AJKD
KDOQI Commentary

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Management of Blood Pressure in CKD

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In response to the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guideline for blood pressure management in patients with chronic kidney disease not on dialysis, the National Kidney Foundation organized a group of US experts in hypertension and transplant nephrology to review the recommendations and comment on their relevancy in the context of current US clinical practice and concerns. The overriding message was the dearth of clinical trial evidence to provide strong evidence-based recommendations. For patients with CKD with normal to mildly increased albuminuria, goal blood pressure has been relaxed to ≤140/90 mm Hg for both diabetic and nondiabetic patients. In contrast, KDIGO continues to recommend goal blood pressure ≤130/80 mm Hg for patients with chronic kidney disease with moderately or severely increased albuminuria and for all renal transplant recipients regardless of the presence of proteinuria, without supporting data. The expert panel thought the KDIGO recommendations were generally reasonable but lacking in sufficient evidence support and that additional studies are greatly needed.
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INDEX WORDS: Kidney Disease: Improving Global Outcomes (KDIGO); guideline; blood pressure.

INTRODUCTION

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative formed to develop and implement clinical practice guidelines for the optimal care of patients with chronic kidney disease (CKD). KDIGO recently published an updated evidence-based practice guideline for the management of blood pressure in individuals with non–dialysis-dependent CKD (CKD ND) of any stage.[1] This report builds upon the previous guideline published by NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) in 2004.[2] In response, the NKF organized a group of US experts in hypertension, nephrology, and transplantation nephrology to review the recommendations and comment on their relevancy and the potential for their implementation in the context of current US clinical practice. This commentary presents the KDIGO guideline recommendations and statements, followed in each topic area by a succinct discussion and commentary of the supporting rationale and potential applicability issues raised by the expert panel.

The genesis and implementation of treatment guidelines are by themselves often a study of bias and belief, but development of guidelines may also lay bare the significant lack of gold-standard studies, in other words, randomized controlled trials (RCTs), that practitioners can use to guide clinical care. Treatment of hypertension, particularly in the setting of CKD ND, is no exception. KDIGO commissioned an evidence review of the recent literature and assembled a writing group to create the current recommendations. While data from RCTs were preferred, the evidence base included published systematic reviews and meta-analyses and selected RCTs that included CKD subgroups or individuals at increased cardiovascular (CV) risk without specific diagnosis of CKD. Outcomes were related to kidney disease progression and CV

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Box 1. Nomenclature and Description for Rating Recommendation Strength and Quality of Evidence

Rating Strength of Recommendation

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

Rating Quality of Evidence

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

Note: 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.

[a]The additional category Not Graded was used typically to provide guidance based on common sense or when 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.

events. Overall, the KDIGO committee did an excellent job of carefully reviewing the evidence and provided an accurate grading of the available data to support their recommendations for the management of blood pressure in patients with CKD ND. However, the final product is disappointing, offering few recommendations that are supported by even moderate-quality evidence. Because many trials routinely excluded patients when their serum creatinine concentration was >1.5-2.0 mg/dL, there is an impressive lack of information in this area in general. This is clearly evident in the current report. This limitation is distinctly highlighted by the use of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence grading scale.[3]

Using GRADE, the strength of each recommendation is indicated as either Level 1, a strong recommendation, indicating that most patients should receive this course of action, or Level 2, a weak or discretionary recommendation, indicating that different choices of therapy would be appropriate for different patients. Strength of recommendation is reflected in the selected wording, with the use of terms such as "recommend" or "should" to imply that most patients should receive this course of action (Level 1) or the use of terms such as "suggest" or "might" to indicate that different choices may be appropriate for different patients depending on their circumstances (Level 2). Moreover, each statement is given a grade reflecting the quality of the supporting evidence: A (high), B (moderate), C (low), or D (very low). The reader should note that none of the graded recommendations received an A grade. Four (23.5%) received a B grade; 3 (17.7%), a C grade; and 10 (58.8%), a D grade. For statements that could not be subjected to systematic evidence review, a "Not Graded" category was assigned (4, or 19.1%, of all recommendations). This system, summarized in Box 1, was used throughout the report.

The guideline was developed to assist health care professionals (nephrologists, other physicians, nurses, and pharmacists) in providing care to patients with CKD. While the ideal is to base all recommendations on RCT-derived data, reality must be taken into consideration and when the data were lacking, the experts thought their clinical acumen and experience would be preferable to leaving gaps with no recommendations. The resulting expert opinion statements are rated with a low strength of recommendation and low strength of evidence. In addition, there are a number

of Not Graded recommendations that provide guidance based on sound clinical judgment in areas lacking in evidence. As stated in the report, the process was not designed or intended to guide regulators or set performance measures. In an area with so little decision making based on optimal data, it is important to accentuate this distinction.

A minor but important point is the discrepancy of the KDIGO guideline with other guidelines in using "less than or equal to" as the goal rather than the generally adopted convention of using "less than" targets. For example, other guidelines use the blood pressure goal <140/90 instead of ≤140/90 mm Hg. As hypertension is defined as blood pressure ≥140/90 mm Hg, in order to achieve a normal blood pressure, the guideline should have recommended a goal of <140/90 mm Hg. This approach runs through the entire document and is relevant to guideline sections 3 through 7. A second difference pertains to the addition of the term "consistently" to all recommendations containing blood pressure goals. Using the argument that blood pressure variability will result in a subset of readings above goal, the KDIGO panel specified the need for more intensive treatment whereby a portion of readings will be below the blood pressure goal in order to meet the consistency requirement. This is a change from other guidelines that may be lost as a subtlety hinging on a single word.

The guideline is consistent with the KDIGO 2012 guideline for the evaluation and management of CKD, which uses a revised terminology for albuminuria based on quantitative measurements.[4] Recommendations are stratified according to urinary albumin excretion <30, 30-300, or >300 mg/24 h, which fits well with the updated classification of normal to mildly increased, moderately, and severely increased albuminuria, respectively, used in the KDIGO CKD guideline. This applies to guideline sections 3 and 4, where recommendations differ by extent of albuminuria.

The guideline recommendations are divided into 5 sections that address specific populations within the total population with CKD according to the presence or absence of diabetes mellitus, with separate guidelines for kidney transplant recipients, children, and the elderly. This division further highlights differences in the strength of evidence and thus the great need for additional trials to address these deficiencies. Each section concludes with a set of recommendations for research. The exercise of defining and grading current evidence flows nicely into a roadmap for areas in need of further study. Clearly the needs are legion and new initiatives will need to prioritize based on the utility and applicability of the knowledge to be gained.

Box 2. KDIGO Recommendations for Lifestyle and Pharmacologic 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)

Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; ND, non–dialysis-dependent.

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REVIEW OF KDIGO BLOOD PRESSURE MANAGEMENT RECOMMENDATIONS

CKD ND Patients

Commentary on Recommendation Statements

KDIGO recommendations on lowering blood pressure in patients with CKD ND are provided in Box 2.

General strategies. Recommendation 2.1 is not graded due to the general lack of RCT data to guide decision making in this area. The recommendation to individualize care and inquire about tolerance of the treatment is considered to be good clinical practice. The authors raise important general concepts: the difficulty reaching blood pressure goals in patients with CKD, concerns regarding the widened pulse pressure associated with arterial stiffness, and the potential to lower diastolic pressures excessively with greater risk for morbidity or mortality. National Health and Nutrition Examination Study (NHANES) data indicate that CKD ND is often associated with resistant hypertension,[5] defined as blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes.[6] The choice of agents must be made after consideration of

comorbidities, including renovascular disease or volume depletion, along with potential drug interactions. Patients with CKD ND are often treated with multiple antihypertensive medications that can each have untoward side effects. Good clinical practice dictates that periodic assessment of medication side effects is an essential feature of management of CKD ND. Although not mentioned, discerning a patient's tolerance to treatment may also improve patient adherence to the prescription, since adverse side effects impose additional burdens.

Recommendation 2.2, which is also not graded, is a reasonable approach, particularly for the elderly or diabetic patient with the potential for autonomic neuropathy, who is prone to develop symptomatic postural hypotension while taking antihypertensive medications. Checking for postural hypotension regularly should be considered good clinical practice.

Lifestyle modifications. Much of this section relies on observational and epidemiologic studies in the general population, including short-term intervention trials. An excellent review and rationale are provided for Recommendation 2.3.1. Application to a CKD population is by extrapolation, with few randomized trials in CKD. While obesity may associate with CKD progression, there remains a lack of high-quality data on interventions in CKD ND. It is worth emphasizing a cautionary note that some popular weight-loss diets emphasize foods high in potassium and protein and may produce hyperkalemia or accelerate kidney disease progression in this patient population.

Regarding Recommendation 2.3.2, abundant preclinical evidence supports a role for restricting dietary salt intake in the control of hypertension and arterial function. Dietary salt restriction is a potentially inexpensive means by which to reduce blood pressure and CV event rates, particularly in high-risk populations.[7] Although some patients with CKD ND may suffer from salt-wasting forms of kidney disease, most patients with CKD ND exhibit salt retention. It is worth noting that the Institute of Medicine recommends limiting sodium intake to 1,500 mg/d,[8] which represents an adequate intake for adults and is lower than the <2-g sodium (<5-g sodium chloride) goal recommended by KDIGO. Debate about the lower limit of salt restriction and individualizing the level of intake continues,[9] but excess salt intake remains an important and economical modifiable risk factor for CV events. While there was an overall lack of high-quality studies to support this practice in the treatment of CKD ND, the committee considered dietary salt restriction in the management of CKD ND to be a Level 1C recommendation.

For Recommendation 2.3.3, high-quality randomized trials involving exercise in CKD ND were lacking. However, randomized controlled trials in the general population support a beneficial effect of physical exercise on blood pressure control. The committee indicated there were no data to suggest that patients with CKD ND might respond differently from the general population and concluded that while the evidence was uncertain, undertaking an exercise program should be a Level 1D recommendation.

For Recommendation 2.3.4, ethanol ingestion can produce acute and chronic increases in blood pressure in the general population and should be restricted to reduce blood pressure. However, there may be an independent effect of red wine polyphenols on blood pressure since dealcoholized red wine promoted significant decreases in both systolic and diastolic blood pressure in men.[10] Because the effects in patients with CKD ND have not been specifically examined, the conclusion that the evidence was 2D was appropriate.

Other interventions: cigarette smoking. The impact of tobacco use on blood pressure in CKD ND has not been examined, but as a known CV risk factor even in the absence of a randomized trial, it is prudent to recommend tobacco cessation in CKD ND.

Other interventions: dietary supplementation. Several studies have examined the effect of potassium supplementation on blood pressure in the general population, with some reporting a salient effect while others suggested no effect. Given the reduced capacity to tolerate dietary potassium intake in CKD ND and in the absence of definitive studies in this population, we agree it is most appropriate not to recommend potassium supplementation in CKD ND to reduce blood pressure. Similarly, without evidence to support other electrolyte or dietary supplements, it is prudent not to recommend them.

Blood pressure–lowering agents. Beyond the use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs) in the setting of albuminuria or proteinuria, RCT-based evidence does not support specific recommendations for antihypertensive drug therapy choices for CKD ND. Nor are there data to support selection of second or third agents in a multiagent regimen. The report provides a clinically useful summary of the pharmacology and practical aspects of medication use in patients with CKD, primarily as an update to the KDOQI 2004 guideline on hypertension and antihypertensive agents in CKD.[2]

The report provides a good summary of clinical use of renin-angiotensin-aldosterone system (RAAS) blockers in practice. For ACEis, this includes metabolism, pharmacokinetics, and side effects (cough and angioedema). Common concerns, such as an increase in serum creatinine level after initiating ACEi/ARB therapy and hyperkalemia, are addressed. Greater

detail on angioedema would be helpful, including the observation that angioedema can occur after a patient has been taking an ACEi for a long time, and the concept of gut angioedema resulting in recurrent episodes of unexplained abdominal pain may be additional helpful information for the practitioner. The role of aldosterone antagonists in resistant hypertension is highlighted, with appropriate cautions for hyperkalemia in the setting of CKD. The more limited role for direct renin inhibitors in the therapeutic armamentarium is reasonable based on the absence of RCT data.

The guideline endorses diuretics as a cornerstone in the management of hypertension in CKD. The concept that diuretics are complementary to ACEis/ARBs in combination is well supported. While metabolic side effects of thiazide diuretics are well known, these are usually easily managed and it is unclear that they pose a major drawback. Increasing interest in chlorthalidone as the thiazide-like diuretic of choice is appropriate given that most of the large clinical trials used chlorthalidone. β-Blockers are still utilized in hypertensive patients with CKD. In primary hypertension, β-blockers are no longer considered first-line therapy in hypertension without a specific indication, such as coronary heart disease or heart failure.[11] Although not specific to CKD, the relevance of this approach to patients with CKD could have been better discussed in the guideline. The differing pharmacokinetics between β-blockers that may accumulate in CKD (such as atenolol) and others that do not (such as metoprolol and carvedilol) is an important concept, as mentioned. The potential for excessive bradycardia when β-blockers are combined with nondihydropyridine calcium channel blockers is an important caution; this may also occur in combination with centrally acting agents such as clonidine.

The guideline provides a good summary for the use of calcium channel blockers, centrally acting agents, α-blockers, and vasodilators in the management of hypertension. The African-American Study of Kidney Disease and Hypertension (AASK) supports the recommendation that dihydropyridine calcium channel blockers should be avoided as monotherapy in proteinuric patients.[12,13] It should be noted that moxonidine and nitrendipine are not available in the United States.

Commentary on Research Recommendations

The recommendations offered cut through the discussion to highlight topics of high priority. Studies of salt restriction in CKD ND could provide evidence to support practical and cost-effective strategies to improve blood pressure control and reduce the risk of progressive renal disease and CV events. Studies to evaluate the benefit of weight loss at different stages of CKD would be valuable in the general management of patients with CKD, but highly challenging. The third recommendation for studies of RAAS blockers in combination may be less pressing, with multiple studies to date suggesting harm from this approach.

CKD ND Patients Without Diabetes Mellitus

Commentary on Recommendation Statements

The KDIGO guideline for the management of hypertension among patients with nondiabetic CKD differs from earlier recommendations in the adoption of a more conservative higher blood pressure goal and the establishment of different blood pressure goals based on the presence of albuminuria (Box 3). For those with normal to mildly increased albuminuria, the guideline recommends blood pressure goals of

Box 3. KDIGO Recommendations for 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 during systole or $>$90 mm Hg during diastole be treated with BP-lowering drugs to maintain a BP that is consistently $\leq$140 mm Hg systolic and $\leq$90 mm Hg diastolic. (1B)
- 3.2: We suggest that non-diabetic adults with CKD ND and with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office BP is consistently $>$130 mm Hg during systole or $>$80 mm Hg during diastole be treated with BP-lowering drugs to maintain a BP that is consistently $\leq$130 mm Hg systolic and $\leq$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 during systole or $>$80 mm Hg during diastole be treated with BP-lowering drugs to maintain a BP that is consistently $\leq$130 mm Hg systolic and $\leq$80 mm Hg diastolic. (2C)
- 3.4: We suggest that an ARB or ACE-I be used as first-line therapy in non-diabetic adults with CKD ND and with 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 as first-line therapy in non-diabetic adults with CKD ND and with urine albumin excretion $>$300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. (1B)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; ND, non–dialysis-dependent.

*The guideline notes that "[a]pproximate 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 provided in the Table 1 of Chapter 1 of the guideline.

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≤140/90 mm Hg. For those who have moderately or severely increased albuminuria, the guideline recommends that ACEis or ARBs be used as first-line therapy. Both these recommendations are graded 1B. For patients with moderately or severely increased albuminuria, the guidelines recommend blood pressure goals that are 10 mm Hg lower than for patients with normal or mildly increased albuminuria (evidence grade Level 2D and Level 2C). For those with moderately increased albuminuria, first-line therapy should also be an ACEi or ARB, but the level of evidence is 2D.

Using the strength of recommendations as a guide, different choices for blood pressure goals and agents may be appropriate for different patients, depending on confounding illnesses or other factors. Accordingly, each patient requires individual consideration to arrive at the treatment approach that is optimal to his or her medical status. Lower blood pressure goals are graded as a Level 2 recommendation, suggesting there is still substantial debate and inadequate evidence on which to base this approach. A blood pressure goal of ≤130/80 mm Hg for those with moderately increased albuminuria received a 2D grade, indicating this recommendation is largely opinion based and the quality of evidence is low. Similarly, a goal blood pressure of 130/80 mm Hg for people who have severely increased albuminuria received a grade of 2C, indicating low-quality evidence to support this recommendation. The selection of an ACEi or ARB for the nondiabetic patient with CKD with moderately increased albuminuria also received a grade of 2D. Taken together, low-quality evidence or lack of evidence for these recommendations suggests that except for those with severely increased albuminuria, there is no compelling reason to use or not use specific agent classes in these patients. Thus, an alternate view and one that may be equally acceptable to many clinicians is that a blood pressure goal of <140/90 mm Hg is acceptable, and for most, the choice of initial agent is not mandated.

The guideline may conflict with other recommendations for the management of elderly patients with nondiabetic CKD. Based on the Hypertension in the Very Elderly Trial (HyVET), a goal blood pressure of 140-145 mm Hg is now recommended for octogenarians in the general population.[14] Given that patients who are elderly and have nondiabetic kidney disease may not tolerate aggressive lowering of blood pressure, higher blood pressure goals may also apply to these individuals.

Overall, the recommendations in this section are reasonable. However the clinician should pay special attention to the grades assigned to each. Given grades of 2C and 2D, there is a substantial role for individualization of therapy in patients with CKD. Policy makers should curb their enthusiasm to recommend implementing the uniform use of ACEis in patients who do not have overt albuminuria or the adoption of aggressive blood pressure targets in patients who have albuminuria. Overall, a blood pressure goal of <140/90 mm Hg appears reasonable for patients with nondiabetic kidney disease, except for the very elderly, for whom a more conservative goal may apply. ACEi use is recommended for patients who have overt albuminuria, but the jury is out on patients who have nondiabetic CKD with less severe degrees of albuminuria.[14]

Commentary on Research Recommendations

The recommendations offered highlight areas of high priority but will be costly. Large RCTs of blood pressure targets and specific antihypertensive agents must be powered to evaluate hard clinical outcomes, including CV and renal events. Hopefully the same trials would provide data needed to develop prediction tools to assist in individual decision making, including prediction of clinical outcomes, likelihood of adverse outcomes, and the predictive value of intermediate outcomes as prognostic tools. Such trials will require multicenter collaborations and federal funding, as in the Systolic Blood Pressure Intervention Trial (SPRINT), which represents collaboration between 4 NIH (National Institutes of Health) institutes and will enroll about 3,000 nondiabetic patients with CKD ND.

CKD ND Patients With Diabetes Mellitus

Commentary on Recommendation Statements

We agree with these recommendations (Box 4) based on the limited available randomized clinical trial data. There are no randomized trials examining the effect of tightened blood pressure control to <140/90 mm Hg on progression of CKD in diabetes, reflected in the 2D recommendation grade for diabetic patients with any degree of increased albuminuria. It could be argued that the diastolic blood pressure goal should be <85 mm Hg based on the target for the intensive arm of the United Kingdom Prospective Diabetes Study (UKPDS).[15] However, this analysis is based on combined reductions in systolic and diastolic pressures (to <150/85 mm Hg) and compared to a much higher target of 180/105 mm Hg with a minority of individuals having nephropathy.

In a recent joint guideline document on CV disease prevention, the European Society of Cardiology in collaboration with 8 other scientific societies proposed a goal of <140/80 mm Hg.[16] The lower diastolic blood pressure goal came from analysis of the diabetes subgroup of the Hypertension Optimal Treatment (HOT) Trial[17] that achieved a mean diastolic

Box 4. KDIGO Recommendations for 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 during systole or >90 mm Hg during diastole 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 during systole or >80 mm Hg during diastole be treated with BP-lowering drugs to maintain a BP 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 30-300mg per 24 hours (or equivalent*). (2D)
- 4.4: We recommend that an ARB or ACE-I be used in adults with CKD ND and diabetes with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; ND, non–dialysis-dependent.

*The guideline notes that "[a]pproximate 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 provided in the Table 1 of Chapter 1 of the guideline.

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pressure of 81 mm Hg and the UKPDS in which achieved diastolic blood pressure from the intensive treatment arm was <85 mm Hg. An updated standards of care document released by the American Diabetes Association in January 2013 recommended treating all patients with diabetes and hypertension to a goal of <140/80 mm Hg regardless of the presence of CKD, with the caveat that a lower systolic target, such as <130 mm Hg, may be appropriate for those with longer life expectancy or at higher risk for stroke.[18] Both guidelines recommend a goal for systolic blood pressure that is concordant with KDIGO. Given that systolic blood pressure in those older than 50 years has greater predictive power for CV mortality, the guidelines can be considered generally in agreement on goal blood pressure. A revised version of the European Society of Hypertension and European Society of Cardiology guideline on hypertension will be published in 2013, and may adopt similar blood pressure goals in diabetes.

The guideline does not specifically recommend the use of ACEis or ARBs in people with normal to mildly increased albuminuria given the lack of outcome data to indicate significant benefit on kidney disease progression beyond blood pressure control and other CV risk factor management (eg, lipids and glucose).[19,20] KDIGO recommends ACEis or ARBs for patients with CKD and moderately increased albuminuria with an evidence strength of 2D based solely on expert opinion. In contrast, there is solid evidence from RCTs to support benefit from ACEis or ARBs in patients with severely increased albuminuria in slowing CKD progression, but not in improved CV outcomes. There are no data to support either ACEis or ARBs over the other drug class, with older studies generally using ACEis and newer studies using ARBs.

The combined use of renin-angiotensin system (RAS) blockers such as an ACEi plus ARB or ARB plus renin inhibitor thus far has failed to show a benefit on nephropathy progression and is associated with increased risk of side effects.[21,22] ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) was a CV and renal outcomes trial in which the direct renin inhibitor aliskiren or placebo was added to RAS-blocking therapy in patients with type 2 diabetes, CKD, and high CV risk. This double-blind placebo-controlled study of 8,561 participants had a primary end point of time to first occurrence of CV death, resuscitated cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease, or doubling of serum creatinine level.[23] The Data Safety Monitoring Committee stopped the trial early after the second interim analysis when no difference in the primary end point was noted despite lower blood pressure and greater albuminuria reduction in the aliskiren group.[22] Those randomly assigned to aliskiren experienced higher rates of hyperkalemia and hypotension than the placebo group.[22] The VA-NEPHRON-D (Diabetes in Nephropathy) study of combined ACEi/ARB therapy to slow diabetic nephropathy set to continue until 2014 was also recently stopped by the Data Safety Monitoring Committee, although details are not yet available.[24] Thus, dual RAAS blockade to date has failed to show a benefit for patients with type 2 diabetes at high CV and renal risk.

Commentary on Research Recommendations

KDIGO calls for more granular studies comparing blood pressure thresholds and goals in patients with diabetes mellitus with varied degrees of albuminuria, stratified by level of glomerular filtration rate. It is important to expand the drug classes of agents tested, to test drug combinations and add-on therapy approaches, and to provide guidance for situations such as obesity, for which drug metabolism/distribution may be different. Certainly, the expanding numbers with diabetes and diabetic CKD would make this

Box 5. KDIGO Recommendations for 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 during systole or >80 mm Hg during diastole 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)

Abbreviations: BP, blood pressure; CKD T, chronic kidney disease: transplant.

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feasible, although not without substantial efforts and costs.

Kidney Transplant Recipients

Commentary on Recommendation Statements

While guideline development requires careful review of the evidence, in many respects the management of hypertension for kidney transplant recipients rests on limited data. Current KDIGO recommendations for the management of blood pressure in kidney transplant recipients provide little new information or direction compared with prior guidelines. Due to the lack of prospective large clinical trials, KDIGO chose to follow the recommendation of the KDIGO guideline specific to the care of kidney transplant recipients published in 2009.[25] The current guideline discusses 2 items: (1) choice of goal blood pressure and (2) treatment strategies with medications (Box 5). The first recommendation receives a grade of 2D, while the second recommendation is not graded.

The suggestion that kidney transplant recipients should have a blood pressure goal ≤130/80 mm Hg is not based on clinical evidence. No RCTs have been conducted to examine whether the level of blood pressure achieved during the course of therapy impacts on either graft or patient survival. The premise that lower levels of blood pressure may be beneficial is based solely on epidemiologic data. Even in patients with native kidney disease, there is a paucity of evidence demonstrating that reducing blood pressure to <140/90 mm Hg is associated with any benefits for CV or renal survival, with the lone exception of patients with proteinuria with protein excretion >1 g/d. From a clinical standpoint, achieving levels of blood pressure <130/80 mm Hg requires a more substantial investment in both lifestyle modification and medications. This is particularly problematic for kidney transplant recipients, who not uncommonly require 10 or more medications for the management of their immunosuppression and concurrent medical comorbidities. The propensity for drug-drug interactions is particularly important in transplant recipients, for whom some medications used for the treatment of blood pressure alter immunosuppressant medication levels. Thus, in the absence of data to support the benefits of a blood pressure goal <140/90 mm Hg, it would seem prudent to individualize blood pressure goal decisions, considering the benefit to risk ratio of additional medications and potential drug-drug interactions against further complexity in the patient's medical regimen.

The optimal strategy for managing blood pressure in adult kidney transplant recipients requires careful individualization. The guideline provides ungraded recommendations that calcium channel blockers and drugs that block the RAS are preferred, noting there may be unique advantages from these agents compared to others. The report acknowledges the lack of RCTs comparing different agent classes and appropriately notes conflicting results from registry data. Clinicians who treat these patients would agree that dietary salt restriction coupled with weight loss enhances the opportunity to achieve blood pressure goals in kidney transplant recipients, while reducing the pharmacologic burden and the associated risks for side effects and drug-drug interactions.

The choice of medications requires care. There are important opportunities to lower blood pressure and proteinuria in a well-tolerated manner using ACEis and ARBs. Negative effects, including hyperkalemia, a 10%-15% reduction in hemoglobin level, and alterations in renal function due to changes in renal hemodynamics, may create clinical complexity. Calcium channel blockers work effectively in lowering blood pressure in kidney transplant recipients and may attenuate the vasoconstrictive influence of calcineurin inhibitors on the preglomerular vascular beds. However, some of these agents may alter the metabolism of calcineurin inhibitors and mTOR (mammalian target of rapamycin) inhibitors and therefore need to be started and adjusted with care. Not discussed in the guideline are the potential benefits of β-blockers in kidney transplant recipients who may have hypertrophic cardiomyopathy, congestive heart failure, or angina pectoris. Likewise, diuretics may be necessary to facilitate reduction in blood pressure in the setting of suboptimal graft function or for those receiving high doses of corticosteroids. α-Blockers may be useful in men with prostatic hypertrophy. Thus, in the absence of clinical data indicating a preferred therapeutic strategy, the combination of lifestyle modifi-

cation and medications based on efficacy, tolerability, and medical comorbidity should be carefully individualized.

Other potential issues of clinical importance include white-coat hypertension, masked hypertension, medication nonadherence, and remediable forms of secondary hypertension. Endocrine causes of hypertension such as hyperaldosteronism and transplant renal artery stenosis occur in kidney transplant recipients and should be considered. Nonsteroidal anti-inflammatory drugs and stimulants, while generally avoided in this patient group, may also increase blood pressure, as do agents that correct anemia (erythropoiesis-stimulating agents). The current guideline offers recommendations for optimal goal blood pressures and types of medications to be used in kidney transplant recipients. Equally important is a discussion of relevant aspects of clinical care encompassing nonpharmacologic factors, such as obesity, exercise, smoking, and dietary factors, along with issues of adherence, timing of blood pressure measurements, and evaluation for causes of resistant hypertension.

Commentary on Research Recommendations

There is great need for prospective randomized trials in kidney transplant recipients. The recommendations offered are appropriate but could better emphasize the need for data and the opportunities to improve care for this patient group, particularly in the area of prolonging allograft function.

Children With CKD ND

Recommendation 6.1 advises initiation of blood pressure treatment when blood pressure is consistently higher than the 90th percentile for age, sex, and height (Box 6). This differs from the currently accepted threshold for diagnosis of childhood hypertension, which is office blood pressure that is repeatedly higher than the 95th percentile for age, sex, and height.[26,27] Thresholds for initiation of pharmacologic treatment differ among current practice guidelines: the Fourth Report indirectly recommends initiation of pharmacologic treatment for children with CKD and prehypertension,[26] whereas the KDOQI and European Society of Hypertension pediatric guidelines do not specifically mention a lower blood pressure threshold for initiation of pharmacologic treatment.[2,27] Thus, implementation of this recommendation might be confusing to clinicians, who may not be accustomed to consideration of pharmacologic treatment in children and adolescents with blood pressure between the 90th and 95th percentiles.

Box 6. KDIGO Recommendations for 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)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; ND, non–dialysis-dependent.

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Recommendation 6.2 is problematic for several reasons. First, there is no scientific evidence to support a measurable benefit from reducing office blood pressure to less than the 50th percentile in children with CKD. In the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of CRF in Pediatric Patients) trial, enhanced blood pressure control, defined as 24-hour mean ambulatory blood pressure lower than the 50th percentile, resulted in a slower rate of progression in children with stages 2-4 CKD.[28] While the Chronic Kidney Disease in Children (CKiD) investigators have published preliminary data in abstract form suggesting reduced progression in children with CKD whose baseline auscultatory office blood pressure was lower than the 50th percentile,[29] these findings have not been subjected to peer review.

Second, the document suggests reducing systolic and diastolic blood pressure to lower than the 50th percentile, while the evidence is based on mean ambulatory blood pressure lower than the 50th percentile. Ambulatory blood pressure values are generally higher than office values in children, as demonstrated within the currently available pediatric ambulatory and office blood pressure normative values.[26,30] This implies that systolic and diastolic blood pressure values back-calculated from the 50th percentile ambulatory mean arterial pressure (MAP) would be higher than the 50th percentile systolic and diastolic blood pressure measured at rest in the office. As such comparisons are not available in the literature and there are no data indicating the level of office systolic or diastolic blood pressure equivalent to the 50th percentile ambulatory MAP, even if one accepted an ambulatory MAP lower than the 50th percentile as of potential benefit, the clinician does not know what level of office systolic or diastolic blood pressure this corresponds to, making implementation of this suggestion challenging. The authors were aware of the discrepancy between trial measurements using ambulatory blood pressure

monitoring (ABPM) and their recommendations but did not recommend ABPM-based targets due to the costs and limited clinical availability of this technique.

Third, normalization of blood pressure in children with CKD may be difficult to achieve due to reluctance of prescribers to utilize multiple drug combinations, compounded by the lack of evidence to guide prescribing of many antihypertensive agents in children.[31] Additional data on the efficacy and safety of multiple-drug regimens and the feasibility of achieving office blood pressure lower than the 50th percentile are needed before this recommendation could be widely implemented.

Recommendation 6.3 is supported by available observational data. Data from the CKiD investigators has shown that better blood pressure control was achieved in pediatric patients with CKD receiving an ACEi or ARB than in those who did not receive such agents.[32] Additionally, some small studies have shown that ACEis and ARBs are effective in lowering proteinuria in pediatric CKD.[33] The ESCAPE trial, which included the ACEi ramipril in all patients, demonstrated an initial reduction in proteinuria and delay in progression of CKD.[28] Thus, there appears to be sufficient evidence to support the use of these classes of agents in pediatric CKD. Surveys have shown that regimens incorporating an ACEi or ARB are favored by pediatric nephrologists when treating hypertensive children with CKD.[34] Thus, even though many children with CKD do not appear to be receiving ACEis or ARBs as part of their treatment regimens,[32] implementation of this suggestion should be feasible in the pediatric population.

However, 2 issues pertaining to the use of ACEis and ARBs in children deserve mention. First is the reversal of initial proteinuria reduction that occurred in the ESCAPE trial,[28] suggesting that reduction of proteinuria in CKD may not be sustained. Further research into the mechanisms of this phenomenon and how to counteract it are needed. Second, many ACEis and ARBs are now classified by the US Food and Drug Administration (FDA) as pregnancy risk category D for use at any time during pregnancy. While this labeling is not consistent for all members of these classes, a study by Cooper et al[35] highlighted potential congenital malformations after ACEi exposure in the first trimester and concluded that such exposure should not be considered safe. Thus, while ACEis and ARBs are recommended for treatment of teenage girls with CKD, strict counseling about the need for pregnancy avoidance should be considered mandatory when prescribing an ACEi or ARB to such patients. In contrast to the discussion in the KDIGO guideline, the category D designation affects all trimesters of pregnancy.

Box 7. KDIGO Recommendations for 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)

Abbreviations: BP, blood pressure, CKD; chronic kidney disease; ND, non–dialysis-dependent.

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Commentary on Research Recommendations

We agree that further randomized trials are needed to examine the effect of strict blood pressure control on progression of CKD in children, and additional evidence is needed to support the proposed blood pressure targets for the pediatric age group. There is a need to validate use of the 90th percentile for the initial diagnosis of hypertension in children and adolescents with CKD. We agree that further work should be done to validate specific blood pressure measurement devices in the pediatric age group and to establish broad-based pediatric ABPM normative data since there is reason to believe that ABPM offers specific advantages to blood pressure assessment in pediatric CKD.[28,30,36]

Elderly Persons With CKD ND

Commentary on Recommendation Statement

This recommendation addresses an important clinical issue commonly faced by clinicians (Box 7). Although mostly opinion based due to lack of data in the elderly with CKD, the statement and discussion provides useful and practical suggestions for the management of hypertension in elderly patients with CKD. It recommends caution in titration of drug therapy, with careful monitoring for potential side effects, and individualization of management based on comorbid conditions. These considerations are reasonable and consistent with good clinical care. There is an excellent discussion of blood pressure goal, although the recommendation does not endorse a specific goal blood pressure for the elderly patient with CKD. In comparison, JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure),[37] and ACC/AHA (American College of Cardiology/American Heart Association) guidelines[14] retain $<$140/90 mm Hg

as the blood pressure goal in the elderly while providing cautions similar to the KDIGO guideline. Endorsing the ACC/AHA goals may have been a reasonable action that would provide consistency across guidelines. Finally, the goal blood pressure for the growing population of "very elderly" (>80 years) remains uncertain.

Not directly addressed in the guideline is the concern raised by clinicians of decreasing the diastolic blood pressure too far as they lower systolic blood pressure.[38] This phenomenon remains a controversial issue with no definitive answers. Home and ambulatory blood pressure measurement may be helpful in assessing the overall burden and profile of hypertension in older patients.[14]

SPRINT, which is ongoing, is enriched with older patients with CKD; this study compares long-term clinical outcomes of strategies targeting blood pressure <140 mm Hg compared to <120 mm Hg.[39] This trial will likely provide the data needed to define blood pressure goals for the elderly with CKD. However, results are not expected until 2018. Pending additional data, the guideline, although opinion based, provides valuable information that clinicians can use at the bedside in managing hypertension in older patients with CKD.

Commentary on Research Recommendations

As elderly patients were excluded from earlier trials, there is little evidence on which to base recommendations. Expanding numbers of elderly and very elderly patients with CKD highlight the need for clinical trials in this group. Arguing that an RCT to determine blood pressure goals alone is not feasible, KDIGO specifically advises trials using fixed sequential agent regimens and inclusion of nearly all patients, excluding only those with angina or cardiomyopathy.

CONCLUSIONS

Under the premise that the primary aim of the KDIGO Blood Pressure Work Group was to provide evidence-based recommendations for the management of blood pressure in patients with CKD, the current recommendations are disappointing. Clearly, there is a lack of high-quality evidence based on prospective clinical trials in the CKD population. CKD was often an exclusion criterion in early blood pressure treatment trials, and the evolution of most pharmacologic agents to generic form reduced industry funding for the large-scale multiagent trials needed to clarify the optimal treatment of patients with CKD.

Certain trends seen in other guidelines are evident in KDIGO. For patients with CKD with normal to mildly increased albuminuria, blood pressure goals have been relaxed to ≤140/90 mm Hg for both diabetic and nondiabetic patients. In contrast, KDIGO continues to recommend blood pressure goals ≤130/80 mm Hg for all renal transplant recipients regardless of the presence of albuminuria, without supporting data. Goals for children with CKD are aggressive without evidence, yet remain vague and individualized for the elderly. A summary of KDIGO recommendations with evidence grade and our conclusions are shown in Table 1.

The commentary on the ACC/AHA summary statement guideline published in 2009 indicated that about one recommendation in 11 (9%) was based on Level

Table 1. Summary of KDIGO Recommendations for Management of Blood Pressure in CKD

Target Population	Goal Blood Pressure	Evidence Level	Commentary
Nondiabetic CKD with normal to mild albuminuria	≤140/90 mm Hg	1B	Evidence based Recommend <140/90 mm Hg
Nondiabetic CKD with moderate to severe albuminuria	≤130/80 mm Hg	2D moderate, 2C severe	Reasonable to select a goal of <140/90 mm Hg, especially for moderate albuminuria
Diabetic CKD with normal to mild albuminuria	≤140/90 mm Hg	1B	Evidence based Recommend <140/90 mm Hg
Diabetic CKD with moderate to severe albuminuria	≤130/80 mm Hg	2D	Reasonable to select a goal of <140/90 mm Hg
Kidney transplant recipients	≤130/80 mm Hg	2D	Reasonable to select a goal of <140/90 mm Hg
Children with CKD	≤90th percentile for age, sex, height ≤50th percentile for age, sex, height with any proteinuria	2D	No evidence to support either recommendation
Elderly with CKD	Individualize	Not available	Reasonable to consider a higher goal, especially for age >80 y

1A evidence.[40] The evidence base for blood pressure management in CKD is not at this standard as there are no 1A recommendations. Thus, we believe the important take-home message in blood pressure management in CKD is the serious paucity of evidence. Hopefully, as the NKF and FDA work out means to lower the bar for what constitutes a valid "kidney outcome" in clinical trials beyond the current measures of halving of estimated glomerular filtration rate, doubling of serum creatinine level, or end-stage renal disease, this will stimulate interest in better treatments (both drug and nondrug) for patients with CKD.[41]

Another hurdle in blood pressure management in CKD is that while it makes intuitive sense to recommend measures to reduce body mass index in obese patients (Recommendation 2.3.1), the better survival of dialysis patients with higher body mass index[42] gives one pause about a blanket implementation of this recommendation. Similarly, while sodium restriction is beneficial for most, it may worsen renal function after renal transplantation or with salt-losing tubulopathies.

One of the more controversial recommendations is to treat patients with CKD with or without diabetes who have moderately to severely increased albuminuria (Recommendations 3.2, 3.3, and 4.2) to a systolic blood pressure $\leq$130 mm Hg (2C and 2D level). Although this may result in less albuminuria than a less stringent goal of $<$140 mm Hg, it is hard to show the benefit of the 130-mm Hg systolic goal and this may conflict with recommendations of the Joint National Committee's upcoming report likely to be released in 2013.

Even with these limitations, we applaud the efforts of the KDIGO Work Group. It is likely more difficult to provide guidance in the face of sparse data than it is when flush with abundant clinical trial evidence. We believe that one of the most substantial messages of KDIGO is to emphasize the need for more data in the nephrology evidence base. Lower systolic blood pressure goals did not protect kidney function in diabetic patients in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study.[43] Creatinine level was higher in the more aggressively treated group who had a lower (but statistically nonsignificant) incidence of CV outcomes. SPRINT is $>$90% through recruitment and should address the 140- versus 120-mm Hg systolic pressure treatment goal in nondiabetic patients with CKD, including the elderly,[39] and will hopefully contribute substantially to the much needed evidence base for blood pressure management in CKD.

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