Objectives

This systematic review evaluates the evidence regarding the potential benefits and harms of: (1) screening adults for early-stage chronic kidney disease (CKD stages 1–3); (2) monitoring adults with CKD stages 1–3 for progression of kidney dysfunction and/or kidney damage; and (3) treating adults with CKD stages 1–3.

This report’s scope is limited to CKD stages 1–3 to inform patient care decisions of primary care physicians. Management of patients with CKD stages 4–5, generally performed by nephrologists, is outside the scope of the report. An additional aim of the report is to provide a synthesis of evidence to assist groups developing clinical practice recommendations regarding CKD screening and management.

Background

Definition of CKD

In CKD, the kidneys are damaged and/or cannot filter blood normally.\(^1\) CKD increases the risk for many adverse health outcomes, including cardiovascular disease, end-stage renal disease (ESRD), and mortality. However, CKD is usually asymptomatic until its most advanced state.
CKD has been defined as decreased kidney function and/or kidney damage persistent for at least 3 months. Kidney dysfunction is indicated by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², while kidney damage most frequently is manifested as increased urinary albumin excretion. Within this framework, CKD has been categorized into five stages:

• Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m².
• Stage 2: Kidney damage with GFR 60–89 mL/min/1.73 m².
• Stage 3: GFR 30–59 mL/min/1.73 m² regardless of kidney damage.
• Stage 4: GFR 15–29 mL/min/1.73 m² regardless of kidney damage.
• Stage 5: GFR <15 mL/min/1.73 m² regardless of kidney damage, or kidney failure treated by dialysis or transplantation.

A recent series of meta-analyses of large prospective cohort studies demonstrated the independent associations of each level of estimated GFR (eGFR) and albuminuria or dipstick proteinuria with total and cardiovascular mortality, ESRD, and acute kidney injury (AKI). These associations were independent of cardiovascular risk factors. Informed by these results, a CKD consensus conference concluded that CKD staging should be modified:

• Divide Stage 3 into 3a (GFR 45–59 mL/min/1.73m²) and 3b (GFR 30–44 mL/min/1.73m²).
• Add albuminuria strata within each GFR stage (urine albumin-creatinine ratio <30 mg/g [normoalbuminuria], 30–299 mg/g [microalbuminuria], or >300 mg/g [macroalbuminuria]).
• Identify the cause of CKD when possible.

Epidemiology of CKD

Approximately 11 percent of U.S. adults age 20 or older (23.5 million persons) have CKD. Of these, nearly half are stage 1 or 2, nearly another half are stage 3, fewer than 4 percent are stage 4, and fewer than 2 percent are stage 5 and receive dialysis. Also, about half have albuminuria without impaired GFR, one-third have decreased GFR without albuminuria, and one-sixth have albuminuria plus impaired GFR. Of individuals with albuminuria, nearly 85 percent have microalbuminuria and the remainder have macroalbuminuria. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that the prevalence of CKD is rising, particularly for stage 3.

Etiology of CKD

Infrequently, CKD is caused by primary kidney disease (e.g., glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease). But in the vast majority of cases, it is associated with other medical conditions, such as diabetes and hypertension. For example, excluding those with ESRD, in 2008, 48 percent of Medicare patients with CKD had diabetes, 91 percent had hypertension, and 46 percent had atherosclerotic heart disease. Other risk factors for CKD include older age, obesity, family history, and African American, Native American, or Hispanic ethnicity.

Screening for Early-Stage CKD

The rationale for considering screening for early-stage CKD includes the high and rising prevalence of CKD, its known risk factors, its numerous adverse health consequences, its long asymptomatic phase, the availability of potential screening tests for CKD, and the availability of treatments that may alter the course of early-stage CKD and reduce complications of early-stage CKD or its associated health conditions.

Some organizations already recommend CKD screening in selected populations. Kidney Disease: Improving Global Outcomes (KDIGO) recommends screening of all patients with hypertension, diabetes, or cardiovascular disease. The American Diabetes Association recommends annual screening of all adults with diabetes, based on “expert consensus or clinical experience.” The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends annual screening of all patients with combined hypertension and diabetes. Also advocating selected screening, the National Kidney Foundation sponsors free CKD screening for all adults with hypertension, diabetes, or a primary relative with a history of kidney disease, hypertension, or diabetes.

Nevertheless, the benefit of screening for early-stage CKD is uncertain. For screening to be beneficial, it should improve important clinical outcomes (while limiting harms) for screened individuals identified with CKD compared with individuals with CKD whose treatment started at a later time or stage. However, potential CKD treatments may be indicated for conditions associated with CKD. So demonstration of benefit from CKD screening requires that the treatment benefits CKD populations who
would have had no indication for such treatment in the absence of CKD or that, among patients with an indication for the treatment, those with CKD have a relatively greater treatment benefit or benefit from the treatment at doses or treatment targets different from those of non-CKD patients.

Monitoring Early-Stage CKD for Progression

In most patients with CKD stages 1–3, GFR declines slowly.\textsuperscript{12} However, the rate of decline varies among individuals, and many factors appear to impact progression.\textsuperscript{13} Because CKD stages 1–3 usually progress asymptptomatically, detection of early-stage CKD requires laboratory testing.

Some organizations recommend monitoring for changes in kidney function or damage in patients with CKD. For example, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends at least annual eGFR measurement in adults with CKD in order to predict onset of ESRD and evaluate the effect of CKD treatments.\textsuperscript{13} JNC7 recommends annual quantitative measurement of albuminuria in all patients with “kidney disease.”\textsuperscript{14} KDOQI also recommends more frequent monitoring of CKD patients with worsening kidney function.\textsuperscript{15}

Confirming the benefits of monitoring patients with CKD stages 1–3 for changes in kidney function or damage requires evidence similar to that for CKD screening. Treatment modified because of monitoring results would need to improve important clinical outcomes more than treatment modified at a later time or stage does, while limiting harms.

Treatment of CKD Stages 1–3

In most patients with nonprimary CKD stages 1–3, treatment is not directed at the CKD but at associated conditions or cardiovascular risk factors, such as diabetes and hypertension.\textsuperscript{16} In efforts to reduce the risk of complications from these conditions, therapeutic goals are sometimes set more strictly for CKD patients than non-CKD patients. For example, JNC7 recommends a blood pressure goal of $<130/80$ mm Hg for patients with CKD or diabetes.\textsuperscript{14} It has been suggested that medications such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may specifically treat CKD. However, whether their impact on CKD outcomes (e.g., incident ESRD) or markers (e.g., albuminuria)\textsuperscript{17} is independent of their effect to lower blood pressure is not clear.\textsuperscript{18}

Analytic Framework and Key Questions

During this project’s topic refinement, we received feedback regarding the scope and relevance of draft Key Questions and feedback regarding the details of a draft protocol. The feedback came from the topic nominators, public reviewers, and a Technical Expert Panel (TEP) composed of researchers, clinicians, and representatives from numerous interested professional organizations and Federal and State agencies. These parties agreed that an independent comprehensive review of the issues introduced above would provide helpful guidance to clinicians and policymakers regarding diagnosis and management of early-stage CKD. There was consensus that the analytic framework, shown in Figure A, and Key Questions addressed the most important issues regarding CKD stages 1–3.

**Key Question 1.** In asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

**Key Question 2.** What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications?

**Key Question 3.** Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

**Key Question 4.** Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function and/or kidney damage?

**Key Question 5.** Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

**Key Question 6.** Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from treatment?
Methods

We searched MEDLINE® and the Cochrane Database of Systematic Reviews (January 1985 to January 2011) to identify randomized controlled trials (RCTs) and controlled clinical trials (CCTs) of screening for and monitoring and treatment of patients with CKD. When no RCTs were identified that evaluated a CKD screening or monitoring intervention and reported outcomes, indirect evidence was reviewed regarding possible benefits and harms. This indirect evidence included observational studies on CKD prevalence, progression, and clinical recognition as well as accuracy and reliability of CKD screening and monitoring tests, and RCTs of CKD treatments. Although these observational studies were not identified through a comprehensive literature search, whenever possible we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs. All titles and abstracts were assessed for eligibility based on Key Question–specific inclusion/exclusion criteria.

For treatment intervention studies, data were extracted pertaining to study quality, trial characteristics, population characteristics, efficacy outcomes, and withdrawals and adverse events. Study quality for each trial was rated to formally assess risk of bias. For each treatment comparison and major outcome, overall strength of evidence for the RCTs was evaluated using methods developed by the Agency for Healthcare Research and Quality and the Effective Health Care Program. Briefly, strength of the evidence was evaluated based on four required domains: risk of bias, consistency, directness, and precision. Based on these four domains, the overall evidence was rated as: (1) high, indicating high

ACEI = angiotensin converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; MI = myocardial infarction; QOL = quality of life.
confidence that further research is very unlikely to change the confidence in the estimate of effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, indicating low confidence that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion. If heterogeneity of patient populations, interventions, and outcomes was minimal, we pooled results using Review Manager 5.0. Random effects models were used to generate pooled estimates of relative risks and 95 percent confidence intervals. Statistical heterogeneity was summarized using the $I^2$ statistic. Additional evidence on CKD screening and monitoring was qualitatively described.

**Results**

We found no direct RCT evidence that addressed whether systematic CKD screening or monitoring improves clinical outcomes or increases harms. Indirect evidence that these interventions improve outcomes would need to include evidence that CKD treatment improves outcomes. Therefore, the ordering of the Results section has been changed from that of the Key Questions to be consistent with this logical flow.

**CKD Treatment Benefits and Harms**

- In RCTs of patients with CKD stages 1–3, several treatments reduced the risk of clinical outcomes, but the benefits appeared to be limited to specific CKD subgroups, some of which already had a clinical indication for the treatment studied (Table A).
- Only limited data addressed whether the relative effectiveness of treatment differed between patients with and without CKD or between patients with different severities of CKD.
- Trials used heterogeneous entrance criteria for renal function and damage, which often did not match KDOQI definitions for CKD stages 1–3 precisely, so we considered reasonable overlap sufficient for inclusion in this evidence synthesis. Because trials also rarely reported outcomes stratified by CKD stage or other CKD markers, it was difficult to determine if trial clinical benefits applied to patients within individual CKD stages or eGFR or albuminuria categories.
  - ACEI and/or ARB treatment significantly reduced ESRD risk in patients with proteinuria (macroalbuminuria), most of whom had diabetes and hypertension. ESRD was not significantly reduced in patients with CKD stages 1–3 who did not have proteinuria. Patients with proteinuria, diabetes, and hypertension may benefit from ACEI or ARB treatment.  
  - ACEI treatment significantly reduced mortality risk in patients known to have microalbuminuria who had either cardiovascular disease or the combination of diabetes and other cardiovascular risk factors. Relative risk reduction was not significantly different than in similar patients who did not have microalbuminuria. Patients who had microalbuminuria and were at high risk for cardiovascular complications may benefit from ACEI treatment at adequate doses.  
  - Statins significantly reduced the risk of mortality, myocardial infarction (MI), and stroke in patients with hyperlipidemia and impaired eGFR or creatinine clearance, including those without coronary artery disease. Patients with hyperlipidemia and no coronary artery disease may not otherwise have an indication for statins, but the subset with CKD may benefit from treatment. No statin trials reported clinical outcomes data for patients with albuminuria.  
  - Beta blockers significantly reduced the risk of mortality, MI, and congestive heart failure (CHF) events in patients with CHF and impaired eGFR or creatinine clearance, including those without coronary artery disease. Patients with systolic CHF already have an indication for beta blockers, regardless of whether they have CKD.  
  - In RCTs that compared different active treatments head to head (e.g., ACEI versus ARB, ACEI versus beta blocker), there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.  
  - In RCTs that compared high- versus low-dose treatment (ARB, statin), strict versus standard control (blood pressure, glycemia), combination versus monotherapy, and intensive multidisciplinary interventions (simultaneous targeting of blood pressure, diabetes, cholesterol, and/or reducing nephrotoxic drug exposure) versus usual care, there was no consistent significant difference in clinical
outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.

- Low-protein diets did not significantly reduce risk of mortality, ESRD, or any clinical vascular outcome compared with usual protein diets; risk for a composite renal outcome was significantly reduced in one trial, but this study also included participants with CKD stages 4–5.

  • Few RCTs reported information on study withdrawals. When reported, withdrawals were often high and infrequently were separated by treatment group.

  • Few trials reported adverse events. When reported, adverse events often did not appear to be predefined, were not systematically collected or reported, and often were not reported separately by treatment group.

  • Although limitations in reporting impeded the quantitative synthesis of withdrawal and adverse events data from different studies, adverse events reported generally were consistent with known potential adverse effects of these treatments (e.g., hypotension with antihypertensives; cough with ACEIs; edema with calcium channel blockers; hyperkalemia with ACEIs, ARBs, and aldosterone).

CKD Screening Benefits and Harms

  • We found no direct RCT evidence that addressed whether systematic screening of adults for CKD improves clinical outcomes or increases harms.

  • Results from studies not directly linking systematic CKD screening to clinical outcomes contributed indirect evidence regarding whether CKD screening improves clinical outcomes.

    - Microalbuminuria and eGFR are sensitive screening tests for detecting one-time kidney abnormalities that may reflect CKD, but false positive rates are substantial, particularly for microalbuminuria; their sensitivity and specificity for CKD as defined by kidney dysfunction or damage lasting 3 months or longer is unknown.

    - Most patients with CKD stages 1–3 are clinically unrecognized. Because even populations with a high CKD prevalence (e.g., diabetes, hypertension, cardiovascular disease, older age) are not routinely tested for CKD, especially for albuminuria, systematic screening likely would lead to a large increase in CKD diagnoses.

- Because of the above-noted treatment benefits in patients who have cardiovascular disease or diabetes combined with other cardiovascular risk factors (e.g., hypertension) and are known to have albuminuria, screening such patients for microalbuminuria or macroalbuminuria could lead to early initiation of ACEI or ARB treatment and reduced risk of mortality or ESRD.

- Because of the above-noted treatment benefits in patients who have hyperlipidemia without cardiovascular disease and are known to have impaired eGFR or creatinine clearance, screening such patients for impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.
- Virtually no RCTs of CKD treatments identified participants through screening, so the generalizability of treatment RCT results to patients with CKD stages 1–3 identified through screening is unknown.

- We found insufficient strength of evidence addressing potential harms associated with systematic CKD screening.

**CKD Monitoring Benefits and Harms**

- We found no direct RCT evidence regarding whether systematic monitoring of adults with CKD stages 1–3 for worsening kidney function or damage improves clinical outcomes.

- Results from studies not directly linking systematic CKD monitoring to clinical outcomes contributed indirect evidence regarding whether CKD monitoring improves clinical outcomes.

- Because of the above-noted treatment benefits in patients with albuminuria who have cardiovascular disease or have diabetes combined with other cardiovascular risk factors (e.g., hypertension), monitoring patients with impaired eGFR for development of albuminuria could lead to early initiation of ACEI or ARB treatment and reduced mortality or ESRD risk.

- Because of the above-noted treatment benefits in patients with hyperlipidemia who have impaired eGFR or creatinine clearance, monitoring such patients for development of impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.

- In patients with CKD stages 1–3, kidney function usually slowly worsens over years, but may worsen faster in selected subgroups (e.g., those with diabetes, proteinuria, hypertension, older age, obesity, or dyslipidemia).

- The sensitivity and specificity of eGFR and albuminuria for identifying CKD progression in patients with CKD stages 1–3 are unknown.

- The vast majority of patients with recognized CKD stages 1–3 have serum creatinine measured regularly, so implementation of systematic eGFR monitoring may have only a limited impact on current practice. Because only a minority of patients with CKD stages 1–3 are annually tested for albuminuria, systematic albuminuria monitoring likely would lead to an increase in patients identified with clinical worsening of CKD.

- We found insufficient strength of evidence addressing potential harms associated with systematic CKD monitoring.

Table A summarizes the evidence for specific comparative effectiveness studies addressed in Key Question 5.
### Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3

<table>
<thead>
<tr>
<th>Treatment, Trials, Number of Patients</th>
<th>Level of Evidence</th>
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</table>
| ACEI vs. placebo 17 trials; 11,661 patients | Mortality: moderate ESRD: moderate | • There was no significant difference in risk of all-cause or cardiovascular mortality, MI, or stroke overall, but significantly reduced risk of mortality in patients at high risk for cardiovascular complications who had microalbuminuria.  
• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, MI, or stroke.  
• ACEI significantly reduced ESRD risk in patients with overt proteinuria.  
• ACEI significantly reduced risk of all examined composite renal outcomes, but of few examined composite vascular outcomes.  
• **Limits:** Few studies were designed to assess clinical outcomes; there was considerable variability in the definitions of clinical outcomes. |
| ACEI vs. ARB 6 trials; 4,799 patients | Mortality: low ESRD: insufficient | • There was no significant difference in risk of all-cause or cardiovascular mortality, MI, or CHF; no data for stroke, ESRD, or composite vascular outcomes.  
• Results from the CKD subset of the ONTARGET study, whether defined by GFR <60 ml/min/1.73m² or albuminuria, showed no difference in risk of composite renal outcome.  
• **Limits:** There were small sample sizes in all but one trial; few trials reported most outcomes; there were few events in trials reporting. |
| ACEI vs. CCB 6 trials; 4,357 patients | Mortality: low ESRD: low | • There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, any composite vascular endpoint, or ESRD.  
• ACEI significantly reduced risk of composite renal outcome in one of three trials.  
• **Limits:** Several studies were not designed for/reported no clinical outcomes; most outcomes were reported in few trials; there were few events in trials reporting. |
| ACEI vs. BB 3 trials; 1,080 patients | Mortality: low ESRD: low | • There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, composite vascular endpoints, or ESRD.  
• In one trial, ACEI significantly reduced risk of composite renal outcome.  
• **Limits:** Only one trial was designed to evaluate clinical vascular outcomes. |
| ACEI vs. diuretic 2 trials; 4,716 patients | Mortality: insufficient ESRD: low | • There was no significant difference in risk of all-cause mortality, stroke, ESRD, or composite vascular or renal outcomes.  
• **Limits:** One trial was not designed for clinical events; one trial was post hoc subgroup analysis with no mortality data by CKD status. |
| ARB vs. placebo 5 trials; 5,769 patients | Mortality: high ESRD: high | • There was no significant difference in risk of all-cause mortality, cardiovascular mortality, MI, or composite vascular outcomes.  
• ARB significantly reduced risk of CHF hospitalization and ESRD; results were mixed regarding risk of composite renal outcomes.  
• **Limits:** Several outcomes came from only one trial or were not reported. |
### Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

<table>
<thead>
<tr>
<th>Treatment, Trials, Number of Patients</th>
<th>Level of Evidence</th>
<th>Summary, Conclusion, Comments</th>
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</table>
| ARB vs. CCB 3 trials; 3,924 patients | Mortality: low ESRD: low | • There was no significant difference in risk of all-cause mortality, stroke, composite vascular outcomes, or ESRD.  
• **Limits:** Most outcomes were uncommon or reported in only one trial. |
| ACEI+ARB vs. ACEI 6 trials; 7,357 patients | Mortality: moderate ESRD: insufficient | • There was no significant difference in risk of all-cause mortality.  
• Few vascular outcomes were reported, although combination significantly reduced risk of composite vascular outcome in one trial.  
• **Limits:** There were few clinical events and little data on renal outcomes. |
| ACEI+ARB vs. ARB 3 trials; approximately 4,300 patients | Mortality: insufficient ESRD: insufficient | • Only one trial reported all-cause mortality (no deaths in any treatment group); no trials reported information on vascular outcomes or ESRD.  
• **Limits:** There were few clinical events. |
| ACEI+ARB vs. ACEI or ARB 1 trial; 8,933 patients | Mortality: moderate ESRD: low | • There was no significant difference in risk of all-cause mortality, cardiovascular mortality, ESRD, or single composite vascular outcome reported.  
• **Limits:** This was a single post hoc analysis. |
| ACEI+CCB vs. ACEI 1 trial; 481 patients | Mortality: insufficient ESRD: insufficient | • No data were reported for mortality or individual vascular or renal outcomes.  
• There was no significant difference in risk of composite vascular outcome of serious cardiovascular events.  
• **Limits:** Few events were reported. |
| ACEI+CCB vs. ACEI+diuretic 2 trials; 1,425 patients | Mortality: insufficient ESRD: insufficient | • There was no significant difference in risk of mortality, “cardiac disorders,” “vascular disorders,” or a single composite renal outcome.  
• **Limits:** There were few deaths or renal events; no other clinical outcomes were reported. |
| ACEI+diuretic vs. placebo 1 trial; 4,526 patients | Mortality: low ESRD: insufficient | • There was no significant difference in risk of all-cause or cardiovascular mortality, MI, stroke, composite vascular outcome, or composite renal outcome.  
• **Limits:** This was a single post hoc analysis. |
| ARB vs. different ARB 2 trials; 1,745 patients | Mortality: Telmisartan vs. losartan low; telmisartan vs. valsartan low ESRD: Telmisartan vs. losartan insufficient; telmisartan vs. valsartan low | • Compared with losartan, telmisartan significantly reduced risk of mortality and one composite vascular outcome but not a composite renal outcome.  
• There was no significant difference between telmisartan and valsartan in risk of all-cause or cardiovascular mortality, MI, stroke, CHF hospitalization, ESRD, or composite vascular or renal outcomes.  
• **Limits:** There were few clinical events; no studies compared losartan and valsartan. |
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<th>Treatment, Trials, Number of Patients</th>
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<th>Summary, Conclusion, Comments</th>
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| ARB vs. ARB (high vs. low dose) 3 trials; 998 patients | Mortality: insufficient ESRD: insufficient | - One trial reported three total deaths; a second trial reported that there were no deaths in any treatment groups.  
- No other cardiovascular or renal outcomes were reported.  
- **Limits:** There were few clinical events. |
| BB vs. placebo 2 trials; 2,173 patients | Mortality: low ESRD: insufficient | - BB significantly reduced risk of all-cause mortality, CHF hospitalizations, and CHF death; reduced composite vascular outcomes risk in one of two trials.  
- There was no significant difference in risk of cardiovascular mortality.  
- Inconsistent data suggested greater relative risk reduction for several clinical vascular outcomes in lower eGFR category.  
- **Limits:** This was a post hoc analysis from two CHF treatment trials in which CKD was defined only by impaired eGFR; no renal outcomes were reported. |
| CCB vs. placebo 2 trials; 1,226 patients | Mortality: low ESRD: low | - There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, ESRD, or composite vascular or renal outcomes.  
- CCB significantly reduced risk of MI.  
- **Limits:** Outcomes were mainly derived from one trial. |
| CCB vs. BB 3 trials; 12,766 patients | Mortality: low ESRD: low | - There was no significant difference in risk of all-cause mortality, ESRD, or composite renal outcome.  
- **Limits:** Most outcomes were not reported by treatment group in more than one study; 95% of subjects were derived from one post hoc analysis, in which it is uncertain if “renal dysfunction” meets CKD criteria. |
| CCB vs. diuretic 1 trial; 4,129 patients | Mortality: insufficient ESRD: low | - There was no significant difference in risk of stroke, ESRD, or any composite clinical vascular or renal outcomes.  
- **Limits:** This was a post hoc subgroup analysis; no results were reported for risk of mortality or MI between treatment groups. |
| Diuretic vs. placebo 1 trial; 393 patients | Mortality: low ESRD: insufficient | - There was no significant difference in risk of all-cause mortality.  
- Diuretic significantly reduced risk of stroke and one of two composite vascular outcomes.  
- **Limits:** There were few patients; this was a single post hoc subgroup analysis; no renal outcomes were reported. |
| ACEI vs. non-ACEI (other BP control) 1 trial; 131 patients | Mortality: insufficient ESRD: low | - There was no significant difference in risk for ESRD or a composite renal outcome.  
- **Limits:** Sample size was small; there were few clinical events; no data were reported for mortality or other clinical vascular or renal outcomes. |
| Strict BP control vs. usual BP control 6 trials; 2,520 patients | Mortality: low ESRD: low | - There was no significant difference in risk of all-cause or cardiovascular mortality, MI, stroke, ESRD, or several composite renal outcomes.  
- **Limits:** Generalizability is limited for some of the older included studies; there was heterogeneity in patient populations and antihypertensive regimens; there were few vascular events. |
Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

<table>
<thead>
<tr>
<th>Treatment, Trials, Number of Patients</th>
<th>Level of Evidence</th>
<th>Summary, Conclusion, Comments</th>
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<tbody>
<tr>
<td>Statins vs. placebo or usual care</td>
<td>Mortality: high ESRD: low</td>
<td>• Statins significantly reduced risk of all-cause mortality, MI, stroke, and most composite vascular outcomes reported.</td>
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<td></td>
<td></td>
<td>• There was no significant difference in risk of CHF hospitalization, ESRD, or composite renal outcome.</td>
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<td>• <strong>Limits</strong>: All but one study were post hoc analyses in which CKD was defined by impaired eGFR or creatinine clearance; most trials excluded patients with moderate or severe renal impairment.</td>
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<tr>
<td>Statin vs. statin (high vs. low dose)</td>
<td>Mortality: low ESRD: insufficient</td>
<td>• There was no significant difference in risk of all-cause mortality.</td>
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<td>• High-dose statin significantly reduced risk of CHF hospitalization and reduced risk of all composite vascular endpoints in one of two trials.</td>
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<td>• <strong>Limits</strong>: These were post hoc analyses; no outcomes were reported for MI, stroke, or renal outcomes.</td>
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<td>Gemfibrozil vs. placebo</td>
<td>Mortality: low ESRD: insufficient</td>
<td>• There was no significant difference in risk of mortality.</td>
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<td>• Gemfibrozil significantly reduced risk of one of two composite vascular outcomes.</td>
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<td>• <strong>Limits</strong>: This was a post hoc analysis; no ESRD events were reported; no data were reported for mortality or clinical vascular outcomes.</td>
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<tr>
<td>Gemfibrozil vs. low-triglyceride diet</td>
<td>Mortality: insufficient ESRD: insufficient</td>
<td>• There was no significant difference in risk of ESRD.</td>
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<td>• <strong>Limits</strong>: There were few patients and only three ESRD events; no data were reported for mortality or clinical vascular outcomes.</td>
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<tr>
<td>Low-protein diet vs. usual protein diet</td>
<td>Mortality: low ESRD: low</td>
<td>• Low-protein diet did not significantly reduce risk of all-cause or cardiovascular mortality, or of ESRD.</td>
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<td>• Low-protein diet was associated with significant reduction in risk of composite renal outcome of dialysis.</td>
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<td>• <strong>Limits</strong>: Few vascular outcomes were reported; at least four trials also included participants with CKD stages 4 and/or 5.</td>
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<tr>
<td>Low-protein diet vs. low-carb, low-iron-available, polyphenol-enriched diet</td>
<td>Mortality: low ESRD: low</td>
<td>• There was no significant difference in risk of all-cause mortality or ESRD.</td>
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<td>• Treatment with low-protein diet significantly increased risk of composite outcome of mortality and ESRD.</td>
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<td>• <strong>Limits</strong>: This was a small trial; there were few outcomes.</td>
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<tr>
<td>Low-protein, low-phosphate diet vs. low-phosphate diet vs. usual diet</td>
<td>Mortality: insufficient ESRD: low</td>
<td>• There was no significant difference in risk of all-cause mortality or ESRD.</td>
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<td>• <strong>Limits</strong>: This was a small trial with few deaths; no data were reported for clinical vascular outcomes; trial was restricted to participants with deteriorating renal function and appears to have included many with eGFR &lt;30 mg/ml/1.73m².</td>
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### Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

<table>
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<tbody>
<tr>
<td>Intensive vs. standard glycemic control studies 2 trials; 1,861 patients</td>
<td>Mortality: insufficient ESRD: insufficient</td>
<td><strong>Limits:</strong> No data were reported for mortality, ESRD, or other clinical vascular or renal outcomes.</td>
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| Intensive multicomponent intervention vs. control studies 4 trials; 892 patients | Mortality: low ESRD: low | • There was no significant difference in risk of all-cause mortality, MI, fatal stroke, or ESRD.  
• Multicomponent intervention significantly reduced risk of nonfatal stroke, a composite vascular endpoint, in single trials reporting that endpoint.  
• **Limits:** There was heterogeneity between interventions. |

**Note:** For all-cause mortality and end-stage renal disease, the strength of the evidence was evaluated based on: (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Based on these four domains, the overall evidence was rated as: (1) high, meaning high confidence that the evidence reflects the true effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; BP = blood pressure; CCB = calcium channel blocker; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MI = myocardial infarction; ONTARGET = Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial.
Discussion

For CKD screening or monitoring to be of benefit, each would need to improve clinically important outcomes, presumably by leading to specific changes in treatment. However, we identified no RCTs that randomized individuals without known CKD to CKD screening, or randomized those with CKD stages 1–3 to CKD monitoring, and collected and reported associated clinical outcomes.

With no direct link between screening or monitoring and clinical outcomes, concluding that there is a likely benefit to screening or monitoring requires, at minimum, the availability of accurate screening tests and sufficient evidence that treatment for CKD stages 1–3 improves clinically important outcomes while limiting harms.

For treatment benefits in CKD patients to be relevant to screening or monitoring, treatments also would need to improve outcomes in individuals who would not otherwise receive them; i.e., patients without specific treatment indications in the absence of a CKD diagnosis. In patients with other treatment indications, diagnosis of CKD or of CKD progression might be beneficial if outcomes in these patients are significantly improved with a higher treatment dose or by treatment to a stricter target than indicated in individuals with no or less severe CKD. Finally, any treatment benefit would need to outstrip treatment harms and potential screening and monitoring harms, and the applicability of treatment RCT results to screening or monitoring would be increased if subjects were identified for participation in these treatment trials through screening.

In this synthesis of RCT evidence, several treatments reduced the risk of clinical events in patients with CKD stages 1–3. Compared with placebo, ACEI and ARB treatment significantly reduced the risk of ESRD in patients with proteinuria, nearly all of whom had concomitant diabetes and hypertension. While there was no significant reduction in the risk of ESRD with ACEIs or ARBs in patients without proteinuria, the present analysis had limited statistical power to detect such a difference because of the low rate of progression to ESRD in these patients. While it does not constitute direct evidence that testing patients with diabetes and hypertension for proteinuria will reduce ESRD risk, it suggests that knowledge of these results might inform the treatment decision in patients not currently being treated with ACEIs or ARBs. Also, compared with placebo, ACEIs significantly reduced the risk of mortality in patients with microalbuminuria who had cardiovascular disease or had diabetes and other cardiovascular risk factors. Although the relative reduction in mortality risk appeared to be slightly greater in patients with microalbuminuria than in those without microalbuminuria, the difference was not statistically significant, suggesting that such patients may have an indication for ACEI treatment regardless of CKD status.

In individuals with hyperlipidemia and impaired eGFR or creatinine clearance, we found that statins significantly reduced the risk of mortality, MI, and stroke compared with placebo, including the risk in patients without coronary artery disease. This does not constitute direct evidence that testing patients with hyperlipidemia for eGFR will reduce the risk of these outcomes, in part because some of these patients already have a clinical indication for statin treatment. Determining CKD status in these patients would not alter their management. Specifically, as previously documented, patients with hyperlipidemia and coronary artery disease randomized to statins have a significantly reduced risk of mortality compared with placebo;23 they have an indication for statin treatment regardless of their CKD status. In contrast, as also previously documented, hyperlipidemic patients without coronary artery disease, taken as a whole, did not have a significant mortality benefit from statins.24 The current results suggest that knowledge of impaired eGFR might inform the treatment decision in patients with hyperlipidemia and no coronary artery disease who are not being treated with a statin.

In individuals with CHF and impaired eGFR, beta blockers significantly reduced the risk of mortality, MI, and CHF events compared with placebo. Patients in all eGFR strata had a significant reduction in the risk of these clinical outcomes. Inconsistent results suggested possibly a greater relative risk reduction with beta blockers in patients with lower eGFR than in those with higher eGFR. However, as patients with systolic CHF already have an indication for beta blocker treatment, testing for eGFR is not likely to inform this treatment decision.

With regard to patients with CKD stages 1–3 already receiving treatments for conditions associated with CKD (e.g., ACEIs for treatment of hypertension), no clear RCT evidence showed whether intensification of treatment improves clinical outcomes. We identified no eligible RCTs that compared clinical outcomes in CKD patients randomized to different fixed ACEI doses, although separate trials suggested that ramipril
at 1.25 mg per day in patients with albuminuria lacks the mortality benefit of ramipril at 10 mg per day in patients with microalbuminuria. For other treatments in CKD patients, we did not find evidence of significant or consistent benefit in clinical outcomes in high-dose versus low-dose ARBs, strict versus standard blood pressure control, high-dose versus low-dose statins, tight versus standard glycemic control, intensive multidisciplinary interventions versus standard care, or combination treatment versus monotherapy. While data limited to these latter trials suggest an absence of evidence for benefit from intensification of therapy as a justification for either CKD screening or monitoring, most had low statistical power to detect a significant difference in clinical outcomes.

In RCTs included in this evidence synthesis, many treatments reduced the risk of doubling of serum creatinine and progression from microalbuminuria to macroalbuminuria. However, these renal endpoints are not clinical outcomes. Although impaired GFR and albuminuria are unquestionably adverse prognostic markers, treatments that target and even improve these measures will not necessarily reduce the risk of mortality, ESRD, or important clinical vascular outcomes. Findings reported from the large Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study— in which patients with diabetes and at least one additional CKD risk factor were randomized to ARB versus non-ARB blood pressure control— illustrated the potential danger of utilizing albuminuria as a surrogate marker for clinical outcomes in kidney disease. Although blood pressure control was significantly better and time to onset of microalbuminuria was significantly delayed in the ARB treatment group, these patients also experienced a significant increase in fatal cardiovascular events.

As we have noted, establishing the benefit of CKD screening and/or monitoring requires evidence of treatment benefit. Yet treatment benefit does not by itself prove screening or monitoring benefit. First, the accuracy of available screening and monitoring measures for persistent CKD and progressive CKD is uncertain. Second, only two of the dozens of RCTs included in this evidence synthesis reported that study participants were identified through screening. Consequently, patients with CKD stages 1–3 enrolled in all these trials may not be representative of those who would be identified through systematic screening. For example, patients identified through screening may be earlier in their course of CKD, less likely to progress during treatment followup, and thus less likely to benefit from treatment intervention than those not identified through screening. In addition, formal diagnosis of CKD requires that impairment in kidney function or kidney damage persist for at least 3 months. The vast majority of trials included in this evidence synthesis categorized patients as having CKD based on one-time abnormalities. Other trials that required repeated or sustained kidney abnormalities for entry did not mandate persistence for 3 months. Study participants thus may have had transient impairments, been more likely to improve regardless of treatment, and been less likely to develop progressive CKD than patients with CKD confirmed over 3 months duration. Finally, we identified no evidence to quantify harms that may be associated with CKD screening and monitoring. Potential harms of systematic CKD screening could include adverse effects from screening and followup tests, including followup of false positive tests, psychological effects from labeling asymptomatic individuals as diseased, medication adverse effects, increased medical visits, and increased difficulty keeping health insurance coverage. Analogously, potential harms of systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or damage could include adverse effects from monitoring and followup tests, including potentially unnecessary testing, medication adverse effects, and increased medical visits. Accurate information on screening and monitoring harms is needed to evaluate their overall impact in CKD.

Considering these issues, if there is a benefit from CKD screening, evidence suggests that the likelihood of benefit is greatest in individuals with diabetes, cardiovascular disease, and possibly hyperlipidemia. For other populations with a high prevalence of CKD, such as patients with hypertension, obesity, and older age, evidence for benefit from screening appears to be weaker. Individuals under 50 years old and without diabetes, hypertension, cardiovascular disease, or obesity infrequently have CKD and seem least likely to benefit from CKD screening, although this also is based only on indirect data.

Finally, because of the imprecision and high intraindividual variability of eGFR and albuminuria, providers who monitor patients with CKD stages 1–3 for worsening kidney function and/or damage will identify both declines and improvements in these measures, including many that are transient and/or clinically insignificant. We identified no RCTs that assigned patients with CKD stages 1–3 to systematic monitoring versus control, or that modified treatment based on followup levels of eGFR or albuminuria and evaluated clinical outcomes. Rather, trials either assigned participants to a fixed dose to be maintained throughout the trial or titrated upward from an initial dose to achieve a specific target dose or clinical
target (e.g., systolic blood pressure less than 140 mm Hg). Although treatment RCT results suggest that monitoring could inform decisions regarding whether to start ACEI or ARB treatment in patients with diabetes and hypertension who develop albuminuria, or statin treatment in patients with hyperlipidemia who develop impaired eGFR, considering the uncertainty in the accuracy of monitoring tests for identifying CKD progression and the uncertainty regarding possible monitoring harms, the relative benefits and harms of CKD monitoring are unclear.

Future Research Recommendations

Key Question 1. CKD Screening Benefits

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening improves clinical outcomes.
- The sensitivity and specificity of one-time measures of microalbuminuria, macroalbuminuria, and eGFR for persistent (at least 3 months’ duration) CKD is unknown; the impact of patient factors on persistence also is unknown.
- Only two trials were performed in patients with CKD identified through screening.

Research Recommendations

- Long-term RCTs of systematic CKD screening versus usual care that are adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high CKD prevalence and high risk for complications.
  - May test different screening measures (e.g., microalbuminuria, macroalbuminuria, eGFR, combination).
- Modeling studies evaluating efficacy and harms of different CKD screening strategies versus usual care. In addition to parameters in published models, consider impact of:
  - Variations in target populations.
  - Variations in screening measures and frequency.
  - Prevalence in the target population of indications for and use of specific CKD treatments.

Yield of one-time screening tests based on actual association with persistent CKD.

Take into account potential screening harms.

- Determine eGFR and albuminuria from baseline and followup blood and urine available from large prospective cohorts or RCT/CCT control groups (or collect new samples).
- Estimate the proportion of individuals with abnormal one-time abnormalities who meet the criteria for CKD for at least 3 months.
- Evaluate the impact of patient factors (e.g., eGFR severity, albuminuria, age) on persistence.

Key Question 2. CKD Screening Harms

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening increases harms.

Research Recommendations

- Long-term RCTs comparing systematic CKD screening versus usual care to assess potential screening harms.
  - Predefine potential harms, and collect and report them in all study participants.
  - May include as potential harms adverse effects from screening/followup tests, including from false positive tests; psychological effects of labeling asymptomatic individuals as diseased; medication adverse effects; increased medical visits; increased costs; difficulty keeping health insurance.
- Prospectively collect predefined harms data from all participants in large observational CKD screening cohort studies.
- Conduct modeling studies evaluating the effectiveness and harms of different CKD screening strategies versus usual care.

Key Question 3. CKD Monitoring Benefits

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD monitoring for worsened kidney function or damage improves clinical outcomes.
- The sensitivity and specificity of changes in eGFR and albuminuria for CKD progression are unknown.
Only limited RCT data address whether treatment relative risk reduction for clinical outcomes differs based on CKD severity. Such information could inform decisions regarding whether to change treatment in patients identified by monitoring with worsened CKD severity.

No RCT data address whether treatments have different relative risk reduction in clinical outcomes for patients with recently worsened kidney function or damage, as detectable by monitoring, compared with those with stable CKD.

Research Recommendations
- Long-term RCTs of systematic CKD monitoring versus usual care that are adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high risk for CKD complications.
  - Consider testing different monitoring measures, alone and in combination (e.g., quantitative microalbuminuria, macroalbuminuria, eGFR).
- Modeling studies evaluating the efficacy and harms of different CKD monitoring strategies compared with usual care. Parameters of these models may include:
  - Variations in monitoring measures and frequency (quantitative albuminuria, eGFR, or a combination).
  - Variations in baseline CKD severity (i.e., stage, eGFR, quantitative albuminuria).
  - Variations in CKD patient characteristics (e.g., diabetes, hypertension, age, cardiovascular disease, hyperlipidemia, race/ethnicity), including possible indications for specific CKD treatments and prevalence of use of these treatments.

Take into account potential monitoring harms.

Key Question 4. CKD Monitoring Harms

Knowledge Gaps
- No RCT evidence directly addresses whether systematic CKD monitoring for worsening kidney function or damage increases harms.

Research Recommendations
- Long-term RCTs comparing systematic CKD monitoring versus usual care to assess potential monitoring harms.
  - Predefine potential harms associated with monitoring, and collect and report them in all study participants.
  - May include as potential harms adverse effects from monitoring/followup tests, including from false positive tests (for progression); medication adverse effects; increased medical visits; increased costs.
- Prospectively collect predefined harms data from all participants in large observational CKD monitoring cohort studies.
- Conduct modeling studies evaluating the effectiveness and harms of different CKD monitoring strategies versus usual care.

Key Question 5. CKD Treatment Benefits

Knowledge Gaps
- Only limited RCT data address whether the relative efficacy of treatments differs between patients with and without CKD.
- Only limited RCT data address whether treatment risk reduction differs based on CKD severity.
- Only limited RCT data address whether treatments improved outcomes in CKD subgroups in which treatments were not already indicated.
- In RCTs of high versus low dose, combination versus monotherapy, and strict versus standard control, it was unclear whether intensification of treatment improves clinical outcomes.
- The effect of diet interventions on clinical outcomes in patients with CKD stages 1–3 is unclear because diet intervention RCTs were small, included patients with both stage 1–3 and stage 4–5 CKD, and did not separate results by CKD stage or severity.
- In head-to-head RCTs, there was little evidence of a significant difference in mortality or any clinical vascular outcome between different active treatment groups.
- Trials used heterogeneous eligibility criteria for kidney function and damage, and rarely reported outcomes stratified by CKD stage or albuminuria category, impeding evidence synthesis.

Research Recommendations
- Post hoc analyses of ongoing or completed RCTs that already have collected or are collecting clinical
outcomes.

- Determine baseline eGFR and quantitative albuminuria, categorize participants by CKD stage and albuminuria category, and perform analyses to evaluate the relative effectiveness of treatment versus control on clinical outcomes within these strata.

- Merge data from large-scale treatment RCTs with Medicare data to identify incident ESRD cases occurring in the post-trial followup period.

- Long-term RCTs of CKD treatment adequately powered to evaluate impact on clinical outcomes.

- In addition to mortality, ESRD, and clinical vascular outcomes, consider additional clinical outcomes for evaluation, including quality of life, acute kidney injury complications (e.g., hospitalization), health care utilization, physical function, and cognitive function.

- If composite outcomes are reported, also report complete data for individual composite components.

- To increase trial relevance to a screened population, consider recruitment using population-based sampling.

- Stratify results by CKD stage, albuminuria category, and other characteristics associated with CKD complications, including diabetes, hypertension, cardiovascular disease, older age, race/ethnicity, obesity, and hyperlipidemia.

- Consider future RCTs of statins in patients with albuminuria, ACEI or ARB treatment in patients with macroalbuminuria, ACEI or ARB treatment in combination with other therapy, and treatments other than ACEIs or ARBs.

- Consider trials of dietary interventions restricted to patients with CKD stages 1–3.

- Consider trials comparing system-level interventions to aid providers in avoidance of nephrotoxic agents, medication renal dose adjustment, and other measures targeted to reduce CKD-associated complications compared with complications in usual care.

- Analysis of administrative data to evaluate the effect of nephrology referral on clinical outcomes, performing propensity analysis to account for factors associated with early referral.

**Key Question 6. CKD Treatment Harms**

**Knowledge Gaps**

Withdrawals and adverse events were reported in few RCTs.

Withdrawals often were not reported separately by treatment group; adverse events often did not appear to be predefined, systematically collected and reported, or separated by treatment group.

**Research Recommendations**

In future RCTs, predefine withdrawals and adverse effects, and collect and report them in all patients with CKD stages 1–3.

May report withdrawal and adverse effects stratified by CKD stage, albuminuria category, and other patient characteristics.

**Glossary**

ACEI  Angiotensin converting enzyme inhibitor  
AKI  Acute kidney injury  
ARB  Angiotensin receptor blocker  
CCT  Controlled clinical trial  
CHF  Congestive heart failure  
CKD  Chronic kidney disease  
eGFR  Estimated glomerular filtration rate  
ESRD  End-stage renal disease  
GFR  Glomerular filtration rate  
JNC7  Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure  
KDIGO  Kidney Disease: Improving Global Outcomes  
KDOQI  Kidney Disease Outcomes Quality Initiative  
MI  Myocardial infarction  
RCT  Randomized controlled trial
References


Full Report
This executive summary is part of the following document:

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