Complete Summary

GUIDELINE TITLE

K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease.

BIBLIOGRAPHIC SOURCE(S)

K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004 May;43(5 Suppl 1):S1-290. [625 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Hypertension
- Chronic kidney disease, including:
  - Diabetic kidney disease
  - Nondiabetic kidney diseases including glomerular diseases, vascular diseases, tubulointerstitial diseases, and cystic diseases
  - Kidney disease in the kidney transplant recipient

GUIDELINE CATEGORY

Diagnosis
Evaluation

Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Nephrology
Nutrition
Pediatrics
Pharmacology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Health Care Providers
Nurses
Pharmacists
Physician Assistants
Physicians
Social Workers

GUIDELINE OBJECTIVE(S)

To develop evidence-based recommendations for the evaluation and management of hypertension and use of antihypertensive agents in chronic kidney disease (CKD)

TARGET POPULATION

Adults or children with chronic kidney disease (CKD) Stages 1-4 (as defined by the Kidney Disease Outcomes Quality Initiative [K/DOQI] Guidelines on CKD).

Note: These guidelines are not intended for patients with CKD Stage 5 (kidney failure).

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Risk Assessment

Initial evaluation and re-evaluations based on clinical condition

1. Measurement of blood pressure (casual blood pressure [CBP]), self-measured blood pressure (SMBP), or ambulatory blood pressure monitoring (ABPM)
2. Type of chronic kidney disease (CKD) (diagnosis), level of glomerular filtration rate (GFR), level of proteinuria

3. Laboratory measurements for all patients at increased risk for CKD, including serum creatinine to estimate GFR; albumin-to-creatinine or protein-to-creatinine ratio in a first-morning or random untimed urine specimen; examination of the urine sediment or dipstick for red blood cells and white blood cells
4. Laboratory measurements for patients found to have CKD, including imaging of the kidneys, usually by ultrasound; serum electrolytes
5. Laboratory measurements for ascertainment of cardiovascular disease (CVD) and CVD risk factors in CKD: 12-lead electrocardiogram (EKG); serum glucose, fasting lipid panel; height and weight to calculate body mass index (BMI)
6. Complications of decreased GFR
7. Risk for progression of kidney disease
8. Presence of clinical CVD and CVD risk factors
9. Presence of comorbid conditions
10. Estimation of probability of renal artery disease (RAD) (predictive index derived from clinical characteristics; noninvasive screening test for RAD)
11. Barriers to self-management, adherence to diet and other lifestyle modifications, and adherence to pharmacological therapy
12. Complications or side effects of pharmacological therapy

Management/Treatment/Secondary Prevention

1. Development of clinical action plan based on the stage of CKD
2. Establishment of target blood pressure
3. Referral to specialists as indicated
4. Coordination with multiple therapies as part of a multi-intervention strategy
5. Patient and family education that is culturally sensitive, sensitive to economic considerations, and based on the patient's level of understanding (how to measure and record blood pressure; self-management behavior; anti-hypertensive therapy)
6. Lifestyle modifications to lower blood pressure and reduce risk of cardiovascular disease (diet; non-dietary approaches, such as weight control, exercise, moderation of alcohol, smoking cessation)
7. Pharmacologic therapy to slow progression of kidney disease
    - Angiotensin-converting enzyme (ACE) inhibitors (Benazepril [Lotensin], Captopril [Capoten], Enalapril [Vasotec]; Fosinopril [Monopril]; Lisinopril {Prinivil, Zestril]; Moexipril [Univasc]; Perindopril [Aceon]; Quinapril [Accupril]; Ramipril [Altace]; Trandolapril [Mavik]
    - Angiotensin-receptor blockers (ARBs) (Candesartan [Atacand]; Eprosartan [Teveten]; Irbesartan [Avapro]; Losartan [Cozaar]; Olmesartan [Micardis]; Telmisartan [Micardis]; Valsartan [Diovan])
8. Other pharmacologic agents to reduce cardiovascular risk and/or achieve blood pressure goals
    - Diuretics, including thiazide-type diuretics, loop diuretics, potassium-sparing diuretics
    - Beta-blockers, including non-selective beta-blockers, selective beta blockers, combined alpha and beta blockers
    - Calcium-channel blockers, including dihydropyridines and nondihydropyridines
    - Alpha-adrenergic blockers
    - Direct acting vasodilators

    - Aldosterone antagonists
    - Combination therapy
9. Strategies to improve adherence to pharmacologic therapy
10. Ongoing monitoring and evaluations (see "Evaluation" section above)
11. Interventions specific to children

MAJOR OUTCOMES CONSIDERED

- Direct health outcomes related to kidney disease progression (kidney failure, changes in glomerular filtration rate [GFR], changes in serum creatinine, mortality)
- Surrogate outcome related to kidney disease progression (proteinuria)
- Direct health outcomes related to cardiovascular disease (CVD) (clinical events, cause-specific mortality, total mortality)
- Surrogate outcomes related to CVD (left ventricular hypertrophy or carotid artery intima thickness)
- Incidence of adverse effects of drug treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Existing Guidelines on Chronic Kidney Disease (CKD)

There were several prior guideline recommendations for blood pressure management in chronic kidney disease (CKD), as well as other documents that became available during the course of guideline development and these were reviewed by the Work Group. The recommendations issued in 1997 by the Sixth Joint National Commission (JNC 6) were considered a reference source. Thus, the search for other guidelines with recommendations on blood pressure management in CKD was restricted to guidelines published since 1997. Searches were conducted through the National Guideline Clearing House on the following keywords: hypertension, kidney disease, diabetes, and cardiovascular disease, spanning the time from 1997 until March 2003. Approximately 150 guideline citations were found. All guidelines that could be downloaded free of charge or retrieved from published medical journals were searched for recommendations for blood pressure management and use of antihypertensive agents in CKD. Through this search, guideline developers found 11 guidelines with pertinent sections and supplemented this with other known recommendations.

Existing Guidelines on Cardiovascular Disease (CVD) in the General Population

The same search that was conducted through the National Guideline Clearinghouse to identify existing guidelines with recommendations on managing blood pressure in CKD (see above) was also screened for sections containing

recommendations on risk reduction for CVD using antihypertensive agents. This yielded 13 guidelines which were abstracted and compiled into tables and reviewed by Work Group experts.

Literature Search of Primary Articles

The Work Group and Evidence Review Team decided in advance that a systematic process would be followed to identify primary studies on the topics of interest. Only fully published articles with original data were included. Review articles, editorials, letters or abstracts were generally excluded. The only exceptions were abstracts of the ALLHAT trial reporting kidney disease progression and CVD outcomes in a large subgroup of individuals with CKD. The Work Group members and Evidence Review Team selected textbooks and review articles based on personal knowledge.

Studies for the literature review were identified primarily through Medline searches of the English language literature. The Medline literature searches were conducted between July 2001 and July 2002 to identify clinical studies published from 1966 through the search dates. Separate search strategies were developed for each topic.

Development of the search strategies was an iterative process that included input from all members of the Work Group. The text words or medical subject headings (MeSH) included kidney or kidney diseases or kidney function tests or hypertension or renal, diabetic nephropathy, renal artery, and ambulatory blood pressure monitoring. The searches were limited to human studies. Studies that focused on hemodialysis or peritoneal dialysis, pregnancy, neonates, malignant hypertension, acute renal failure, or pharmacokinetics were excluded.

The Evidence Review Team screened citations identified by the Medline search. Potentially relevant articles were identified from abstracts and titles, based on study population, relevance to specific guideline topics, and the study design. In general, studies with fewer than 10 subjects per treatment arm were excluded. However, for pediatric topics, due to the small number of articles, only case reports were excluded. Relevant articles known to domain experts and reviewers supplemented these searches. After retrieval, each paper was screened according to the established criteria to verify its relevance and appropriateness. Work Group members assigned to the specific topic reviewed the articles and made the final decision for inclusion or exclusion of articles. However, they had to provide the reason for rejection. Data extraction was performed on all included articles and their data compiled into evidence tables. Additional relevant studies published since July 2002 were added by experts.

NUMBER OF SOURCE DOCUMENTS

- Primary articles
    - Abstracts screened = 11,688
    - Articles retrieved and reviewed = 899
    - Articles where data were extracted = 177
    - Articles added by Work Group = 47
    - Articles systematically reviewed and listed in summary tables = 76
- Existing guidelines on chronic kidney disease (CKD): 18 guidelines

- Existing guidelines on cardiovascular disease (CVD) in the general population: 13 guidelines

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Strong

Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assesses effects on health outcomes.

Moderately Strong

Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; OR evidence is from a population other than the target population, but from well-designed, studies on surrogate endpoints for efficacy and/or safety in the target population.

Weak

Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; OR the evidence is only for surrogate measures in a population other than the target population; OR the evidence is from studies that are poorly designed and/or analyzed.

The strength of evidence for a group of studies was graded using a rating system that takes into account

1. methodological quality of the studies
2. target population (patients with chronic kidney disease or other populations)
3. study outcomes (health outcomes or surrogate measures for those outcomes).

(See Table 183 in the original guideline document)

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Two types of tables were prepared using data extracted from accepted articles. Evidence tables contain data derived from the data extraction forms that covered features of the study design, patient demographics, disease characteristics, interventions, definitions of the outcomes, and their results. These detailed evidence tables, with information spanning across several pages for each study, were made available to Work Group members for the purpose of reviewing the data and writing of guidelines. The evidence tables are not published along with the guidelines.

Using the information in the evidence tables, the Evidence Review Team also prepared a set of summary tables that succinctly describe the characteristics for each study in six areas: study size; applicability (type of study subjects); baseline information (kidney function, level of proteinuria, and blood pressure in comparator group one); information on therapy in each treatment arm (antihypertensive agents or blood pressure targets tested as well as the blood pressure at the end of the study); results of the primary outcome (the main or composite primary outcome and the magnitude of the effect); and methodological quality.

Grading of Individual Studies

Study Size

The number of patients (N, sample size) is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of effects or associations. In addition, results from large studies are more likely to be applied to a broader population; however, large size alone does not guarantee a high degree of applicability. A study that enrolls a large number of selected patients may be less generalizable than several smaller studies that include a broad spectrum of patient populations.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study sample is sufficiently broad so that the results can be applied to the population of interest at large. The study sample is defined by the inclusion and exclusion criteria. The target population was defined to include patients with chronic kidney disease (CKD) and those at increased risk of CKD, except where noted. A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as were the stated causes of CKD and prior treatments. If the study is not considered broadly generalizable, reasons for the limited applicability are reported. Table 178 in Appendix 1 of the original guideline document describes the Work Group's approach to assessing applicability.

Results

The type of results available in each study is determined by the study design, the purpose, and the question(s) being asked. The Work Group decided that the outcomes of interest were primary outcomes documenting effects on kidney disease progression, all-cause mortality, or cardiac outcomes in randomized controlled trials. Given the large spectrum of different outcomes, results were

collapsed into four categories: direct health outcomes related to kidney disease progression (kidney failure, changes in glomerular filtration rate [GFR], changes in serum creatinine), surrogate outcome category related to kidney disease progression (proteinuria), direct health outcomes related to cardiovascular disease (CVD) (clinical events), and surrogate outcomes related to CVD (left ventricular hypertrophy or carotid artery intima thickness). Table 179 in Appendix 1 of the original guideline document shows the approach in reporting comparisons of blood pressure targets or antihypertensive agents. For studies reporting adverse effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), the incidence of adverse effects (i.e., drug reduction or discontinuation for hyperkalemia, for early decrease in GFR or for any adverse effect) were reported as percentages

Methodological Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a generic three-level classification of study quality was devised (see Table 180 in appendix 1 of the original guideline document).

Summarizing Review Articles and Selected Original Articles

Work Group members had wide latitude in summarizing review articles. They selected original articles for topics that were determined, a priori, not to require a systematic review of the literature. The use of published or derived tables and figures was encouraged to simplify the presentation.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Overview of Process

The development of these guidelines followed four basic principles set forth by Kidney Disease Outcomes Quality Initiative (K/DOQI):

1. The guidelines were developed using a scientifically rigorous process, and the rationale and evidentiary basis for each guideline is clearly explained.
2. A multidisciplinary Work Group, with expertise in the management of chronic kidney disease (CKD), blood pressure, and cardiovascular disease (CVD), developed the guidelines.
3. The Work Group members worked independently from organizational affiliations and had final responsibility for determining guideline content.
4. The guidelines have undergone widespread critical review before they were finalized.

The guidelines were developed using an evidence-based approach similar to that endorsed by the Agency for Healthcare Research and Quality. Development of the

guideline and evidence report required many concurrent steps. The Work Group reviewed all pertinent, published evidence, and critically appraised the quality of studies and the overall strength of evidence supporting each recommendation.

Refinement of Topics and Development of Materials

The Work Group and Evidence Review Team developed (1) draft guideline statements; (2) draft rationale statements that projected the pertinent evidence; (3) mock summary tables providing a shell for the expected evidence; and (4) data extraction forms prompting the reviewers for relevant data elements to be retrieved from the primary articles. The development process included creation of initial mock guidelines and tables by the Work Group Chair and Evidence Review Team, followed by iterative refinement by the Work Group members. The refinement process began prior to literature retrieval and continued through all stages of the project until the drafting of the final report. The refinement occurred by e-mail, telephone, and in-person communication regularly with local experts and with all experts during in-person meetings of the Evidence Review Team and Work Group members. Throughout the process of topic refinement, the type of study design that would be appropriate to address the topics of interest was carefully considered.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade A

It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.

Grade B

It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.

Grade C

It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effect.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines underwent widespread critical review before they were finalized. A list of individuals and organizations who reviewed draft guidelines is provided in the acknowledgements section of the original guideline document.

In addition, the guidelines were compared with other published guidelines and recommendations on hypertension and antihypertensive agents in chronic kidney disease (CKD), including those from the following guidelines and groups: the Sixth and Seventh Reports of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6 and JNC-7); National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease; Department of Veterans Affairs; Veterans Health Administration; New Zealand Guidelines Group; American Society of Transplantation; Report of Management of Hypertension in Adults with Renal Disease and Diabetes by the Executive Committee of the National Kidney Foundation Councils on Hypertension and on Diabetic Kidney Disease; Scottish Intercollegiate Guidelines Network; American Diabetes Association; National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines on CKD; Institute for Clinical Systems Improvement; British Renal Association; Caring for Australians with Renal Impairment (CARI) guidelines; NKF-K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in CKD; National Kidney Disease Education Program, National Institute of Diabetes, Digestive, and Kidney Disease.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the Recommendations Ratings (A-C) are provided at the end of the "Major Recommendations" field.

Guideline 1: Goals of Antihypertensive Therapy in Chronic Kidney Disease (CKD)

Hypertension is common in CKD and is a risk factor for faster progression of kidney disease and development and worsening of cardiovascular disease (CVD). Some antihypertensive agents also slow the progression of kidney disease by mechanisms in addition to their antihypertensive effect.

1.1 Antihypertensive therapy should be used in CKD to:

1.1.a. Lower blood pressure (**A**)

1.1.b. Reduce the risk of CVD, in patients with or without hypertension (**B**) (see Guideline 7)

1.1.c. Slow progression of kidney disease, in patients with or without hypertension (**A**) (see Guidelines 8, 9, 10)

1.2. Modifications to antihypertensive therapy should be considered based on the level of proteinuria during treatment (**C**) (see Guidelines 8, 9, 10, 11).

1.3. Antihypertensive therapy should be coordinated with other therapies for CKD as part of a multi-intervention strategy (**A**).

1.4. If there is a discrepancy between the treatment recommended to slow progression of CKD and to reduce the risk of CVD, individual decision-making should be based on risk stratification (**C**).

Guideline 2: Evaluation of Patients With Chronic Kidney Disease or Hypertension

Careful initial evaluation and frequent re-evaluation are essential for effective treatment of hypertension and use of antihypertensive agents in CKD. Because CKD and hypertension are often present together and both are generally asymptomatic, Guideline 2 considers evaluations of patients with either condition.

2.1. Blood pressure should be measured at each health encounter (**A**).

2.2. Initial evaluation should include the following elements:

2.2.a. Description of CKD

2.2.a.i. Type (diagnosis), level of glomerular filtration rate (GFR), and level of proteinuria (see table below titled "Laboratory Measurements for Ascertainment of CKD") (**A**)

2.2.a.ii. Complications of decreased GFR (**A**)

2.2.a.iii. Risk for progression of kidney disease (**A**)

- 2.2.b. Presence of clinical CVD and CVD risk factors (see table below titled "Measurements for Ascertainment of CVD and CVD Risk Factors in CKD) (**A**)
- 2.2.c. Comorbid conditions (**A**)
- 2.2.d. Barriers to self-management, adherence to diet and other lifestyle modifications, adherence to pharmacological therapy (see Guidelines 5, 6, and 7) (**B**)
- 2.2.e. Complications of pharmacological therapy (see Guidelines 7, 11-12) (**A**)

2.3. A clinical action plan should be developed for each patient, based on the stage of CKD (see table below titled "Stages of CKD: A Clinical Action Plan") (**B**).

2.4. Recommended intervals for follow-up evaluation should be guided by clinical conditions (see table below titled "Recommended Interval for Follow-up Evaluation in CKD") (**C**).

2.5. Patients with resistant hypertension should undergo additional evaluation to ascertain the cause (**B**).

2.6. Patients should be referred to specialists, when possible, for certain indications (see table below titled "Recommendations for Referral to Specialists for Consultation and Co-Management of CKD").

Table. Laboratory Measurements for Ascertainment of CKD

For all patients at increased risk for CKD:
• Serum creatinine to estimate GFR
• Albumin-to-creatinine or protein-to-creatinine ratio in a first-morning or random untimed "spot" urine specimen
• Examination of the urine sediment or dipstick for red blood cells and white blood cells
For patients found to have CKD:
• Imaging of the kidneys, usually by ultrasound
• Serum electrolytes (sodium, potassium, chloride, and bicarbonate)

Table. Measurements for Ascertainment of CVD and CVD Risk Factors in CKD

• 12-lead electrocardiogram (EKG)
• Serum glucose
• Fasting lipid panel
• Height and weight to calculate body mass index (BMI)

Table. Stages of CKG: A Clinical Action Plan

Stage	**Description**	**GFR (mL/min/1.73m^2**	**Action***
1	Kidney damage with normal or increased GFR	$\geq$90	Diagnosis and treatment; Treatment of comorbid conditions; Slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60-89	Estimating progression

Stage	Description	GFR (mL/min/1.73m^2	Action*
3	Moderate decreased GFR	30-59	Evaluating and treating complications
4	Severe decreased GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Notes: CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for $\geq$3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
*Includes actions from preceding stages.

Table. Recommended Interval for Follow-up Evaluation in CKD

Clinical Condition	After Initiation or Increase in Dose of Antihypertensive Therapy	
	4-12 weeks	**<4 weeks**
Systolic blood pressure (SBP) (mm Hg)	120-139*	$\geq$140 or <120
GFR (mL/min/1.73 m^2)	$\geq$60	<60
Early GFR decline (70)	<15	$\geq$15
Serum potassium (meq/L0	>4.5[a] or $\leq$4.5[b]	$\leq$4.5[a] or >4.5[b]
	After Blood Pressure is at Goal and Dose is Stable	
	6-12 months	**1-6 months**
GFR (mL/min/1.73 m^2)	$\geq$60	<60
GFR decline mL/min/1.73 m^2 per year)	<4 (slow)	$\geq$4 (fast)
Risk factors for faster progression of CKD	No	Yes
Risk factors for acute GFR decline	No	Yes
Comorbid conditions	No	Yes

Notes: Clinicians are advised to evaluate each parameter and select the follow-up interval for the parameter that requires the earliest follow-up [a]for thiazide or loop diuretic therapy, [b]for angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) therapy.
* 120-129 mm Hg, to monitor for hypertension; 130-139 mm Hg to reach blood pressure goal.

Table. Recommendations for Referral to Specialists for Consultation and Co-Management of CKD*.

Indication	Specialist
Evaluation and management of CKD, as described in Kidney Disease Outcomes Quality Initiative CKD Clinical Action Plan	Kidney disease specialist (**C**); Other specialists as appropriate (**C**)
GFR <30 mL/min/1.73 m^2	Kidney disease specialist (**B**)
Spot urine total protein-to-creatinine ration >500-1,000 mg/g	Kidney disease specialist (**C**)

Indication	Specialist
Increased risk for progression of kidney disease	Kidney disease specialist (**C**)
GFR decline >30% within 4 months without explanation**	Kidney disease specialist (**C**)
Hyperkalemia (serum potassium concentration >5.5 mEq/L) despite treatment	Kidney disease specialist (**C**)
Resistant hypertension	Kidney disease or hypertension specialist (**C**)
Difficult-to-manage drug complications	Kidney disease or hypertension specialist (**C**)
Acute presentations of CVD	Cardiovascular disease specialist (**C**)
Complex or severe chronic CVD conditions	Cardiovascular disease specialist (**C**)
Age <18 years	Pediatric kidney disease specialist (**C**)

* Availability of specialists may vary, depending on location.
** Defined as "fast" GFR decline (>4 mL/min/1.73 m^2 per year) or risk factors for fast GFR decline. Short-term decline in GFR up to 30% may be seen after initiation of ACE inhibitor or ARB and does not require referral to specialists in the absence of other indications.
Note: Letters in parentheses indicate strength of recommendations.

Guideline 3: Measurement of Blood Pressure in Adults

Blood pressure can be determined by resting blood pressure measurement in the health-care provider's office (casual blood pressure [CBP]), self-measured blood pressure (SMBP), or ambulatory blood pressure monitoring (ABPM).

3.1. Blood pressure should be measured according to the recommendations for indirect measurement of arterial blood pressure of the American Heart Association and Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) (**A**).

3.2. Patients should be taught to measure and record their blood pressure, whenever possible (**C**).

3.3. Ambulatory blood pressure monitoring should be considered for patients with CKD for the following indications (**C**):

3.3.a. Suspected white coat hypertension

3.3.b. Resistant hypertension

3.3.c. Hypotensive symptoms while taking antihypertensive medications

3.3.d. Episodic hypertension

3.3.e. Autonomic dysfunction

Guideline 4: Evaluation for Renal Artery Disease

Renal artery disease (RAD) is a cause of CKD and hypertension and can be present in patients with other causes of CKD, such as diabetes or hypertensive nephrosclerosis, and CKD in the kidney transplant.

4.1. For patients in whom there is a clinical suspicion of RAD, the clinician should do one or more of the following:

4.1.a. Estimate the probability of RAD using a predictive index derived from clinical characteristics (**B**)

4.1.b. Obtain a noninvasive screening test for RAD (**A**)

4.1.c. Refer to a kidney disease or hypertension specialist for evaluation (**C**).

4.2. Patients found to have hemodynamically significant RAD should be referred to a kidney disease or hypertension specialist for management (**C**).

Guideline 5: Education on Self-Management Behavior

Antihypertensive therapy must take into consideration the patient's perception of the health-care provider's advice and prescriptions, factors that may influence self-management behaviors, and the likelihood that the patient will adhere to recommendations.

5.1. Self-management principles should be incorporated into the treatment plan (**B**).

5.2. Patient and family education about antihypertensive therapy should be culturally sensitive, sensitive to economic considerations, and based on the patient's level of understanding (**B**).

5.3. All patients should be assessed for barriers to adherence and self-management (**B**), and referred for further counseling as needed to a nurse practitioner, registered nurse, registered dietitian, masters prepared social worker, pharmacist, physician assistant, or other professional (**C**).

Guideline 6: Dietary and Other Therapeutic Lifestyle Changes in Adults

Dietary and other therapeutic lifestyle modifications are recommended as part of a comprehensive strategy to lower blood pressure and reduce CVD risk in CKD.

6.1. Dietary sodium intake of less than 2.4 g/d (less than 100 mmol/d) should be recommended in most adults with CKD and hypertension (**A**).

6.2. Other dietary recommendations for adults should be modified according to the stage of CKD (see table below titled "Macronutrient Composition and

Mineral Content of the Dietary Approaches to Stop Hypertension [DASH] Recommended by JNC 7, with Modifications for Stages 3-4 of CKD") (**B**).

6.3. Lifestyle modifications recommended for CVD risk reduction should be recommended as part of the treatment regimen (see table below titled "Other Lifestyle Modifications Recommended by JNC 7") (**B**).

6.4. Referral to a registered dietitian should be considered to help patients achieve dietary recommendations (**C**).

Table. Macronutrient Composition and Mineral Content of the Dietary Approaches to Stop Hypertension (DASH) Recommended by JNC 7, with Modifications for Stages 3-4 of CKD

Nutrient	Stage of CKD	
	Stages 1-4	
Sodium (g/day)*	<2.4	
Total Fat (% of calories)	<30	
Saturated Fat (% of calories)	<10	
Cholesterol (mg/day)	<200	
Carbohydrate (% of calories)**	50-60	
	Stages 1-2	**Stages 3-4**
Protein (g/kg/day, % of calories)	1.4 (approximately 18)	0.6-0.8 (approximately 10)
Phosphorus (g/day)	1.7	0.8-1.0
Potassium (g/day)	>4	2-4

*Not recommended for patients with "salt-wasting."
**Adjust so total calories from protein, fat, and carbohydrate is 100%.

Table. Other Lifestyle Modifications Recommended by JNC 7

Lifestyle Component	Recommendation
Weight maintenance if BMI <25 mg/m^2	Balanced diet to maintain desirable body weight
Weight loss if overweight or obese (BMI $\geq$ 25 kg/m^2)	Calorie restricted, balanced diet
Exercise and physical activity	Moderate intensity for 30 minutes/day, most days of week
Moderation of alcohol intake	$\leq$2 drinks/day (men), $\leq$1 drink per day (women)
Smoking cessation	Counseling, nicotine supplementation

Guideline 7: Pharmacological Therapy: Use of Antihypertensive Agents in CKD

All antihypertensive agents can be used to lower blood pressure in CKD. Multi-drug regimens will be necessary in most patients with CKD to achieve

therapeutic goals. Patients with specific causes of kidney disease and CVD will benefit from specific classes of agents.

7.1. Patients with CKD should be considered in the "highest-risk" group for CVD for implementing recommendations for pharmacological therapy, irrespective of cause of CKD (**A**).

7.2. Target blood pressure for CVD risk reduction in CKD should be <130/80 mm Hg (**B**).

7.3. Antihypertensive agents should be prescribed as follows, when possible:

7.3.a. Preferred agents for CKD should be used first (see Guidelines 8, 9, 10, 11) (**A**).

7.3.b. Diuretics should be included in the antihypertensive regimen in most patients (**A**).

7.3.c. Choose additional agents based on cardiovascular disease-specific indications to achieve therapeutic and preventive targets (see table below titled "Preferred Antihypertensive Agents for CVD") and to avoid side-effects and interactions (**B**).

7.4. The antihypertensive regimen should be simplified as much as possible (**B**).

7.4.a. Long-acting (once-daily agents) should be used when possible (**B**).

7.4.b. Two agents, either as separate prescriptions or as a fixed-dose combination containing preferred agents, may be considered as initial therapy for systolic blood pressure (SBP) >20 mm Hg above goal according to the stage of CKD and CVD risk (**C**).

7.4.c. Fixed-dose combinations may be used for maintenance therapy after the antihypertensive regimen has been established (**B**).

Table. Preferred Antihypertensive Agents for CVD

Types of CVD	Thiazide or Loop Diuretics	ACE Inhibitors or ARBs	Beta-Blockers	Calcium-Channel Blockers	Aldosterone Antagonists
Heart Failure with Systolic Dysfunction	X	X	X[a]		X
Post Myocardial Infarction (MI) with Systolic Dysfunction		X	X		X
Post MI			X		
Chronic Stable			X	X	

Types of CVD	Thiazide or Loop Diuretics	ACE Inhibitors or ARBs	Beta-Blockers	Calcium-Channel Blockers	Aldosterone Antagonists
Angina					
High-Risk for Coronary Artery Disease	X	X	X	X	
Recurrent Stroke Prevention	X	X			
Supraventricular Tachycardia			X	X[b]	

[a] Only some beta-blockers (carvedilol, bisoprolol, metoprolol succinate)
[b] Nondihydropyridine calcium-channel blockers

Guideline 8: Pharmacological Therapy: Diabetic Kidney Disease

Diabetes mellitus is the most common cause of kidney failure in the United States. Diabetic kidney disease is characterized by the early onset of albuminuria, hypertension, and a high risk of coexistent or subsequent CVD.

8.1. Target blood pressure in diabetic kidney disease should be <130/80 mm Hg (Guideline 7) (see table below titled "Hypertension and Antihypertensive Agents in Diabetic Kidney Disease").

8.2. Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB (see table below titled "Hypertension and Antihypertensive Agents in Diabetic Kidney Disease ").

Table. Hypertension and Antihypertensive Agents in Diabetic Kidney Disease

Clinical Assessment	Target Blood Pressure	Preferred Agents for CKD	Other Agents to Reduce CVD Risk and Reach Target Blood Pressure
Blood pressure ≥130/80 mm Hg	<130/80 mm Hg **(B)**	ACE inhibitor or ARB **(A)**	Diuretic preferred, then beta-blocker or calcium-channel blocker **(A)**
Blood pressure <130/80 mm Hg		ACE inhibitor or ARB **(A)**	

Note: Letters in parentheses denote strength of recommendations.

Guideline 9: Pharmacological Therapy: Nondiabetic Kidney Disease

Nondiabetic kidney diseases include glomerular diseases other than diabetes, vascular diseases other than renal artery disease, tubulointerstitial diseases, and cystic disease. Among these diseases, the level of proteinuria is useful for diagnosis and prognosis. Glomerular diseases are characterized by higher levels of proteinuria than other diseases. Higher levels of proteinuria are

associated with faster progression of kidney disease and increased risk of CVD.

9.1. Target blood pressure in nondiabetic kidney disease should be <130/80 mm Hg (Guideline 1) (see table below titled "Hypertension and Antihypertensive Agents in Nondiabetic Kidney Disease").

9.2. Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio ≥200 mg/g, with or without hypertension, should be treated with an ACE inhibitor or ARB (see table below titled "Hypertension and Antihypertensive Agents in Nondiabetic Kidney Disease").

Table. Hypertension and Antihypertensive Agents in Nondiabetic Kidney Disease

Clinical Assessment	Target Blood Pressure	Preferred Agents for CKD	Additional Agents to Reduce CVD Risk and Reach Target Blood Pressure
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g	<130/80 mm Hg **(A)**	ACE inhibitor or ARB **(A)**	Diuretic preferred, then beta-blocker or calcium-channel blocker **(A)**
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g	<130/80 mm Hg **(B)**	None preferred	Diuretic preferred, then ACE inhibitor, ARB, beta-blocker or calcium-channel blocker **(A)**
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g		ACE inhibitor or ARB **(C)**	Diuretic preferred, then beta-blocker or calcium-channel blocker **(A)**
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g		None preferred	

Note: Letters in parentheses denote strength of recommendations.

Guideline 10: Pharmacological Therapy: Kidney Disease in the Kidney Transplant Recipient

Most kidney transplant recipients have CKD and hypertension. High blood pressure in kidney transplant recipients is a risk factor for faster progression of CKD and development of CVD.

10.1. The target blood pressure in kidney transplant recipients should be <130/80 mm Hg (see Guideline 7) (see table below titled "Hypertension and Antihypertensive Agents in Kidney Disease in the Kidney Transplant Recipient").

10.2. Patients with CKD in the kidney transplant should be treated with any of the following to reach the target blood pressure: calcium channel blocker (CCB), diuretics, ACE inhibitor, ARB, or beta-blocker (see table below titled "Hypertension and Antihypertensive Agents in Kidney Disease in the Kidney Transplant Recipient").

Table. Hypertension and Antihypertensive Agents in Kidney Disease in the Kidney Transplant Recipient

Clinical Assessment	Target Blood Pressure	Preferred Agents for CKD	Additional Agents to Reduce CVD Risk and Reach Target Blood Pressure
Blood pressure ≥130/80 mm Hg	<130/80 mm Hg **(B)**	None preferred	CCB, diuretics, ACE inhibitor, ARB, beta-blocker **(B)**
Blood pressure <130/80 mm Hg		None preferred	

Note: Letters in parentheses denote strength of recommendations.

Guideline 11: Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in CKD

ACE inhibitors and ARBs can be used safely in most patients with CKD.

11.1. ACE inhibitors and ARBs should be used at moderate to high doses, as used in clinical trials (**A**).

11.2. ACE inhibitors and ARBs should be used as alternatives to each other, if the preferred class cannot be used (**B**).

11.3. ACE inhibitors and ARBs can be used in combination to lower blood pressure or reduce proteinuria (**C**).

11.4. Patients treated with ACE inhibitors or ARBs should be monitored for hypotension, decreased GFR, and hyperkalemia (**A**).

11.5. The interval for monitoring blood pressure, GFR, and serum potassium depends on baseline levels (see table below titled "Recommended Intervals for Monitoring Blood Pressure, GFR, and Serum Potassium for Side Effects of ACE Inhibitors or ARBs in CKD") (**B**).

11.6. In most patients, the ACE inhibitor or ARB can be continued if:

11.6.a. GFR decline over four months is <30% from baseline value (**B**).

11.6.b. Serum potassium is <5.5 mEq/L (**B**).

11.7 ACE inhibitors and ARBs should not be used or used with caution in certain circumstances (see table below titled "Circumstances in which ACE Inhibitors and ARBs Should Not Be Used").

Table. Recommended Intervals for Monitoring Blood Pressure, GFR, and Serum Potassium for Side Effects of ACE Inhibitors or ARBs in CKD

Baseline Value	**SBP (mm Hg)**	≥120*	<120
	GFR (mL/min/1.73 m^2)	≥60	<60
	Early GFR Decline (%)	<15	≥15
	Serum Potassium (mEg/L)	≤4.5	≥4.5
Interval	**After Initiation or Increase in Dose of ACE inhibitor or ARB**	4-12 weeks	≤4 weeks
	After Blood Pressure is at Goal and Dose is Stable	6-12 weeks	1-6 months

*See Guideline 7 for recommended intervals to reach blood pressure goal.

Table. Circumstances in which ACE Inhibitors and ARBs Should Not Be Used

	Do Not Use	**Use with Caution**
ACE Inhibitor	Pregnancy **(A)** History of angioedema **(A)** Cough due to ACE inhibitors **(A)** Allergy to ACE inhibitor or ARB **(A)**	Women not practicing contraception **(A)** Bilateral renal artery stenosis***(A)** Drugs causing hyperkalemia **(A)**
ARB	Allergy to ACE inhibitor or ARB **(A)** Pregnancy **(C)** Cough due to ARB **(C)**	Bilateral renal artery stenosis***(A)** Drugs causing hyperkalemia **(A)** Women not practicing contraception **(C)** Angioedema due to ACE inhibitors **(C)**

*Including renal artery stenosis in the kidney transplant or in a solitary kidney.
Note: Letters in parentheses denote strength of recommendations.

Guideline 12: Use of Diuretics in CKD

Diuretics are useful in the management of most patients with CKD. They reduce extracellular fluid (ECF) volume; lower blood pressure; potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents; and reduce the risk of CVD in CKD. Choice of diuretic agents depends on the level of GFR and need for reduction in ECF volume.

12.1. Most patients with CKD should be treated with a diuretic (**A**).

12.1.a. Thiazide diuretics given once daily are recommended in patients with GFR ≥30 mL/min/1.73 m^2 (CKD Stages 1-3) (**A**).

12.1.b. Loop diuretics given once or twice daily are recommended in patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4-5) (**A**).

12.1.c. Loop diuretics given once or twice daily, in combination with thiazide diuretics, can be used for patients with ECF volume expansion and edema (**A**).

12.1.d. Potassium-sparing diuretics should be used with caution:

12.1.d.i. In patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4-5) (**A**)

12.1.d.ii. In patients receiving concomitant therapy with ACE inhibitors or ARBs (**A**)

12.1.d.iii. In patients with additional risk factors for hyperkalemia (**A**)

12.2. Patients treated with diuretics should be monitored for:

12.2.a. Volume depletion, manifest by hypotension or decreased GFR (**A**)

12.2.b. Hypokalemia and other electrolyte abnormalities (**A**)

12.2.c. The interval for monitoring depends on baseline values for blood pressure, GFR, and serum potassium concentration (see table below titled "Recommended Intervals for Monitoring Blood Pressure, GFR, and Serum Potassium for Side Effects of Diuretics in CKD") (**B**).

12.3. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence (**B**).

Table. Recommended Intervals for Monitoring Blood Pressure, GFR, and Serum Potassium for Side Effects of ACE Diuretics in CKD

Baseline Value	**Baseline SBP (mm Hg)**	≥120*	<120
	Baseline GFR (mL/min/1.73 m^2)	≥60	<60
	Early GFR Decline (%)	<15	≥15
	Baseline Serum Potassium (mEg/L) for Thiazide and Loop Diuretics	>4.5	≤4.5
	Baseline Serum Potassium (mEg/L) for Potassium-Sparing Diuretics	≤4.0	>4.0
Interval	**After Initiation or Increase in Dose**	4-12 weeks	≤4 weeks
	After Blood Pressure is at Goal and Dose is Stable	6-12 weeks	1-6 months

*See Guideline 7 for recommended intervals to reach blood pressure goal.

Guideline 13: Special Considerations in Children

Hypertension is common in children with CKD. Because of their young age at onset of CKD and hypertension, children have a high lifetime exposure to risk factors for CVD. Thus, children with CKD are at high risk of complications from hypertension.

13.1. Measurement of blood pressure in children should be performed with age- and size-appropriate equipment, and blood pressure values should be interpreted according to normal values adjusted for age, gender, and height percentile, as recommended by the 1996 Update on the Task Force Report on High Blood Pressure in Children and Adolescents: A Working Group Report from the National High Blood Pressure Education Program (**A**).

13.2. The cause of CKD and age of the child should be considered in selecting the class of antihypertensive agent (**A**).

13.3. Target blood pressure in children should be lower than the 90th percentile for normal values adjusted for age, gender, and height or 130/80 mm Hg, whichever is lower (**B**).

13.4. Because of the specialized nature of CKD and blood pressure management in children, a pediatric kidney disease specialist should be involved in their care, when possible (**C**).

Definitions:

Recommendations Rating Scheme

Grade A

It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.

Grade B

It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.

Grade C

It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effect.

CLINICAL ALGORITHM(S)

The following algorithms are provided in the original guideline:

- General approach to hypertension and use of antihypertensive agents in chronic kidney disease (CKD) (see Figure 28 in the original guideline document)
- Evaluation for proteinuria for evaluation of hypertension and use of antihypertensive agents in CKD (see Figure 30 in the original guideline document)
- Evaluation of patients with CKD for treatment of hypertension and use of antihypertensive agents (see Figure 31 in the original guideline document)
- Hypertension and antihypertensive agents in CKD (see Figure 34 in the original guideline document)
- Hypertension and antihypertensive agents in diabetic kidney disease (see Figure 43 in the original guideline document)
- Hypertension and antihypertensive agents in nondiabetic kidney disease (see Figure 51 in the original guideline document)
- Hypertension and antihypertensive agents in kidney transplant recipients (see Figure 53 in the original guideline document)

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations were based primarily on a comprehensive review of published reports. In cases where the data did not appear conclusive, recommendations were based on the consensus opinion of the group.

The rationale for each of the 13 guidelines contains a section on the strength of the evidence. The strength of the evidence includes a series of specific "rationale statements," each supported by evidence, and "summary tables" (if appropriate) compiling and evaluating original reports of studies.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Potential Benefits

- Evaluation of patients with chronic kidney disease (CKD) or hypertension can help define prognosis and guide treatment.
- The goals of antihypertensive therapy in CKD are to lower blood pressure, slow progression of kidney disease, and reduce risk of cardiovascular disease (CVD).
- Self-management is a theory-based approach to health care that recognizes the central role played by the patient in health promotion, disease prevention, and successful management of illness.

Specific Potential Benefits

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) slow the progression of diabetic kidney disease and nondiabetic kidney disease with proteinuria, and in addition, they reduce proteinuria, irrespective of the type of kidney disease.
- Diuretics are useful in the management of most patients with CKD. They reduce extracellular fluid (ECF) volume, lower blood pressure, potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents and reduce the risk of CVD in CKD.
- Refer to the original guideline document for specific potential benefits on individual agents.

POTENTIAL HARMS

Side Effects of Medication

- *Peripheral alpha-adrenergic blockers*. Side effects include postural hypotension, diarrhea, decrease in clearance of verapamil (prazosin only), nasal congestion (reserpine only), sedation (reserpine only, incontinence priapism).
- *Central alpha-adrenergic agonists*. Side effects include sedation, dry mouth, bradycardia, withdrawal hypertension, concomitant beta-blocker therapy), increase serum lithium levels (methyldopa only), hepatic and autoimmune disorders (methyldopa).
- *Directly acting vasodilators*. Side effects include headaches, fluid retention, tachycardia, lupus-like syndrome (hydralazine), hirsutism and pericardial effusion (minoxidil only).
- *Non-selective aldosterone antagonists (spironolactone)*: Side effects include hyperkalemia, metabolic acidosis, gynecomastia, impotence, and hypermenorrhea.
- *Selective aldosterone antagonists (eplerenone)*. Side effects include hyperkalemia, metabolic acidosis, hypertriglyceridemia.
- *Thiazide and loop diuretics*. Side effects include extracellular fluid (ECF) volume depletion, increase in cholesterol, increase in glucose, increase in uric acid, increase in calcium (not with loop diuretics), increase in lithium, decrease in potassium, decrease in sodium, decrease in magnesium; rarely causes blood dyscrasias, photosensitivity, pancreatitis, hyponatremia, erectile dysfunction.
- *Potassium-sparing diuretics*. Side effects include hyperkalemia, metabolic acidosis, folate deficiency (triamterene), and kidney stones (triamterene).
- *Non-selective beta-blockers (and high-dose selective beta-blockers*. Side effects include bronchospasm, impairment of peripheral circulation, and hyperkalemia.
- *Lipid-soluble (metabolized in the liver) beta-blockers*. Side effects include impotence, fatigue, decreased exercise tolerance, and insomnia.
- *All beta-blockers*. Side effects include bradycardia, masking of and prolonging of insulin-induced hypoglycemia, and hyperkalemia.

- *Combined alpha and beta-blockers*. Side effects include postural hypotension and bronchospasm.
- *Angiotensin-converting enzyme (ACE) inhibitors*. Side effects include cough, angioedema (very rare) hyperkalemia, rash, loss of taste, leucopenia, increase in lithium levels.
- *Angiotensin receptor blockers*. Side effects include cough, angioedema (very rare), hyperkalemia, increase in lithium levels.
- *Dihydropyridine calcium-channel blockers*. Side effects include edema of the ankle, flushing, headache, increase in cyclosporine levels (nicardipine only), gingival hypertrophy, "dose dumping" (nifedipine, nisoldipine, felodipine).
- *Non-dihydropyridine calcium channel blockers (CCBs) (e.g., diltiazem, mibefradil, verapamil)*. Side effects include the following: Nausea, headache (diltiazem); constipation (verapamil); conduction defects; worsening of systolic dysfunction; increased levels of other drugs metabolized by the same hepatic enzyme system; decreased serum lithium levels (verapamil only); increase in cyclosporine levels; gingival hyperplasia, constipation.

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Angiotensin-converting enzyme (ACE) inhibitor*. Do not use in pregnancy, history of angioedema, cough due to ACE inhibitors, allergy to ACE or angiotensin receptor blocker (ARB). Use with caution in women not practicing contraception, individuals with bilateral renal artery stenosis, or with drugs causing hyperkalemia.
- *Angiotensin Receptor Blocker*. Do not use in allergy to ACE inhibitor or ARB, pregnancy, cough due to ARB. Use with caution in bilateral renal artery stenosis, drugs causing hyperkalemia, women not practicing contraception, angioedema due to ACE inhibitors.
- *Thiazide and loop diuretics*. Avoid with gout.
- *Potassium-sparing diuretics*. Use with caution in chronic kidney disease (CKD) Stages 3-4 and in patients at increased risk for hyperkalemia.
- *Non-selective beta-blockers (and high-dose selective beta-blockers*. Avoid with asthma, chronic obstructive pulmonary disease, and with severe peripheral vascular disease
- *Lipid-soluble beta-blockers*. Avoid with depression and liver disease (labetalol only).
- *All beta-blockers*. Avoid with bradycardia, second or third degree heart block, and heart failure (except carvedilol, extended release metoprolol, and bisoprolol).
- *Non-dihydropyridine calcium-channel blockers (CCBs)*. Avoid with second and third degree heart block, congestive heart failure due to systolic dysfunction
- *Peripheral alpha-adrenergic system*. Avoid with depression (reserpine only) and peptic ulcer disease (reserpine only)
- *Central alpha-adrenergic blockers*. Avoid with depression and liver disease (methyldopa only).
- *Directly acting vasodilators*. Avoid in lupus (hydralazine only)

- *Non-selective (spironolactone)*. Use with caution in CKD Stages 3-4 and in patients at increased risk for hyperkalemia
- *Selective (eplerenone)*. Use with caution in CKD Stages 3-4 and in patients with increased risk of hyperkalemia

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Use of the Guidelines

These guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management. Individual judgment by responsible clinicians is paramount in treatment of chronic kidney disease.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

Guideline 2: Evaluation of the Patient with Chronic Kidney Disease (CKD)

The risks of hypertension and the need for prompt recognition and evaluation in the general population are well documented. Far less evidence specific to the CKD population is available, and it must be acknowledged that many of the major hypertension trials upon which Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) guidelines are based specifically excluded patients with kidney disease. Nevertheless, the casual blood pressure (CBD) and CKD progression risks are well documented, and so it seems prudent to the guideline developers to follow accepted recommendations in this patient population.

Guideline 3: Measurement of Blood Pressure in Adults

Ambulatory blood pressure monitoring (ABPM) is becoming more widely used, yet important limitations remain such as the expense of equipment and software, and personnel required to apply the equipment; high test-retest variability in some individuals, and reimbursement issues.

Guideline 4: Evaluation for Renal Artery Disease

Recommendations for the optimal management of patients with renal artery disease (RAD) are limited by the absence of long-term, randomized trials comparing medical management versus revascularization interventions upon blood pressure control, glomerular filtration rate (GFR), and cardiovascular

morbidity and mortality. Similarly, the absence of long-term, randomized trials of the medical management of RAD comparing therapy with or without angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) precludes recommending ACE inhibitors or ARBs as preferred antihypertensive agents in RAD.

Guideline 5: Education on Self-Management

Research that pertains to CKD and hypertension is limited. However, data obtained from other clinical populations can be extrapolated for use with the CKD population. Much research has been done in other clinical populations related to lifestyle modifications and behavioral factors that are implicated in an individual's management of hypertension.

Guideline 6: Dietary and Other Therapeutic Lifestyle Changes in Adults

There are few controlled trials designed to determine the effectiveness and safety of dietary therapies to lower blood pressure in patients with CKD.

Guideline 7: Pharmacological Therapy: Use of Antihypertensive Agents in CKD

There are few studies on the treatment of hypertension in CKD. Most of the largest clinical studies in patients with CKD were designed to evaluate the efficacy of therapy in slowing the progression of CKD rather than reducing risk of CVD. Therefore, most of the recommendations in Guideline 7 are extrapolated from clinical studies performed in the general population.

Guideline 8: Pharmacological Therapy: Diabetic Kidney Disease

Recommendations regarding pharmacological therapy in diabetic kidney disease need to be qualified based upon the available data. First, no claims of superiority between ACE inhibitors and ARBs can be made since no randomized trials have compared these agents "head-to-head" in slowing the progression of kidney disease. Second, efficacy of therapy in many studies of diabetic kidney disease with microalbuminuria, efficacy of antihypertensive agents was based on reduced risk of kidney disease progression, as assessed by development of microalbuminuria, rather than decline in glomerular filtration rate (GFR) or onset of kidney failure. It is not practical, however, to conduct studies for the duration of follow-up required to observe a reduction in GFR decline or onset of kidney failure in patients with microalbuminuria; this would take more than 20 years of follow-up. Consequently, evidence from such studies was graded "strong." Moreover, since the level of albumin excretion in normotensive patients with diabetic kidney disease generally does not exceed "microalbuminuria," the recommendation for treating patients without hypertension is graded as "A."

Guideline 9: Pharmacological Therapy: Nondiabetic Kidney Disease

One of the challenges in creating guidelines for pharmacological therapy in nondiabetic kidney disease is that nondiabetic kidney disease encompasses a diverse array of diseases. Differentiating the type of nondiabetic kidney disease is another challenge. As described in the original guideline document, the urine sediment, and kidney imaging procedures may be useful. However, there is large variation in urine protein excretion in types of kidney disease. Therefore, urine protein cut-off values to suggest types of nondiabetic kidney disease are not precise, and urine sediment examination and kidney imaging may not be diagnostic. Another limitation in approaching nondiabetic kidney disease is that there are few large studies of a single type of nondiabetic kidney disease. Further modifications of these recommendations will require the development of more discriminating diagnostic techniques and large studies focusing on single types of nondiabetic CKD.

Guideline 10: Pharmacological Therapy: Kidney Disease in the Kidney Transplant Recipient

There are few randomized, controlled studies of the treatment of hypertension in kidney transplant recipients. Although it is clear from the data that dihydropyridine calcium-channel blockers are effective in controlling blood pressure and maintaining GFR in the posttransplant setting, long-term data are lacking on their effectiveness in slowing progression of kidney disease.

Guideline 11: Use of ACE Inhibitors and ARBs in CKD

Compared to the wealth of data on antihypertensive agents in the general population, there are few data that examine the use of antihypertensive agents in CKD, and fewer data on the adverse effects of those agents. Many of the randomized trials do not provide adequate definitions of the key adverse effects, such as hypotension, decreased kidney function, and hyperkalemia. Data concerning the allergic reactions and fetal abnormalities are derived primarily from observational studies. There are few comparative data either within groups of ACE inhibitors or ARBs, or among agents from different classes. It is unclear whether substitution of one agent from a different class will attenuate an adverse effect. Risk factors for adverse effects need clarification.

Guideline 12: Use of Diuretics in CKD

There is limited information from controlled trials to guide diuretic dosing for blood pressure control. In addition, there are very limited data concerning the antiproteinuric effects of diuretics and the combination of diuretics and ACE inhibitors or ARBs. Moreover, the role of diuretic therapy in CKD progression when congestive heart failure coexists needs to be better clarified.

Guideline 13: Special Considerations in Children

There are virtually no studies in children that evaluate the effect of antihypertensive therapy on progression of CKD or the incidence of cardiovascular disease. Multiple studies demonstrate that antihypertensive therapy is effective in lowering blood pressure in children and some studies

demonstrate that antihypertensive therapy with an ACE inhibitor is effective in reducing proteinuria. Thus, the recommendations in this guideline are based upon studies in adults and studies in children using surrogate markers.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation issues related to each of the guidelines are discussed in the original guideline document. In addition, recommendations for clinical performance measures are provided for guidelines 2, 7, 8, 9, and 13.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004 May;43(5 Suppl 1):S1-290. [625 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 May

GUIDELINE DEVELOPER(S)

National Kidney Foundation - Disease Specific Society

SOURCE(S) OF FUNDING

National Kidney Foundation (NKF)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The National Kidney Foundation makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

Specifically, all members of the Work Group are required to complete, submit, and sign a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. All affiliations are published in their entirety at the end of the original guideline document in the biographical sketches of the Work Group members.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the National Kidney Foundation (NKF) Web site.

Print copies: Available from the National Kidney Foundation (NKF), 30 East 33rd St., New York, NY 10016. These guidelines are also available on CD-ROM from NKF.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on February 23, 2005.

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Date Modified: 9/22/2008