Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease?

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The Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for management of blood pressure (BP) in chronic kidney disease (CKD) supersedes the 2004 Kidney Disease Quality Outcomes Initiative document on this topic. The new guideline has been designed to assist clinical decision making in patients with CKD who are not receiving dialysis. The recommendations in the guideline acknowledge that no single BP target is optimal for all CKD patients and encourage individualization of treatment depending on age, the severity of albuminuria, and comorbidities. In general, the available evidence indicates that in CKD patients without albuminuria the target BP should be $\leqslant$140 mm Hg systolic and $\leqslant$90 mm Hg diastolic. However, in most patients with an albumin excretion rate of $\geqslant$30 mg/24 h (i.e., those with both micro- and macroalbuminuria), a lower target of $\leqslant$130 mm Hg systolic and $\leqslant$80 mm Hg diastolic is suggested. In achieving BP control, the value of lifestyle changes and the need for multiple pharmacological agents is acknowledged. Use of agents that block the renin–angiotensin–aldosterone system is recommended or suggested in all patients with an albumin excretion rate of $\geqslant$30 mg/24 h. Recommendations are almost identical in CKD patients with and without diabetes. Special considerations relevant to children and those of older age and those who have received a kidney transplant are included. Ongoing controversies in BP management in the context of CKD are highlighted along with key areas for future research.

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BACKGROUND

Most nephrologists believe that lowering blood pressure (BP) is worthwhile in patients with chronic kidney disease (CKD), both to slow the progressive decline in kidney function and to reduce the risk of cardiovascular complications. Less clear is the optimal BP target, the best method of achieving this target, and the true benefits (and risks) of doing so. The new *Kidney Disease: Improving Global Outcomes* (*KDIGO*) *Clinical Practice Guideline for Management of Blood Pressure in Chronic Kidney Disease*, published as a *Kidney International* Supplement,[1] addresses these issues. A literature search commissioned for the guideline updated the evidence review conducted for the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline published by the National Kidney Foundation in 2004.[2] Using strict criteria for selecting appropriate randomized controlled trials, 55 studies relevant to BP management in CKD patients were identified, most of which compared different BP-lowering agents, rather than treatment to different targets. Furthermore, most studies examined change in kidney function or albuminuria rather than the development of end-stage kidney failure or cardiovascular outcomes. An additional 14 studies that did not primarily recruit individuals with CKD but that reported results by CKD subgroups were reviewed.

The new KDIGO guideline (here called the 'KDIGO BP Guideline') is aimed at patients with CKD and healthcare professionals responsible for their care. It is focused on the management rather than assessment of BP, unlike the previous KDOQI document that covered both topics. The term 'hypertension' is avoided because it implies a threshold value above which BP readings are associated with an increased risk of adverse outcomes. In common with other KDIGO guidelines, the recommendations (Appendix 1) are graded using the GRADE system,[3] which separately rates the strength of the recommendation and the quality of the evidence upon which it is based. The Work Group could also issue ungraded recommendations to provide guidance based on common sense and in areas where formal evidence review was not conducted. Gaps in the evidence are identified, controversies are highlighted, and specific recommendations

for future research are included. By interpreting the growing evidence base in this particular area and providing recommendations for treatment, KDIGO seeks to assist clinical decision making, and in so doing to benefit CKD patients around the world, including those managed in less well-developed healthcare systems.

HOW WAS THE GUIDELINE DEVELOPED?

The methods of KDIGO guideline development have been described in detail elsewhere.[4] This new KDIGO BP Guideline was developed by an international Work Group comprising individuals with a broad range of expertize including representatives of other guideline groups (Joint National Committee, International Society of Hypertension) in liaison with a member of the World Health Organization. The group included individuals with expertize in pediatrics, diabetes, and kidney transplantation. The group worked closely with an evidence review team with expertize in nephrology and in systematic review methods, meeting in person three times. Before the first meeting, the Work Group chairs commissioned the evidence report with rigorous prespecified criteria to enrich the evidence base with clinical outcome studies. Thus, to be included in the evidence review, trials need to include at least 50 patients in each arm, and these individuals needed to be followed up for at least 3 months for changes in urinary albumin excretion, or for 1 year for changes in kidney function or for clinical outcomes. The exception was trials of lifestyle modification, which needed to be of 6 weeks duration and could include BP changes as an endpoint. The draft guideline document was presented to the KDIGO Board in December 2010, and further changes were made at the request of Board members. The guideline subsequently went out for public review. A total of 198 responses were received from a total of 829 invitations, yielding a return rate of 24%, which compares favorably to the public response to the review of previous KDIGO guidelines. In addition to providing comment, respondents were asked to assess whether the recommendations were acceptable or not. None of the recommendations received an approval rating lower than 93%. Further modifications to the recommendations and accompanying text were made in response to the public review process and new data were incorporated.

WHAT ARE THE HEADLINES IN THE NEW KDIGO GUIDELINE?

Many of the recommendations contained in the older KDOQI Clinical Practice Guideline have been updated by the KDIGO Work Group, based on the newer data that are now available. For example, little evidence was found to support the KDOQI recommendation that a target BP of $\leqslant$130/80 mm Hg is more beneficial than $\leqslant$140/90 mm Hg in CKD patients without abnormally elevated urinary albumin excretion. The evidence supporting the newly recommended target of $\leqslant$140/90 mm Hg is outlined in a meta-analysis of three trials including 2272 patients, which has already been published by the evidence review team.[5] However, lower-quality evidence from subgroups of these trials suggests that a lower target of $\leqslant$130/80 mm Hg may be beneficial for patients with proteinuria greater than 30 mg/day. It was recognized that 24-h urinary samples are not always available when assessing patients. To provide the healthcare professional with practical assistance, a table from the forthcoming KDIGO guideline on classification and management of CKD[6] is provided (Table 1). This suggests equivalent cutoffs for albuminuria or proteinuria when assessed using 'spot' samples or dipstick analysis.

The use of albuminuria to stratify target BP introduces the concept of individualized therapy, a recurrent theme in the new KDIGO BP Guideline. The available evidence reviewed by the Work Group supports individualization of treatment based not only on urinary albumin excretion but also on age and the presence or absence of cardiovascular comorbidities, for example, heart failure. Although the Work Group considered stratifying recommendations according to the stage of CKD, the evidence review team was unable to find data to support this approach.

The concept of individualization is also applied to the choice of therapeutic agents used to control BP to the appropriate target level. There are a wide range of therapeutic options, not all of which are appropriate in certain patients. The Work Group recognized the importance of lifestyle modifications, particularly maintaining a healthy weight, restricting dietary salt intake, taking regular exercise,

Table 1 | Relationship among categories for albuminuria and proteinuria[a]

Measure	Categories: Normal to mildly increased	Moderately increased	Severely increased
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Abbreviations: ACR, albumin/creatinine ratio; AER, albumin excretion rate; PCR, protein/creatinine ratio; PER, protein excretion rate.
Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact.
The relationships between AER and ACR, and between PER and PCR are based on the assumption that average creatinine excretion rate is ~1.0 g/24 h or 10 mmol/24 h. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship among these categories is approximate only. ACR<10 mg/g is considered normal; ACR 10–29 mg/g is considered 'high normal.'
The relationship between urine reagent strip results and other measures depends on urine concentration.
[a]Tentatively adopted by the KDIGO CKD Work Group.

cessation of smoking, and moderating alcohol consumption. Although no trials to date have proved that these lifestyle changes improve clinical outcomes in CKD patients, there were several studies indicating useful reductions in BP.

Most CKD patients will need pharmacological therapy and the use of multiple therapeutic agents to achieve target BP. In terms of BP lowering, the guideline concludes that all classes of agents (including diuretics) are effective in the context of CKD, providing a wide choice for the healthcare professional. With respect to clinical outcomes, with the exception of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), there was no strong evidence to support the use of any particular agent. As in the previous KDOQI guideline, the new KDIGO document recommends the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as the preferred agent in patients with urinary albumin excretion $\geqslant$30 mg/day, a slightly lower threshold than previously recommended by KDOQI (the cutoff was a protein-to-creatinine ratio of $\geqslant$200 mg/g equivalent to an albumin excretion rate of $\geqslant$40 mg/day). This recommendation applies to patients with and without diabetes and is based largely on studies examining the progressive loss of kidney function rather than cardiovascular complications (Table 2). No other recommendations about the use of any specific drug class could be made, owing to the lack of suitably robust evidence.

DOES THE PRESENCE OF DIABETES CHANGE THE RECOMMENDATIONS?

The simple answer is 'no'. The Work Group acknowledged that many CKD patients with a diagnosis of diabetes do not undergo kidney biopsy, and that if they did changes other than those associated with diabetes would often be reported by the pathologist. Predicting that the available evidence might lead to different recommendations in patients with CKD with diabetes as compared with those with CKD without diabetes, the Work Group separately summarized the evidence and drafted the recommendation for these two groups of patients. As it turned out, the recommendations for both these groups did not substantially differ in content, with just minor differences in evidence rating (see Recommendation 3.3 and 4.3). Thus, although the recommendations for CKD patients with and without diabetes appear in separate chapters in the KDIGO BP Guideline, the presence of diabetes does not change the management of BP in patients with CKD.

Table 2 | Summary of recommendations for management of blood pressure in adult CKD patients with and without diabetes

Albuminuria (mg/day)[a]	BP Target mm Hg	Preferred agent
$<$30	$\leqslant$140/90 mm Hg	None
30–300	$\leqslant$130/80 mm Hg	ACE-I or ARB
$>$300	$\leqslant$130/80 mm Hg	ACE-I or ARB

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease.
[a]Approximate equivalents for albumin excretion rate per 24 h—expressed as protein excretion rate per 24 h, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1.

HOW SHOULD BLOOD PRESSURE BE MANAGED IN KIDNEY TRANSPLANT RECIPIENTS?

Evidence for the management of BP after kidney transplantation is limited. The few trials that have been conducted have tended to study interventions during the first year post transplantation and have been of short duration. Most of these trials did not fulfill the prespecified criteria for inclusion in the evidence review. On balance, the Work Group felt that the target BP in these patients should be $\leqslant$130/80 mm Hg regardless of other factors, in keeping with the recommendation published in another KDIGO guideline focussed on care of the transplant recipient.[7] With respect to individualizing therapy, the Work Group recognized that time after transplantation, the use of calcineurin inhibitors, the presence of albuminuria, and other comorbidities may influence the choice of the BP-lowering agent, but were unable to be any more precise on this issue owing to the lack of robust clinical trials assessing relevant clinical endpoints.

HOW SHOULD BLOOD PRESSURE BE MANAGED IN CHILDREN?

BP measurements in children (defined as individuals $\leqslant$18 years of age) are usually corrected for age, gender, and height, and this needed to be reflected in the recommendations. The Work Group felt that a separate set of recommendations was required for children. Extrapolating from one large study in children, which assessed changes in 24-h mean arterial pressure measured by an ambulatory method, the guideline recommends starting treatment in children when BP is consistently above the 90th percentile for age, gender, and height, and treating to achieve systolic and diastolic readings that are less than or equal to the 50th percentile for age, gender, and height.

HOW SHOULD BLOOD PRESSURE BE MANAGED IN THE ELDERLY?

The Work Group considered that there were also important issues relevant to BP management at the other end of the age spectrum. For example, as arteries stiffen with age, pulse pressure widens, meaning that target systolic, and diastolic BP derived from studies in younger cohorts may not be relevant. Thus, the elderly, defined as $\geqslant$65 years of age, are covered in a separate chapter in the guideline. The available evidence did not allow specific recommendations to be made with respect to BP management, but the Work Group provides an ungraded statement reflecting the increased hazards of trying to achieve target BP in these patients and the importance of individualizing treatment accordingly.

WHY ARE THERE NO RECOMMENDATIONS FOR BLOOD PRESSURE MANAGEMENT IN CKD PATIENTS RECEIVING HEMODIALYSIS?

The KDIGO policy has been to ensure that sufficient evidence is available before embarking on the development of a

particular Clinical Practice Guideline.[4] Lack of evidence inevitably leads to 'opinion-based' suggestions that reflect the consensus view of the Work Group. It could be argued that providing healthcare professionals with some guidance based on the views of 'experts' is helpful and better than providing no guidance at all. However, expert opinion without sufficient supporting evidence may be subsequently proven to be wrong, and development of such 'opinion-based' guidance can impair the development of clinical trials designed to properly address the relevant question.

Before the development of the BP Guideline, KDIGO organized a consensus conference on the topic of BP management in CKD 5 patients receiving dialysis, held in New York in March 2009. The conference report concluded that there was uncertainty about how to measure BP in hemodialysis patients, a poor understanding of the association between BP and risk of adverse outcomes, and a complex interplay of factors influencing both systolic and diastolic pressure.[8] As a result, the KDIGO executive decided that it was premature to make recommendations regarding BP management in CKD Stage 5D patients.

WHAT ARE THE MAJOR ONGOING CONTROVERSIES IN BLOOD PRESSURE MANAGEMENT IN CKD?

Although most of the recommendations in the KDIGO BP Guideline are based on reasonably strong evidence, there were many questions that arose during discussion that could not be answered on the basis of the available data. In an effort to influence the future research agenda, specifically the design of randomized controlled trials, the Work Group has provided a list of research priorities at the end of each of the major chapters.

Many of these 'evidence gaps' proved to be controversial, and the Work Group decided to highlight these in a separate chapter (Chapter 8). Some of these controversies (Table 3) cover surprisingly basic issues such as how best to measure BP in CKD patients and whether measurements other than those taken in the office or clinic are useful. There was discussion as to the role of ambulatory BP monitoring and the alternative methods of assessing the health of the arterial system (e.g., by assessment of arterial stiffness). However, as these methods had not been studied in the context of large clinical studies involving CKD patients, no recommendations could be made.

Table 3 | Controversies in the management of blood pressure in CKD patients not receiving dialysis

What is the best method for measuring blood pressure in CKD patients?
Is there an evidence-based lower limit for BP reduction?
Should reduction in albuminuria be a target for treatment with agents that modify BP?
Should renin–angiotensin–aldosterone inhibition be maximized in CKD patients?
Should ACE-Is and ARBs be discontinued in CKD Stage 5 because they compromise residual kidney function?
Should ethnicity or other genetic factors influence the approach to BP management?
What are the barriers to the implementation of BP guidelines at a global level?

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease.

Although the Work Group set an upper target for BP control, there proved to be insufficient evidence to provide a generic lower target value below which further lowering of BP is inappropriate. However, the problem of overtreatment was recognized and is highlighted throughout the guideline. The Work Group decided to include a nongraded recommendation (Recommendation 2.2) reminding healthcare professionals to inquire about postural symptoms when assessing patients receiving BP-lowering medications. This issue is emphasized in Chapter 7 that covers the management of the elderly, who are particularly prone to postural symptoms and more often injured as a consequence.

The controversies most hotly debated by the Work Group were related to the use of agents that block the renin–angiotensin–aldosterone system. Some members of the group strongly believed that a reduction in albuminuria should be a target of treatment with these agents, regardless of BP. The arguments for this approach have been rehearsed elsewhere[9] and were only briefly summarized in the guideline. The available studies did not qualify for the evidence review process, and no recommendations were possible on this topic.

Also relevant to the management of albuminuria (as well as BP) was the view that renin–angiotensin–aldosterone system blockade should be maximized using multiple agents that target different steps in this pathway. Although early small trials in this area were promising, more recent larger studies, which have included CKD patients, have dampened enthusiasm for such a strategy. One of these trials would have fulfilled the criteria for evidence review, but was not published at the time the guideline went to press, and even if it had been it would not have changed the recommendations.[10]

As covered in the guideline, the healthcare professional needs to be aware that lowering blood pressure may lead to elevations in serum creatinine. This may be particularly obvious when using angiotensin-converting enzyme inhibitor and angiotensin receptor blockers, which reduce estimated glomerular filtration rate (eGFR) as a direct result of their mechanism of action. There are anecdotal reports suggesting that withdrawal of these agents in CKD 4–5 leads to an 'improvement' in eGFR and protects residual kidney function, delaying the need for renal replacement therapy. Contrary clinical data that do not support this approach exist, and robust studies validating hard clinical endpoints are required before any recommendations can be made.

HOW SHOULD THIS GUIDELINE BE USED?

The KDIGO BP Guideline is designed to support patient and healthcare professionals' decisions related to the management of BP in nondialysis dependent CKD patients of any stage (CKD ND). As with all guidelines, the healthcare professional is still required to use clinical judgement when managing an

individual patient, using the recommendations from the guideline to support decision making. The healthcare professional will thus need to decide when to apply the recommendations in a given clinical situation or when an alternative approach is more appropriate. Such individualization of care is encouraged in the recommendations, particularly in elderly individuals. Examples of how the guideline might be used in individual patients are given in Appendix 2.

Implementation of a clinical guideline on a global scale is inevitably challenging and falls within the remit of the KDIGO Implementatation Task Force. Previous KDIGO guidelines have been generally well received by the nephrology community as indicated by the numerous commentaries that have been published and the number of translations into different languages (available at www.kdigo.org). KDIGO is keen to engage nephrology societies around the world in the dissemination of the guideline in an effort to maximize patient benefit.

DISCLOSURE

DCW reported receiving consultancy fees from Amgen, honoraria from Abbott, Amgen, Fresenius, Otsuka and Shire; travel stipends from Amgen, Merck Sharp and Dohme and Shire; and grant/research support from Abbott and Genzyme. GJB reported no relevant financial relationships.

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APPENDIX 1
SUMMARY OF RECOMMENDATION STATEMENTS

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, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, the 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 20–25). *(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 min, five 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 nondiabetic adults with CKD ND and urine albumin excretion <30 mg per 24 h (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 $\leqslant 140$ mm Hg systolic and $\leqslant 90$ mm Hg diastolic. *(1B)*.

3.2: We suggest that nondiabetic adults with CKD ND and urine albumin excretion of 30–300 mg per 24 h (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 $\leqslant 130$ mm Hg systolic and $\leqslant 80$ mm Hg diastolic. *(2D)*.

3.3: We suggest that nondiabetic adults with CKD ND and urine albumin excretion >300 mg per 24 h (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 $\leqslant 130$ mm Hg systolic and $\leqslant 80$ mm Hg diastolic. *(2C)*.

3.4: We suggest that an ARB or ACE-I be used in nondiabetic adults with CKD ND and urine albumin excretion of 30–300 mg per 24 h (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 nondiabetic adults with CKD ND and urine albumin excretion >300 mg per 24 h (or equivalent*) in whom treatment with BP-lowering drugs is indicated. *(1B)*.

*Approximate equivalents for albumin excretion rate per 24 h—expressed as protein excretion rate per 24 h, 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 h (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 $\leqslant 140$ mm Hg systolic and $\leqslant 90$ mm Hg diastolic. *(1B)*.

4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 h (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 $\leqslant 130$ mm Hg systolic and $\leqslant 80$ 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 30–300 mg per 24 h (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 h (or equivalent*). *(1B)*.

*Approximate equivalents for albumin excretion rate per 24 h—expressed as protein excretion rate per 24 h, 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 $\leqslant 130$ mm Hg systolic and $\leqslant 80$ 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, the use of calcineurin inhibitors, the presence or absence of persistent albuminuria, and other comorbid 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 be 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 be 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, comorbidities, 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)*.

APPENDIX 2

Example of the application of the KDIGO guideline for management of blood pressure in CKD

Case 1

A 67-year-old male patient with Type II diabetes (requiring insulin treatment) and Stage 4 CKD (eGFR 22 ml/min/1.73 m^2) is reviewed in clinic. His BP is measured using an automated sphygmomanometer on two occasions 1 min apart after he has been seated for 5 min in accordance with local practice. The BP readings obtained are 145/85 and 142/87 mm Hg. On further examination, his weight is 96 kg and he has a body mass index of 33 kg/m^2. He has no ankle edema. Dipstick analysis of his urine reveals protein, and the result of a spot urine available later that day demonstrates a urinary to creatinine ratio of 105 mg/g (equivalent to 10.5 mg/mmol). In addition to insulin, he is receiving simvastatin 40 mg once daily and ramipril 2.5 mg once daily.

The healthcare professional needs to know the appropriate target BP for this patient, which will depend on his level of albuminuria. On the basis of Table 1, his urinary excretion of 105 mg/g is equivalent to a 24-h albumin excretion rate above the threshold of 30 mg/day, and according to **Recommendation 4.1** the suggested BP target is $\leqslant 130/80$ mm Hg, unless there were other factors that might make this inappropriate as suggested in **Recommendation 2.1**.

The next question is how should this target be achieved? Assuming that lifestyle changes have already been initiated (**Recommendations 2.3.1–2.3.4**) and that the patient is attempting to comply with these, it is possible that additional pharmacological agents may be required. Many clinicians will be more comfortable in obtaining a second and/or third office (clinic) BP recording on a separate occasion before initiating therapeutic changes, or ask the patient to provide BP readings taken at home, or even check a 24-h ambulatory recording, accounting for the fact that home and ambulatory BP readings are generally lower than clinic BP readings. Assuming that the need to additional treatment is established, the healthcare professional will need to decide whether to increase doses of agents already prescribed or whether to add a new class of agents. The guideline does not make specific recommendations on treatment regimens because of a lack of evidence, the exception being the use of ACE-Is or

ARBs in patients with elevated urinary albumin levels. The patient in question is already receiving an ACE-I. As stated in Chapter 2 of the guideline, the Work Group did not identify any trials (that fulfilled inclusion criteria for evidence review) that might be useful to guide the choice of second- or third-line therapy in this clinical scenario. The antihypertensive and antialbuminuric effects of ACE-Is and ARBs are augmented by both dietary salt restriction and diuretic therapy, and thus a diuretic could be considered as a logical choice of additional medication, despite the tendency of these agents to cause hyperglycemia. The addition of a calcium channel blocker is also a reasonable strategy. According to a *post hoc* analysis of a large trial of different fixed-dose combination therapies that was not included in the evidence review, the use of a calcium antagonist with an ACE-I was more likely to slow progression of CKD than an ACE-I combined with a diuretic.[11]

Case 2

An 87-year-old female patient with CKD 3 (eGFR 32 ml/min/1.73 m^2) lives independently. She is known to have osteoporosis, but apart from a previous hip fracture that was treated by internal fixation she has been fit and well. The patient, who avoids adding salt to food and walks for 30 min each day, is taking 5 mg bendrofluazide once daily and 50 mg atenolol once daily. She has no proteinuria on dipsticks testing of urine. Previous investigations include an ultrasound that revealed small nonobstructed kidneys and a screen for immune-mediated kidney disease and myeloma, which was negative. At a routine clinic appointment, her BP is recorded at 155/74 mm Hg, consistent with readings obtained at two previous clinical encounters. She has a regular pulse of 60 beats/min, suggesting adequate beta-blockade and no ankle edema.

Recommendation 7.1 would encourage the healthcare professional to consider the risks and benefits of lowering BP in this elderly patient. This patient's wide pulse pressure is likely to reflect a stiff arterial tree. Although the patient's diastolic BP is within the target of $\leqslant$90 mm Hg for a non-proteinuric patient, the systolic exceeds 140 mm Hg. The target for treatment in individuals with CKD and no albuminuria is $\leqslant$140/90 mm Hg (**Recommendation 3.1**). The Work Group did not find sufficient evidence upon which to base recommendations for the treatment of systolic hypertension in the context of CKD, and the decision as to whether or not to add additional therapy must lie with the healthcare professional and patient. This decision must take into account the risk of postural hypotension in a patient with osteoporosis, set against the risk of a disabling or fatal cardiovascular event such as a stroke. If additional pharmacological agents are used, the guidelines do not help in selecting a third agent, although an ACE-I or ARB would seem an obvious choice, despite the lack of albuminuria. As stated in **Recommendation 2.2**, the healthcare professional should regularly inquire about symptoms suggesting postural hypotension and should monitor for electrolyte abnormalities and other side effects as mentioned in **Recommendation 7.1**.