this Guideline shows that many RCTs excluded patients >70 years of age. The mean age of participants rarely exceed 65 years with the upper limit of the 95% CI (i.e., the mean ± 2 SD) very uncommonly being ≥85 years, meaning no more than about 2.5% of the study population had an age above this cut-off point (Supplementary Table 65 online). We therefore cannot draw much direct evidence from these RCTs to indicate how to properly manage BP in elderly CKD patients, although some inferences might be drawn from BP studies in elderly populations not specifically chosen for the presence of CKD.

Measurement of BP in the elderly. Assessment of BP in the elderly is made more difficult by such common issues as the presence of atrial fibrillation (as seen in 25% of patients ≥70 years in the Chronic Renal Insufficiency Cohort (CRIC) study372), orthostatic hypotension34,45 and the tendency for pulse pressure to widen with arterial stiffening, resulting in systolic hypertension.32,42,373,374

The literature on management of elderly patients has thus been focused more on systolic than diastolic BP. There is relevant observational evidence from the SHEP study.374 In an analysis of 2181 persons >65 years of age in the placebo arm of this study, systolic BP was more predictive of decline in kidney function (i.e., rise in SCr by ≥0.4 mg/dl [35.4 μmol/l] over 5 years) than diastolic BP, pulse pressure, or MAP. The mean age was 72 years and patients with ‘renal
failure’ were excluded. Among those enrolled, the initial SCr level was $1.04 \pm 0.23$ mg/dl ($92 \pm 20 \mu$mol/l). Hence, most subjects probably had normal kidney function or CKD stages 1–3.

**CKD in the elderly.** There are clear differences in the causes of CKD when comparing elderly and younger cohorts. Autopsy studies indicate that arteriolar sclerosis, global glomerulosclerosis, and tubular atrophy are more common in the elderly, as are renal artery stenosis and cholesterol embolization. Although selection bias is likely, a kidney biopsy series of 413 patients aged 66 to 79 years showed nephrosclerosis in 34% of patients >80 years and in 7% of those 66 to 79 yrs. According to registries of kidney failure patients, ‘arteriopathic disease’ was the diagnosis in 17 to 38% of patients commencing dialysis on three continents. Although a discussion as to whether or not nephrosclerosis is an aspect of aging kidney is beyond the scope of this Guideline, vascular disease within the kidney is often regarded as a major factor contributing to decline in kidney function. This predisposition to vascular disease may influence the response of the aging kidney to low BP and renin–angiotensin blockade, with the attendant risks of acute reduction in GFR and hyperkalemia. This has led to questions regarding the safety of renin-angiotensin-blocking agents such as ACE-Is and ARBs in the elderly.

**GFR estimation in the elderly.** Most equations used to estimate GFR have been primarily developed in younger populations, although subgroup analyses show that these equations perform reasonably well in older people. Co-morbidities. Co-morbidities are frequently present in the elderly and may influence BP management. Macrovascular disease is particularly common. This might influence BP targets or the preferred agents to control BP, especially if heart failure, angina, cerebral vascular insufficiency, or peripheral vascular diseases are prominent. The presence of heart failure or cardiomyopathy may lead clinicians to initiate ACE-Is, ARBs, or diuretics independently of BP treatment. Similarly, angina may be an indication for beta-blockers or calcium-channel blockers. Hypotension (orthostatic or persistent) due to BP-lowering treatment may exacerbate the risk of falls and fractures in the elderly, especially in patients with co-morbidities such as cerebrovascular disease, osteoporosis, or vitamin D deficiency.

**Drugs and the elderly.** The pharmacology and pharmacodynamics of BP drugs also change with age, mainly because of reduced GFR, but also due to changes in hepatic function, volume of distribution, and other issues that are less well characterized. Side-effect profiles may also vary, either owing to altered end-organ sensitivity to the drugs, co-morbidities, or interactions with other medications, such as diuretics, NSAIDs and COX-2 inhibitors which may accentuate the adverse kidney effects of renin-angiotensin blockade.

**Goals of BP management in the elderly.** It is particularly important to individualize care in the elderly, bearing co-morbidities in mind. A philosophy of patient-centered care (rather than disease-directed care) is particularly relevant as the elderly become very elderly. The high likelihood of elderly patients developing cardiac and cerebrovascular complications in the context of a high BP, along with evidence that kidney function may decline more slowly in the elderly than in younger patients (particularly when the GFR is $\geq 45$ ml/min/1.73 m$^2$) should lead to a greater emphasis on vascular rather than kidney outcomes. Moreover, particularly in the very elderly, possible beneficial effects of therapy on morbidity and mortality should be balanced against any negative effects on quality of life.

**BP TARGETS IN THE ELDERLY**

Although there have been many studies of treatment of high BP in the elderly, there is little evidence specific to the elderly with known CKD. Most relevant information comes from observational studies and RCTs involving entire populations of older hypertensive patients not specifically chosen on the basis of kidney function (Supplementary Table 66 online). ‘Renal failure’ or a designated upper limit for the SCr concentration have been an exclusion criterion in many studies, reducing the applicability of the data to CKD patients.

A meta-analysis of observational studies conducted prior to 2002, including nearly 1 million subjects selected for having no previously known vascular disease, indicated that the rates of stroke, ischemic heart disease, and overall mortality increased with increasing BP, even among subjects 60 to 89 years of age, although the RR decreased with increasing age.

RCTs involving elderly patients not selected for having CKD indicate that it is beneficial to treat high BP in patients >60 years of age. A 2009 Cochrane review of 15 RCTs in which persons >60 years of age with a systolic BP $\geq 140$ mm Hg or a diastolic BP $\geq 90$ mm Hg at baseline received either placebo or a BP-lowering agent indicated that active treatment reduced total mortality (RR 0.90; 95% CI 0.84–0.97) and total cardiovascular mortality and morbidity (RR 0.72; 95% CI 0.68–0.77), particularly due to a reduction in the incidence of stroke. Withdrawals due to adverse events were poorly documented, but in three RCTs that did report these data, treatment was associated with 111 events/1000 patient-years, as compared with 65 events/1000 patient-years with placebo (RR 1.71; 95% CI 1.45–2.00). Although these findings support treatment of high BP in subjects >60 years of age, they do not inform us specifically about patients with CKD nor about the target BP and they suggest that some patients will have adverse reactions to drug therapy.

Of concern is that in this Cochrane review, when patients aged $\geq 80$ years were specifically considered, there was no overall reduction in the risk of total mortality with treatment of BP vs. no treatment (RR 1.01; 95% CI 0.90–1.13), although the reduction in risk of cardiovascular mortality (RR 0.75; 95% CI 0.65–0.87) was similar to that seen in patients 60 to 80 years of age. This is in accordance with a 1999 subgroup meta-analysis of seven RCTs representing 1670 patients aged $\geq 80$ years (who had participated in trials of anti-hypertensive agents) indicating that treatment...
vs. no treatment was associated with a decrease in the rates of strokes, major cardiovascular events and heart failure but, similar to the Cochrane findings, there was no benefit of treatment in terms of cardiovascular death or overall mortality.355 Similarly, a 2010 meta-analysis of 8 RCTs involving treatment of BP in subjects 80 years and older found that treatment of high BP reduced the risk of stroke, cardiovascular events and heart failure, but had no effect on total mortality.390 Meta-regression analysis suggested that mortality reduction was achieved in the trials with the least BP reductions and lowest intensity of therapy. These findings suggest that there might be deleterious effects resulting from BP treatment in the very elderly undermining the advantages brought about by the reduced risk of cardiovascular events.

An observational cohort study involving 4071 hypertensive individuals aged 80 years or older (mainly men, since they were recruited from the Veterans Affairs Administration) supports this notion.43 All subjects were classified as ‘hypertensive’ according to the International Classification of Diseases (ICD-9) code, 9.9% as having ‘chronic renal failure;’ and 84.5% were taking anti-hypertensive medications. A J-shaped relationship between BP and survival was seen. Patients with BP $<130–139$ mm Hg systolic or $<70–79$ mm Hg diastolic were more likely to die during 5 years of follow-up than those with BP $130–139$ mm Hg systolic or $70–79$ mm Hg diastolic. With each further 10 mm Hg decrease in systolic or diastolic BP to $<100$ mm Hg systolic or $<50$ diastolic the risk increased, suggesting that overly aggressive BP control might be harmful in this age group.

A series of retrospective analyses of INVEST has further highlighted the issue of J-shaped relationships between systolic BP, diastolic BP and outcomes in elderly hypertensive patients with CAD.40,42,231 The risk of all-cause mortality and myocardial infarction, but not stroke, increased with reductions in diastolic BP in the patient group as a whole, all of whom had CAD and were being treated for high BP.40 In elderly patients included in the study, nadirs of risk occurred at particular systolic and diastolic BP levels, with the nadirs generally increasing with age. In patients aged 70 to 80 years, risk increased once systolic BP was less than 135 mm Hg or diastolic BP $<75$ mm Hg, while the risk increasing when systolic BP was $<140$ mm Hg or diastolic BP $<70$ mm Hg in patients $\geq80$ yrs.42 These relationships may be due to confounding and should not be used to set BP targets in this population.

In preparing the evidence review for this guideline, the ERT found four studies involving elderly patients in which treating to differing targets for BP was part of the study design (Supplementary Table 67 online).149,389,391–393 The Shanghai Trial of Nifedipine in the Elderly (STONE) involved 1632 patients aged 60–79 years with a systolic BP $\geq160$ mm Hg, or a diastolic BP $\geq96$ mm Hg, who were randomized to nifedipine or placebo.392 The mean achieved BP was $147/85$ mm Hg in the nifedipine group and $156/92$ mm Hg in the placebo group and although there was no significant difference in all-cause mortality, there were reductions in the rates of stroke and severe arrhythmia in the lower-BP nifedipine treated group. Exclusion criteria included ‘secondary hypertension’ and a blood urea nitrogen level $\geq40$ mg/dl (14.3 mmol/l).

The Hypertension in the Very Elderly Trial (HYVET), involving patients 80 years of age or older, provided further assurance that BP lowering treatment of very elderly patients with a sustained BP of $\geq160$ mm Hg is beneficial.149,391 Aiming to treat to a target BP of systolic $<150$ mm Hg and diastolic $<80$ mm Hg in the active-treatment group, the investigators achieved a BP of $145/79$ mm Hg with indapamide plus perindopril (if needed), compared to $159/83$ mm Hg with placebo. They demonstrated a reduction in the rates of all-cause mortality and stroke in the low-BP active-treatment group over a median 1.8 years of follow-up. Patients were withdrawn if systolic BP fell to $<110$ mm Hg. However, exclusion criteria included secondary hypertension (which might be of kidney origin) and a SCr level $>1.7$ mg/dl (>150 $\mu$mol/l) (which represents a GFR of 39 or 37 ml/min/1.73 m² for an 80-year-old white man, as estimated by either the MDRD or CKD Epidemiology Collaboration (CKD-EPI) equation, respectively and a GFR of 29 or 28 ml/min/1.73 m² for an 80-year-old white woman as estimated by the MDRD and CKD-EPI equations, respectively). The mean baseline creatinine levels were $88.6$ $\mu$mol/l (1.0 mg/dl) and $89.2$ $\mu$mol/l (1.0 mg/dl) in the active-treatment and placebo groups, respectively which were well below the exclusion level. Accordingly, direct extrapolation of these data to patients with known advanced CKD is not possible.

Although this evidence provides some reassurance regarding treatment of high BP in the very elderly, it only does so with respect to treatment to a BP target level of 150/80 mm Hg, and it does not specifically address CKD patients with a GFR $<40$ and $<30$ ml/min/1.73 m² for men and women, respectively. Very importantly, however, the evidence challenges any tendency toward ‘therapeutic nihilism’ in the very elderly with high BP and CKD 1–3.

Two Japanese studies failed to show any benefit or harm from reducing systolic BP to $<140$ mm Hg in otherwise healthy elderly patients.393,394 The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) aimed to assess optimal systolic BP in elderly hypertensive patients and randomized 4418 patients with ‘essential hypertension’ aged 65 to 85 years with a systolic BP $>160$ mm Hg to ‘strict’ BP control (target systolic BP $<140$ mm Hg) or ‘mild’ BP control (target systolic BP 140–160 mm Hg).393 Patients with SCr of $\geq1.5$ mg/dl (133 $\mu$mol/l) were excluded, as were patients with multiple co-morbidities. Achieved mean $\pm SD$ systolic BP was $135.9 \pm 11.7$ mm Hg in the strict-control group and $145.6 \pm 11.1$ in the mild-control group ($P<0.001$), with significantly more drugs required in the strict-control group. There was no difference in cerebrovascular, cardiac, or kidney end points, nor in total mortality between the two groups at 2 years of follow-up. ‘Renal failure’ occurred in 8 and
9 patients, respectively. Rates of treatment withdrawal due to adverse events did not differ between the groups.

The Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study involved 3260 Japanese participants aged 70 to 84 years, with systolic BP $\geq 160$ mm Hg. Like JATOS, this study did not demonstrate any differences in outcomes or adverse events between the strict-control group (systolic BP goal $<140$ mm Hg, achieved mean systolic BP was 136.6 mm Hg) and the moderate-control group (systolic BP goal 140–150 mm Hg, achieved mean systolic BP was 142.0 mm Hg) after a median follow-up period of 3.07 years. Although 43 of the 3260 patients had 'kidney insufficiency' (undefined) at study entry, none had a SCr level $\geq 2$ mg/dl (177 $\mu$mol/l) since this was an exclusion criterion, as were many other co-morbidities. Doubling of the SCr, an increase in the SCr level to 2.0 mg/dl (177 $\mu$mol/l), or dialysis occurred in 5 and 2 patients, respectively (non-significant). The authors concluded that in relatively healthy elderly Japanese patients, a BP $<140$ mm Hg is safely achievable, but that the trial was underpowered to assess outcome benefits. No difference was seen between the two groups in terms of adverse event rates (18.2% with strict control and 17.9% with mild control, $P = 0.851$).

Thus BP targets in the elderly, with or without CKD, should be set only after consideration of co-morbidities and should be achieved gradually. Based on the evidence on BP in the elderly (not selected for CKD), recent guidelines and consensus documents generally agree that $<140/90$ mm Hg should be the target in uncomplicated hypertension. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA), in collaboration with a large group of other American and European bodies, acknowledge in their consensus document on hypertension in the elderly that although 'there is limited information for evidence-based guidelines to manage older hypertensive patients,' a target of $<140/90$ mm Hg is recommended in uncomplicated hypertension for the age range 65–79 years. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA), in collaboration with a large group of other American and European bodies, acknowledge in their consensus document on hypertension in the elderly that although 'there is limited information for evidence-based guidelines to manage older hypertensive patients,' a target of $<140/90$ mm Hg is recommended in uncomplicated hypertension for the age range 65–79 years. This document acknowledges that the target for $>80$ years is unclear, and refers to expert opinion and observational data (including KDOQI 2002 and JNC 7) suggesting $<130/80$ mm Hg as a target in CKD, irrespective of albuminuria.

From the UK, NICE has published a comprehensive guideline for management of hypertension in adults which also recommends BP $<140/90$ mm Hg for 'primary' hypertension up to 80 years of age, and for those over 80 years who are continuing therapy. Caution is recommended when starting BP medications in those over 80 years of age, and no recommendation is given with respect to the elderly with CKD.

Although intuitively there must be a lower limit for safe BP control in the elderly and very elderly, there will probably never be an RCT designed specifically to address this limit in these populations. We can, however, gain insights from observations among elderly patients on treatment as outlined above. While these data do not allow us to recommend a lower BP limit on treatment, they do suggest that in the elderly, it may be prudent not to reduce BP much below the target BP $<140/90$ mm Hg as recommended by ACCF/AHA and NICE. In addressing the risks associated with low BP in the elderly, it is relevant that orthostatic hypotension is more common than in younger populations, particularly among those treated for high BP or diabetes and those receiving sedatives. As well as causing postural dizziness, low BP is associated with a higher risk of falls and fractures in elderly persons in studies that are likely to have included individuals with and without CKD. An additional consideration when treating elderly CKD patients is that they may differ from those with well preserved kidney function in terms of their response to BP lowering agents.

The Work Group decided that it was not possible to recommend specific BP targets in the elderly with CKD. A reasonable approach might be to use BP targets as recommended in the younger CKD population ($\leq 140/90$ mm Hg in non-albuminuric CKD and $\leq 130/80$ mm Hg in albuminuric CKD as in Chapters 3 and 4), but to reach these targets gradually, bearing in mind that they may not be achievable without adverse effects particularly in a patient with multiple age-related co-morbidities. It is even more difficult to make recommendations in patients over 80 years of age with CKD due to the lack of evidence.

With consideration given to the adverse effects of treatment, the Work Group felt that it was good practice to ask elderly patients treated for high BP about postural dizziness and to measure BP immediately (within 1 minute) and a few minutes after standing as well as in the sitting position.

METHODS FOR BP REDUCTION IN THE ELDERLY

Lifestyle modifications in the elderly, although often recommended, can compromise quality of life and may impair nutrition. The place of salt restriction, exercise and weight control is detailed in the aforementioned ACCF/AHA document. Given that there is very little evidence to support lifestyle modifications in the treatment of BP in CKD patients in general, the Work Group decided not to make any such recommendations in the elderly with CKD. Although salt restriction might seem to be the most attractive intervention, it may impact the quality of life, particularly enjoyment of food. A recent observational study of elderly persons ($\geq 65$ years of age) does not support alcohol restriction as an intervention to reduce decline in GFR.

The Work Group felt that drug regimens should be tailored by carefully considering the elderly patient's co-morbidities and any changes in treatment should be very gradual. Close attention should be paid to potential adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function and orthostatic hypotension. Although many elderly patients with CKD will require several agents, studies comparing use of various agents in the elderly without CKD have produced somewhat conflicting results (see Supplementary Tables 66–68 online). The ability of the patient to adhere to complex poly-pharmacy should be taken into consideration. Some clinicians have expressed concerns about the use...
of drugs that block the renin-angiotensin system in the elderly with CKD. This concern is largely due to the perceived potential for these agents to cause more frequent adverse events in this population. A recent Cochrane review addressing pharmacotherapy of all types for treatment of hypertension in the elderly reported an increased risk of withdrawals due to adverse effects (RR 1.71; 95% CI 1.45–2.00). Since quality of life is particularly important in the elderly, it may be worth avoiding drugs that may have negative quality of life implications, but no clear advice can be given.

Thus given the many differences between the elderly (particularly the very elderly) with CKD and younger patients with CKD, it is not possible to recommend any particular drug class for the reduction of BP in older CKD patients. However, it is advisable to consider the severity of CKD, presence of albuminuria, and co-morbidities and their treatment when prescribing. Therapeutic changes should be made gradually, with close monitoring for adverse effects due to low BP or side effects from prescribed agents.

RESEARCH RECOMMENDATIONS

An important NIH funded trial- SPRINT- is currently ongoing in the United States randomizing patients without diabetes or significant proteinuria to a systolic BP of <140 mm Hg or <120 mm Hg. Since it contains both elderly patients and those with CKD, it is likely to provide important evidence to guide BP management in this subpopulation.

A workshop on kidney disease including the American Society of Nephrology, the National Institute on Aging, the American Geriatrics Society, and the National Institute of Diabetes and Digestive and Kidney Diseases resulted in the 2009 publication of a list of priority areas for research in kidney disease in the elderly (Table 3). Although BP was not specifically addressed, it highlighted the many areas of ignorance regarding CKD in the elderly.

Important areas for future research suggested by this KDIGO Work Group include:

- The effects of different BP targets (e.g., 150/90 mm Hg vs. 140/90 mm Hg) in elderly and very elderly patients with advanced CKD (CKD 3–4) should be assessed by prospective RCTs using a fixed-sequential BP-agent protocol (e.g., diuretic, ACE-I or ARB, beta-blocker, and calcium-channel blocker) excluding only patients with angina or cardiomyopathy.

- The effect of various combinations of agents in the elderly and very elderly populations should be examined.

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SUPPLEMENTARY MATERIAL

Table 3 | Questions for future research

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<td>Is CKD in elderly people the same condition as CKD in young adults?</td>
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<td>How do age-related mechanisms such as fibrosis and cellular senescence interact with mechanisms underlying CKD progression?</td>
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<td>Do age- and CKD-associated changes in vascular biology differ from other parenchymal kidney disease changes associated with age?</td>
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<td>What are the morphologic correlates of CKD in elderly people?</td>
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<td>Are there other markers that can contribute to assessment of CKD prognosis in elderly people, beyond GFR and cystatin?</td>
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<td>What are the age-related changes in non-traditional cardiovascular risk factors in patients with CKD?</td>
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<td>How can geriatricians, internists, general family practitioners, and nephrologists work together to optimize the care of elderly patients with CKD and kidney failure?</td>
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Other comorbidities

The consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer’s own published literature.

SUPPLEMENTARY MATERIAL

Supplementary Table 65. Age restriction in all RCTs for DM CKD, non-DM CKD, Transplant and CKD subgroups.

Supplementary Table 66. PICO criteria for blood pressure targets in elderly studies.

Supplementary Table 67. Ages and BP targets in elderly studies.

Supplementary Table 68. PICO criteria for blood pressure agents in elderly studies.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php
INTRODUCTION
In this chapter, we discuss issues regarding BP management and the use of BP-lowering drugs in CKD patients that are currently the subject of ongoing research or controversy and for which there is insufficient evidence upon which to base a recommendation at this time.

8.1: ASSESSMENT OF BP
The RCTs on which this Guideline is based involved standard office BP measurements, with the exception of the ESCAPE trial in children. In clinical practice BP assessment typically involves measurements made in the clinic or ‘office.’ In RCTs, the protocols for BP measurement usually require one or more BP readings taken after a period of rest and avoiding prior activities that may have effects on BP. As far as it is possible these protocols should be followed in clinical practice if this evidence is used to guide management. The techniques for office BP measurement and associated problems are well described in the hypertension literature. There is no reason to believe that office BP measurement should be performed differently in CKD patients than in non-CKD patients, other than a strong emphasis be placed on measuring supine or sitting and standing BP because of the increased likelihood of orthostatic hypotension associated with volume depletion, autonomic neuropathy, older age, and drug effects.

Measuring BP in the general community and in particular, patients with 'essential' hypertension, is becoming increasingly sophisticated. Examples include technologies that assess 'usual' BP as distinct from the BP measured at an office visit and new ways of measuring BP beyond just systolic and diastolic pressures. Gradually, these advances are being implemented in research and BP management in CKD patients.

Ambulatory BP monitoring and self-monitoring at home.
There is a long history of assessing BP by means other than the BP measurement taken at an office visit. The 'gold standard' is automated ABPM, the techniques for which have been well described and self-monitoring using automated devices, which is increasingly used. Recommendations and guidelines for the use of ABPM and self-monitoring are accumulating in the hypertension literature (Table 4).

There have been a limited number of studies conducted in CKD patients but data suggest that in CKD, high ABPM systolic pressures, and nocturnal ‘non-dipping’ (i.e., the absence of a drop in BP during sleep) are associated with increased risks of mortality (as in other populations) and of decline in GFR or kidney failure. As has been found for non-CKD patients, office BP measurements are commonly overestimates (in the case of white-coat hypertension) or underestimates (in the case of masked hypertension) of ‘usual’ BP when compared with ambulatory BP assessments.

A recent paper highlights the interest in ABPM in CKD. 436 hypertensive CKD patients were prospectively followed using ABPM and this was shown to be much more accurate in predicting both renal and cardiovascular outcomes than office BP. White coat hypertension was common, and ABPM indicated that non-dipping and reverse dipping of nocturnal BP were particularly predictive of cardiovascular and renal outcomes. Future trials are needed to assess the best means of measuring BP in CKD patients by randomizing patients to ABPM, home BP or office BP directed therapy and to address whether evening dosing to encourage ‘dipping’ is advantageous as recently demonstrated in non-CKD hypertensive individuals.

Given the technical and economic barriers to routine measurement of ambulatory BP, self-BP recording using automated BP devices has been introduced because these give readings that are more in line than with ABPM than those achieved by office BP measurements.

Self-BP measurement and ABPM are being used increasingly in BP management and the devices for measuring them usually rely on oscillometric assessment of BP at the elbow. Atrial fibrillation and very high pulse pressures can lead to inaccuracies and hence, re-calibration against traditional methods of BP measurement is important. While it is unlikely that self-BP monitoring or ABPM will become part of mainstream CKD monitoring in developing countries in the near future, they are likely to become more widely used if further research indicates the value of these techniques in CKD management.

Measurement of pulse pressure and pulse wave velocity.
The stiffening of arterial walls that accompanies CKD (as well as aging and chronic high BP) causes a loss of the volume compliance in the large arteries such as the aorta, reducing their ability to effectively buffer the systolic pressure wave generated by the left ventricle and thus resulting in higher systolic BP. In diastole, the loss of elastic recoil leads to a reduced diastolic pressure. These changes together contribute to a higher pulse pressure and faster pulse wave velocity, since the pulse wave travels more rapidly when the larger arteries are less compliant. Measurement of pulse pressure or pulse wave velocity can therefore offer insights into vascular structure and function. Studies of pulse pressure or
ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

### Table 4: Existing guidelines on ambulatory BP monitoring (ABPM) and home BP monitoring

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<tr>
<th>Society or authors</th>
<th>Measurement recommendations</th>
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<td><strong>British Hypertension Society</strong>&lt;sup&gt;406&lt;/sup&gt;</td>
<td>Home BP monitoring: Accuracy of at-home recordings can be improved by calibration of the home instrument with a known standard, but even so, a lower threshold for treatment is recommended (i.e., less than 135/85 mm Hg) because of inaccuracies in home measurements and the tendency for home readings to be lower than office readings.</td>
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<td><strong>Japanese Society of Hypertension Guidelines for self-monitoring of BP at home</strong>&lt;sup&gt;425&lt;/sup&gt;</td>
<td>Home BP monitoring: 1. Arm-cuff devices based on the cuff-oscillometric method that have been validated officially and the accuracy of which has been confirmed in each individual should be used for home BP measurement. 2. The BP should be measured at the upper arm. Finger-cuff devices and wrist-cuff devices should not be used for home BP measurements. 3. Devices for home BP measurement should be adapted to the American Association for Medical Instrumentation standards and the British Hypertension Society guidelines. In addition, the difference between the BP measured by the auscultatory method and the device should be within 5 mm Hg in each individual. The home measurement device should be validated before use and at regular intervals during use. 4. Home BP should be monitored under the following conditions: The morning measurement should be made within 1 h after waking, after micturition, sitting after 1 to 2 min of rest, before drug ingestion, and before breakfast. The evening measurement should be made just before going to bed, sitting after 1 to 2 min of rest. 5. Home BP should be measured at least once in the morning and once in the evening. 6. All home BP measurements should be documented without selection, together with the date, time, and pulse rate. Use of devices with a printer or an integrated circuit memory is useful to avoid selection bias. 7. The home BP in the morning and evening should be averaged separately for a certain period. The first measurement on each occasion should be used for totalizing. 8. Home BP values averaged for a certain period ≥ 135/80 mm Hg indicate hypertension and ≥ 135/85 mm Hg, definite hypertension. Normotension is defined as less than an average BP &lt; 125/80 mm Hg and definite normotension as &lt; 125/75 mm Hg.</td>
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<td><strong>American Society of Hypertension</strong>&lt;sup&gt;408&lt;/sup&gt;</td>
<td>ABPM: Ambulatory BP monitors measure BP by means of auscultatory or oscillometric methods. Auscultatory monitors use a microphone on the bladder cuff to detect the Korotkoff sounds. The advantage of this technique is that arm movement does not interfere with the recording; however, these monitors are sensitive to background noise. Oscillometric monitors sense arterial pressure vibrations and calculate systolic and diastolic values using an algorithmic approach. They are unaffected by background noise, but arm movement can cause errant readings. Both types of monitors are validated by the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Patients wear the monitor for a 24-hour period, usually a workday. The monitor is preprogrammed to record BP, usually every 15 to 20 minutes during daytime hours and every 20 to 30 minutes during night-time hours. Patients are instructed to keep an activity log throughout the testing period for evaluation of stress- and activity-related BP changes.</td>
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<td><strong>Pickering et al.</strong>&lt;sup&gt;409&lt;/sup&gt;</td>
<td>ABPM: Currently available ambulatory monitors are fully automatic and can record BP for 24 hours or longer while patients go about their normal daily activities. Most monitors use the oscillometric technique. They can be worn on a belt or in a pouch and are connected to a sphygmomanometer cuff on the upper arm by a plastic tube. Subjects are asked to keep their arm still while the cuff is inflating and to avoid excessive physical exertion during monitoring. The monitors are programmed to take a reading every 15 to 30 minutes throughout the day and night. At the end of the recording period, the readings are downloaded into a computer. Standard protocols are used to evaluate the accuracy of the monitors, and approved devices are usually accurate to within 5 mm Hg of readings taken with a mercury sphygmomanometer. The daytime level of ambulatory BP that is usually considered the upper limit of the normal range is 135/85 mm Hg.</td>
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<td><strong>The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure</strong>&lt;sup&gt;413&lt;/sup&gt;</td>
<td>ABPM is warranted for evaluation of white-coat hypertension in the absence of target-organ injury. It is also helpful in patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, or autonomic dysfunction. Ambulatory BP values are usually lower than office readings. Individuals with hypertension have an average BP of 135/85 mm Hg when awake and ≥ 120/75 mm Hg during sleep. The level of BP measurement by using ABPM correlates better than office measurements in patients with target organ injury. ABPM also provides data on the percentage of BP readings that are elevated, the overall BP load, and the extent of BP reduction during sleep. In most individuals, BP decreases by 10 to 20% during the night; those in whom such reductions are not present are at increased risk for cardiovascular events.</td>
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<td><strong>European Society of Hypertension</strong>&lt;sup&gt;417,401,403&lt;/sup&gt;</td>
<td>1. Refers to: <a href="http://www.dabbledental.org.uk">http://www.dabbledental.org.uk</a> for UK available ABPM and home measuring devices. 2. Details proper equipment and technique. 3. Outlines accepted and potential clinical indications for ABPM.</td>
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<td><strong>NICE Guideline</strong>&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Out-of-office BP measurements are now recommended as part of the proper diagnosis of hypertension. ABPM should be offered to confirm the diagnosis of hypertension if two BP measurements during an office consultation are ≥ 140/90 mm Hg. If ABPM is used, at least two measurements per hour must be taken during waking hours (08:00 to 22:00). The average value at least 14 measurements taken during the waking hours is needed to confirm the diagnosis of hypertension. Home BP monitoring is a suitable alternative to ABPM and requires two consecutive BP measurements a minute apart in the seated position, taken twice daily (usually morning and evening) for at least 4 days (but ideally 7). The first day’s measurements are discarded and the average of the remaining measurements are used to confirm a diagnosis of hypertension. Stage 1 hypertension is diagnosed if average BP from ABPM or home monitoring is ≥ 135/85 mm Hg. When using ABPM or home BP monitoring to assess response to treatment, the target average BP during waking hours should be &lt; 135/85 mm Hg for people aged under 80 years and &lt; 145/85 mm Hg for people aged ≥ 80 years.</td>
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pulse wave velocity have been widely performed in the general, hypertensive, and diabetic populations as well as to a limited extent, in hemodialysis patients, in whom the correlation of pulse wave velocity with mortality has been well documented.32,35

Pulse wave velocity may be increased in early CKD34,404,405 but it is unclear what this means in terms of CVD risk and kidney-disease prognosis. It is also unclear whether treatment of BP will alter pulse wave velocity in the longer term for CKD 1-5 patients and if so, whether this might influence the prognosis. While sophisticated studies such as pulse wave velocity are unlikely to become widespread in the global CKD community, especially in less economically advanced communities, further research is likely to lead to better use of this tool for assessment of BP related changes in the cardiovascular system in CKD patients and possibly to treatment changes based on pulse wave velocity indices.

8.2: IS THERE AN EVIDENCE-BASED LOWER LIMIT FOR BP REDUCTION?

The Work Group discussed whether it would be preferable to recommend a target range (lowest to highest) for BP rather than just a single target for highest acceptable BP. Although the benefits of lowering BP in CKD have been demonstrated, allowing us to recommend that we should aim for BP consistently ≤140/90 mm Hg when albumin excretion is <30 mg per 24 hours and ≤130/80 mm Hg if albumin excretion is ≥30 mg per 24 hours in both non-diabetic (Chapter 3) and diabetic (Chapter 4) adults with CKD ND, we were unable to give any recommendations for a lower BP target level due to a lack of evidence.

There are observational data that support the intuitive notion that excessive BP reduction might be harmful, at least in trials that have not specifically recruited CKD patients. In a cohort of 4071 very elderly (≥80 years) ambulatory American veterans (hence 96.6% males) with hypertension on 1.7 ± 1.2 (mean ± SD) antihypertensive medication classes, a J-shaped survival curve was noted when the relationship between both systolic and diastolic pressure and survival was examined. The optimum survival was associated with the ranges of diastolic BP between 70–79 mm Hg and systolic BP between 130–139 mm Hg.43 In another smaller study (n = 331) of mortality with 2 year follow-up in elderly hospitalized subjects >70 years with vascular disease or hypertension, the longest survival was observed when diastolic BP was in the range 71–80 mm Hg, with a pronounced increase in risk with diastolic BP ≤60 mm Hg.410

Further evidence to discourage aggressive reduction in BP in high risk groups comes from secondary analyses of outcomes associated with achieved BPs in the context of large RCTs. Such analyses are retrospective in nature and the trials themselves have not specifically recruited (and often excluded) patients with reduced GFR, so they cannot be used to formulate a guideline for a lower BP target in the context of CKD. One example of such a study is a retrospective analysis of the active treatment group of the SHEP trial. In this study, 4736 subjects aged ≥60 years with a systolic BP >160 mm Hg and diastolic <90 mm Hg were randomized to placebo or BP reduction with chlorthalidone with or without atenolol to reduce systolic BP. Perhaps surprisingly, a low diastolic BP on treatment was associated with an increased risk of stroke, coronary heart disease and CVD.41 Likewise in INVEST, a multi-national RCT comparing verapamil sustained-release and atenolol-based treatment in 22,576 patients with hypertension and CAD, BP control and outcomes were equivalent between the groups, but the risk of the primary outcome (all-cause death, non-fatal myocardial infarction and non-fatal stroke) progressively increased with a BP lower than 119/84 mm Hg, although taken alone, stroke risk did not increase with lower BP. After adjustment for multiple variables the relationship between low diastolic BP and primary outcome persisted.40 Further analysis of the above association including only the 2699 patients with peripheral artery disease also showed a J-shaped relationship, such that the primary outcome occurred least frequently at a systolic BP of 135-145 mm Hg and a diastolic BP of 60-90 mm Hg, with the effect most strongly related to systolic BP.411 Stratifying patients into those aged <60, 60 to <70, 70 to <80 and ≥80 years and plotting survival versus diastolic BP produced a pronounced J-curve effect with a HR nadir at 75 mm Hg up to 80 years, then 70 mm Hg for subjects >80 years. For systolic BP the HR nadir increased with increasing age: 115 mm Hg up to 70 years, 135 mm Hg for 70 to <80 years, and 140 mm Hg for ≥80 years.42

In ONTARGET involving 25,588 patients with atherosclerotic disease or diabetes with organ damage, a J-shaped relationship between on-treatment systolic BP (nadir around 130 mm Hg) and all outcomes except stroke was observed in a retrospective analysis.412 Data from IDNT showed that a systolic BP below 120 mm Hg was associated with an increased risk of cardiovascular deaths and congestive heart failure, but not myocardial infarction in hypertensive type 2 diabetics.228

Finally, in the ACCORD study, while targeting a systolic BP of <120 mm Hg rather than <140 mm Hg did not reduce cardiovascular outcomes, serious adverse events occurred in 3.3% of the lower BP group compared with 1.3% (p < 0.001) in the higher BP target group indicating the potential penalty paid for aggressive BP reduction.159

In CKD ND patients, there is observational evidence from two community-based longitudinal studies including 1549 subjects with CKD 3-4. In one study, a J-shaped relationship between stroke and systolic BP was observed, with lowest stroke risk in the range of systolic BP between 120 and 129 mm Hg, and higher risk above and below this.58 A cohort study of 860 US veterans (comprising mainly men) with CKD (GFR <60 and a subset with GFR <30 ml/min/1.73 m²) showed greater mortality when systolic BP was <133 mm Hg or diastolic BP <65 mm Hg, although it appeared that the association might not be causal but instead related to atherosclerotic CVD as a co-morbidity.113

In summary, with respect to a lowest BP target, most of the relevant evidence is observational, derived from retrospective analyses, and nearly all involves non-CKD populations. No studies to date have specifically tested a strategy of
reducing blood-pressure-lowering drug treatment if the BP falls below a certain limit. We anticipate that there would be major practical difficulties in implementing such a practice, particularly in patients with reduced conduit artery compliance and consequent increased pulse pressure (in whom a lower limit for diastolic BP might entail accepting an systolic BP much higher than the current targets). Although the available evidence is enough to support our guideline statements advising caution in those with co-morbidity, we do not consider it is robust enough to allow us to specify a lower limit for either systolic BP or diastolic BP, even though other organizations have done so. Although inferences can be drawn when treatment-related BP is too low, especially in patients with diabetes, the elderly and those with CVD, we are left without a lowest BP target.

The NIH funded SPRINT trial currently recruiting patients in the US may clarify this issue. It will randomize over 7500 patients with systolic BP to targets of <140 mm Hg or <120 mm Hg, deliberately including approximately 1750 patients over 75, and followed for cardiovascular, cognitive and kidney end points over a period of 9 years, commencing 2010.

8.3: SHOULD A REDUCTION IN ALBUMINURIA BE A TARGET FOR TREATMENT WITH AGENTS THAT MODIFY BP?

As outlined elsewhere in this Guideline, RAAS intervention is effective in not only lowering BP but also protecting individual patients with CKD from further decline in kidney function. Although the BP-lowering effect of RAAS inhibition contributes to renoprotection, a component of the protective effect may be independent of the effect on BP. Thus, to achieve maximum renoprotection using a RAAS inhibitor, the clinician might consider monitoring the reduction in urine albumin excretion (an ‘off target’ effect). This is particularly important in macroalbuminuric and microalbuminuric hypertensive subjects with type 2 diabetes, in whom the BP response to RAAS inhibitors may be discordant with the anti-albuminuric response. Studies in such patients indicate that those in whom urine albumin was lowered without significant lowering of BP gained some renoprotection, whereas patients who did not have urine albumin lowered in spite of BP-lowering did not have renoprotection. Thus, albuminuria may be an independent factor in renoprotection. In a prospective study supporting this concept, Hou et al. detected nearly 50% additional renoprotection with a dose of a RAAS inhibitor titrated to maximally reduce urine albumin levels as compared to a standard dose used for the BP lowering effect.

There have been no RCTs assessing hard renal or cardiovascular outcomes, in which patients have been randomized to different targets of urinary albumin excretion irrespective of BP.

8.4: SHOULD RAAS INHIBITION BE MAXIMIZED IN CKD PATIENTS?

Accepting that RAAS inhibitors may be used to both lower BP and urine albumin excretion, options are available to optimize the albuminuria lowering effect of these agents. For example, it is well recognized that co-administration of a low-sodium diet or the addition of a diuretic enhances the effect of both ACE-Is and ARBs on lowering urine albumin excretion. Such therapeutic combinations make good sense and are unlikely to be associated with harmful side effects.

Whether more aggressive blockade of the RAAS using supramaximal doses of ACE-Is or ARBs is beneficial is less certain. Recently, Burgess et al. showed that increasing the dose of candesartan well beyond the guideline-recommended dose for BP-lowering resulted in further reduction of the urine albumin levels.

The substantial evidence suggesting that RAAS inhibition using ACE-Is or ARBs has renoprotective effects when these agents are used individually has led to the hypothesis that combining the two classes of agents, or adding an aldosterone antagonist or a DRI, may provide additional benefit. Interest in this approach has been increased by the evidence that individuals treated with ACE-Is may have ‘aldosterone breakthrough’ with angiotensin I to angiotensin II conversion occurring via other pathways and by the fact that there may be other active receptors for angiotensin II that may have a range of roles.

A number of moderate-sized studies, mostly in patients with diabetes, have demonstrated that proteinuria levels may be further lowered by combining ACE-Is and ARBs than by using each agent alone. Aldosterone antagonists may substantially lower proteinuria when used on top of ACE-Is or ARBs. Similarly when the DRI, aliskiren, was added to an ARB, proteinuria was reduced.

The optimism generated by these findings has recently been seriously dampened. The ONTARGET trial did not demonstrate any cardiovascular benefit for dual RAAS blockade (with the ACE-I ramipril and the ARB telmisartan), in a population at high risk of CVD, but did suggest an increased risk of major renal outcomes with dual RAAS blockade.

The ALTITUDE trial randomized type 2 diabetic participants to receive either aliskiren or matching placebo on top of an ACE-I or ARB and included a large number of diabetic individuals with CKD. Although the results have not been published at the time of writing this Guideline, the trial was recently stopped early due to a low likelihood of ever demonstrating benefit and a suggestion of an increased risk of some adverse outcomes, including non-fatal stroke, renal complications, hyperkalemia and hypotension, resulting in the US FDA counselling against this practice.

As a result, any benefits of combined blockade of the RAAS for clinically important renal outcomes currently remain unproven, and the safety issues should be taken into account prior to using this therapeutic approach.

8.5: SHOULD ACE-IS AND ARBS BE DISCONTINUED IN CKD 5 BECAUSE THEY COMPROMISE RESIDUAL KIDNEY FUNCTION?

It has long been recognized that commencing ACE-Is and ARBs can lead to an acute reduction in GFR that may be
reversed if the dose is reduced or if the drug is discontinued. This phenomenon has been observed in the context of RCTs such as the RENAAL trial. In a post hoc analysis of this study, an initial fall in GFR was found to predict better long-term renoprotection.87 Such acute changes in GFR are likely to reflect the hemodynamic changes that accompany initiation of RAAS blockade.88,428 However, since a reduction in GFR is not usually considered beneficial, observers have recently questioned the value of commencing or continuing BP-lowering regimens based on an ACE-I or ARB in elderly patients with advanced CKD and have specifically suggested that use of such agents in CKD 4–5 patients may compromise residual kidney function or even accelerate its rate of decline in both diabetic429 and non-diabetic patients.430

This opinion is based on uncontrolled observations and is contrary to the observations made from the RENAAL RCT in patients approaching renal replacement therapy.431 For example in one such observational study, discontinuation of ACE-I and ARBs in 52 patients with CKD 4–5 was followed by a greater than 25% increase in the GFR in 61.5% of patients, and a greater than 50% increase in 36.5% of patients.23 An RCT that specifically randomized patients with advanced CKD to benazapril or placebo did not support this.432 The study reported that 112 predominantly CKD 4 patients with a mean GFR of 26 ml/min/1.73 m² receiving benazapril had a lower risk of doubling of SCr, kidney failure, or death compared with the same number of patients receiving placebo. A small study of 60 peritoneal dialysis patients showed better preservation of residual kidney function among patients randomized to ramipril as compared to no treatment.432

Thus, the current evidence does not support the discontinuing ACE-I and ARBs in patients with advanced CKD in an effort to preserve residual kidney function, although hyperkalemia or hypotension may be a specific reason for discontinuation in some patients.

8.6: ETHNICITY, RACE, AND GENES
In this Guideline, the individualization of BP control is emphasized, yet specific advice to tailor therapy according to ethnicity, race, or genetic influences is not available. In lieu of such advice, we have drawn on RCTs specific to various racial and ethnic populations: African-American, Chinese, Japanese, Pakistani, and European whites (sometimes from a single country). We have generalized the observations derived from these ethnicity- or race-specific RCTs to management advice applicable to all ethnic and racial groups. However, there is good reason—but not good evidence—to believe that ethnicity, race, and genotype influence elevated BP and CKD, with familial aggregation and ethnic–racial disparities in both conditions. Currently, it is difficult to disentangle ethnic–racial disparities from social, economic, and environmental disparities.

The evidence for ethnic or racial influence on CKD is mainly epidemiological. The incidence of kidney failure requiring dialysis is higher in a wide variety of non-white groups (African-American, Asian, Native American, Native Australian, and Pacific Islander) than in white groups of European heritage in North America, Europe, and the Asia–Pacific region.366,433–435 Hypertension is also more common, develops earlier in life, and manifests with a higher average BP among African-Americans than whites in the United States.436

Although profound environmental and socioeconomic issues are clearly involved, information is gradually being gathered that enlightens us about some of the links among genetics, high BP and kidney disease in the African-American population.437 Genetic variance in the non-muscle myosin heavy chain 9 gene (MYH9) was reported to be partly responsible for progressive kidney disease in hypertensive African-Americans.438 This might provide a rationale for lower BP targets in hypertensive African-Americans than other racial groups,439 especially in African-Americans with genetic variation in the MYH9 gene. More recently, polymorphisms in the apolipoprotein L-1 gene (APOL1), which is located immediately upstream to MYH9, has been implicated in this process, with the APOL1 G1 and G2 alleles associating with focal segmental glomerulosclerosis in African-Americans.440 Intriguingly, these variants seem to confer resistance to Trypanosoma brucei rhodesiense, which may explain the persistence of this seemingly otherwise disadvantageous gene in West Africans, but this hypothesis does not clarify the association between APOL1 and focal segmental glomerulosclerosis.

Epidemiological evidence is suggestive of many other ethnic–racial differences among individuals with CKD. In addition to the differences in the prevalence of types of kidney diseases in different groups, there appear to be differences in the rates of CKD progression, in the effects of BP control on CKD progression, in BP responses to various antihypertensive regimens, and in cardiovascular risk associated with a particular BP level. Outlining this evidence is beyond the scope of this Guideline, but clearly the scientific community is currently only scratching the surface of the links among BP, CKD, race, ethnicity, genes, and epigenetics. In the future evidence may become available regarding how to modify BP control in CKD according to an individual’s genetic profile, or ethnic or racial background. In the meantime, we must pay greater attention to socioeconomic and environmental issues related to ethnicity or race, which are more immediately amenable to modification.

8.7: BARRIERS TO IMPLEMENTATION
Although several guidelines on BP management in CKD have been published, BP management in CKD patients is often suboptimal and audit studies suggest that the target readings are not achieved in many patients.441 The reasons why it is challenging to implement recommendations and to achieve target BP in CKD (and other) patient populations are multiple and complex, but are likely to include the issues listed below. Because of these uncertainties we cannot suggest that the recommended BP targets in this Guideline should be
used as performance measures in the management of CKD patients.

**The credibility of the guideline is questioned.** Not all clinicians agree with the currently recommended BP targets, at least not for all of their patients. The evidence supporting current BP targets in CKD has been challenged, reinforcing clinicians’ concerns.\(^{22}\) However, surveys have shown that less stringent BP targets, such as 160/90 mm Hg, are also not regularly achieved.\(^{441}\) The BP targets recommended in this guideline are higher than those in some previous publications and it remains to be seen whether this will result in a higher proportion of CKD patients achieving them.

**The trial data are not directly relevant to a real world setting.** There are few systematically collected data to support the notion that BP control cannot be achieved in most patients. However several important issues need to be considered when extrapolating from clinical trials to a ‘real world’ setting. Firstly, patients recruited into RCTs are selected for characteristics that increase the likelihood of BP control. These include a lack of co-morbidities, an absence of previous adverse reactions to the BP-modifying agents used in the trial, good BP control during a run-in or washout period and high motivation, reflected by the patients’ willingness to enroll. Secondly, patients participating in trials are often micro-managed in specialized clinics, where frequent reinforcement and pill-counting increases the likelihood of adherence to the drug regimen. Thirdly, patients who drop out because of drug-related side effects or non-adherence are usually accounted for in intention-to-treat analyses and the overall proportion of dropouts is not often reported (although may be 10% or more of the recruited population). Finally, although the mean achieved BP is often close to the intended target, the SD of the reported BP measurements is often large, suggesting that the recorded values in many patients are well above the mean and hence well above the target.\(^{22}\) Only rarely is the actual number of patients not achieving the target BP reported. Taken together, these factors indicate that the proportion of patients with CKD in whom BP cannot be controlled to a specified target may be much higher than indicated by the data derived from RCTs.

**Patients do not adhere to the treatment.** The reasons why patients do or do not adhere to medical advice are believed to depend in part on cost-benefit analysis by the patients themselves. This is particularly relevant to the use of BP-modifying drugs that do not provide immediately perceivable improvement in quality of life or relief of symptoms, yet have immediately observable negative effects in terms of expense and inconvenience, even if there are no adverse side effects. The literature contains many reports of poor adherence to BP-modifying drug regimens and suboptimal BP control in CKD patients is known to be associated with poor adherence to medication.\(^{442}\)

**BP fluctuates.** In a usual clinical setting, if a BP target is set, a clinician will gradually increase the number of drugs prescribed to a given patient until this target is achieved. The regimen will not then be altered again unless several BP readings are above (sometimes well above) that target. Because BP fluctuates, there is a good chance that a proportion of the subsequent BP readings will inevitably be above a previously achieved target. One way to circumvent this problem is to set a threshold level for treatment that is lower than the desired target. This strategy has been used in several health care recommendations, including the WHO nutrition goals and the 1997 NKF-Dialysis Outcomes Quality Initiative Hemodialysis Adequacy guideline. As previously stated and in line with several previous guidelines on BP management in CKD, we have set the same values for the threshold for treatment and desired target systolic and diastolic levels. We emphasize the value of checking for consistency by using repeated BP measurements to direct therapy and believe that this strategy will improve target attainment.

**BP is measured infrequently.** Traditionally, BP control is assessed by measuring the BP in a patient or a group of patients on just one occasion. In an individual patient, the BP can be better assessed by means of repeated clinical measurements over a period of time or by more sophisticated techniques such as home self-measurement of BP or ABPM. Evaluating guideline implementation in a group of patients is difficult, as repeated or more sophisticated measurements are not possible in everyone. We have insufficient knowledge of what proportion of patients at any one time will have a BP level above the target value, even when guidelines have been closely followed and adherence has been high. In a post hoc analysis of a large RCT of essential hypertension, a single elevated office BP reading in a patient with previously well controlled BP was unlikely to indicate a persistent loss of BP control, but rather reflect day-to-day variation.\(^{443}\)

**DISCLAIMER**

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Methods for guideline development


AIM
The overall aim of this project was to develop an evidence-based CPG for the use of BP-lowering agents in individuals with CKD. The guideline consists of recommendation statements, rationale, and a summary of systematically generated evidence on relevant pre-defined clinical topics.

OVERVIEW OF PROCESS
The development process for the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease included the following steps:

- Appointing Work Group members and the ERT.
- Discussing process, methods, and results.
- Developing and refining topics.
- Identifying populations, interventions or predictors, and outcomes of interest.
- Selecting topics for systematic evidence review.
- Standardizing quality assessment methodology.
- Developing and implementing literature-search strategies.
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria.
- Creating data extraction forms.
- Extracting data and performing critical appraisal of the literature.
- Grading the methodology and outcomes in individual studies.
- Tabulating data from individual studies into summary tables.
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles.
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations.
- Finalizing guideline recommendations and supporting rationales.
- Sending the guideline draft for peer review to the KDIGO Board of Directors in December 2010 and for public review in July 2011.
- Publishing the final version of the guideline.

The Work Group, KDIGO Co-Chairs, ERT, and KDIGO support staff met for three 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Commissioning of Work Group and ERT
The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, cardiology, hypertension, pharmacology, epidemiology, and endocrinology. The Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA, was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician-methodologists with expertise in nephrology, a project coordinator and manager, and a research assistant. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

Defining scope and topics
The Work Group Co-Chairs first defined the overall scope and goals of the guideline and then drafted a preliminary list of topics and key clinical questions. The Work Group and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms (Table 5).

Given the lack of robust evidence, the Work Group decided not to make guideline recommendations for patients with kidney failure (CKD 5D). The Work Group decided instead to refer readers to the KDIGO Controversies Conference paper on this topic.

Establishing the process for guideline development
The ERT performed literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes and defined and standardized the methodology for performing literature review, data extraction, and summarizing the evidence. Throughout the project, the ERT offered suggestions for guideline development and led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. The Work Group took the primary role of writing the recommendation statements and rationale and retained final responsibility for their content.

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of open-ended questions to be considered by Work Group members. At their first 2-day meeting, members added further questions until the
initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

Formulating questions of interest

Questions of interest were formulated according to the PICODD (Population, Intervention, Comparator, Outcome, study Design and Duration of follow-up) criteria. Details of the criteria are presented in Table 5.

Ranking of outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 6). Doubling of SCr level or halving of GFR was upgraded from ‘high’ to ‘critical’ importance in studies where the baseline GFR was <60 ml/min/1.73 m² or SCr >2 mg/dl (177 μmol/l), given the known adverse consequences of advanced CKD.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Systematic review topics and screening criteriaa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet or lifestyle modification</strong></td>
<td>CKD ND: CKD 1–5, non-dialysis, adults and children, with or without hypertension, any type of CKD</td>
</tr>
<tr>
<td>Population</td>
<td>CKD ND: CKD 1–5, non-dialysis, adults and children, with or without hypertension, any type of CKD</td>
</tr>
<tr>
<td>Intervention</td>
<td>Salt restriction, weight loss, diet, exercise</td>
</tr>
<tr>
<td>Comparator</td>
<td>Active or control</td>
</tr>
<tr>
<td>Outcome</td>
<td>Blood pressure, mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events</td>
</tr>
<tr>
<td>Study design</td>
<td>RCTs with parallel-group design; cross-over trials</td>
</tr>
<tr>
<td>Minimum duration of follow-up</td>
<td>6 weeks for blood pressure, 3 months for proteinuria, 1 year for other outcomes</td>
</tr>
<tr>
<td>Minimum N of subjects</td>
<td>≥50 per arm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure targets</th>
<th>CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD but organized by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD but organized by</td>
</tr>
<tr>
<td>Intervention</td>
<td>Lower or lower BP target</td>
</tr>
<tr>
<td>Comparator</td>
<td>Higher or usual BP target</td>
</tr>
<tr>
<td>Outcome</td>
<td>Mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events</td>
</tr>
<tr>
<td>Study design</td>
<td>RCTs with parallel-group design</td>
</tr>
<tr>
<td>Minimum duration of follow-up</td>
<td>3 months for proteinuria, 1 year for other outcomes</td>
</tr>
<tr>
<td>Minimum N of Subjects</td>
<td>≥50 per arm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agents</th>
<th>CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD but organized by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD but organized by</td>
</tr>
<tr>
<td>Intervention</td>
<td>Any anti-hypertensive agent (single or in combination, any dose) as well as specific searches for ACE-I, ARB, aldosterone antagonist, beta-blocker, calcium-channel blocker, diuretic</td>
</tr>
<tr>
<td>Comparator</td>
<td>Active or placebo</td>
</tr>
<tr>
<td>Outcome</td>
<td>Mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events</td>
</tr>
<tr>
<td>Study design</td>
<td>RCTs with parallel-group design</td>
</tr>
<tr>
<td>Minimum duration of follow-up</td>
<td>3 months for proteinuria, 1 year for other outcomes</td>
</tr>
<tr>
<td>Minimum N of Subjects</td>
<td>≥50 per arm</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CKD ND, non-dialysis-dependent CKD; CKD T, non-dialysis-dependent CKD with a kidney transplant; DKD, diabetic kidney disease; DM, diabetes mellitus; N, number; RCTs, randomized controlled trials.

aIncludes CKD subgroups from ‘general population’ studies (not exclusively in CKD patients).

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Hierarchy of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hierarchya</strong></td>
<td>Outcomesb</td>
</tr>
<tr>
<td>Critical importance</td>
<td>Mortality, cardiovascular mortality, cardiovascular events, kidney failure, composite including clinical events</td>
</tr>
<tr>
<td>High importance</td>
<td>Doubling of SCr or halving of GFR, proteinuria (categorical)</td>
</tr>
<tr>
<td>Moderate importance</td>
<td>Kidney function (continuous), urine protein level (continuous)</td>
</tr>
<tr>
<td>Importance dependent on severity</td>
<td>Adverse events: drug discontinuation or dose decrease, hyperkalemia, early rise of SCr or decrease of GFR</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; SCr, serum creatinine.

aDoubling of SCr or halving of GFR is of ‘critical’ importance in those studies with baseline GFR <60 ml/min/1.73 m² or SCr >2 mg/dl (177 μmol/l).

bThe lists are not meant to reflect outcome ranking for other areas of kidney disease management. The Work Group acknowledges that not all clinicians, patients or families, or societies would rank all outcomes the same.

Literature searches and article selection

The Work Group sought to build on the evidence base from the previous KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.1 As the first search for the KDOQI guideline was conducted in
Table 7 | Relevant systematic reviews and meta-analyses

<table>
<thead>
<tr>
<th>Topic</th>
<th>Title</th>
<th>Reference</th>
<th>Databases and cut-off dates of literature search</th>
<th>Use in Work Group deliberation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topic 1. Low sodium diet or lifestyle modification and change in BP</td>
<td>Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials</td>
<td>Dickinson et al.53</td>
<td>Cochrane CENTRAL MEDLINE Embase 1998-2003</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td></td>
<td>Systematic review of long term effects of advice to reduce dietary salt in adults</td>
<td>Hooper et al.62</td>
<td>Cochrane CENTRAL MEDLINE Embase CAB abstracts CVRCT registry SIGLE 1982-1998 Further search on sodium restriction and BP: Cochrane CENTRAL MEDLINE Embase Up to July 2002</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td>Topic 2. BP target and kidney outcomes</td>
<td>Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient level meta-analysis</td>
<td>Jafar et al.96</td>
<td>MEDLINE 1977-1999</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td>Topic 3. ACE-I or ARB on CVD and CKD progression</td>
<td>RAS blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis</td>
<td>Balamuthasamy et al.27</td>
<td>OVID MEDLINE Embase 1975-2006</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td></td>
<td>Angiotensin receptor blockers as anti-hypertensive treatment for patients with diabetes mellitus: meta-analysis of controlled double-blind randomized trials</td>
<td>Siebenhofer et al.450</td>
<td>Cochrane CENTRAL MEDLINE Embase Cochrane Controlled Trials Register PubMed DARE NHSEED HTA 1992-2002</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td>Topic 4. ACE-I or ARB on CKD progression</td>
<td>Effect of inhibitors of the renin-angiotensin system and other anti-hypertensive drugs on renal outcomes: systematic review and meta-analysis</td>
<td>Casas et al.451</td>
<td>Cochrane CENTRAL MEDLINE Embase 1960-Jan. 31, 2005</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-converting enzyme inhibitors and progression of non-diabetic renal disease. A meta-analysis of patient-level data</td>
<td>Jafar et al.141</td>
<td>MEDLINE May 1977-September 1997</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
<tr>
<td>Topic 5. ACE-I on CKD progression in CKD without DM</td>
<td>Anti-hypertensive agents in kidney-transplant recipients</td>
<td>Cross et al.191</td>
<td>Cochrane Renal Group Specialized Register Cochrane CENTRAL MEDLINE Embase Up to July 1, 2008</td>
<td>References used to check and supplement reference list of ERT systematic review</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ERT, evidence review team; RAS, renin-angiotensin system.

Table 8 | Literature yield

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Abstracts identified</th>
<th>Articles retrieved</th>
<th>Studies with data extracted</th>
<th>Studies included in summary tables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DKD</td>
<td>Non-DKD</td>
<td>Transplant</td>
<td>General population studies in summary tables</td>
</tr>
<tr>
<td>Agents</td>
<td>10, 657</td>
<td>247</td>
<td>55</td>
<td>23 22 6 13</td>
</tr>
<tr>
<td>Targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| DKD, diabetic kidney disease.
BP targets in CKD without DM
BP target in adults + + (3 studies)
BP target in children + – (single study)
Adverse events of target RCTs + – a

Agents in CKD without DM, non-transplant
ACE-I or ARB versus CCB + + (7 studies)
ACE-I or ARB versus placebo + + (6 studies)
High-dose ACE-I versus low-dose ACE-I + + (2 studies)
ACE-I versus ARB + + (3 studies)
ACE-I versus beta-blocker + – (single study)
High-dose ARB versus low-dose ARB + + (3 studies)
(ACE-I + CCB) versus ACE-I + – (single study)
(ACE-I + CCB) versus CCB + – (single study)
Beta-blocker versus CCB + – (single study)
CCB versus CCB + – (single study)
Central-acting agent versus CCB + – (single study)
Adverse events of agent RCTs + – a

Agents in CKD with DM, non-transplant
Aldosterone antagonist versus placebo + – (single study)
ACE-I or ARB versus CCB + + (7 studies)
ACE-I or ARB versus placebo + + (9 studies)
ACE-I versus ARB + + (3 studies)
ARB versus ARB + + (3 studies)
CCB versus placebo + – (single study)
Direct renin inhibitor versus placebo + – (single study)
Endothelin antagonist versus endothelin antagonist + – (single study)
Endothelin antagonist versus placebo + – (single study)
Adverse events of agents in RCTs + – a

Agents in CKD in kidney transplant recipient
ACE-I versus ARB + – (single study)
ARB versus placebo + – (single study)
ACE-I versus CCB + + (2 studies)
CCB versus placebo + + (3 studies)
Adverse events of agents in RCTs + – a

CKD subgroups from general population studies
BP target + (1 study)
ACE-I + diuretic versus placebo in DM + (4 studies)
ACE-I or ARB versus control + (5 studies)
ACE-I or ARB versus ACE-I + (1 study)
ARB versus CCB + (1 study)
CCB versus control + (2 studies)
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; RCTs, randomized controlled trials; +, work product is indicated for the topic of interest; –, work product is not indicated for the topic of interest.

July 2002, the search for the current KDIGO Guideline included publications since January 2002. Search strategies were developed by the ERT with input from the Work Group. The text words or medical subject headings (MeSH) that were included are provided in the Supplementary Appendix 1 online. Non-human studies and those focusing on dialysis, pregnancy, neonates, malignant hypertension, acute kidney injury, or drug pharmacology were excluded.

The MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched by the ERT to capture all RCTs on the use of BP-lowering agents in CKD. The first search was conducted in November 2009 and was subsequently updated in April and August of 2010; the final update was done in January 2011. Additional focused searches were conducted to identify RCTs evaluating lifestyle interventions of salt restriction, weight loss, and diet and exercise in CKD and to look for reviews of adverse effects of anti-hypertensive agents. The ERT relied on Work Group members to identify large, general population RCTs reporting on subgroup analyses based on CKD, GFR, or proteinuria status. Additional pertinent articles were added from the reference lists of JNC 7 and relevant meta-analyses and systematic reviews (Table 7). The search yield was also supplemented by articles provided by Work Group members through February 2012.

A total of 10,657 citations were initially screened. Journal articles reporting original data, meta-analyses, and systematic reviews were selected for evidence review. Editorials, letters, abstracts, unpublished reports, and articles published in non-peer-reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they get solicited, selected, reviewed, and edited compared to peer-reviewed publications. Post hoc analyses were also excluded, however, after discussion with the Work Group, it was decided that exception would be made for post-trial observational follow-up reports from RCTs looking at BP targets as BP interventions may take longer time to influence outcomes. These studies were downgraded one level to designate that they are of lesser quality than the original RCT. The overall search yield along with the number of abstracts identified and articles reviewed for each topic are presented in Table 8.

Data extraction
Data extraction was done by the ERT. The ERT, in consultation with the Work Group, designed forms to capture data on design, methodology, sample characteristics, interventions, comparators, outcomes, results, and limitations of individual studies. Methodology and outcomes were also systematically graded (see the section on grading below) and recorded during the data extraction process.

Summary tables
Summary tables were developed for each comparison of interest (Table 9). Studies included in the evidence base for the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease were also incorporated if they fulfilled the inclusion criteria for the current KDIGO Guideline.

Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator, results, and quality grading for each outcome. Categorical and continuous outcomes were summarized separately. Studies done exclusively in patients of a single race or ethnicity and studies reporting effect modifications by baseline urine protein level were annotated. Studies were also
For studies not exclusively examining CKD population, only those reporting analysis by CKD subgroups were tabulated. Studies including both diabetes mellitus and non-diabetes mellitus populations were included in summary tables for the CKD without diabetes mellitus topic unless results of subgroup analysis by diabetes mellitus status was provided.

Work Group members proofed all summary table data and quality assessments. Summary tables are available at www.kdigo.org.

**Evidence profiles**

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and the Work Group. When the body of evidence for a particular comparison of interest consisted of only one study, the summary table provided the final level of synthesis and an evidence profile was not generated. Evidence profiles were also not created for studies that did not exclusively examine CKD population. Each evidence profile was initially constructed by the ERT and then reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base are listed in Table 9.

**Grading of quality of evidence for outcomes of individual studies**

**Methodological quality.** Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 10). Variations of this system have been used in most KDOQI and all KDIGO guidelines and have been recommended for the US Agency for Healthcare Research and Quality Evidence-based Practice Center program.444

Each study was given an overall quality grade based on its design, methodology (randomization, allocation, blinding, definition of outcomes, appropriate use of statistical methods, etc.), conduct (dropout percentage, outcome assessment methodologies, etc.) and reporting (internal consistency, clarity, thoroughness and precision, etc.). Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality of evidence for summarizing the evidence base are listed in Table 9.

**Table 10 | Classification of study quality**

| Good quality | Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention, must be RCT. |
| Fair quality | Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective. |
| Poor quality | High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective. |

*RCT, randomized controlled trial.*

**Table 11 | GRADE system for grading quality of evidence**

<table>
<thead>
<tr>
<th>Step 1: Starting grade for quality of evidence based on study design</th>
<th>Step 2: Reduce grade</th>
<th>Step 3: Raise grade</th>
<th>Final grade for quality of evidence and definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials = High</td>
<td>Study quality</td>
<td>Strength of association</td>
<td>High = Further research is unlikely to change confidence in the estimate of the effect</td>
</tr>
<tr>
<td></td>
<td>–1 level if serious limitations</td>
<td>+1 level if strong(a), no plausible confounders</td>
<td>Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate</td>
</tr>
<tr>
<td></td>
<td>–2 levels if very serious limitations</td>
<td>+2 levels if very strong(b), no major threats to validity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consistency</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–1 level if important inconsistency</td>
<td>1 level if evidence of a dose-response gradient</td>
<td></td>
</tr>
<tr>
<td>Observational study = Low</td>
<td>Directness</td>
<td>1 level if all residual plausible confounders would have reduced the observed effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–1 level if some uncertainty</td>
<td>Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–2 levels if major uncertainty</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other evidence = Very Low</td>
<td>1 level if sparse or imprecise data(c)</td>
<td>Very Low = Any estimate of effect is very uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–1 level if high probability of reporting bias</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*GRADEx Grade of Recommendations Assessment, Development and Evaluation.

\(a\)Strong evidence of association is defined as ‘significant relative risk of \(> 2 (< 0.5)\)’ based on consistent evidence from two or more observational studies, with no plausible confounders.

\(b\)Very strong evidence of association is defined as ‘significant relative risk of \(> 5 (< 0.2)\)’ based on direct evidence with no major threats to validity.

\(c\)Sparse if there is only one study or if total N < 500. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range > 1. Adapted by permission from Macmillan Publishers Ltd, *Kidney International*. Uhlig K, Macleod A, Craig J et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058-2063.157 accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf.*
grade of an individual outcome could not exceed the quality grade for the overall study.

**Grading the quality of evidence and the strength of a guideline recommendation**

A structured approach, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and facilitated by the use of evidence profiles was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The ‘strength of a recommendation’ indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The ‘quality of a body of evidence’ refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.

---

**Table 12 | Final grade for overall quality of evidence**

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

**Table 13 | Balance of benefits and harms**

When there was evidence to determine the balance of medical benefits and harms of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit or harm, report as ‘benefit [or harm] of drug X.’
- For non-statistically significant benefit or harm, report as ‘possible benefit [or harm] of drug X.’
- In instances where studies are inconsistent, report as ‘possible benefit [or harm] of drug X.’
- ‘No difference’ can only be reported if a study is not imprecise.
- ‘Insufficient evidence’ is reported if imprecision is a factor.

**Table 14 | KDIGO nomenclature and description for grading recommendations**

<table>
<thead>
<tr>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Clinicians</td>
</tr>
<tr>
<td>Policy</td>
</tr>
<tr>
<td>Level 1 ‘We recommend’</td>
</tr>
<tr>
<td>Level 2 ‘We suggest’</td>
</tr>
</tbody>
</table>

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*The additional category ‘Not Graded’ was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.*
Table 16 | Existing major guidelines and recommendations on hypertension and anti-hypertensive agents in CKD

<table>
<thead>
<tr>
<th>Year</th>
<th>Group</th>
<th>Target CKD population</th>
<th>Recommended BP goal (mm Hg)</th>
<th>Recommended preferred anti-hypertensive agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) [441]</td>
<td>Stage 3 CKD, macroalbuminuria, kidney-transplant recipients</td>
<td>&lt;130/80</td>
<td>CKD 3 or macroalbuminuria: ACE-I or ARB in combination with a diuretic Kidney-transplant recipients: No particular class of agents superior</td>
</tr>
<tr>
<td>2003</td>
<td>World Health Organization/International Society of Hypertension (WHO/ISH) [442]</td>
<td>Type 1 DM with nephropathy Type 2 DM with nephropathy Non-diabetic nephropathy</td>
<td>&lt;130/80</td>
<td>Type 1 DM with nephropathy: ACE-I Type 2 DM with nephropathy: ARB Non-diabetic nephropathy: ACE-I</td>
</tr>
<tr>
<td>2003</td>
<td>European Society of Hypertension-European Society of Cardiology Guidelines for the Management of Arterial Hypertension (ESH-ESC) [443]</td>
<td>DM, CKD</td>
<td>&lt;130/80 (if urine protein &gt; 1 g/d is present, lower target to lower protein if possible)</td>
<td>CKD: Diuretic Type 1 DM with nephropathy: ACE-I Type 2 DM with nephropathy: ARB Non-diabetic nephropathy: ACE-I Proteinuria: ACE-I or ARB</td>
</tr>
<tr>
<td>2006</td>
<td>Caring for Australasians with Renal Impairment (CARI) Guidelines: Prevention of Progression of Kidney Disease [444]</td>
<td>DM, CKD</td>
<td>CKD in general: &lt;125/75 (or mean BP &lt; 92) if urine protein &gt; 1 g/d &lt;130/80 (or mean BP &lt; 97) if urine protein 0.25–1 g/d &lt;130/85 (or mean BP &lt; 100) if urine protein &lt; 0.25 g/d DKD: &lt;130/85 for patients &gt; 50 years of age &lt;120/70–75 for those &lt; 50 years of age</td>
<td>Non-DKD: Regimens including ACE-I more effective than those not including ACE-I in slowing CKD progression in non-DKD Combination therapy of ACE-I and ARB slows progression of non-DKD more effectively than either single agent ACE-I more effective than beta-blockers and dihydropyridine CCB in slowing progression of CKD Beta-blockers more effective than dihydropyridine CCB in slowing CKD progression, especially in the presence of proteinuria DD: ACE-I for all patients with diabetes and hypertension ACE-I for all patients with diabetes and microalbuminuria or overt nephropathy, independent of BP and GFR ARB provides specific renoprotection in diabetic nephropathy, beyond their anti-hypertensive benefit There is insufficient evidence that ACE-I and ARB combination are of additive specific benefit in diabetic nephropathy, beyond additional anti-hypertensive benefit</td>
</tr>
<tr>
<td>2008</td>
<td>Canadian Society of Nephrology Guidelines on Management of CKD [445]</td>
<td>DM, CKD</td>
<td>&lt;130/80</td>
<td>Non-DKD: ACE-I or ARB should be included in the regimen if urine ACR &gt; 30 mg/mmol (&gt; 300 mg/g) ACE-I, ARB, thiazides, long-acting CCB, or beta-blockers (for patients older than 60 years) should be included in the regimen if urine ACR &lt; 30 mg/mmol (&lt; 300 mg/g) DD: ACE-I or ARB should be included in the regimen</td>
</tr>
<tr>
<td>2009</td>
<td>Reappraisal of European Guidelines on Hypertension Management: a European Society of Hypertension Task Force Document [446]</td>
<td>DM, CKD</td>
<td>Initiate treatment for systolic BP &gt; 130 and diastolic BP &gt; 85</td>
<td>ACE-I or ARB, but combination therapy with other agents most likely needed to control BP</td>
</tr>
<tr>
<td>2009</td>
<td>Japanese Society of Hypertension Guidelines for the Management of Hypertension [447]</td>
<td>CKD</td>
<td>&lt;130/80 For those with urine protein ≥ 1 g/d: target &lt; 125/75</td>
<td>ACE-I or ARB should be the first choice of therapy and dose should be titrated by urinary albumin excretion (&lt; 30 mg/g for diabetic nephropathy and &lt; 300 mg/g for glomerulonephritis) For diuretics, thiazides should be used if GFR ≥ 30 ml/min/1.73 m², and loop diuretics should be used if GFR &lt; 30 ml/min/1.73 m²</td>
</tr>
</tbody>
</table>

Table 16 continued on following page
Table 16 | Continued

<table>
<thead>
<tr>
<th>Year</th>
<th>Group</th>
<th>Target CKD population</th>
<th>Recommended BP goal (mm Hg)</th>
<th>Recommended preferred anti-hypertensive agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>The Renal Association (UK) CKD Guidelines&lt;sup&gt;SM&lt;/sup&gt; <a href="http://www.renal.org/Clinical/GuidelinesSection/Detection-Monitoring-and-Care-of-Patients-with-CKD.aspx">http://www.renal.org/Clinical/GuidelinesSection/Detection-Monitoring-and-Care-of-Patients-with-CKD.aspx</a> (accessed August 28, 2012)</td>
<td>CKD</td>
<td>For the majority, systolic BP: &lt; 140 mm Hg (target range 120-139 mm Hg), and diastolic BP: &lt; 90 mm Hg for the majority. For those with DM or proteinuria ≥ 1g/24h, systolic BP: &lt; 130 mm Hg (target range 120-129 mm Hg) and diastolic BP: &lt; 80 mm Hg unless the risks are considered to outweigh the potential benefits. Antihypertensive therapy should be individualized and lowering the systolic blood pressure to &lt; 120 mm Hg should be avoided</td>
<td>ACE-I or ARB</td>
</tr>
<tr>
<td>2012</td>
<td>Canadian Hypertension Education Program Recommendations <a href="http://www.hypertension.ca/chep-recommendations">http://www.hypertension.ca/chep-recommendations</a> (accessed August 20, 2012)</td>
<td>Non-DKD and DKD</td>
<td>CKD in general: &lt; 140/90 DKD: &lt; 130/80</td>
<td>Non-DKD: ACE-I or ARB (if ACE-I intolerant) as a first choice agent if urine ACR &gt; 30 mg/mmol (&gt; 300 mg/g) or urine protein &gt; 500 mg/24 h. DKD: For patients with persistent microalbuminuria (urine ACR &gt; 2 mg/mmol [&gt; 20 mg/g] in men and &gt; 2.8 mg/mmol [&gt; 28 mg/g] in women), ACE-I or ARB is recommended as initial therapy</td>
</tr>
<tr>
<td>2012</td>
<td>American Diabetes Association&lt;sup&gt;453&lt;/sup&gt; <a href="http://care.diabetesjournals.org/content/35/Supplement_1/S11.full.pdf">http://care.diabetesjournals.org/content/35/Supplement_1/S11.full.pdf</a> (accessed August 20, 2012)</td>
<td>DM with microalbuminuria or overt nephropathy</td>
<td>&lt; 130/80</td>
<td>ACE-I or ARB should be considered for patients with microalbuminuria or macroalbuminuria. If ACE-I or ARB is not tolerated, then diuretics, CCBs, and beta-blockers should be considered</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; DKD, diabetic kidney disease; DM, diabetes mellitus; GFR, glomerular filtration rate.

account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: ‘A’, ‘B’, ‘C’ or ‘D’ (Table 12).

**Assessment of the net health benefit across all important clinical outcomes.** The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 13). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

**Grading the strength of the recommendations.** The strength of a recommendation is graded as level 1 or level 2. Table 14 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Table 15 shows that the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments regarding the size of the net medical benefit, values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

**Ungraded statements.** This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

**Format for guideline recommendations.** Each chapter contains one or more specific 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. The recommendation statements and grades are followed by a brief background with relevant definitions of terms and then the rationale starting with a ‘chain of logic,’ which consists of declarative sentences summarizing the key points of the
Table 17 | The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Discussed in KDIGO Management of Blood Pressure in Chronic Kidney Disease Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview material</td>
<td>Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.</td>
<td>Abstract and Methods for Guideline Development.</td>
</tr>
<tr>
<td>2. Focus</td>
<td>Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventive, diagnostic or therapeutic interventions that were considered during development.</td>
<td>Management of blood pressure and the use of anti-hypertensive agents in adults and children with CKD ND, including those with kidney transplants.</td>
</tr>
<tr>
<td>3. Goal</td>
<td>Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.</td>
<td>This clinical practice guideline is intended to assist the practitioner caring for patients with non-dialysis CKD and hypertension to prevent deaths, CVD events, and progression to kidney failure while optimizing patients' quality of life.</td>
</tr>
<tr>
<td>4. User/setting</td>
<td>Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.</td>
<td>Providers: Nephrologists (adult and pediatric), Internists, and Pediatricians. Patients: Adults and children with CKD at risk for hypertension. Policy Makers: Those in related health fields.</td>
</tr>
<tr>
<td>5. Target population</td>
<td>Describe the patient population eligible for guideline recommendations and list any exclusion criteria.</td>
<td>Adults and children with CKD, not on dialysis; kidney transplant recipients.</td>
</tr>
<tr>
<td>6. Developer</td>
<td>Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.</td>
<td>Organization: KDIGO Names/credentials/potential conflicts of interest.</td>
</tr>
<tr>
<td>7. Funding source/sponsor</td>
<td>Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.</td>
<td>KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Bayer Schering Pharma, Belo Foundation, Bristol-Myers Squibb, Chugai Pharmaceutical, Coca-Cola Company, Dole Food Company, Fresenius Medical Care, Genzyme, Hoffmann-LaRoche, JC Penney, Kyowa Hakko Kirin, NATCO—The Organization for Transplant Professionals, NKF-Board of Directors, Novartis, Pharmacosmos, PUMC Pharmaceutical, Robert and Jane Cizik Foundation, Shire, Takeda Pharmaceutical, Transwestern Commercial Services, Vifor Pharma, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review.</td>
</tr>
<tr>
<td>8. Evidence collection</td>
<td>Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.</td>
<td>Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews on treatment with different anti-hypertensive agents or to different BP targets, we searched for RCTs in MEDLINE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria are outlined in the Methods for Guideline Development chapter. The search was updated through January 2011 and supplemented by articles identified by Work Group members through February 2012. We also searched for pertinent existing guidelines and systematic reviews.</td>
</tr>
<tr>
<td>9. Recommendation grading criteria</td>
<td>Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.</td>
<td>Quality of individual studies was graded in a three-tiered grading system (see Table 10). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 12 and 14). The Work Group could provide general guidance in ungraded statements.</td>
</tr>
<tr>
<td>10. Method for synthesizing evidence</td>
<td>Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.</td>
<td>For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.</td>
</tr>
<tr>
<td>11. Prerelease review</td>
<td>Describe how the guideline developer reviewed and/or tested the guidelines prior to release.</td>
<td>The guideline had undergone internal review at the 2010 KDIGO Board of Directors meeting and external public review in July 2011. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.</td>
</tr>
<tr>
<td>12. Update plan</td>
<td>State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.</td>
<td>There is no date set for updating. The need for updating of the guideline will depend on the publication of new evidence that would change the quality of the evidence or the estimates for the benefits and harms. Results from registered ongoing studies and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline.</td>
</tr>
</tbody>
</table>

Table 17 continued on following page
evidence base and the judgments supporting the recommendation. This is followed by a narrative in support of the rationale. In relevant sections, research recommendations suggest future research to resolve current uncertainties.

**Comparison with other guidelines**
We tabulated recommendations from other key English-language guidelines pertinent to the use of blood-pressure-lowering agents in individuals with CKD (Table 16). This served to inform topic selection and scope. Also, after recommendations had been drafted, the Work Group reviewed them in the context of the existing guideline recommendations to avoid unnecessary or unwarranted discrepancies.

**Limitations of approach**
Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

**Review of guideline development process**
Several tools and checklists have been developed to assess the quality of the methodological process for guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria, the Conference on Guideline Standardization (COGS) checklist, and the Institute of Medicine’s recent Standards for Systematic Reviews and Clinical Practice Guidelines We Can Trust.

Table 17 and Supplementary Appendix 2 online show, respectively, the COGS criteria and the Institute of Medicine standards, and how each one of them is addressed in this Guideline.

**SUPPLEMENTARY MATERIAL**
Supplementary Appendix 1. Online search strategies.
Supplementary Appendix 2. Concurrence with Institute of Medicine standards for systematic reviews and for guidelines.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php
Biographic and disclosure information


Gavin J Becker, MD, FRACP (Work Group Co-Chair), is Professor and Director of Nephrology at the Royal Melbourne Hospital and Clinical Director of Renal and Endocrinology Services at Melbourne Health. He maintains an active role in numerous professional societies including serving as a current member of the International Society of Nephrology (ISN) Executive Committee, Cochrane Renal Collaboration Advisory Board and Co-Chair of the World Health Organization ICD-11Renal Diseases Working Group. He is a Past President of the Asian Pacific Society of Nephrology. Dr Becker has published over 300 papers, chapters and books and presently serves as Associate Editor for Nephrology Dialysis Transplantation. He has served as Editor of Nephrology, Associate Editor or on the editorial boards of the Journal of the American Society of Nephrology, Clinical Journal of the American Society of Nephrology, American Journal of Kidney Diseases, Nephron, and Journal of Nephropathy. His research interests center on the progression of kidney failure, development of guidelines for renal care, promotion of renal physician education and the development of nephrology in the Asian Pacific region. In recognition for his work, he was awarded the International Distinguished Medal by the US National Kidney Foundation in 2002. He was also a recipient of an Honorary Fellowship of the Ceylon College of Physicians in 2003, the Oshima Award from the Asian Pacific Society of Nephrology in 2005 and Chairman's ‘Best of Health’ Award from Melbourne Health in 2002 and again in 2009.

Dr Becker reported no relevant financial relationships

David C Wheeler, MD, FRCPP (Work Group Co-Chair), holds an academic position in Nephrology (Reader) at University College London, UK and is an Honorary Consultant Nephrologist at the Royal Free Hospital. His research is focused on the cardiovascular complications of CKD and the role of vascular risk factors in progression of kidney damage. Dr Wheeler is a member of the International Steering Committee of the Study of Heart and Renal Protection (SHARP) and was UK National Coordinator for the trial. He is involved in several other randomized trials and observational studies involving patients with CKD.

Dr Wheeler is Co-Chair of KDIGO, having served previously on its Executive Committee and Board. He received an International Distinguished Medal from the US National Kidney Foundation in recognition of his contribution to guideline development. In the UK, he has been elected President of the Renal Association for the term 2012–2014.

Dr Wheeler has served on the editorial boards of American Journal of Kidney Diseases and Journal of the American Society of Nephrology and is presently Co-Editor for Nephrology Dialysis Transplantation.

Advisor/Consultant: Amgen

Honoraria: Abbott; Amgen; Fresenius; Otsuka; Shire

Travel Stipend: Amgen; Merck Sharp & Dohme; Shire

Grant/Research Support: Abbott; Genzyme

Dick de Zeeuw, MD, PhD, earned his MD from the University of Groningen in 1975. He completed his PhD thesis in 1980 on the topic of renal hypertension at the Renal Department of the Groningen University. He later obtained training in clinical and experimental renal research at the Renal Department in Groningen and clinical pharmacology at the University of Dallas (1984–1985) and was board certified in 1996 at the University of Groningen. Dr de Zeeuw is currently Professor and Chair of the Department of Clinical Pharmacology with a joint appointment in the Department of Nephrology. He has served on the editorial board of several international journals, including Clinical Nephrology, Current Opinion in Nephrology and Hypertension, Journal of Geriatric Urology and Nephrology, Journal of Hypertension, Journal of the Renin-Angiotensin-Aldosterone System, Kidney International, NDT Plus, and Nephron.

Dr de Zeeuw is Director of the Groningen University Institute for Drug Exploration (GUIDE), and member of ISN Council. His research interests include: optimizing current therapies and finding new therapeutic approaches to reduce the progressive loss of cardiovascular and renal function, both in diabetic and non-diabetic renal disease. The role of albuminuria/proteinuria and microalbuminuria as biomarkers for cardiac and renal disease progression has been his particular interest, not only in trying to establish the independent 'causal' role of albumin leakage in renal and CVD progression, but also to establish intervention strategies that lower albuminuria/proteinuria with the supposed organ protective results. In his ‘albuminuria’ quest he initiated large cohort studies such as PREVEND (in general population) and GIANTT (type 2 diabetes), and is involved in the leadership of several clinical trials on preventing diabetic cardiovascular and renal disease progression such as RENAAL (angiotensin II receptor antagonist), PLANET (statin), TREAT (darbepoetin), VITAL (vitamin D), SUN (sulodexide), ALTITUDE (renin-inhibition), CANVAS (SGLT2-inhibition), RADAR (atrasentan) and BEACON (bardoxolone).
Unraveling the reasons for individual therapy resistance and creating a response score to evaluate the total effect of drugs are the topics that he judges to be of important focus for the next decade. He has authored more than 440 international scientific publications and more than 60 book chapters, and received the Lennart Hansson Memorial Lecture Award from the European Society of Hypertension, the International Distinguished Medal from the US National Kidney Foundation, and a special lecture award from the Japanese Society of Nephrology.

Toshiro Fujita, MD, is Professor and Chairman of the Department of Internal Medicine and Chief of the Department of Nephrology and Endocrinology at the University of Tokyo. He qualified in medicine in 1972 at the Keio University School of Medicine, Japan and remained in Keio until 1976, during which time he completed his medical internship and residency. Between 1976 and 1978, he was a Research and Clinical Fellow at National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA. Upon his return to Japan, he was appointed Assistant Professor of Internal Medicine, firstly at the University of Tsukuba and later at the University of Tokyo School of Medicine. Since 1995, Professor Fujita has been Chairman of the Department of Internal Medicine at the Graduate School of Medicine and Faculty of Medicine, University of Tokyo, and is Chief of the Department of Nephrology and Endocrinology at the University of Tokyo Hospital.

In 1980, Fujita and Bartter at NIH demonstrated the pathophysiology of salt-sensitive hypertension (Am J Med 1980). Since then, he has been continuing research on renal and metabolic aspects of hypertension. His research interests include nephrology, endocrinology, metabolic science and cardioangiology. Dr Fujita's group has reported the involvement of aldosterone/mineralocorticoid receptor (MR) activation in salt-sensitive hypertension and metabolic syndrome. Recently, they found an alternative pathway of MR activation: modification of MR function by Rac1 GTPase (Nat Med 2008). Most recently, his group clarified the involvement of aberrant renal β adrenergic receptor-WNK4 pathway in salt-induced hypertension (Nat Med 2011).

A renowned expert in his field, Professor Fujita has been actively contributing to professional associations and scientific publications and his contribution to the study of hypertension and kidney diseases has been widely recognized. In 2009, Professor Fujita was awarded Arthur Carcoran Lecture Award by the Council for High Blood Pressure Research, American Heart Association (AHA). Over the past 30 years, Professor Fujita has published over 500 scientific articles and has been a member of the Committee of the High Blood Pressure Council, AHA. Professor Fujita is currently serving as a Consulting Editor for Hypertension and an Editorial Board member for Diabetes. He was Past President of the Japanese Society of Hypertension (2003–2005), the Japanese Society of Internal Medicine (2004–2006), the Japanese Society of Endocrinology (2006–2007), and the Japanese Society of Nephrology (2009–2010). He was also Vice-President, International Society of Hypertension (2008–2010).

Speaker: Astellas; Boehringer Ingelheim; Daiichi Sankyo; Merck; Mitsubishi Tanabe; Mochida; Novartis; Pfizer; Takeda
Grant/Research Support: Astellas; Boehringer Ingelheim; Daiichi Sankyo; Merck; Mitsubishi Tanabe; Mochida; Novartis; Pfizer; Takeda

Susan L Furth, MD, PhD, is Chief, Division of Pediatric Nephrology at Children’s Hospital of Philadelphia and Professor, Department of Pediatrics and Epidemiology, Perelman School of Medicine at University of Pennsylvania School of Medicine, where she is also currently a Senior Scholar and faculty member at the institution’s Center for Clinical Epidemiology and Biostatistics. Dr Furth received her medical degree from University of Pennsylvania and doctorate degree from Johns Hopkins University School of Hygiene and Public Health. She maintains a longstanding interest in the studies of children and adolescents with kidney disease, particularly their risk factors and consequences, including pediatric hypertension. As Principal Investigator of CKID, she directs a multidisciplinary team for one of the largest multicenter, prospective cohort studies of children with CKD to better identify risk factors for CKD progression, neurocognitive deficits and CVD. Dr Furth is also a recipient of an National Institute of Diabetes and Digestive and Kidney Diseases Investigator Award in Clinical Research to mentor fellows and junior faculty on the evaluation of hypertension and risk of kidney dysfunction using national pediatric data.

In addition to being a peer reviewer for 20 academic journals, Dr Furth has authored over 100 publications and served as a thesis advisor to more than 30 students. As an acknowledgment for her contribution, Dr Furth was awarded ‘Pediatric Leaders for the 21st Century’ by the American Society of Pediatric Nephrology and American Academy of Pediatrics and is currently President of the Society for Pediatric Research.

Dr Furth reported no relevant financial relationships

Hallvard Holdaas, MD, PhD, is senior consultant in Nephrology at Department of Transplant Medicine, Oslo University Hospital, Rikshospitalet, Norway, where he also received his training in transplant medicine. His primary research interests are immunosuppression, dyslipidemia, and CVD in renal transplant recipients. He was the principal investigator in the ALERT trial (fluvastatin) and co-investigator in the AURORA and SHARP trials.

Dr Holdaas is a member of numerous professional organizations including American Society of Nephrology, American Society of Transplantation, European Dialysis and
Transplant Association and European Society for Organ Transplantation. He has published more than 170 original articles, reviews and book chapters in the fields of nephrology, dialysis and transplantation.

Advisor/Consultant: Merck (Schering Plough); Novartis
Speaker: AstraZeneca; Bristol-Myers Squibb; Novartis

Shanthi Mendis, MBBS, MD, FRCP, FACC, is Senior Advisor for Cardiovascular Diseases and Coordinator, Chronic Disease Prevention and Management at the World Health Organization (WHO) in Geneva, Switzerland. Prior to taking up the position in WHO, she was Professor of Medicine at Peradeniya Medical School in Sri Lanka from 1991–2000. As a specialist in cardiology and public health with expertise in policy development, she has written extensively on the prevention and management of CVD in a global context. In particular, she has advocated for the development of national policies and strategies to combat non-communicable diseases which strike disproportionately in low- and middle-income countries.

Dr Mendis reported no relevant financial relationships

Suzanne Oparil, MD, is Professor of Medicine, Professor of Cell, Developmental and Integrative Biology, and Physiology & Biophysics, and Director of the Vascular Biology and Hypertension Program of the Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham. She earned her medical degree at Columbia University College of Physicians and Surgeons, New York and completed her medical residency at Columbia Presbyterian Hospital and cardiology fellowship at Massachusetts General Hospital. Dr Oparil is Past President of the American Heart Association (AHA) and American Society of Hypertension, and a member of numerous editorial boards, societies and important advisory positions with the NIH (Co-Chair, JNC 8). She has published over 700 journal articles, books, and book chapters on topics in clinical cardiology, vascular biology and hypertension. Dr Oparil has received a number of honorary memberships, lectureships, and distinguished awards for her contributions to hypertension research, including the Irving Page-Alva Bradley Lifetime Achievement Award, given by the AHA Council for High Blood Pressure Research (2002); the 2008 Harriet Dustan Award, sponsored by the AHA Council for High Blood Pressure Research; the Virginia Frantz ‘22 Award for Distinguished Women in Medicine (2010) presented by Columbia University College of Physicians and Surgeons; and the ICS Distinguished Lecture Award (2011), sponsored by the Institute of Cardiovascular Sciences.

Dr Oparil is a cardiologist with a special interest in the fundamental mechanisms of CVD and in applying this information to the development of novel treatments. Her research ranges from molecular and cellular studies to whole animal studies to clinical trials. She has made a number of innovative discoveries with major clinical impact: 1) observing that angiotensin-converting enzyme (ACE) is involved in vascular disease, leading to the development of ACE-Is; 2) identifying endothelin as the major mediator of pulmonary hypertension and pulmonary vascular disease, leading to the development of a class of drugs for patients with pulmonary hypertension; and 3) defining novel pathways by which blood vessels are protected from injury by estrogens, providing crucial information on potential targets for future gene therapy. She has made many significant contributions to vascular biology and hypertension research.

Advisor/Consultant: BackBeat Medical; Bayer; Boehringer Ingelheim; Daiichi Sankyo; Eli Lilly; Forest Laboratories; Medtronic; Merck; NicOx; Novartis; Omron Healthcare; Pfizer
Grant/Research Support: Daiichi Sankyo; Merck; Novartis; Takeda

Vlado Perkovic, MBBS, FRACP, FASN, PhD, is Executive Director, George Clinical at The George Institute for International Health and Staff Specialist in Nephrology and Hypertension at the Royal North Shore and Sydney Adventist Hospitals. Dr Perkovic received his medical and doctorate degrees from University of Melbourne and completed his training in nephrology and general medicine at the Royal Melbourne Hospital. His research interests include elucidating the roles of BP and lipid management and their impact on CVD in CKD patients. In this vein, Dr Perkovic is a committee member of the ALTITUDE and SHARP trials and an organizer of the Cardiovascular Guideline Group for Caring for Australasians with Renal Impairment (CARI). As an author of over 75 publications, Dr Perkovic also serves as a peer reviewer to numerous journals and a grant reviewer for the National Health and Medical Research Council.

Advisor/Consultant: Abbott; Baxter; Boehringer Ingelheim; Johnson & Johnson; Vitae
Honoraria: AstraZeneca; Roche; Servier
Grant/Research Support: Baxter; Johnson & Johnson

Cibele Isaac Saad Rodrigues, MD, PhD, is a full Professor of Nephrology at the Faculdade de Ciências Médicas e da Saúde – Pontifícia Universidade Católica de São Paulo – (PUC-SP), Brazil where she also graduated and completed her Residency in Internal Medicine and Nephrology. She obtained her master’s and doctorate degrees in Nephrology at the Federal University of São Paulo, Brazil. Currently she is the academic coordinator of Santa Lucinda Hospital in Sorocaba–São Paulo, coordinator of the Hypertension Department of the Brazilian Society of Nephrology, and member of the Scientific Council of the Brazilian Society of Hypertension. From 2001 to 2009 she was the dean of the Centro de Ciências Médicas e Biológicas (PUC-SP) and President of the Administration Council of Santa Lucinda Hospital. Her primary research
interests are hypertension, diabetic nephropathy and CKD. Professor Rodrigues has published more than 40 journal articles and contributed 15 book chapters in the field of nephrology and hypertension. She is a member of numerous professional organizations in Brazil and abroad, and has served as peer reviewer for many scientific journals and an advisory committee member to various organizations.

Dr Rodrigues reported no relevant financial relationships

Mark J Sarnak, MD, MS, is Professor of Medicine at Tufts University School of Medicine in Boston, Massachusetts, USA and Director of Research in the Division of Nephrology at Tufts Medical Center. He obtained his medical degree from Columbia University College of Physicians and Surgeons and master’s degree in clinical care research from Tufts University of Medicine. His current research encompasses various topics including the role of aging in CKD, the relationship between cognition and CKD, and CVD in CKD. He has lectured extensively on the epidemiology and management of traditional and non-traditional cardiovascular risk factors in CKD. Dr Sarnak has authored more than 175 publications and is a peer reviewer for more than a dozen journals. He was Co-Editor for American Journal of Kidney Disease between 2006–2007 and presently serves on the Editorial Board of the Annals of Internal Medicine. Among the recent honors he has received include Best Teacher Award for the Medical Residents in 2008, Excellence in Teaching in the Medical Clerkship in 2009, and an acknowledgment in Boston Magazine Best Doctors in both 2010 and 2011.

Dr Sarnak reported no relevant financial relationships

Guntram Schernthaner, MD, became Professor of Medicine at the University of Vienna, Austria in 1987. Since 1988 he has been Head of the Department of Medicine I at the Rudolfstiftung Hospital in Vienna and between 1982 and 1988 he served as Head of the Division of Metabolism & Endocrinology at the University of Vienna. Professor Schernthaner’s main research interests are diabetes mellitus (including diabetic nephropathy, diabetic retinopathy, insulin resistance, CVD, hemostasis, immunotherapy of type 1 diabetes, gestational diabetes), hypertension and morbid obesity.

Professor Schernthaner has held various prestigious positions, including serving as Council Member and Vice-President of the European Society for Clinical Investigation; President of the Austrian Diabetes Association; President of the first Joint Congress of the German and Austrian Diabetes Associations; Council Member of the European Diabetes Association; and President of the 32nd European Diabetes Congress (EASD, Vienna 1996).

Professor Schernthaner has authored more than 350 publications in peer-reviewed journals and has presented invited lectures at many international congresses, symposia and universities in more than 50 countries. According to the Citation Index of Web of Science his papers were cited 8300 times, with a Hirsch index of 43. He was also the principal investigator of more than 40 studies (e.g., Canadian-Cyclosporin Trial; Diapep277 Study; IDNT; IRMA 2; QUARTET; PROactive; GUIDE; ORIGIN; LEAD-6; DIRECT; EUREXA; DURATION; GENERATION). Professor Schernthaner was awarded the Bertram Award of the German Diabetes Association in 1982 and the Albert Renold Medal of the European Association for the Study of Diabetes in 1997. He is currently the Liaison Editor for Diabetology for Nephrology Dialysis Transplantation.

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Charles R V Tomson, DM, FRCP, completed his undergraduate studies at Cambridge University and attended medical school at University of Oxford. Dr Tomson has worked as a Consultant Nephrologist at Southmead Hospital since April 1991. Between 1997 and 2004 he was course director for the Renal Association’s Advanced Nephrology Course, and between 1998 and 2002 he was Secretary of the Renal Association’s Audit and Standards Subcommittee, developing the 3rd edition of the Association’s Standards document. In 2001 he set up and chaired the group that developed the first UK guidelines on identification, management and referral of patients with CKD. In 2004–5 he was a Health Foundation Quality Improvement Fellow at the Institute for Healthcare Improvement in Boston, USA. From 2006–2010 he was Chairman of the UK Renal Registry, which measures and reports on the quality of care achieved by all renal centers in the UK. He became President of the Renal Association in May 2010.

Dr Tomson reported no relevant financial relationships

Carmine Zoccali, MD, is Director of the Division of Nephrology, Hypertension and Renal Transplantation and Chief of the Clinical Epidemiology of Renal Diseases and Hypertension Unit of the National Research Council-IBIM at Riuniti Hospital, Calabria. He is Professor of Nephrology at the Postgraduate School of Nephrology, Universities of Palermo and Messina, Sicily, Italy. Having trained in medicine at the University of Rome, he completed specialist training in renal diseases, hypertension, internal medicine and clinical epidemiology.

Dr Zoccali’s research interests cover hypertension, cardiovascular complications in chronic renal failure, kidney disease progression and the epidemiology of chronic renal failure. He has contributed over 600 publications in these areas, including more than 400 papers in international peer-reviewed journals with a Hirsch index of 52.

Dr Zoccali founded NDT-Educational in 2004 and directed its online educational resources between 2004–2009, and he is presently the Editor-in-Chief of Nephrology Dialysis Transplantation. Dr Zoccali also holds editorial positions in several national and international nephrology journals including Clinical Nephrology, Clinical
Dr Zoccali reported no relevant financial relationships

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Bertram L. Kasiske, MD, is Professor of Medicine at the University of Minnesota, USA. He received his medical degree from the University of Iowa and completed his Internal Medicine residency and fellowship training in Nephrology at Hennepin County Medical Center where he is currently Director of Nephrology.

Dr Kasiske is former Deputy Director of the United States Renal Data System and former Editor-in-Chief of American Journal of Kidney Diseases. He has served as Secretary/Treasurer and on the Board of Directors of the American Society of Transplantation, and on the Organ Procurement and Transplantation Network/United Network of Organ Sharing Board of Directors, and the Scientific Advisory Board of the US National Kidney Foundation. He is currently serving on the Board of Councilors of the International Society of Nephrology. He is the Principal Investigator for a National Institutes of Health-sponsored, multi-center study of long term outcomes after kidney donation and he is the Director of the Scientific Registry of Transplant Recipients. He has over 160 scientific publications in major peer reviewed journals, and 230 review articles, editorials and textbook chapters. Dr Kasiske is also a recipient of the US National Kidney Foundation’s Garabed Eknoyan Award in 2003.

Advisor/Consultant: Litholink

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Katrin Uhlig, MD, MS, is the Director, Guideline Development at the Tufts Center for Kidney Disease Guideline Development and Implementation, Boston, MA, Associate Professor of Medicine at Tufts University School of Medicine, and a staff nephrologist at Tufts Medical Center. Dr Uhlig completed her training in internal medicine, nephrology, and rheumatology in Germany (Aachen University Hospital and Munich University Hospital) and the USA (Georgetown University Medical Center and Tufts Medical Center). Since 2001, she has been participating in or directing the evidence review for KDOQI and KDIGO guidelines. As Director of Guideline Development, Dr Uhlig has a substantial role in coordinating the ERT. She orchestrates and supervises the guideline development process and didactic curriculum that provides Work Group members with formal instruction on topics related to guideline development. As project director on individual guidelines, she directs and supervises the collection, evaluation, grading, and synthesis of evidence and the drafting and revisions of the final evidence report. She provides methodological guidance and training to Work Group members at meetings regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. She provides nephrology expertise in the interpretation and review of guideline recommendations and evidence reports. In this capacity, Dr Uhlig possesses unique knowledge as a methods expert in evidence synthesis and critical literature appraisal in the domain of nephrology.

In 2005, she co-chaired the KDIGO Evidence Rating Group to develop a consensus on grading of KDIGO guidelines and also co-chaired the KDIGO Consensus Conference on Guideline Methodology in October 2007. From 2006 to 2007, she served as Co-Editor of American Journal of Kidney Diseases. Her teaching and research focus includes evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal. Dr Uhlig lectures on guideline topics and is a co-instructor of an annual course on meta-analysis in the Master of Science Program at the Sackler School of Graduate Biomedical Sciences at Tufts University.

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Ashish Upadhyay, MD, is Assistant Professor, Renal Section and Associate Director, Internal Medicine Residency Program at Boston University School of Medicine, Boston, MA, USA. Dr Upadhyay was previously Assistant Professor at Tufts University School of Medicine and staff physician in the William B Schwartz, MD, Division of Nephrology at Tufts Medical Center. He joined the ERT in July 2009 and served as the Assistant Project Director for the KDIGO Management of Blood Pressure in CKD and Anemia in CKD Guidelines. Dr Upadhyay coordinated and assisted in the collection, evaluation, grading, and synthesis of evidence, and played a critical role in the revisions of the final evidence report. He also provided methodological guidance and training of Work Group members on topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. Dr Upadhyay’s past research involved studying kidney disease epidemiology in the Framingham Heart Study. He has published in areas ranging from arterial stiffness in CKD and inflammation in kidney disease to dialysis complications and epidemiology of hyponatremia.

Dr Upadhyay reported no relevant financial relationships
Amy Earley, BS, is a project coordinator at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She is key in coordinating the guideline development activities within the ERT, especially in the development of the evidence reports for all guidelines. Ms Earley also heads the actual evidence review, which includes running searches, screening, data extraction, drafting of tables and methods sections, proofing of guideline drafts and critical literature appraisals. She participates in the conduct of research projects at the Center and actively collaborates with other members of the Center on independent research topics and manuscript submissions.

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Shana Haynes, MS, DHSc, is a research assistant at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development. She screens abstracts and articles, extracts data, and assists in the drafting and editing of evidence tables. Dr Haynes also assists in the development of clinical practice guidelines and conducts systematic reviews and critical literature appraisals.

Dr Haynes reported no relevant financial relationships

Jenny Lamont, MS, is a project manager and medical writer at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development, assists in the preparation of talks and manuscripts, and edits KDIGO draft guidelines currently in progress.

Ms Lamont reported no relevant financial relationships
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Participation in the review does not necessarily constitute endorsement of the content of this report by the above individuals, or the organization or institution they represent.
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