**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** Click here to enter NQF number

**Measure Title**: Adult Kidney Disease: Angiotensin Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Click here to enter composite measure #/ title

**Date of Submission**: 2/27/2015

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| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Health outcome: [**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4)that the measured intermediate clinical outcome leads to a desired health outcome. * Process: [**5**](#Note5) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured structure leads to a desired health outcome. * Efficiency: [**6**](#Note6) evidence not required for the resource use component.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Outcome

Health outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors*

Intermediate clinical outcome (*e.g., lab value*): Click here to name the intermediate outcome

Process: increasing the number of patients with CKD and albuminuria who are prescribed ACE inhibitor or ARB therapy. ACE inhibitors and ARBs are recommended as preferred agents for diabetic kidney disease and nondiabetic kidney diseases with proteinuria

Structure: Click here to name the structure

Other: Click here to name what is being measured

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**HEALTH OUTCOME/PRO PERFORMANCE MEASURE**  *If not a health outcome or PRO, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

This is a process measure aimed at increasing the number of patients with CKD and albuminuria who are prescribed ACE inhibitor or ARB therapy. ACE inhibitors and ARBs are recommended as preferred agents for diabetic kidney disease and nondiabetic kidney diseases with proteinuria, even in the absence of hypertension. In these diseases, they lower blood pressure, reduce proteinuria (albuminuria), slow the progression of kidney disease, and likely reduce CVD risk by mechanisms in addition to lowering blood pressure. (National Kidney Foundation. (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. May:43(5 Suppl 1):S1-S290.)

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (*i.e., influence on outcome/PRO*).**

The guideline recommendations supporting this measure are focused on the use of ACE inhibitors and ARBs in patients with CKD, with or without hypertension. The guideline focuses on the adult CKD population but also includes special considerations for the pediatric CKD population. This measure specifically focuses on patients with CKD stages 1-5 that are not receiving renal replacement therapy. The measure also includes patients that have proteinuria, and is therefore, more specific, with regards to the patient population. Proteinuria, which includes the measurement of all proteins in the urine, is discussed in the guideline with regards to therapy and improved outcomes for CKD patients. The requirement for proteinuria in the denominator for these measures is based on growing controversy regarding the appropriateness of prior recommendations for a BP <130/80 and for the use of ACE inhibition/angiotensin receptor blockade in non-proteinuric kidney disease (Chang TI, Cheung AK, Chertow GM. Blood pressure control in type 2 diabetes mellitus. Am J Kidney Dis 2010; 56: 1029-1031 & Agarwal R. Blood pressure goal in chronic kidney disease: what is the evidence? Current Opinion in Nephrology & Hypertension 2011; 20:229–232).

The evidence cited in support of the measure, demonstrates the association between patients with chronic kidney disease and hypertension. The guideline states that patients with CKD should be considered in the "highest risk" group for cardiovascular disease, that the target blood pressure for CVD risk reduction in CKD should be <130/80 mmHg, that patients with diabetic kidney disease (with or without hypertension) should be treated with an ACE inhibitor or an ARB, that ACE inhibitors and ARBs are effective in slowing the progression of kidney disease with microalbuminuria due to type 1 and type 2 diabetes, that 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, that ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases, and that the beneficial effect is greater in patients with higher levels of proteinuria. The measure numerator captures patients with CKD and albuminuria who were prescribed ACE inhibitor or ARB therapy within a 12-month period.

The recommendation statements from the guideline 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 macroalbuminuria, rather than decline in 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." A 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.

KDOQI 2012 Update: The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent\*) in whom treatment with BP-lowering drugs is indicated. (2D)

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

*Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

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**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes**. Include all the steps between the measure focus and the health outcome.

Measure addresses underuse of effective services (evaluation and treatment strategies)

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

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**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

National Kidney Foundation. (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. May:43(5 Suppl 1):S1-S290. <http://www.ajkd.org/issue/S0272-6386%2800%29X0083-2>

#### National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. American Journal of Kidney Diseases , Volume 60 , Issue 5 , 850 - 886 <http://www.ajkd.org/article/S0272-6386%2812%2900957-2/fulltext#sec12>

KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414. <http://www.guideline.gov/content.aspx?id=39430>

James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311(5):507-520. doi:10.1001/jama.2013.284427 (<http://jama.jamanetwork.com/article.aspx?articleid=1791497>)

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

**KDOQI 2012: 6.2: We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels ≥30 mg/g who are at high risk of DKD or its progression. (**2C**)**

KDIGO: **Blood Pressure Management in CKD ND Patients without Diabetes Mellitus**

The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent\*) in whom treatment with BP-lowering drugs is indicated. (2D)

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

KDIGO: **Blood Pressure Management in CKD ND Patients with Diabetes Mellitus**

The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent\*). (2D)

The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent\*). (1B)

JNC 8: Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

JNC 8: Recommendation 8

In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

KDIGO:

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| **Level 1** 'The Work Group recommends' | 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** 'The Work Group suggests' | 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 debate and involvement of stakeholders before policy can be determined. |

Grade 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.

Grade C: Low: The true effect may be substantially different from the estimate of the effect.

Grade D: Very Low: The estimate of effect is very uncertain, and often will be far from the truth.

JNC Grade B: Moderate Recommendation

There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

Grade A: High: The Work Group is confident that the true effect lies close to that of the estimate of the effect.

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

Yes **→ *complete section*** [***1a.7***](#Section1a7)

No **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

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**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

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**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

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**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

*If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.*

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

KDOQI:

1. Establishment of individualized target blood pressure (BP)
2. Inquiring about dizziness and postural hypotension when BP-lowering drugs are used
3. Lifestyle modification
   * Achieving/maintaining healthy body weight
   * Lowering salt intake
   * Exercise program
   * Limiting alcohol intake
4. Use of BP-lowering drugs:
   * Angiotensin converting enzyme inhibitors (ACE-Is)
   * Angiotensin receptor blockers (ARBs)
   * Other BP-lowering drugs or combinations (aldosterone antagonists, beta-blockers, calcium-channel blockers, diuretics)
5. Blood pressure management in patients without diabetes mellitus
6. Blood pressure management in patients with diabetes mellitus
7. Blood pressure management in kidney transplant recipients
8. Blood pressure management in children
9. Blood pressure management in the elderly

KDIGO: The 2012 guideline update effort was a voluntary and multidisciplinary undertaking that included input from NKF scientific staff, an evidence review team from the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, and a Work Group of experts in relevant disciplines. The approach to the systematic literature review and the comprehensive findings prepared for this update are reported in detail elsewhere.[7](javascript:void(0);) Briefly, MEDLINE was searched to identify randomized controlled trials published between January 2003 and October 2010 that related to albuminuria, glycemic and lipid management in patients with diabetes. All titles and abstracts were assessed for their appropriateness to address key questions that were developed by the multidisciplinary team and outlined in [Fig 1](http://www.ajkd.org/cms/attachment/2009271352/2032268933/gr1.jpg). Study reference lists, reviews, and meta-analyses were evaluated and references to other clinical trials were elicited from members of the Work Group. Data from each study that pertained to study quality, trial characteristics, population characteristics, efficacy, outcomes, withdrawals, and adverse events were extracted. Evidence tables were created to address the key questions. Study quality was rated as good, fair, or poor according to criteria suggested by the Cochrane Collaboration, and included information on adequate allocation concealment, method of blinding, use of the intention-to-treat principle for data analysis, reporting of dropouts, and reasons for attrition.

JNC: This evidence-based hypertension guideline focuses on the panel’s 3 highest-ranked questions related to high BP management identified through a modified Delphi technique.[5](http://jama.jamanetwork.com/article.aspx?articleid=1791497#jsc130010r5) Nine recommendations are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

See above

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

See above

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**: 1966-2012

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

Overall, for KDOQI´s clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease, 11,688 abstracts were screened by the Evidence Review Team, 899 articles were retrieved and reviewed, and data were extracted from 177 articles. Forty-seven articles were added by the Work Group. Finally, results from 76 articles were systematically included in the guideline. The total number of studies reviewed was not specified. (2004) quality (highest first), then by applicability (widest first), and then by study size (largest first). (2004)

KDOQI 2012 Update: This report builds upon the previous guideline published by NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) in 2004.[2](javascript:void(0);) 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.

KDIGO 2012*:* A total of 10,657 citations were initially screened, and 247 articles were retrieved. Data extraction was performed on 55 studies. The overall search yield along with the number of abstracts identified and articles reviewed for each topic are presented in Table 8 of the original guideline document.

JNC8: Initial search dates for the literature review were January 1, 1966, through December 31, 2009. The search strategy and PRISMA diagram for each question is in the online Supplement. To ensure that no major relevant studies published after December 31, 2009, were excluded from consideration, 2 independent searches of PubMed and CINAHL between December 2009 and August 2013 were conducted with the same MeSH terms as the original search. Three panel members reviewed the results. The panel limited the inclusion criteria of this second search to the following. (1) The study was a major study in hypertension (eg, ACCORD-BP, SPS3; however, SPS3 did not meet strict inclusion criteria because it included nonhypertensive participants. SPS3 would not have changed our conclusions/recommendations because the only significant finding supporting a lower goal for BP occurred in an infrequent secondary outcome).[7](http://jama.jamanetwork.com/article.aspx?articleid=1791497#jsc130010r7),[8](http://jama.jamanetwork.com/article.aspx?articleid=1791497" \l "jsc130010r8) (2) The study had at least 2000 participants. (3) The study was multicentered. (4) The study met all the other inclusion/exclusion criteria. The relatively high threshold of 2000 participants was used because of the markedly lower event rates observed in recent RCTs such as ACCORD, suggesting that larger study populations are needed to obtain interpretable results. Additionally, all panel members were asked to identify newly published studies for consideration if they met the above criteria. No additional clinical trials met the previously described inclusion criteria. Studies selected were rated for quality using NHLBI’s standardized quality rating tool (see Supplement) and were only included if rated as good or fair.

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB. ACE inhibitors and ARBs are effective in slowing the progression of kidney disease with microalbuminuria due to type 1 and type 2 diabetes (Strong). 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. ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases (Strong). The beneficial effect is greater in patients with higher levels of proteinuria (Strong). All these recommendations are "Strong," indicating that the evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes.

For Patients with Diabetic Kidney Disease:

A large number of epidemiological studies and controlled trials have defined risk factors for progression of diabetic kidney disease, and response to treatment. Because of the high prevalence of diabetes in the population, many individuals with other types of CKD may also have diabetes. In general, the guidelines for use of antihypertensive agents in kidney disease due to diabetes and due to other causes do not conflict. For GUIDELINE 8: PHARMACOLOGICAL THERAPY: DIABETIC KIDNEY DISEASE, ACE inhibitors and ARBs are compared to other classes of antihypertensive agents. There are few studies directly comparing these two classes to each other in diabetic kidney disease, and no comparative outcome studies. In these studies, diuretics were frequently used as an additional antihypertensive agent to achieve blood pressure control. In addition, some data are provided comparing other classes of antihypertensive agents. ACE inhibitors and ARBs lower urine albumin excretion, slow the rise in albumin excretion and delay the progression from microalbuminuria to macroalbuminuria in kidney disease due to type 1 and type 2 diabetes. Follow-up in these studies was generally in the range of 2 to 4 years, so in most studies GFR was stable and there was no difference in GFR decline between the ACE inhibitor or ARB groups and control groups. Because of the long duration of follow-up necessary to ascertain an effect of interventions on GFR decline in a study of patients with microalbuminuria, and the proven beneficial effect of ACE inhibitors and ARBs in later stages of diabetic kidney disease, the [Guideline Development] Work Group considered that these studies provided "strong" evidence, even though they are based on a surrogate endpoint. Because of the early stage of kidney disease, some patients in these studies were not hypertensive. Consequently, patients in the ACE inhibitor or ARB group had lower mean blood pressure during follow-up than patients in the control group. In some studies, the beneficial effect of ACE inhibitors or ARBs appeared greater than the difference in mean follow-up blood pressure or persisted after adjustment for follow-up blood pressure in multiple regression analysis, suggesting that the benefit is due to mechanisms in addition to the antihypertensive effect. An individual patient meta-analysis of 646 patients in 10 randomized clinical trials confirmed these results. Consequently, the [Guideline Development] Work Group concluded that ACE inhibitors and ARBs are preferred agents for diabetic kidney disease with microalbuminuria and should be prescribed for patients with or without hypertension.

There are conflicting data on the efficacy of ACE inhibitors in kidney disease due to type 2 diabetes. Some studies show greater reduction in albuminuria and slowing the decline in GFR. However, the small sample size, the use of surrogate outcomes, and inconsistent results on surrogate outcomes preclude definitive conclusions. In contrast, a recent analysis of the large subgroup of patients with type 2 diabetes and estimated GFR <60 mL/min/1.73 m2 enrolled in ALLHAT showed no beneficial effects of an ACE inhibitor (lisinopril) compared to a diuretic (chlorthalidone) on decline in GFR or onset of kidney failure over a 4-year interval when each agent was used separately. There are insufficient data on the efficacy of ARBs in kidney disease due to type 1 diabetes. The [Guideline Development] Work Group found no long-term, controlled trials on the use of ARBs in patients with kidney disease due to type 1 diabetes. However, based on the shared properties of both drug classes in inhibiting the RAS, it may also be extrapolated that ARBs may be as effective as ACE inhibitors and more effective than other antihypertensive classes in slowing the progression of kidney disease due to type 1 diabetic kidney disease. Thus, it is the opinion of the [Guideline Development] Work Group that ARBs can be used as an alternative class of agents to slow kidney disease progression if ACE inhibitors cannot be used.

Two meta-analyses have demonstrated a greater effect of ACE inhibitors compared to other classes of antihypertensive agents on reducing proteinuria in diabetic kidney disease. Other studies show a larger effect of ARBs compared to other classes.

KDIGO 2012 update: The Work Group sought to build on the evidence base from the previous KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. As the first search for the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline was conducted in July 2002, the search for the current KDIGO Guideline included publications since January 2002. Search strategies were developed by the Evidence Review Team (ERT) with input from the Work Group. The text words or medical subject headings (MeSH) that were included are provided in Supplementary Appendix 1 online (see the "Availability of Companion Documents" field). Non-human studies and those focusing on dialysis, pregnancy, neonates, malignant hypertension, acute kidney injury, or drug pharmacology were excluded.

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

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

In general, the guidelines for use of antihypertensive agents in kidney disease due to diabetes and due to other causes do not conflict.

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.

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

Use of an ACEI or an ARB will commonly increase serum creatinine and may produce other metabolic effects such as hyperkalemia, particularly in patients with decreased kidney function. Although an increase in creatinine or potassium level does not always require adjusting medication, use of renin-angiotensin system inhibitors in the CKD population requires monitoring of electrolyte and serum creatinine levels, and in some cases, may require reduction in dose or discontinuation for safety reasons.

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

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**1a.8 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.8.1** **What process was used to identify the evidence?**

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**