Draft Comparative Effectiveness Review
Number XX

Screening for and Management of Chronic Kidney Disease Stages 1-3

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.tov/referencepurpose.cfm .

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Structured Abstract

Objective: To conduct a systematic review and synthesize evidence regarding benefits and harms of screening for, and monitoring and treatment of chronic kidney disease (CKD) stages 1-3.

Data Sources: Trials were identified from the MEDLINE® and Cochrane Database of Systematic Reviews electronic databases, from hand searching of references from relevant systematic reviews and eligible trials, and from expert consultants.

Review Methods: Standard Evidence-based Practice Center (EPC) methods were employed. Screening of abstracts and full articles to identify eligible studies was performed by one reviewer with duplicate review of a 10 percent sample. Conditional on the sample discrepancies, all initial abstract and article reviews were repeated. Randomized controlled trials (RCTs) were searched for all key questions. When no RCTs were identified for key questions 1-4, observational data were reviewed for indirect evidence to address the questions. Data extraction was completed and quality was checked by a second reviewer. Quality ratings and strength of evidence grading was performed on included trials. Evidence on screening and monitoring was qualitatively described. Evidence on CKD treatments was quantitatively synthesized where possible.

Results: There was no direct evidence regarding the benefits or harms of systematic screening for CKD. Screening with creatinine-based glomerular filtration rate (GFR) and urinary albumin excretion (urine albumin-creatinine ratio) tests appears sensitive for detection of kidney abnormalities that may reflect undiagnosed CKD. Such screening will produce a high yield in high-risk subgroups (e.g., diabetes, hypertension, old age), but is associated with a non-negligible false positive rate. There was no direct evidence regarding the benefits or harms of systematic monitoring of patients with CKD stages 1-3 for worsening kidney function/damage. Targeting subgroups at risk for worsening CKD severity will increase monitoring yield, though GFR testing already is common in usual care, and sensitivity and false positive rates for detection of significant decline (e.g., CKD stage change) is unknown. In placebo-controlled RCTs, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) significantly reduced risk of end-stage renal disease (ESRD) in patients with proteinuria; beta blockers significantly reduced risk of mortality, mycocardial infarction (MI), and congestive heart failure (CHF) in CKD patients with well controlled CHF (usually on ACEI or ARB); and HMG-CoA reductase inhibitors (statins) significantly reduced risk of all-cause mortality and MI in CKD patients with hyperlipidemia. There was no evidence for the superiority of one active treatment over another or of any combination treatment versus monotherapy, and no treatments other than ACEI and ARB were found to protect against ESRD. Adverse event reporting was limited.

Conclusions: No direct data currently exist regarding benefits and harms of screening for or monitoring of CKD. Studies to determine the actual sensitivity and false-positive rates of CKD screening and monitoring, and updated modeling studies incorporating estimated GFR, albuminuria, and testing related harms would be informative. ACEI, ARB, and beta blockers improve important clinical outcomes in subgroups of CKD patients, with evidence suggesting treatments may be more effective in patients with more advanced CKD. Statins also lower risk of

important health outcomes in CKD patients. New, well-designed RCTs of other treatments, and combination treatments should inform clinical practice.

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Effective Health Care

Comparative Effectiveness of "Screening for and Management of Chronic Kidney Disease Stages 1-3"

Executive Summary

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Objectives

This systematic review evaluates the evidence regarding the potential benefits and harms of: (1) screening adults for chronic kidney disease (CKD); (2) monitoring adults with early stage CKD (stages 1-3) for progression of kidney dysfunction and/or kidney damage; and (3) treatment of adults with early stage CKD. This report's scope is limited to early stage CKD because it is intended to inform patient care decisions of primary care physicians. This report is intended as background to material to assist groups developing clinical practice recommendations.

Background

Definition of Chronic Kidney Disease (CKD)

CKD is a condition in which the kidneys are damaged and/or cannot filter blood normally.[1] CKD increases risk for many adverse health outcomes, including cardiovascular disease, end-stage renal disease (ESRD), and mortality. However, early stage CKD has no hallmark symptoms, and the condition's progression usually remains asymptomatic until its most advanced state. As a result, diagnosing CKD generally requires laboratory tests.

In that context, CKD has been operationally defined as the persistence of decreased kidney function and/or kidney damage for at least 3 months. Kidney dysfunction is indicated by a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, while kidney damage

most frequently is manifested by abnormally increased excretion of urinary albumin.[2] Within this framework, CKD has been categorized into five stages:

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

Results of a recent meta-analysis of multiple large prospective cohort studies clearly demonstrated the graded, independent, and multiplicative associations of each level of GFR and albuminuria with mortality.[3] Based on these results, a consensus conference on CKD concluded that CKD staging should be modified as follows:[4]

- Divide Stage 3 into 3a (GFR 45-59 mL/min/1.73m^2) and 3b (GFR 30-44 mL/min/1.73m^2).
- 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]).

Epidemiology of CKD

Data from the 1999-2006 National Health and Nutrition Examination Survey (NHANES) shows that approximately 11 percent (23.5 million) of U.S. adults aged 20 or older have CKD.[5] Of these, nearly 50 percent have stage 1 or 2 CKD, nearly another half have stage 3, fewer than four percent have stage 4, and less than 2 percent have stage 5 CKD and receive dialysis. Among individuals with CKD, about half have albuminuria without impaired GFR, one-third have decreased GFR without albuminuria, and one-sixth have both abnormalities. Of individuals with albuminuria, nearly 85 percent have microalbuminuria. Additional analyses of NHANES data suggest that the prevalence of CKD is rising, with more individuals being classified into every stage of CKD from 1999-2004 than from 1988-1994.[6]

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. Other risk factors for CKD include older age, cardiovascular disease, obesity, and, possibly, gender.

CKD Screening

Rationale exists for considering the merits of CKD screening. Reasons behind the rationale include: the high and rising prevalence of CKD; its association with 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 CKD or its associated health conditions.

In fact, some organizations already recommend screening to diagnose CKD. Kidney Disease: Inspiring Global Outcomes (KDIGO) recommends screening for all patients with hypertension, diabetes, or cardiovascular disease, with consideration also given to other risk groups.[7] 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.[8]

Nevertheless, it is unclear whether screening for CKD is beneficial. In the strictest sense, for screening to be beneficial, it must improve important clinical outcomes (while limiting harms) for individuals diagnosed with CKD through screening compared to outcomes of treatment started at a later time or stage. The effect of screening on treatment outcomes should be examined for specific risk groups as well as for the broader population. A further intricacy is that potential CKD treatments may be indicated for conditions associated with CKD. Therefore, demonstration of benefit from CKD screening may require further evidence: First, that treatment benefits CKD populations with no other indication for their use; and second that, among patients with another indication, those with CKD have a relatively greater benefit from treatment than those without CKD.

Monitoring Early Stage CKD (1-3) for Progression

Most CKD patients experience a slow decline in GFR.[9] However, rate of decline shows substantial variability among individuals, and a number of risk factors appear to impact progression.[10] Because CKD stages 1-3 usually progresses asymptomatically, detection of this progression requires laboratory testing.

Some organizations advocate such testing and recommend monitoring for changes in kidney function or damage in patients with CKD. For example, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that adults with CKD receive monitoring of GFR at least annually in order to predict the interval until onset of ESRD, as well as to evaluate the effect of any CKD treatments on kidney function.[10] Both KDOQI and the U.K. National Health Service guidelines recommend more frequent monitoring of CKD patients with worsening kidney function.[11]

Confirming the actual benefits of monitoring CKD patients for changes in kidney function and/or damage requires evidence similar to that described for CKD screening. For monitoring to be deemed beneficial, it would be necessary to show that treatment modified due to results of monitoring improves important clinical outcomes more than treatment modified at a later time or stage, while limiting harms.

CKD Treatment

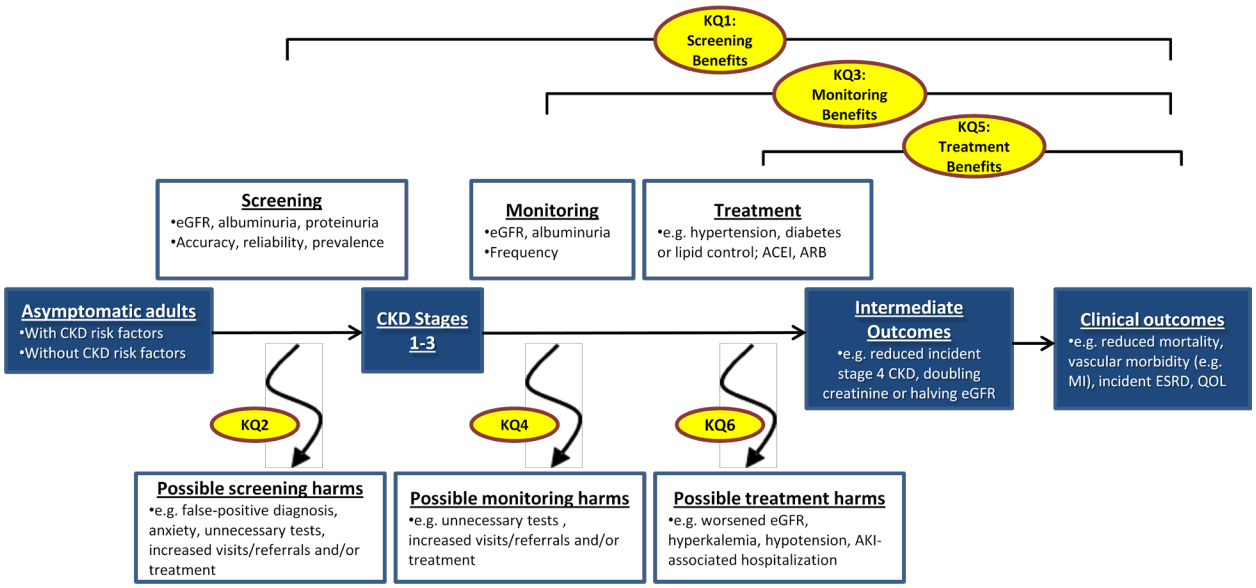
In most patients treated for nonprimary CKD, treatment is not directed specifically at the CKD. Instead, treatment is aimed at associated underlying conditions or cardiovascular risk factors, such as hypertension, diabetes, and/or dyslipidemia.[12] Therapeutic goals for these conditions are sometimes set more strictly for CKD patients than for non-CKD patients.[13] It has been suggested that medications such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may specifically treat CKD. However, whether their impact on CKD outcomes or markers (e.g., incident ESRD), albuminuria severity)[14] is independent of their blood pressure lowering effect is not clear.[15]

Key Questions

During this project's topic development phase, the topic nominators and other interested 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 general consensus that the analytic framework (Executive Summary Figure 1) and the following key questions addressed the most important issues regarding CKD stages 1-3:

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?
2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?
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?
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?
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?
6. Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

Executive Summary Figure 1. Analytic Framework



KQ1: In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?
KQ2: What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?
KQ3: 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?
KQ4: 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/kidney damage?
KQ5: 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?
KQ6: 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 November 2010) to identify randomized controlled trials (RCTs) and controlled clinical trials (CCTs) related to screening for, and monitoring and treatment of, patients with CKD. 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.[16] For each treatment comparison and each major outcome, the overall strength of evidence for the RCTs was evaluated using methods developed by the Evidence-based Practice Center program at the Agency for Healthcare Research and Quality.[17] If heterogeneity of patient populations, interventions, and outcomes was minimal, we pooled results using Review Manager 5.0.[18] Random effects models were used to generate pooled estimates of relative risks (RR) and 95 percent confidence intervals (CI). Statistical heterogeneity was summarized using the I^2 statistic.[19]

Results

Key Findings

Screening Benefits and Harms.

- We found insufficient evidence regarding whether systematic screening of adults for CKD improves clinical outcomes or increases harms.
- Indirect evidence suggests benefits from CKD screening are more likely in populations at higher risk for CKD, its progression, its complications, and/or for whom RCT evidence suggests treatment benefit. Such populations may include older patients and those with hypertension, diabetes, cardiovascular disease, or hyperlipidemia.
- Indirect evidence suggests that potential harms of screening include adverse effects from increased medication use, additional testing, and additional renal biopsies.
- An additional potential harm is labeling asymptomatic individuals as diseased, some of whom will not experience worsening of kidney function even without treatment.

Monitoring Benefits and Harms.

- We found insufficient evidence regarding whether systematic monitoring of patients with CKD stages 1-3 for worsening kidney function and/or damage improves clinical outcomes or increases harms.
- Indirect evidence suggests that monitoring of patients with CKD stages 1-3 for worsening of kidney function and/or damage is feasible, but it is uncertain whether such monitoring will improve clinical outcomes.
- Indirect evidence suggests that potential harms of monitoring include adverse effects from increased medication use and additional testing.

Treatment Benefits and Harms.

- ACEI and ARB significantly reduced risk of ESRD in patients with proteinuria, risk of macroalbuminuria in patients with microalbuminuria, and doubling of serum creatinine in CKD patients overall; risk of mortality and vascular outcomes was not reduced versus placebo.
- BB treatment significantly lowered risk of mortality, MI, and CHF complications versus placebo in patients with CHF, most of whom were already being treated with ACEI. There was insufficient evidence regarding whether BB improve clinical renal outcomes.
- HMG-CoA reductase inhibitors (statins) significantly lowered risk of mortality and MI versus placebo in patients with hyperlipidemia. There was insufficient evidence regarding whether statins improve clinical renal outcomes.
- Treatments for which RCTs do not show significant reduction in risk of ESRD, conversion from micro- to macroalbuminuria, or significant worsening of GFR include: CCB, BB, diuretics, HMG-CoA reductase inhibitors, gemfibrozil, strict hypertension control versus standard hypertension control, tight versus standard glycemic control, and low protein diet versus other diet.

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?

- We found insufficient evidence regarding whether systematic screening of adults for CKD improves clinical outcomes.
- No direct evidence addressed this question: no RCTs compared CKD screening to no CKD screening, usual care, or an alternative CKD screening regimen and evaluated clinical outcomes.
- Indirect evidence suggests systematic CKD screening is feasible, but it is uncertain whether screening will improve clinical outcomes.
  - The prevalence of CKD is high, particularly in certain groups (e.g., diabetes, hypertension, cardiovascular disease, and older age) and, based on administrative and provider awareness data, most CKD appears undiagnosed and/or unrecognized.
  - Estimated GFR and albuminuria are sensitive for detection of one-time kidney abnormalities that may reflect CKD. Sensitivity of these screening tests for CKD as defined by persistent kidney dysfunction and/or damage is unknown.
  - The false positive rates of one-time estimated GFR, microalbuminuria, and macroalbuminuria for CKD as defined by persistent kidney dysfunction and/or damage are unknown.
  - The false positive rate of one-time estimated GFR for one-time measured GFR <60 ml/min/1.73 m^2 is approximately 15 percent. The false positive rate of one-time microalbuminuria for microalbuminuria on repeat testing exceeds 30 percent. The false positive rate of one-time macroalbuminuria is likely to be lower since it is less likely to detect transiently elevated albuminuria.
  - In a single RCT that enrolled CKD patients identified by systematic screening, results showed no significant differences in clinical outcomes between ACEI and placebo.
  - Very limited data address whether treatments shown in RCTs to improve clinical outcomes in patients with CKD have a different relative reduction in risk compared to treatment in non-CKD patients.
  - Very limited data address whether treatments shown in RCTs to improve outcomes in CKD stage 1-3 patients do so in subgroups in whom these treatments might not otherwise be clinically indicated, or in whom the treatments would be indicated for just one of multiple options (e.g. no CHF or hypertension for ACEI or ARB).

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?

- We found insufficient evidence regarding whether systematic screening of adults for CKD causes harms.

- No direct evidence addressed this question: no RCTs compared systematic CKD screening to no CKD screening, versus usual care, or versus an alternative CKD screening regimen and evaluated harms.
- We identified virtually no data on the harms of CKD screening, but potential harms may include:
  - Adverse physical effects of screening tests, and of any further evaluations (e.g., blood draws, renal biopsies)
  - Adverse effects associated with treatment of diagnosed CKD (e.g., medication side effects)
  - Adverse psychological effects of screening tests, of CKD diagnostic label, and of any further evaluations following CKD diagnosis
  - Misclassification/false positive diagnosis
  - Unnecessary tests performed to follow up abnormal screening tests
  - Increased visits to primary provider and to kidney specialists
  - Increased costs to patient and health system
  - Increased difficulty of obtaining/keeping health insurance coverage

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?

- We found insufficient evidence regarding whether systematic monitoring of adults with CKD stages 1-3 for worsening kidney function and/or kidney damage improves clinical outcomes.
- No direct evidence addressed this question, as no RCTs compared systematic monitoring of adults with CKD stages 1-3 for worsening kidney function and/or damage versus no CKD monitoring, versus usual care, or versus an alternative CKD monitoring regimen and evaluated clinical outcomes.
- Indirect evidence suggests that systematic monitoring of patients with CKD stages 1-3 for worsening of kidney function and/or damage is feasible, but we did not identify evidence regarding how it would improve clinical outcomes.
  - The natural course of CKD stages 1-3 is usually of slow worsening over years, but with high inter-individual variability and with faster GFR decline in certain risk groups (e.g., diabetes, proteinuria, increased blood pressure, older age, obesity).
  - In usual care, most patients with CKD stages 1-3 undergo annual measurement of estimated GFR. A minority of patients undergo annual measurement of albuminuria. We did not identify data regarding whether providers recognize when patients experience substantial worsening in CKD (e.g., a decline in CKD stage).
  - The sensitivity and specificity of one-time estimates of GFR and quantitative albuminuria (i.e., urine albumin-creatinine ratio) to detect substantial worsening in CKD is unknown.
  - We identified very limited RCT data regarding whether treatments have different relative reductions in risk between patients at different levels within CKD stages 1-3.

- We did not identify RCT data regarding whether treatments have a different relative reduction in risk for clinical outcomes between recent decliners and those whose CKD has not recently worsened.

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?

- We found insufficient evidence regarding whether systematic monitoring of adults with CKD stages 1-3 for worsening kidney function and/or damage causes harms.
- No direct evidence addressed this question, as no RCTs compared systematic monitoring of patients with CKD stages 1-3 for worsening kidney function and/or damage versus no CKD screening, usual care, or an alternative CKD monitoring regimen and evaluated harms.
- We identified virtually no data on the harms of monitoring patients with CKD stages 1-3 for worsening kidney function and/or damage, but potential harms may include:
  - Adverse physical effects of monitoring tests, and of any further evaluations (e.g., blood draws, renal biopsies)
  - Adverse effects associated with modifying CKD treatment (e.g., medication side effects)
  - Adverse psychological effects of monitoring tests, of label of more advanced CKD, and of any further evaluations following monitoring results
  - Incorrect reclassification of CKD severity
  - Unnecessary tests performed to follow up abnormal monitoring tests
  - Increased visits to primary provider and to kidney specialists
  - Increased costs to patient and health system
  - Increased difficulty of obtaining/keeping health insurance coverage

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?

- In RCTs that enrolled patients with CKD stages 1-3, we found mixed results.
  - ACEI and ARB significantly reduced risk of ESRD in patients with proteinuria, progression to macroalbuminuria in patients with microalbuminuria, and doubling baseline creatinine in CKD patients overall; no other treatment was shown to protect against ESRD in patients with CKD.
  - Beta blockers significantly reduced risk of mortality, MI, and CHF within CKD patients with controlled CHF (including, nearly always, treatment with ACEI or ARB). Relative risk reduction for mortality and vascular outcomes with BB versus placebo was significantly greater in CHF patients with CKD versus without CKD. However, BB was still superior to placebo in all GFR categories studied.
  - Statins significantly reduced risk of mortality and MI in CKD patients with hyperlipidemia. Effect size appeared similar in patients with or without coronary

artery disease. Relative reduction in risk of mortality with statin versus placebo did not differ significantly between patients with and without CKD.

- Collectively, there was little evidence of significant differences in any mortality or clinical vascular outcome between active treatment groups.
- The following interventions did not significantly lower risk of mortality or of clinical vascular or renal outcomes in CKD patients: CCB, gemfibrozil, strict blood pressure control versus standard blood pressure control, tight glycemic control versus usual care, low protein diet, or intensive multi-component interventions versus usual care.
- Very limited RCT data address whether the relative benefit of any treatment differs between CKD and non-CKD patients.
- Limited data addresses whether treatments shown in RCTs to improve outcomes in CKD stage 1-3 patients do so in subgroups in which treatments might not otherwise be indicated or would be indicated for just one of multiple options (e.g., no CHF or hypertension for ACEI or ARB).
- We identified very limited RCT data regarding whether treatments have different relative reductions in risk between patients at different levels within CKD stages 1-3.
- We did not identify RCT data regarding whether treatments have a different relative reduction in risk for clinical outcomes between recent decliners and those whose CKD hasn't recently worsened.

Executive Summary Table 1 summarizes the evidence for specific comparative effectiveness studies addressed in KQ5.

Executive Summary Table 1. Summary of evidence

Key Question 5 Benefits of Treatment of CKD Stage 1-3 Patients	Level of Evidence	Summary/Conclusion/Comments
Angiotensin converting enzyme inhibitor (ACEI) versus placebo (n=17 trials; 10,845 patients)	Moderate for mortality and ESRD	• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, MI, or stroke. • 2/7 trials reported significantly reduced risk for composite vascular outcome in participants randomized to ACEI. • ACEI significantly reduced risk of ESRD versus placebo by 35%, a result driven by trials restricted to patients with overt proteinuria. • ACEI significantly reduced risk of doubling serum creatinine, conversion from micro- to macroalbuminuria, and multiple composite renal outcomes. • Limits: Few studies designed to assess clinical outcomes; considerable variability in the definitions of clinical outcomes
ACEI versus angiotensin receptor blocker (ARB) (n=6 trials; 4,799 patients)	Low for mortality Insufficient for ESRD	• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, MI, or CHF versus ARB. • There were no data for stroke, ESRD, or any composite vascular outcome. • Results from CKD subset of the ONTARGET study, whether defined by GFR <60 ml/min/1.73m^2 or by albuminuria, appeared to show no difference in risk of composite renal outcome of doubling creatinine, dialysis, renal transplant, or death. • Limits: Small sample sizes in all but one trial; reporting of most outcomes in few trials; small number of events among trials reporting.

Key Question 5 Benefits of Treatment of CKD Stage 1-3 Patients	Level of Evidence	Summary/Conclusion/Comments
ACEI versus calcium channel blocker (CCB) (n=6 trials; 4,357 patients)	Low for mortality and ESRD	• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, stroke, CHF, any composite vascular endpoint, or ESRD versus CCB. • ACEI significantly reduced risk of composite renal outcome in 1/3 trials. • Limits: Several studies not designed for/reported no clinical outcomes; reporting of most outcomes in few trials; small number of clinical events in trials reporting.
ACEI versus beta blocker (BB) (n=3 trials; 1,080 patients without diabetes)	Low for mortality and ESRD	• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, stroke, CHF, or either of two composite vascular endpoints versus BB. • ACEI did not significantly reduce risk of ESRD versus BB. • In one trial reporting, ACEI significantly reduced risk of composite renal outcome versus BB. • Limits: Only one study, the AASK trial, designed to evaluate effect of ACEI and BB treatment on clinical vascular outcomes.
ACEI versus diuretic (n=2 trials; 4,716 patients with hypertension)	Insufficient for mortality, low for ESRD	• ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, MI, stroke, ESRD, or other composite vascular or renal outcomes versus diuretic. • Limits: One trial was bioequivalence study not designed for clinical events; one trial was post hoc subgroup analysis with no mortality data by CKD status.
ARB versus placebo (n=4 trials; 3,778 patients with type 2 diabetes)	Moderate for mortality, high for ESRD	• ARB did not significantly reduce risk of all-cause mortality, MI, or of at least two defined composite vascular outcomes versus placebo. No trials reported results for stroke. • ARB significantly reduced risk of CHF hospitalization, ESRD, doubling of serum creatinine, and conversion from micro- to macroalbuminuria, but results mixed regarding risk of composite renal outcomes versus placebo. • Limits: Several outcomes from only one trial or not reported
ARB versus CCB (n=3 trials; 3,924 patients with hypertension and type 2 diabetes)	Low for mortality and ESRD	• ARB did not significantly reduce risk of all-cause mortality, MI, stroke, or at least two defined composite vascular outcomes versus CCB. • ARB did not significantly reduce risk of ESRD, or conversion from micro- to macroalbuminuria, but did reduce risk of doubling serum creatinine versus CCB. • Limits: Most outcomes were reported in only one trial or were uncommon.
Combination ACEI+ARB therapy versus ACEI (n=6 trials; 7,357 patients)	Moderate for mortality, insufficient for ESRD	• Combination therapy did not significantly reduce risk of all-cause mortality. • Few vascular outcomes reported, though one trial reported a significant reduction in the combination group for a composite vascular endpoint. • Limited data on renal outcomes. • Limits: Few clinical events
Combination ACEI+ARB therapy versus ARB (n=3 trials; approximately 4,300 patients)	Low for mortality, insufficient for ESRD	• One trial reported that there were no deaths; no trials reported information on vascular outcomes or ESRD. • Limits: Few clinical events

Key Question 5 Benefits of Treatment of CKD Stage 1-3 Patients	Level of Evidence	Summary/Conclusion/Comments
Combination ACEI+aldosterone antagonist therapy versus ACEI+ARB (n=1 trial; 54 patients with hypertension)	Insufficient for mortality and ESRD	• Few clinical outcomes occurred and there were no apparent difference between treatment groups.
Combination ACEI+aldosterone antagonist therapy versus ACEI+placebo (n=1 trial; 54 patients with hypertension)	Insufficient for mortality and ESRD	• Few clinical outcomes occurred and there were no apparent difference between treatment groups.
Combination ACEI+CCB therapy versus ACEI (n=1 trial; 481 patients with hypertension, type 2 diabetes, and no cardiovascular disease)	Insufficient for mortality and ESRD	• No data reported for mortality or individual vascular or renal outcomes. • Combination therapy did not significantly reduce risk of composite vascular outcome of serious cardiovascular events compared to ACEI. • Limits: Few events reported
Combination ACEI+CCB versus ACEI+diuretic therapy (n=1 trial; 332 patients with hypertension)	Insufficient for mortality and ESRD	• Combination ACEI+CCB therapy did not significantly reduce risk of all-cause mortality, "cardiac disorders," or "vascular disorders" versus combined ACEI+diuretic therapy. • No significant difference in risk of progression from micro- to macroalbuminuria between treatment groups, but wide confidence intervals. • Limits: Very few deaths or renal events; no data for other important clinical outcomes.
ARB versus different ARB (n=2 trials; 1,745 patients with hypertension and type 2 diabetes)	Low for mortality, insufficient for ESRD	• Telmisartan significantly reduced risk of all-cause mortality and composite vascular outcome of cardiovascular morbidity or mortality versus losartan. • Telmisartan did not significantly reduce risk of the composite renal endpoint of doubling of serum creatinine, ESRD or death versus losartan. • Telmisartan did not significantly reduce risk of all-cause and cardiovascular mortality, MI, stroke, and CHF versus valsartan. • Limits: Small sample size; few clinical events, with most outcomes from one trial; no studies compared losartan and valsartan
ARB (High Dose) versus ARB (Standard Dose) (n=1 trial; 269 patients with hypertension)	Insufficient for mortality and ESRD	• The trial reported no deaths in any of the treatment groups. • No other cardiovascular or renal outcomes reported. • Limits: One small trial of short duration with no clinical events
Aldosterone antagonist (+ACEI/ ARB) versus placebo (+ACEI/ARB) (n=1 trial; 59 patients with type 2 diabetes)	Insufficient for mortality and ESRD	• No significant difference between groups in risk of fatal MI. • No other clinical vascular or renal events reported. • Limits: One small study with low power for clinical events
BB versus placebo (n=1 trial; 1,469 patients with CHF)	Low for mortality, insufficient for ESRD	• BB significantly reduced risk of all-cause mortality, CHF hospitalizations, CHF deaths, and composite vascular outcomes of all cause mortality or CHF hospitalization, and of cardiac death or nonfatal MI. • Relative risk reduction between BB and placebo for several cardiac

Key Question 5 Benefits of Treatment of CKD Stage 1-3 Patients	Level of Evidence	Summary/Conclusion/Comments
		events appeared greatest in patients with lowest baseline GFR. • No data reported on clinical renal outcomes. • Limits: Post hoc subgroup analysis from one CHF treatment trial.
CCB versus placebo (n=2 trials; 1,226 patients with hypertension)	Low for mortality and ESRD	• CCB did not significantly reduce risk of all-cause or cardiovascular mortality, stroke, CHF, or two different composite vascular outcomes versus placebo. • CCB significantly reduced risk of MI versus placebo. • Risk between treatments appeared similar for ESRD, doubling of creatinine, and a composite renal outcome including both of these events as well as death. • Limits: Outcomes mainly derived from one trial.
CCB versus BB (n=3 trials; 12,766 patients with hypertension)	Low for mortality and ESRD	• CCB did not significantly reduce risk of all-cause mortality versus BB. • CCB did not significantly reduce risk of ESRD or of composite renal outcome of ESRD, death, or halving GFR. • Limits: Most outcomes not reported by treatment group in more than one study; 95 percent of subjects derived from ASCOT-BPLA post hoc analysis, in which it is uncertain whether "renal dysfunction" meets criteria for CKD.
CCB versus diuretic (n=1 trial; 4,129 patients with hypertension)	Insufficient for mortality, low for ESRD	• No significant difference between CCB and diuretic for risk of stroke, ESRD, or any composite clinical vascular or renal outcomes. • Limits: Post hoc subgroup analysis; no results reported for risk of mortality or MI between treatment groups.
Diuretic versus placebo (n=1 trial; 393 patients with hypertension)	Low for mortality, insufficient for ESRD	• No significant difference between treatments for all-cause mortality. • Diuretic significantly reduced risk of stroke. • Diuretic significantly reduced risk of “any vascular event,” but not of “fatal or nonfatal coronary heart disease.” • Renal outcomes not reported. • Limits: few patients; single post hoc subgroup analysis
ACEI versus non-ACEI (other BP control) (n=1 trial; 131 patients with hypertension)	Insufficient for mortality, low for ESRD	• ACEI did not significantly reduce risk for MI, ESRD, halving of GFR, or of a composite renal outcome including ESRD and GFR. • Mortality data and other vascular or renal outcomes not reported. • Limits: Small sample size; few clinical events.
Strict BP control versus usual BP control (n=6 trials; 2,520 patients with hypertension)	Low for mortality and ESRD	• There was no significant difference between treatment groups in all-cause or cardiovascular mortality, MI, stroke, ESRD, or in several composite renal outcomes. • Limits: Limited generalizability of some of the older included studies; heterogeneity in patient populations and antihypertensive regimens; few vascular events
HMG-CoA reductase inhibitors (statins) versus placebo or usual care (n=11 trials; 14,193 patients with hyperlipidemia)	High for mortality, low for ESRD	• Statins significantly reduced risk of all-cause mortality and MI versus control. • Statin did not significantly reduce risk of stroke or risk of CHF hospitalization versus control. • For most composite vascular outcomes reported, risk significantly lower with statin treatment versus control. • In results available from only one trial, there was no significant difference between statin and control treatment groups regarding risk of ESRD or a composite outcome of ESRD or halving GFR. • Limits: All but one study was a post hoc subgroup analysis; most trials excluded patients with moderate and/or severely impaired renal function, limiting generalizability to these populations
High dose versus low dose HMG-CoA Reductase Inhibitors	Low for mortality, insufficient for	• High dose statin did not significantly reduce risk of all-cause mortality. • High dose statin significantly reduced risk of CHF hospitalization and risk of all defined composite vascular endpoints.

Key Question 5 Benefits of Treatment of CKD Stage 1-3 Patients	Level of Evidence	Summary/Conclusion/Comments
(n=1 trial; 3,107 patients with hyperlipidemia and coronary artery disease)	ESRD	• No data reported for MI, stroke, or renal outcomes. • Limits: Single post hoc analysis; no data for renal outcomes
HMG-CoA Reductase Inhibitors versus Bile Acid Sequestrant (n=1 trial; 86 patients with hypertension and type 2 diabetes)	Insufficient for mortality or ESRD	• Statin significantly reduced risk of conversion from micro- to macroalbuminuria. • No data reported for mortality or other clinical vascular or renal outcomes. • Limits: Single small study, few outcomes reported
Gemfibrozil versus placebo (n=1 trial; 470 patients with coronary artery disease)	Low for mortality, insufficient for ESRD	• Gemfibrozil did not significantly reduce risk of mortality, but did significantly reduce risk of one of two composite vascular outcomes. • No patients developed ESRD. • No information on other renal outcomes was reported. • Limits: Single post hoc not designed for renal patients or renal outcomes
Gemfibrozil versus low triglyceride diet (n=1 trial; 57 patients without diabetes)	Insufficient for mortality and ESRD	• No data reported for mortality or vascular outcomes. • Three participants developed ESRD, with no apparent difference between treatment groups. • Limits: Few patients; few outcomes reported
Low protein diet versus usual protein diet (n=6 trials; 1,480 patients)	Low for mortality and ESRD	• Low protein diet did not significantly reduce risk of all-cause or cardiovascular mortality, or of ESRD. • Low protein diet associated with significant reduction in risk of composite outcome of dialysis or doubling of creatinine. • Limits: Few vascular outcomes reported
Low protein diet versus carbohydrate-restricted, low-iron-available, polyphenol-enriched diet (n=1 trial; 191 patients)	Low for mortality and ESRD	• No significant difference between the diets for risk of all-cause mortality, ESRD. • Treatment with low protein diet significantly increased risk of composite outcome of mortality and ESRD compared with other diet. • Limits: small trial, few outcomes
Low protein-low phosphate diet versus low phosphate diet versus unrestricted diet (n=1 trial; 98 patients)	Insufficient for mortality, low for ESRD	• All-cause mortality was 3, 13, and 3 percent, respectively. • ESRD developed in approximately half of participants in each diet treatment group. • Limits: Small trial, restricted to participants with deteriorating renal function and appears to have included many with GFR <30 mg/ml/1.73m^2
Intensive versus standard glycemic control studies (n=2 trials; 1,861 patients with diabetes)	Insufficient for mortality and ESRD	• Intensive glycemic control did not significantly reduce risk of conversion from micro- to macroalbuminuria. • No data reported for mortality, vascular outcomes, ESRD, or other renal outcomes. • Limits: Few outcomes reported
Intensive multi-component intervention versus control studies (n=4 trials; 892 patients)	Low for mortality and ESRD	• No significant difference between treatment groups in risk of all-cause mortality, MI, fatal stroke, or ESRD. • Individual trials reported significant reductions with multi-component interventions in risk of nonfatal stroke, a composite vascular endpoint, and conversion from micro- to macroalbuminuria. • Limits: Heterogeneity between interventions

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?

- Few trials reported information on withdrawals. When reported, withdrawals were often high and infrequently separated by treatment group.
- Few trials reported adverse events. When reported, adverse events were not separated by treatment group and were not systematically reported.
- In general, we were not able to quantitatively synthesize the withdrawal and adverse events data from the different studies.
- The types of adverse events reported were consistent with known potential adverse effects of these treatments:
  - Multiple anti-hypertensive treatments were associated with syncope or hypotension.
  - ACEI, ARB, ACEI+ARB, and ACE+aldosterone were associated with hyperkalemia.
  - Cough was a consistently reported side effect for ACEI; angioedema also was noted.
  - CCBs were associated with edema.
  - Gemfibrozil increased withdrawals due to gastrointestinal side effects in one trial.
  - Neither intensive glycemic control nor intensive multifactorial treatment programs were associated with increased risk of hypoglycemia.

Discussion

Clinical Implications

Is screening for CKD of benefit to patients?

No direct RCT evidence addresses the potential benefits of CKD screening. Such a trial would face enormous and possibly insurmountable logistical challenges. Therefore, decisions regarding whether CKD screening is worthwhile will need to be informed by indirect evidence. Providers who look for CKD will find it. This is in part because CKD is common, and in part because CKD screening tests, also used to define CKD if abnormal results persistent, are quite sensitive. However, knowledge of a patient's CKD status, while it facilitates risk stratification, cannot directly benefit the patient unless it leads to a change in his or her treatment that is itself of benefit.

Will identification of CKD from screening change treatment?

In subgroups of CKD patients, RCTs of BB (patients with systolic CHF, nearly all on ACEI or ARB) and statins (patients with hyperlipidemia) have reported significant reductions in MI and mortality. However, we found insufficient evidence that higher doses produce better outcomes than lower doses. Therefore, benefits are not likely to be gained from screening for CKD in patients already receiving these treatments for these conditions. Regarding patients with systolic CHF currently treated with ACEI or ARB but not on BB, mortality risk is significantly reduced with BB treatment compared to placebo, whether or not GFR is impaired. Along similar lines, most statin trials were comprised of patients with coronary artery disease, who therefore already had an indication for statins whether or not they had CKD. In the primary prevention trials (mean LDL range 117 to 155 mg/dl), data are limited by the small number of

cardiovascular events. However, in most of these post hoc primary prevention studies, risk appears reduced for CKD patients allocated to statins, with no significant difference in relative risk reduction between the patients with and without CKD. A CKD diagnosis would mark these patients at higher absolute risk for cardiovascular events, and might be used to inform a decision regarding whether to treat with statins.

RCTs have reported a significantly reduced risk of ESRD but not of mortality or cardiovascular events in CKD patients treated with ACEI or ARB versus placebo. This result appears driven by studies that restricted entry to patients with overt proteinuria. ESRD has not been reduced in trials that enrolled patients with microalbuminuria. This finding is not a surprise, given that such progression is relatively infrequent and the median time to ESRD in these patients far exceeds the followup duration of all studies reviewed. Even pooling all microalbuminuria RCTs, our analyses had very low statistical power to detect a between-group difference in ESRD of 40 percent as observed in the proteinuria RCTs. Most patients in these proteinuria RCTs had both diabetes and hypertension. Screening patients with these diagnoses for proteinuria could identify those in whom ACEI or ARB would be protective. While ACEI and ARB reduced risk of surrogate renal outcomes in CKD patients without proteinuria, mortality and clinical vascular outcomes were not reduced. In the case of such patients, whether benefits of long-term treatment with ACEI or ARB would outweigh harms remains unknown.

We evaluated multiple patient subgroups to investigate whether there were patient characteristics that were not automatic indications for the treatments reviewed in this report, but for which treatment significantly improved clinical outcomes in CKD patients. No trials reported stratified analyses by such patient characteristics, and studies restricted by co-morbid condition (e.g., limited to diabetics) either reported few clinical outcomes or did not find significant reductions in risk of clinical events.

Altogether, RCT data do not provide clear guidance regarding whether screening for CKD beyond these limited circumstances is beneficial. In great part, this is a function of the heterogeneity in trial populations and outcomes, and limitations in events and in reporting. New, well-designed trials would have a high likelihood of impacting conclusions about treatment efficacy, especially in patient subgroups. Updated modeling studies may be the most efficient strategy to address this question.

Will results from monitoring patients with CKD stages 1-3 for worsening kidney function and/or damage change treatment?

Providers who test patients with CKD stages 1-3 for worsening kidney function and/or damage will find changes in these measures. This is virtually guaranteed by the tests' imprecision and high intra-individual variability. Rationale offered for monitoring has included predicting the interval until the onset of ESRD and evaluating the effect of interventions to slow GFR decline.[10] Another possible rationale would be evidence that, within patients with CKD stages 1-3, certain treatments do not improve clinical outcomes when damage is less or function is better but do improve these outcomes when damage or function is worse.

With regard to forecasting ESRD, most patients with CKD stages 1-3 never progress to ESRD, and those that do progress to ESRD do so over many years. How much benefit patients perceive from predictions estimating onset of ESRD perhaps 20 years in the future remains unclear. With regard to monitoring to evaluate treatment interventions, we identified no RCT that assigned patients with CKD stages 1-3 to systematic monitoring versus another intervention, or that as part of trial protocol implemented treatment changes based on followup GFR or

albuminuria results and evaluated clinical outcomes. Even in the absence of such trials, providers wishing to start a treatment such as ACEI or ARB to decrease albuminuria and GFR decline may not need to retest these CKD measures to guide treatment. Almost all of the trials included in this review prescribed ACEI and ARB treatments at a fixed dose throughout the trial. Less often, the initial dose was adjusted or another agent was added to achieve a specific blood pressure target. Studies have shown greater reductions in albuminuria with higher doses of these medications,[20] but it has not been established that their impact on potential monitoring measures such as albuminuria severity is independent of their blood pressure lowering effects.[15] Consequently, the point when such test results would warrant a change in treatment remains unknown, as does the question of whether monitoring patients with CKD stages 1-3 for worsening kidney function and/or damage would benefit the patient.

Do treatments for patients with CKD stages 1-3 improve patient outcomes?

As discussed above, ACEI and ARB significantly reduce risk of ESRD in patients with proteinuria. BB significantly reduced risk of mortality, MI, and CHF complications in patients with CKD and stable CHF already being treated with ACEI or ARB as tolerated. Statins significantly reduce risk of mortality and MI in patients with CKD and hyperlipidemia. To date, no treatments other than ACEI and ARB have been found to reduce risk of ESRD. In trials involving head-to-head comparisons of active treatments and combination treatments, there was little direct evidence for the superiority of one active treatment over another. Insufficient data addresses whether treatments shown in RCTs to improve outcomes in CKD stage 1-3 patients do so in subgroups in which these treatments might not otherwise be clinically indicated, or would be indicated for just one of multiple options (e.g., no CHF or hypertension for ACEI or ARB).

Future Research

Given the absence of direct evidence regarding the benefits and harms of screening for CKD, a number of research directions could be considered. The most direct would be to conduct a large-scale RCT of CKD screening plus treatment for confirmed diagnoses versus usual care. Current knowledge is sufficient to decide on many of the parameters for such a trial, such as the target risk groups for screening, the screening tests, the timing of the confirmatory tests, and at least some aspects of treatment. However, such an RCT likely would require tens of thousands of participants followed for a dozen or more years to have adequate power to evaluate final clinical outcomes such as mortality, cardiovascular events (e.g., MI), and ESRD. Such a study is not likely to be feasible. Alternatively, research could seek to refine published modeling studies of CKD screening. Previous modeling studies evaluating proteinuria screening[21] and microalbuminuria screening[22,23] have taken into account an exhaustive set of factors and concluded that such screening is not likely to be cost effective unless targeted to populations with an increased prevalence of CKD, including individuals with diabetes, hypertension, and older age. These models could be expanded to evaluate the impact of incorporating both estimated GFR and measurement of urinary albumin excretion in the screening algorithm. Models could also include potential harms so as to not inappropriately bias results. Additional screening-related research could determine the actual rather than assumed proportion of individuals with abnormal one-time screens for impaired GFR and/or micro- and macroalbuminuria who go on to meet CKD criteria based on persistent abnormalities for at least 3 months. This research should further seek to quantify the impact of various patient factors on

these persistence rates, including the level of GFR and albuminuria at screening, diabetes, hypertension, age, and gender. Research in large screened cohorts, such as the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), should be conducted to try to quantify harms associated with CKD screening.

As with screening, the most direct way to address the absence of direct evidence regarding the benefits and harms of monitoring patients with CKD stages 1-3 for progression would be to conduct a large-scale RCT of CKD monitoring plus treatment modification for confirmed progression versus usual care. This likely would be more difficult to conduct than a screening trial. Challenges would include distinguishing the monitoring arm from usual care, given that the vast majority of early stage CKD patients receive annual estimated GFR measures and, within a year of documented CKD stage 1-2 diagnosis, approximately 60 percent of patients have received either ACEI or ARB and 50 percent have received a statin.[1] Monitoring could certainly be targeted to CKD patients predicted to have the highest rate of progression. However, a CKD severity threshold or progression rate would need to be established, upon which to base changes in the patient's treatment regimen. A modeling study could be developed. In that case, determining the effect of treatment changes due to monitoring findings might require prior studies to determine whether treatments have differential effects on clinical outcomes for patients with recent declines in their CKD severity as compared to those whose CKD has remained stable.

Many RCTs have contributed data to help determine whether treatments of CKD patients improve clinically relevant outcomes, including mortality, and clinical vascular and renal outcomes. However, the vast majority of these trials either did not collect many of these outcomes, are small and/or included too few participants with these outcomes to draw meaningful conclusions, or have methodological flaws, including high withdrawal rates and exclusions of randomized participants from analyses. Post hoc analyses of completed large trials may still continue to be an efficient means for providing partial information regarding the efficacy of different interventions on clinical vascular and renal outcomes. Where data allow, investigators of completed trials could reanalyze results after categorizing participants by CKD stage and albuminuria category as proposed by KDIGO. There may be some large trials for which a merger with Medicare data would be a feasible means of identifying incident ESRD cases over a long followup period. Nevertheless, many studies will remain constrained by their original designs and collected data. Future RCTs should follow standardized methods to address these issues. Studies of treatments other than ACEI or ARB, and involving combinations of ACEI or ARB with an additional agent, should be considered.

Glossary

ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers
ACP	American College of Physicians
BB	Beta blocker
CCB	Calcium channel blocker
CCT	Controlled clinical trial
CI	Confidence interval
CKD	Chronic kidney disease
ESRD	End-stage renal disease

GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Inspiring Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
NHANES	National Health and Nutrition Examination Survey
RCT	Randomized controlled trial
RR	Relative risk
USPSTF	United States Preventive Services Task Force

Introduction

Scope and Purpose

The objective of this systematic review is to evaluate the evidence for the potential benefits and harms of: (1) screening adults for chronic kidney disease (CKD) stages 1-3, (2) monitoring adults with CKD stages 1-3 for progression of kidney dysfunction and/or damage, and (3) treatment of adults with CKD stages 1-3. The evidence presented will be used to inform development of clinical practice recommendations.

Definition of CKD

CKD is a condition in which the kidneys are damaged and/or cannot filter blood normally.[24] CKD usually is asymptomatic, except in its most advanced state. Consequently, blood and/or urine tests generally are required to make a diagnosis.

There has been substantial debate regarding how to define early stages of CKD. The definition of CKD developed by Kidney Disease Outcomes Quality Initiative (KDOQI)[2] was:

1. Kidney damage present at least 3 months, as defined by structural or functional abnormalities (most often based on increased albuminuria, e.g. urinary albumin-creatinine ratio [UACR] ≥30 mg/g); and/or
2. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 present at least 3 months.

Within this framework, KDOQI then classified CKD into five stages, as follows:

- Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m^2
- Stage 2: Kidney damage with GFR 60-89 mL/min/1.73 m^2
- Stage 3: GFR 30-59 mL/min/1.73 m^2
- Stage 4: GFR 15-29 mL/min/1.73 m^2
- Stage 5: GFR <15 mL/min/1.73 m^2 or kidney failure treated by dialysis or transplantation

A limitation of the KDOQI definition and staging was that they were based on cross sectional data, and that there were limited data associating adverse clinical outcomes with specific levels of GFR, albuminuria, or proteinuria. However, a recently published meta-analysis examined the longitudinal association of reduced GFR and albuminuria with total and cardiovascular mortality in 1.5 million individuals.[3] Based on these data, a consensus conference led by Kidney Disease: Improving Global Outcomes (KDIGO), on Chronic Kidney Disease: Definition, Classification and Prognosis, concluded that the current CKD definition should be preserved. However, the conference recommended that staging be altered to subdivide stage 3 into 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2), to add albuminuria strata within each GFR stage (UACR <30 mg/g, 30-299 mg/g, or ≥300 mg/g), and to assign a cause of CKD when possible.[4]

Prevalence of CKD

In the United States, based on data from the 1999-2006 National Health and Nutrition Examination Survey (NHANES) study, an estimated 11.1 percent (22.4 million) of adults aged 20 or older have CKD stages 1-3. [5] Because this estimate was based on one-time measurements of urinary albumin-creatinine ratio (UACR) and serum creatinine, and the definition of CKD requires persistent kidney abnormalities, statistical adjustments were made to estimate persistence. An additional 0.8 million U.S. adults aged 20 or older have CKD stage 4, and more than 0.3 million have stage 5 CKD and receive hemodialysis.[25]

Among adults with CKD stages 1-3, approximately half have either stage 1 or 2 CKD (increased albuminuria with normal GFR), and half have stage 3 CKD (low GFR, with approximately one third of these having increased albuminuria and two thirds having normal albuminuria).[5] Of individuals with albuminuria, nearly 85 percent have microalbuminuria (UACR 30-299 mg/g).

Analyses of NHANES data also suggest that the prevalence of CKD is rising, with more individuals being classified into every stage of CKD from 1999-2004 than from 1988-1994.[6] The number of patients with stage 5 CKD requiring dialysis also has increased.[25] It has been estimated that more than 700,000 individuals will have end-stage renal disease (ESRD) by 2015.[26]

Factors Associated with CKD

Prevalence of CKD stages 1-3 in U.S. adults rises from 3.1 percent among those aged 20-39 years, to 6.7 percent in those aged 40-59, 17.6 percent in those aged 60-69, and 44.4 percent among adults aged 70 years or older.[5] CKD prevalence is somewhat higher in women (12.6 percent) than in men (9.7 percent) and is similar in whites (11.6 percent) and blacks (11.2 percent).

Although CKD can be caused by primary kidney disease (predominantly glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease), in the vast majority of patients with CKD, the kidney damage is associated with other medical conditions such as diabetes and hypertension. For example, based on NHANES 1999-2006 data, prevalence of diabetes was approximately 5 percent in individuals without CKD and 20 percent in individuals with CKD stages 1-3.[1] Prevalence of hypertension was 24 percent among individuals without CKD, but rose from 36 percent in those with CKD stage 1 to 64 percent in those with CKD stage 3. Similarly, prevalence of cardiovascular disease was 6 percent among individuals without CKD, and rose from 7 percent in those with CKD stage 1 to 36 percent in those with CKD stage 3. Compared to the NHANES population, the prevalence of comorbidities was higher in the older Medicare population. 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.[1]

Association of CKD with Adverse Outcomes

CKD has been associated with numerous adverse health outcomes. Many studies have reported that a GFR of 30-59 mL/min/1.73 m^2 is associated with an increased risk of

mortality,[3,27] cardiovascular disease,[28] fractures,[29] bone loss,[30] infections,[31] cognitive impairment,[32] and frailty. Similarly, there appears to be a graded relationship between the severity of proteinuria or albuminuria and adverse health outcomes, including mortality,[3,33] ESRD,[34] and cardiovascular disease.[35] Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria (or proteinuria) appears to be independent and multiplicative.[3,34]

A number of possible explanations exist for the observed association of CKD with adverse health outcomes. First, CKD shares many of the same risk factors as other vascular diseases, such as older age, hypertension, and diabetes, so CKD may be a marker for undiagnosed vascular disease or for a worsened prognosis among individuals with known vascular disease. Second, CKD may be associated with a number of nontraditional risk factors for vascular disease and mortality, such as increased inflammation or bone mineral disorders. Third, CKD may be a marker for individuals less likely to receive proven medical therapies. For example, among individuals with myocardial infarction, those with CKD are less likely to receive proven effective therapies such as coronary artery bypass grafting, angiotensin converting enzyme inhibitors (ACEI), beta-blockers, or HMG CoA-reductase inhibitors (i.e., statins).[36] Therefore, systematic undertreatment may in part underlie the association between CKD and adverse health outcomes. Finally, the associations of CKD with adverse health outcomes and increased healthcare costs may be related to a combination of the above mechanisms.

Rationale for CKD Screening

Factors that impact the potential benefit of screening adults for CKD stages 1-3 include: (1) whether undiagnosed CKD is sufficiently prevalent in the population, overall or in certain high risk groups; (2) whether CKD is associated with significant adverse health consequences and/or healthcare costs; (3) whether CKD is diagnosable while asymptomatic; (4) whether there are valid and reliable screening tests for CKD that are acceptable to patients and available in primary care settings; and (5) whether there are treatments for patients with CKD that improve clinically important health outcomes.

Going further, determination that CKD screening is beneficial would require evidence that treatment of screen-detected CKD is associated with an improvement in health outcomes compared to treatment initiated once an individual is symptomatic or has CKD detected through usual care, while limiting harms. In addition, since potential CKD treatments often are indicated for conditions associated with CKD, such as diabetes, hypertension, or cardiovascular disease, demonstration that CKD screening is beneficial may require evidence that treatment benefits CKD populations who don't have another indication for treatment or, that among patients with another indication for treatment, those with CKD experience a greater relative treatment benefit than those without CKD. Alternatively, because patients with diabetes, hypertension, and/or cardiovascular disease who also have CKD are at significantly higher risk for adverse health outcomes than patients with these comorbid conditions who don't have CKD, diagnosis of CKD resulting from screening patients with these conditions would identify a group, if currently untreated, who could derive a greater absolute benefit in health outcomes even if the relative benefit of treatment versus no treatment was similar in CKD and non-CKD patients.

Several organizations have made recommendations regarding screening for CKD. KDIGO recommends screening for CKD in patients with hypertension, diabetes, or cardiovascular disease using both a urine test for proteinuria and a blood test for creatinine to estimate GFR.[7]

KDIGO further recommends that CKD screening be considered in patients who are older, have a family history of kidney disease, have other cardiovascular disease risk factors, have certain chronic infections or cancers, or are treated with potentially nephrotoxic drugs, and that screening need not be performed more often than annually. The American Diabetes Association (ADA) recommends that all adults with diabetes undergo annual measurement of serum creatinine to estimate GFR, and that all type 2 diabetics and all type 1 diabetics with a diabetes duration of at least 5 years undergo annual measurement of urinary albumin excretion.[37] Ongoing CKD screening programs include the National Kidney Foundation's Kidney Early Evaluation Program (KEEP®), which offers free screening for all adults with hypertension, diabetes, or a first degree relative with a history of kidney disease, hypertension, or diabetes.[8]

Rationale for Monitoring for Progression of CKD

Because CKD in stages 1-3 is usually asymptomatic, monitoring these patients for worsening kidney function or damage requires laboratory testing (i.e., measures to estimate GFR, albuminuria).

Factors that impact the potential benefit of monitoring adults with CKD stages 1-3 for worsening kidney function or damage include: (1) whether undiagnosed progression of patients with CKD stages 1-3 to worse kidney function or damage is sufficiently frequent in the population, overall or in certain high risk groups; (2) whether CKD that has progressed from stages 1-3 is associated with significant adverse health consequences and/or healthcare costs; (3) whether CKD that has progressed from stages 1-3 is diagnosable while asymptomatic; (4) whether there are valid and reliable monitoring tests for CKD stages 1-3 that are acceptable to patients and available in primary care settings; and (5) whether there are treatments for patients whose CKD has progressed from stages 1-3 that improve clinically important health outcomes.

Strictly considered, determination that monitoring patients with CKD stages 1-3 for worsened kidney function or damage is beneficial would require evidence that modified treatment of worsened CKD detected by monitoring is associated with an improvement in health outcomes compared to treatment modified once an individual becomes symptomatic or has CKD worsening detected through usual care, while limiting harms.

Several organizations have made recommendations regarding monitoring kidney function and/or damage in patients with CKD. KDOQ/I recommends that adults with CKD receive monitoring of urinary albumin or protein to creatinine ratio, though no frequency of monitoring was recommended.[10] The U.K. National Health Service (NHS) National Institute for Health and Clinical Excellence (NICE) guidelines suggest "more frequent monitoring" in CKD patients with worsening kidney function and a "relaxed frequency" of estimated GFR measurements in patients with stable kidney function.[11]

Rationale for Treatment of CKD

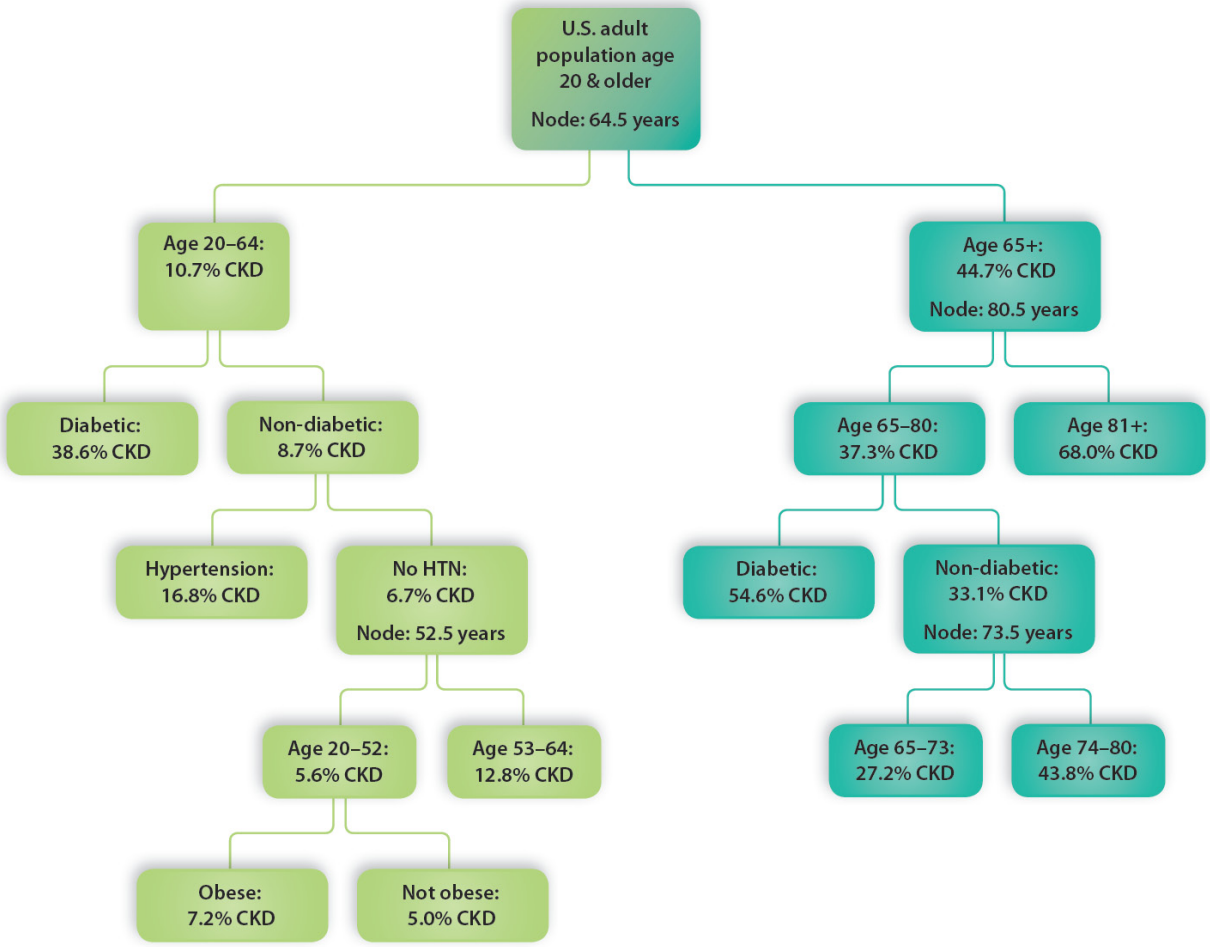
In patients treated for nonprimary CKD, treatment most often is not directed specifically at the CKD but rather at the associated underlying conditions or cardiovascular risk factors, such as hypertension or diabetes,[12] with therapeutic goals for these conditions sometimes set more strictly for CKD patients than for non-CKD patients.[13] An aim of this systematic review is to evaluate the evidence regarding whether the benefits and harms of treatment differ between patients with and without CKD, both in patients with and without other indications for treatments. Medications such

as ACEI and angiotensin receptor blockers (ARB) potentially could be directed specifically towards treatment of CKD. However, whether their impact on CKD outcomes or markers (e.g., incident end stage renal disease (ESRD), albuminuria severity[14]) is independent of their blood pressure lowering effect is not clear.[15] Additional nonspecific therapies may include other medications and nonpharmacological interventions targeted, for example, at blood pressure control, glycemic control, cholesterol control, and obesity treatment.

Key Questions

1. In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?
   - In asymptomatic adults with or without risk factors for CKD incidence, progression, or complications, what is the accuracy and reliability of CKD screening and the prevalence of CKD identifiable by screening?
   - Does initiating treatment for CKD as a result of systematic screening improve clinical outcomes compared to treatment initiated after incidental CKD diagnosis during routine clinical practice?
   - How do patient factors and CKD screening thresholds modify the yield of CKD screening and its association with clinical benefits?
2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?
   - How do patient factors and CKD screening thresholds modify the association of CKD screening with harms?
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?
   - How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with clinical benefits?
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/kidney damage?
   - How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with harms?
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?
   - Does the presence of CKD modify the likelihood of improvement in clinical outcomes associated with treatment of vascular disease or vascular risk factors?
   - Among adults with CKD, what patient factors modify the association of specific treatments with improved clinical outcomes?
6. Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from treatment?
   - Does the presence of CKD modify the likelihood of harms associated with treatment of vascular disease or of vascular risk factors?
   - How do patient factors and CKD severity/stage modify the association of CKD treatment with harms?

Figure 1. Prevalence of CKD in U.S. adults age 20 and older as a function of age, diabetes, hypertension, and obesity[25]



Methods

Topic Refinement

The initial nominator of this topic, first titled "Management of Mild Renal Impairment," proposed questions related to clinical typology, frequency of monitoring, calculation of creatinine clearance, management, and secondary prevention of mild renal impairment. Subsequently, a second nominator proposed questions related to screening for and treatment of screen-detected CKD. It was determined to be feasible to combine the two sets of questions. The scope of the combined questions was explicitly not to include management of patients with more advanced kidney disease.

Subsequently, to clarify the purpose of this project, its title and the language used throughout were changed to be consistent with the currently accepted terminology for referring to impairments in kidney function and kidney damage as established by the National Kidney Foundation's KDOQI[2] and later modified by the KDIGO.[4]

The initial key questions were drafted with input from representatives of the nominating organizations. The key questions and project scope were submitted for AHRQ approval and then posted on the Effective Health Care web site for public comment. These public comments were reviewed with AHRQ and the nominators, and incorporated as appropriate in a draft protocol. The draft protocol was circulated to a Technical Expert Panel (TEP) composed of researchers, clinicians, and representatives from professional organizations and federal and state agencies, and was revised based on feedback received from the TEP. A final protocol, including the revised key questions and proposed project methods, was then approved by AHRQ and posted on the Effective Health Care website.

Systematic Review

Search Strategy

We developed separate search strategies for the screening, monitoring, and treatment key questions. Search strings were developed and tested to identify randomized controlled trials (RCTs) or controlled clinical trials (CCTs). We included studies that enrolled an adult population (18 years of age and older), were published since 1985, and were written in the English language. Evidence suggests that for systematic reviews of conventional medicine, as were evaluated in the present review, restriction to include only English language trials should not bias estimates of the effectiveness of the interventions.[38] Only full articles were included. We searched MEDLINE® and the Cochrane Database of Systematic Reviews. Details of the major search strategies are provided in Appendix A.

To identify systematic reviews related to the three topic areas, we completed a search of MEDLINE® and the Cochrane Database of Systematic Reviews using the same search strategies as above with the addition of publication type terms to identify systematic reviews. We manually searched the reference lists of the identified systematic reviews to identify any RCTs or CCTs not detected in our electronic literature search. We also manually searched reference lists of the primary reports that were eligible for inclusion in the review. Per project protocol, because we did not find evidence from RCTs or CCTs to directly address whether screening or monitoring

impact clinical outcomes or harms, we conducted a nonsystematic search for observational studies to identify indirect evidence regarding the benefits and harms of screening for and monitoring of CKD. All citations then were imported into EndNote X and Excel for abstract review and database management.

A broad search of the grey literature was completed by the AHRQ Scientific Resource Center librarian. In addition, scientific information packets were sought from pharmaceutical companies that have developed medications related to treatments evaluated in this topic.

We conducted the initial searches in March and April of 2010. All searches were updated in November 2010.

Inclusion/Exclusion Criteria

We developed criteria for inclusion and exclusion of studies based on patient populations, interventions, outcome measures, and types of evidence relevant to the key questions (see below). We retrieved full-text articles of potentially relevant abstracts and conducted a second review for inclusion by reapplying the inclusion criteria. If no abstract was available electronically, the full text of the article was obtained for review.

Key Questions 1 and 2

Patients.

We restricted the review to studies that enrolled adults who were without known CKD, were with or without recognized risk factors for CKD, and who were systematically screened for CKD. Because much of our search period preceded the development and wide implementation of the current CKD staging system, studies whose definitions of CKD at least closely approximated the current KDOQI and KDIGO definitions for CKD stages 1-3 were considered eligible.

Study selection.

We sought RCTs or CCTs that assessed the direct impact of systematic screening for CKD stages 1-3 on clinical outcomes and harms. Examples of tests to screen for CKD that were considered eligible were direct measurements of GFR or creatinine clearance, estimation of GFR or creatinine clearance with creatinine-based formulae, serum creatinine, albuminuria, proteinuria, albumin/creatinine ratio, and cystatin C. The screening method must have been feasible within a primary care setting. Our exclusion criteria were as follows: nonadult population, study participants already diagnosed with CKD, not an RCT that assigned participants to systematic screening for CKD versus usual care or a comparator intervention, study followup duration less than 1 year, and sample size less than 1,000 randomized participants.

We did not identify any RCTs of CKD screening that assessed clinical outcomes and harms. Therefore, per protocol, we employed a nonsystematic search for studies that might provide indirect evidence regarding potential benefits and harms of screening. These studies may have addressed the prevalence of CKD stages 1-3, the validity and reliability of tests to identify CKD stages 1-3 while asymptomatic, and the frequency at which tests to identify CKD were performed in individuals without diagnosed CKD in clinical practice. We already were performing a systematic search for RCTs that evaluated the effect of treatment of patients with CKD stages 1-3 on clinical outcomes to address Key Questions 5 and 6.

Comparators.

Studies were to compare systematic screening for CKD stages 1-3 with no CKD screening, usual care, or an alternative CKD screening regimen. Any monitoring or treatment interventions that followed screening were allowed.

Outcomes.

We restricted the review to studies that reported clinical outcomes or harms.

Study designs.

We initially included only RCTs. As described above, when no relevant RCTs were identified, we expanded our search to include observational studies that could provide indirect evidence regarding these questions.

Key Questions 3 and 4

Patients.

We restricted the review to studies that enrolled adults with CKD stages 1-3 who were systematically monitored for worsening of kidney function and/or damage. As above, studies whose definitions of CKD stages 1-3 at least closely approximated the current KDOQI and KDIGO definitions were considered eligible.

Study selection.

We sought RCTs or CCTs that assessed the direct impact of monitoring on clinical outcomes and harms. Examples of tests to monitor for worsening kidney function and/or damage that were considered eligible were direct measurements of GFR or creatinine clearance, estimation of GFR or creatinine clearance with creatinine-based formulae, serum creatinine, albuminuria, proteinuria, albumin/creatinine ratio, and cystatin C. The monitoring method must have been feasible within a primary care setting. Our exclusion criteria were as follows: nonadult population, population entirely or predominately not CKD stages 1-3, not an RCT that assigned participants to systematic monitoring for worsening of kidney function and/or damage versus usual care or a comparator intervention, and sample size of less than 50 randomized participants.

We did not identify any RCTs of CKD monitoring that assessed clinical outcomes and harms. Therefore, per protocol, we employed a nonsystematic search for studies that might provide indirect evidence regarding potential benefits and harms of monitoring. These studies may have addressed the incidence of progression of CKD stages 1-3 to worse kidney function and/or damage, the validity and reliability of tests to identify progression of patients from CKD stages 1-3 to worse kidney function and/or damage while asymptomatic, and the frequency at which tests to identify CKD progression were performed in individuals with CKD stages 1-3 in clinical practice. We already were performing a systematic search for RCTs that evaluated the effect of treatment of patients with CKD stages 1-3 on clinical outcomes to address Key Questions 5 and 6.

Comparators.

Studies were to compare systematic monitoring of patients with CKD stages 1-3 for changes in kidney function and/or damage with usual care or an alternative CKD monitoring regimen. Any interventions that followed CKD monitoring were allowed.

Outcomes.

We restricted the review to studies that reported clinical outcomes or harms.

Study designs.

We initially included only RCTs. As described above, when no relevant RCTs were identified, we expanded our search to include observational studies that could provide indirect evidence regarding these questions.

Key Questions 5 and 6

Patients.

We restricted the review to studies that enrolled adults with CKD stages 1-3. Again, studies whose definitions of CKD stages 1-3 at least closely approximated the current KDOQI and KDIGO definitions were considered eligible.

Interventions.

We included studies of both CKD specific and nonspecific treatments. Specifically, we attempted to identify studies of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), aldosterone antagonists, alpha blockers, beta blockers (BB), loop diuretics, thiazide and related diuretics, combination antihypertensive regimens, targeting thresholds of blood pressure control independent of specific antihypertensive agent(s), insulin, sulfonylureas, thiazolidinediones, biguanides (e.g., Metformin), targeting thresholds for glycemic control, HMG CoA-reductase inhibitors (i.e., statins), bile acid sequestrants, cholesterol absorption inhibitors (e.g., Ezetimibe), anorexiants, lipase inhibitors, low protein diets, and other diets.

Comparators.

These studies compared active treatment of patients with CKD stages 1-3 with placebo, usual care/no treatment, or with other active treatments, including combination treatment and comparisons with the same active treatments using different dose levels or targeting different treatment thresholds.

Outcomes.

We restricted the review to studies that reported clinical outcomes or harms.

Study designs.

We only included RCTs.

Study Selection

Separate literature searches were completed for the three main topic areas: screening, monitoring, and treatment. Results of each literature search were imported to a spreadsheet for screening. Trained reviewers examined all titles and abstracts for eligibility based on the inclusion/exclusion criteria for the topic area of the search. Titles and abstracts with insufficient information to determine eligibility were pulled for full article text review. If the initial reviewer was uncertain about eligibility, one of the physician project leads reviewed the abstract (or article) and made a final decision about inclusion or exclusion. We selected a 10 percent sample (representing the work of all abstract reviewers) for repeat review. Based on discrepancies between the results of one initial reviewer and the second reviewer, all abstracts reviewed by that initial reviewers were reviewed a second time. Overall, we asked abstract reviewers to err on the side of inclusion rather than exclusion. Reasons for exclusion were tallied in the spreadsheet and entered in an EndNote file for reference list management. We also applied the inclusion/ exclusion criteria to studies identified in the hand search of reference lists and in the review of studies cited in relevant systematic reviews. Additional references suggested by members of our TEP and by the public during the comment period also were reviewed for eligibility. A list of excluded studies is included in Appendix B.

Data Extraction

For the treatment interventions, trained clinicians or research assistants extracted data onto a spreadsheet. After verifying study eligibility, we extracted the following data from each trial:

- **Study quality**: Allocation concealment, intention-to-treat analysis, blinding, withdrawals, and dropouts adequately described;
- **Study characteristics**: Location, number of sites, subject inclusion and exclusion criteria, source of study subjects, total number randomized, details of treatment and control group interventions;
- **Baseline participant data**: age, weight, body mass index, gender, race/ethnicity, CKD stage, estimated or directly measured GFR, serum creatinine, urinary albumin or protein excretion rate, creatinine clearance, urine albumin or protein creatinine ratio, glycosylated hemoglobin, blood pressure, cholesterol, smoking status, and history of diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure (CHF), peripheral arterial disease, myocardial infarction (MI), stroke, and history of acute kidney injury;
- **Efficacy outcomes**: Duration of followup, all-cause mortality, cardiovascular mortality, MI (any, fatal, nonfatal), stroke (any, fatal, nonfatal), CHF (hospitalization, death), composite vascular outcomes, ESRD (progression to kidney transplant or dialysis), progression to stage 4 or stage 5 kidney disease, composite renal outcomes, doubling of serum creatinine or halving of GFR, conversion from microalbuminuria to macroalbuminuria, whether continuous renal outcomes were reported, and whether quality of life, physical function or activities of daily living were reported; and
- **Withdrawals and adverse events**: any withdrawals, withdrawals due to adverse events, any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Articles identified as not meeting eligibility criteria during the extraction phase were tallied and documented on the study flow diagram. In preparing the tables and text, a second clinician or research assistant confirmed the accuracy of the extracted information by comparing the extracted information with the original article. A physician project lead verified all entries in tables included in the review and appendices.

Quality Assessment

Study quality for the individual RCTs was rated by using the following criteria based on the domains the Cochrane Collaboration recommends to assess the risk of bias of studies included in a systematic review:[16] (1) adequate allocation concealment, based on the approach by Schulz and Grimes;[39] (2) blinding methods (participant, investigator, and/or outcome assessor); (3) how incomplete data are addressed (did the study analyze the data based on the intention-to-treat principle, i.e., were all participants who were randomized included in the outcomes analyses); and (4) whether reasons for dropouts/attrition were reported. Studies were rated as good, fair, or poor quality. A rating of good generally indicated that the trial reported adequate allocation concealment, blinding, analysis by intent-to-treat, and reasons for dropouts/attrition were reported. Studies were generally rated poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intent-to-treat was not utilized, and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition.

Rating the Body of Evidence

The overall strength of evidence for the randomized trials was evaluated using methods developed by the Evidence-based Practice Center at the Agency for Healthcare Research and Quality (AHRQ).[17] For each of several important clinical outcomes within each comparison evaluated, the strength of the evidence was evaluated based on four required domains: (1) risk of bias (do the studies for a given outcome or comparison have good internal validity); (2) consistency (the degree of similarity in the effect sizes, i.e., same direction of effect, of the included studies); (3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and (4) precision (degree of certainty surrounding an effect estimate of a given outcome). The risk of bias, based on study design and conduct, is rated low, medium, or high. Consistency is rated consistent, inconsistent, or unknown/not applicable (e.g., a single study was evaluated). Directness can either be direct or indirect and precision is either precise or imprecise. A precise estimate is one that would yield a clinically meaningful conclusion. Based on these four domains, the overall evidence was rated as: (1) high, indicating high confidence that further research is very unlikely to change the confidence in the estimate of effect, meaning 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, 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, 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. An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains.

Applicability

Applicability of the results reported in this review is affected by the representativeness of the patient samples in the included studies to general populations and specific subpopulations of nonstudy patients with CKD stages 1-3, both those identified through screening and through other means. All treatment trials included patients with CKD stages 1-3, but because of the variability in CKD definitions used in identified studies, some trials also included some patients outside the bounds defined by CKD stages 1-3. This may limit the applicability of results reported here to patients who meet the currently accepted definition for CKD stages 1-3. Incomplete reporting of patient characteristics in many included trials also limits our ability to judge applicability of study results to specific CKD patient populations. The evidence tables in Appendix C identify reported details on the patient inclusion and exclusion criteria, as well as baseline patient characteristics.

Data Synthesis

Text; evidence, outcomes, and summary tables; and figures were organized by intervention. If clinical heterogeneity of patient populations, interventions, and outcomes was minimal, we pooled results. For many interventions, there were only one or two trials and reported outcomes did not overlap. Narratives provide details on study populations, interventions, clinical outcomes, and harms. Data were analyzed in Review Manager 5.0.[18] Random effects models were used to generate pooled estimates of relative risks (RR) and 95 percent confidence intervals (CI). Statistical heterogeneity was summarized using the I^2 statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).[19]

Publication Bias

Grey literature was searched for relevant trials and other material to estimate the likelihood of publication bias. Sources of regulatory documents included Federal Drug Administration – Medical Reviews and Statistical Reviews, Health Canada – Drug Monographs, and Authorized Medicines for the European Union. Clinical trial registries accessed were ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, and World Health Organization's Clinical Trials. Conference papers and abstracts were identified from the CSA Conference Papers Index and Scopus.

Results

Our literature search was designed to identify RCTs and CCTs of screening to identify patients with CKD stages 1-3, and monitoring and treatment of patients with CKD stages 1-3. For the screening questions, our search yielded 324 references (Key Questions 1 and 2; Figure 2). We excluded 315 references in the initial review of titles and abstracts and we excluded the remaining nine references based on a full text review. The results were similar for the monitoring questions (Key Questions 3 and 4; Figure 3). Of 816 references identified in the search, we excluded 803 in title and abstract review and excluded the remaining 13 after obtaining the full text. For the treatment questions, 4,706 references were identified by the literature search (Key Questions 5 and 6; Figure 4). We excluded 3,676 references during title and abstract review and excluded an additional 939 when we reviewed the full text. In addition to the 91 eligible references identified from the literature search, an additional eight eligible references were identified by hand searching reference lists of related articles or systematic reviews or were suggested by members of our TEP or reviewers of our protocol.

The grey literature search yielded 1,899 documents or citations; 1,065 from regulatory sources, 416 from clinical trials, and 418 conference papers and abstracts. Of the treatments analyzed for this report, our literature review yielded the most references for ACEIs. We therefore looked at the grey literature for ACEI studies not identified in our literature search. In the conference abstract and papers grey literature, there were 74 references pertaining to ACEIs. Ten of the references were identified in our literature search. The remainder did not meet inclusion criteria. In the clinical trials grey literature, there were 13 citations pertaining to ACEIs. Nine did not meet inclusion criteria. The four remaining studies are in progress with no results reported, to date. We concluded that our literature search adequately identified the relevant studies.

Figure 2. Reference flow chart for CKD literature search - screening

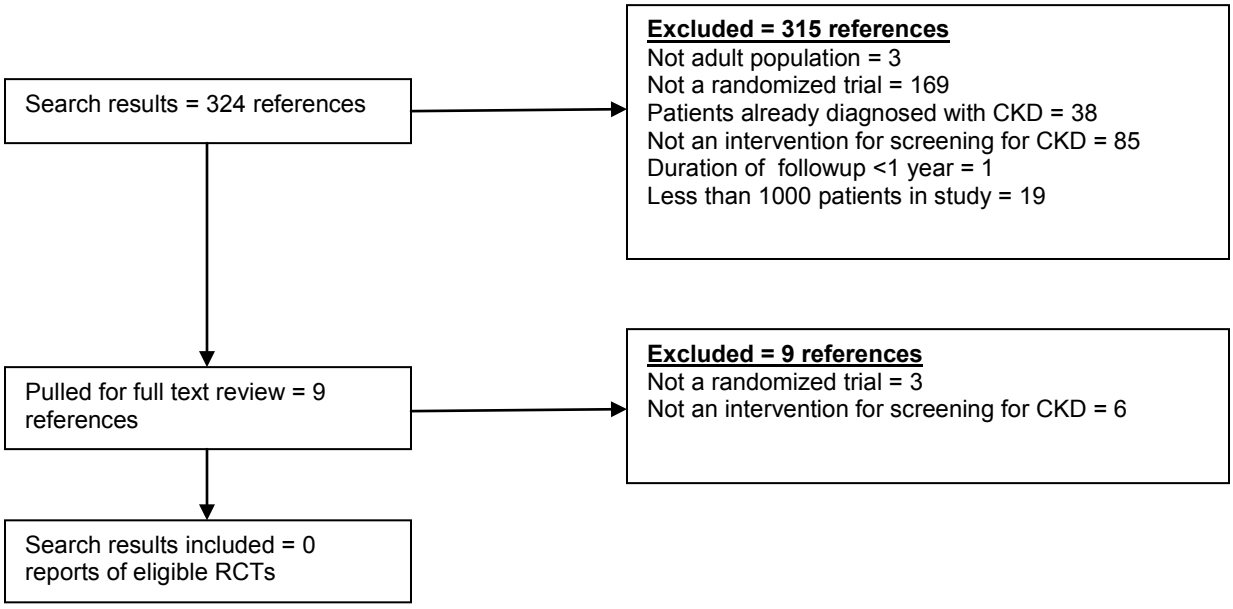


Figure 3. Reference flow chart for CKD literature search - monitoring

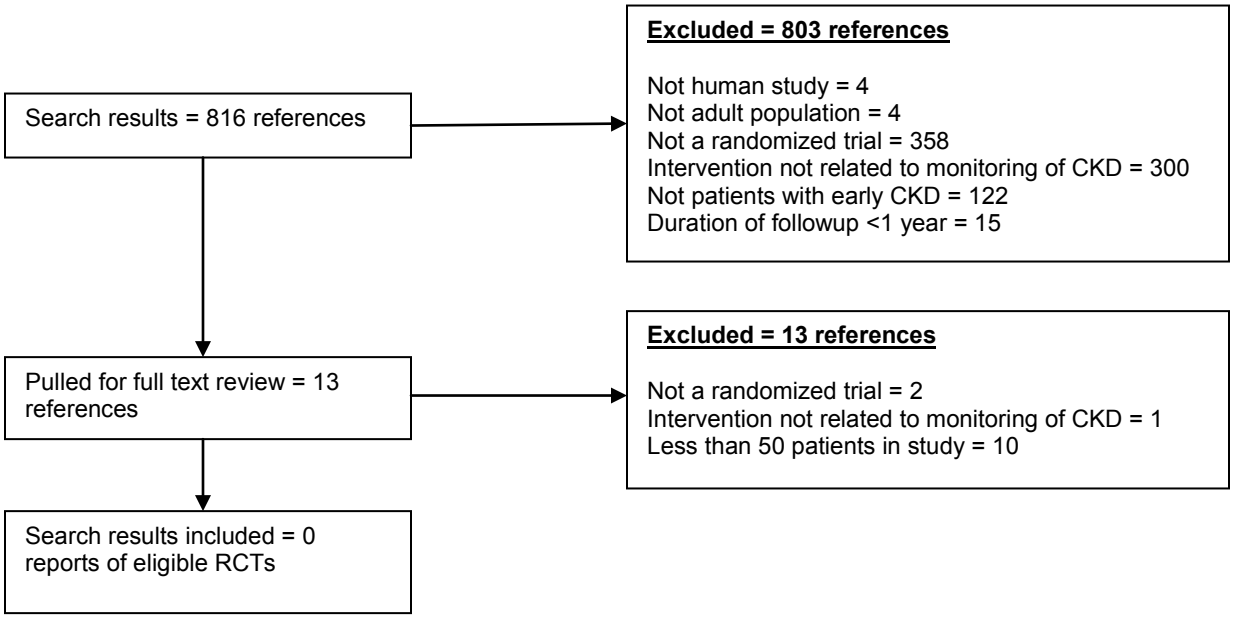
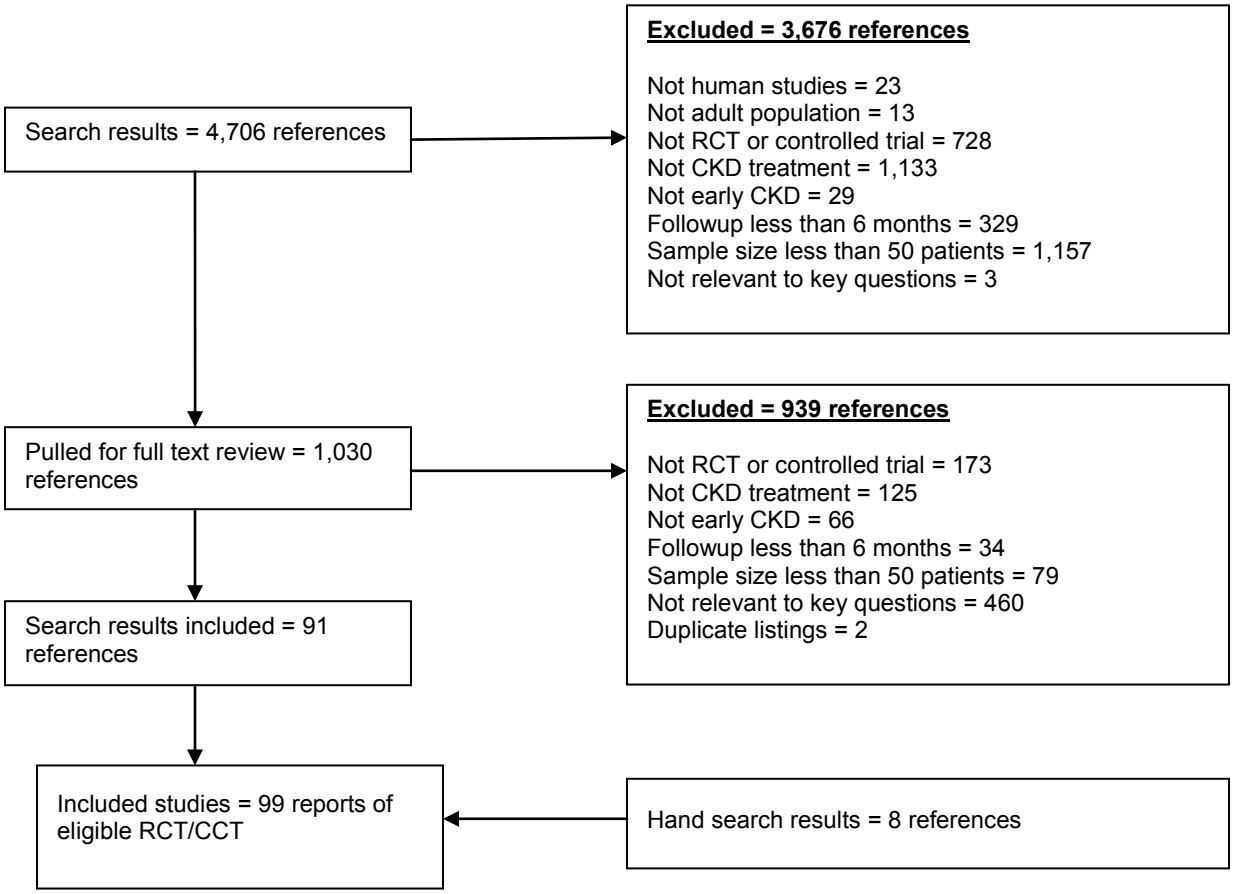


Figure 4. Reference flow chart for CKD literature search - treatment



Key Question 1: In Asymptomatic Adults with or without Recognized Risk Factors for Chronic Kidney Disease (CKD) Incidence, Progression or Complications, What Direct Evidence is there that Systematic CKD Screening Improves Clinical Outcomes?

We found insufficient evidence regarding whether systematic screening for CKD improves clinical outcomes.

Direct Evidence

We identified no RCTs that compared systematic CKD screening versus no CKD screening, versus usual care, or versus an alternative CKD screening regimen and evaluated clinical outcomes.

Indirect Evidence

Not finding direct evidence regarding whether systematic CKD screening improved clinical outcomes, we nevertheless identified data to address at least some parameters that would be needed to indirectly assess the potential clinical benefits of systematic CKD screening.

Is undiagnosed CKD stages 1-3 sufficiently prevalent?

Determination of how many individuals need to be screened to identify each new case of CKD in the population overall and within high risk groups will be a function both of the prevalence of undiagnosed CKD in these groups and the frequency with which such patients already are tested for CKD in usual practice.

As described earlier, approximately 11.1 percent (22.4 million) of U.S. adults aged 20 or older have CKD stages 1-3.[5] This estimate is derived from the NHANES population by using the CKD-EPI formula to estimate GFR and the urine albumin-creatinine ratio to estimate kidney damage. Of individuals with CKD stages 1-3, half have increased albuminuria only (nearly all with microalbuminuria), one-third have decreased GFR only, and the remainder have both abnormalities. Of individuals with albuminuria, nearly 85 percent have microalbuminuria, with the remainder (approximately 1 percent of NHANES participants) having macroalbuminuria. In another population-based sample, prevalence of macroalbuminuria among adults aged 28 to 75 years was 0.6 percent.[40] Compared to the overall population, prevalence of CKD stages 1-3 is higher among older adults, including 17.6 percent in those aged 60-69, and 44.4 percent among adults aged 70 years or older[5] Also based on NHANES data, prevalence of CKD stages 1-3 is 41.1 percent in patients with diabetes, 27.8 percent in patients with hypertension, and 39.3 percent in those with cardiovascular disease.[41] Combining these risk factors, NHANES data have been used to stratify individuals into different groups with respect to their likelihood of having CKD (Figure 1).[25] For example, only 5 percent of individuals less than 52 years old and without diabetes, hypertension, or obesity were estimated to have CKD compared to 68 percent of those aged 81 years or older.

Other data suggest that most individuals with CKD stages 1-3 are not clinically recognized to have this diagnosis. In one study, among patients with GFR <60 ml/min/1.73m^2, just 26.5 percent were documented to have a clinical diagnosis of CKD.[42] In 2008 data from the VA

system, even in patients with CKD stages 3-5, only 33 percent had a provider-coded ICD-9 diagnosis for CKD.[43] Awareness of CKD appears even lower in patients. According to the CDC CKD Surveillance Project 2009 Report, among NHANES participants in 1999-2006, fewer than 5 percent with proteinuria and an estimated GFR ≥60 ml/min/1.73m^2 (based on a single measurement) reported being aware of having CKD, and only 7.5 percent of participants with a GFR between 30-59 ml/min/1.73m^2 were aware of having CKD.[43]

Most patients without CKD, even those in high risk groups, do not appear to be undergoing CKD testing in usual clinical care. Based on 2007-2008 Medicare data, among patients without CKD who had diabetes, the annual probability of urine microalbumin testing was just over 30 percent.[1] In those without CKD who had hypertension, the annual probability of urine microalbumin testing was 4 percent. Based on 2004 Medicare data, among patients without CKD who had either diabetes or hypertension, the annual probability of serum creatinine measurement was less than 20 percent.[44]

Is CKD stages 1-3 associated with sufficient adverse health consequences?

As described earlier, early stage CKD is usually asymptomatic. However, data from many studies indicate that a GFR 30-59 mL/min/1.73 m^2 (stage 3 CKD) is associated with an increased risk of mortality,[3,27] cardiovascular disease,[28] fractures,[29] bone loss,[30] infections,[31] cognitive impairment,[32] and frailty. Similarly, albuminuria and proteinuria (stage 1-4 CKD) are associated with an increased risk of mortality,[3,33] ESRD,[34] and cardiovascular disease,[35] with risk increasing according to the severity of albuminuria or proteinuria. Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria or proteinuria appear independent and multiplicative.[3,34]

Are there valid, reliable, and clinically available CKD screening tests?

Serum creatinine is measured from a simple blood test. Formulas to estimate GFR are now automatically reported in many clinical labs from serum creatinine and are highly correlated (i.e., greater than 0.9)[45] with direct GFR measurement based on urinary clearance of ^{125}I-iothalamate. A large external validation study indicated that compared to measured GFR the CKD-EPI formula had a small median bias (measured GFR minus estimated GFR) of +/-4 ml/min/1.73m^2 or less at all levels of measured GFR.[46] This represents a significant improvement in accuracy compared to the Modification of Diet in Renal Disease (MDRD) formula for measured GFR ≥30 ml/min/1.73m^2, which is known to underestimate measured GFR above this level, particularly in individuals with GFR ≥60 ml/min/1.73m^2. However, the precision of both formulas are limited in that the percentage of their estimates that diverge by more than 30 percent from measured GFR exceeds 15 percent.[5] Framed differently, the sensitivity and specificity of a one-time estimate of GFR <60 mL/min/1.73m^2 for detection of a one-time direct measurement of GFR <60 mL/min/1.73m^2 were 91 percent and 87 percent according to the CKD-EPI equation and 95 percent and 82 percent according to the MDRD Study equation.[5] These data correspond to a false-positive rate of 13 percent and 18 percent for GFR estimation with CKD-EPI and MDRD, respectively. We did not identify studies that compared estimated GFR with directly measured GFR based on two or more measurements three or more months apart as would be consistent with the definition of CKD. It would be expected that when compared to persistently abnormal measured GFR, the false-positive rate of one-time estimated GFR would be higher.

There are many sources of variability in measurement of urinary albumin excretion. Intra-individual variability is high, with many published coefficients of variance estimates clustering

around 30 to 50 percent.[47] Factors that can impact urinary albumin excretion include body position, exercise, and fever.[47] While most groups recommend use of spot tests and calculation of the urine albumin-creatinine ratio, methodology for its collection and for measurement of both urinary albumin and creatinine has yet to be standardized. Although these are additional sources of variation, they appear considerably smaller in magnitude than the intra-individual variability.[47-49] Impacted by these issues, among individuals with one-time microalbuminuria and GFR ≥60 ml/min/1.73m^2 in the NHANES study, only 63 percent had either microalbuminuria or macroalbuminuria on repeat testing two months later.[50] Further, even in a diabetic population with persistent microalbuminuria, as defined by repeated UACR measurements during a 2 year period, regression of the microalbuminuria to normal occurred in 59 percent patients over a subsequent 6 year evaluation period.[51]

Unfortunately, we did not identify any population-based studies that tested the sensitivity or specificity of one-time screening using both estimated GFR and albuminuria for diagnosis of CKD as defined by persistence of impaired GFR and/or albuminuria for at least three months (the current "gold standard"). We also did not identify any data on the validity and reliability of repeated screening for CKD.

Do treatments for screen-detected CKD patients improve important clinical outcomes?

We did not identify RCTs involving treatment of CKD patients identified through systematic screening, but did systematically review the RCT evidence on the effectiveness of treatments of CKD patients identified more generally in the Results section for Key Question 5.

Table 1. Prevalence of CKD stages by age, gender, race, and comorbidities using the creatinine based CKD-Epi formula for estimating GFR (Adapted from USRDS Annual Report 2010)[1]

	Stage 1	Stage 2	Stage 3	Stages 4-5
Overall	4.3	3.2	6.3	0.6
Age 20-39	4.7	0.7	0.2*	0.1*
Age 40-59	4.9	2.5	2.0	0.2
Age 60+	2.4	8.6	24.3	2.1
Male	3.5	3.4	5.2	0.6
Female	5.0	3.0	7.4	0.6
Non-Hispanic white	3.2	3.3	7.4	0.6
Non-Hispanic African American	6.3	3.4	4.9	1.2
Diabetes (SR)	11.8	10.2	17.0	3.1
Hypertension (SR)	5.4	5.9	14.6	1.7
CVD (SR)	3.3	8.7	25.9	4.3
Current smoker	5.9	2.3	2.4	0.5
Obese (BMI ≥30)	5.5	4.2	6.6	0.6

*Not Reliably Estimated. SR= Self-Reported
CKD Stages defined as:
Stage 1: eGFR ≥90 mL/min/1.73 m^2, UACR ≥30 mg/g
Stage 2: eGFR 60-89 mL/min/1.73 m^2, UACR ≥30 mg/g
Stage 3: eGFR 30-59 mL/min/1.73 m^2
Stage 4: eGFR 15-29 mL/min/1.73 m^2
Stage 5: eGFR <15 with dialysis patients excluded from this analysis

Table 2. Sensitivity and specificity of different population characteristics for identifying individuals who would have one-time eGFR <60 ml/min/1.73 m^2: using creatinine and CKD-Epi formula (Adapted from USRDS Annual Report 2010)[1]

Screened Population	Sensitivity of Demographic Characteristics	Specificity of Demographic Characteristics
Age 20+	100.0	0
Age 50+	94.6	65.7
Age 50+ or <50 with DM or HTN	98.0	55.4
Age 50+ or <50 with DM, HTN, or CVD	98.6	54.7
Age 60+	85.3	82.3
Age 60+ or <60 with DM or HTN	94.6	65.5
Age 60+ or <60 with DM, HTN, or CVD	95.4	64.2

CKD-Epi Formula: estimated GFR = 141 * min(Scr /κ, 1)**α* max(Scr/κ, 1)**(-1.209) * 0.993**age * 1.018 [if female] * 1.159 [if African American], where Scr is standardized serum creatinine in mg/dl, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/κ or 1.
DM=Diabetes Mellitus, HTN=Hypertension, CVD=Cardiovascular Disease.

Table 3. Sensitivity and specificity of different population characteristics for identifying individuals who would have one-time UACR ≥30 mg/g (Adapted from USRDS Annual Report 2010)[1]

Screened Population	Sensitivity	Specificity
Age 20+	100.0	0
Age 50+	60.5	64.3
Age 50+ or <50 with DM or HTN	73.3	54.9
Age 50+ or <50 with DM, HTN, or CVD	73.9	54.1
Age 60+	44.9	80.5
Age 60+ or <60 with DM or HTN	67.6	65.1
Age 60+ or <60 with DM, HTN, or CVD	68.6	63.7

ACR: urinary Albumin (mg/l) to urinary Creatinine (mg/dl) Ratio.
DM=Diabetes Mellitus, HTN=Hypertension, CVD=Cardiovascular Disease.

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?

We found insufficient evidence to address the question regarding whether systematic CKD screening causes adverse effects for patients.

Direct Evidence

We identified no RCTs that compared systematic CKD screening versus no CKD screening, versus usual care, or versus an alternative CKD screening regimen and evaluated adverse effects for patients.

Indirect Evidence

We considered numerous potential adverse effects of systematic CKD screening (Table 4), but found only very limited literature addressing this issue.[21] The primary harms from CKD screening are likely to be misclassification of patients with CKD, unnecessary tests and their associated adverse effects (e.g., from phlebotomy or renal biopsies), psychological effects of being labeled with CKD, adverse events associated with pharmacological treatments initiated or changed following a CKD diagnosis, and possible financial and insurance ramifications of a new CKD diagnosis.

Table 4. Potential harms associated with screening for CKD

A)	Psychological effects of screening tests
B)	Adverse physical effects of screening tests (e.g. phlebotomy-associated bruising)
C)	Misclassification/false positive diagnosis
D)	Unnecessary tests to further evaluate patients with positive screening test and their associated effects, e.g., phlebotomy-associated bruising; pain, bleeding with need for transfusion, and infection associated with renal biopsy
E)	Psychological effects associated with CKD diagnostic label and of further evaluations following diagnosis
F)	Increased visits to primary provider, increased referrals to specialists
G)	Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
H)	Increased costs to patient and health system
I)	Increased difficulty and costs of obtaining/keeping health insurance coverage

Psychological effects of screening.

We did not identify any studies that reported on the psychological effects of screening tests for CKD.

Adverse physical effects of screening tests and of followup tests to evaluate abnormal screening test.

Phlebotomy required to measure serum creatinine may be associated with a small degree of bruising or discomfort. In a small number of patients, post-screening evaluation will include a renal biopsy, which has an associated risk of pain, bleeding, and infection.

Misclassification/false positive test for CKD.

We did not identify any studies that reported on the effects of a false positive result from tests used to screen for CKD. False positive results may be common with tests for microalbuminuria. As described above, intra-individual variability in albuminuria is high. In one study, more than one-third of individuals with microalbuminuria and normal GFR on first testing regressed to normoalbuminuria on repeat testing two months later.[50] Raising questions about the sufficiency of the requirement that albuminuria be persistent for at least 3 months to diagnose CKD, in a second study, 59 percent of individuals with persistent microalbuminuria over a 2 year period regressed to normal during a subsequent 6 year evaluation period.[51] We did not identify any studies that reported the specificity of a single measurement of GFR estimated from serum creatinine for a diagnosis of CKD defined by abnormalities in kidney function or damage that persist for at least 3 months.

Labeling of an individual with CKD.

We did not identify any studies that reported on the effects of labeling an individual with CKD.

Increased clinic visits to primary and/or specialist providers.

We did not identify any studies that reported on the effect of CKD screening tests on subsequent patient visits to primary or specialist providers. However, to the extent that their provider is aware of it, individuals who have an abnormal result on CKD screening, seem likely to be seen more frequently in primary and specialty clinics. These visits may be for further evaluation to confirm the abnormal screening test, or providers may follow and treat these patients under the assumption that they have diagnosed CKD. According to recent U.S. Renal Data System (USRDS) data, in the year following a claim-documented CKD diagnosis, approximately 90 percent of individuals have at least one physician visit and 30 percent have a visit with a nephrologist.[1]

Adverse effects associated with treatment.

We systematically reviewed the RCT evidence on adverse effects of treatments of CKD patients in the Results section for Key Question 6.

Increased costs to patient, healthcare system, and impact on insurance coverage.

These questions were considered outside the scope of this AHRQ review.

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?

We found insufficient evidence regarding whether systematic monitoring of individuals with CKD stages 1-3 for worsening kidney function and/or kidney damage improves clinical outcomes.

Direct Evidence

We identified no RCTs that compared systematic monitoring of individuals with CKD stages 1-3 for changes in kidney function and/or damage versus no CKD monitoring, versus usual care, or versus an alternative CKD monitoring regimen and evaluated clinical outcomes.

Indirect Evidence

Though we did not find direct evidence regarding whether systematic monitoring of individuals with CKD stages 1-3 for changes in kidney function and/or damage improved

clinical outcomes, we identified data to address at least some parameters that would be needed to indirectly assess the potential clinical benefits of such systematic monitoring in these patients.

Is undiagnosed worsening of kidney function and/or damage sufficiently frequent in patients with CKD stages 1-3?

Determination of whether and how frequently individuals with CKD stages 1-3 need to be monitored to identify patients with CKD progression, overall and within high risk groups, will be a function both of the incidence of undiagnosed CKD progression in these groups, the incidence of CKD regression (e.g., to normoalbuminuria), and the frequency with which these patients already have their level of kidney function and/or damage tested in usual practice.

In patients with CKD, reported rates of CKD progression vary widely. Mean annual GFR decline may range from approximately 1 to >10 ml/min/1.73m^2.[10] Factors shown in at least some studies to predict faster decline include diabetes, proteinuria, increased blood pressure, older age, obesity, dyslipidemia, smoking, male gender, and etiology of primary kidney disease. The high intra-individual variation in albuminuria makes it harder to estimate rates at which albuminuria increases in CKD. However, in several RCTs that randomized individuals with diabetes and microalbuminuria to either ACEI or ARB versus placebo,[52-57] the average annual progression rate to macroalbuminuria was approximately 5 to 9 percent (Table 5). A lower annual conversion rate of 2.8 percent was reported in the United Kingdom Prospective Diabetes Study.[58] However, these estimates of progression in albuminuria from RCTs are limited both in that being derived from RCTs they may not be representative of all patients with microalbuminuria, and in that a substantial portion of individuals with microalbuminuria also will regress (i.e., to normoalbuminuria) over time.

Contrasted to the lower frequency of testing among individuals who do not carry a CKD diagnosis, most patients with CKD stages 1-3 appear to be undergoing at least some CKD testing in usual clinical care. Based on 2008 data, the annual probability that patients with CKD stages 1-3 receive serum creatinine testing is about 95 percent in the Medicare population and about 80 percent in a younger privately insured population.[1] By comparison, the annual probability that patients with CKD stages 1-3 get albuminuria measured is between 30 and 40 percent.

In patients with CKD stages 1-3, is CKD progression associated with sufficient adverse health consequences?

As described earlier, data from many studies indicate that a GFR 30-59 mL/min/1.73 m^2 (stage 3 CKD) is associated with an increased risk of mortality,[3,27] cardiovascular disease,[28] fractures,[29] bone loss,[30] infections,[31] cognitive impairment,[32] and frailty. Similarly, albuminuria and proteinuria are associated with an increased risk of mortality,[3,33] ESRD,[34] and cardiovascular disease,[35] with risk increasing according to the severity of albuminuria or proteinuria. Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria or proteinuria is independent and multiplicative.[3,34]

We did not identify studies that longitudinally recalibrated risk of adverse health consequences among individuals with CKD stages 1-3 as their CKD progressed. However, a large, recent meta-analysis of prospective cohort studies reported risk of all-cause and cardiovascular mortality for different strata defined by baseline eGFR and albuminuria as follows:[3]

- Within individuals who had albuminuria and GFR >60 ml/min/1.73m^2 (CKD stages 1-2):

- Mortality risk was higher in those with macroalbuminuria than in those with microalbuminuria.
- A lower GFR within this range was not associated with a higher mortality risk.
- Mortality is increased for each lower level of eGFR below 60 ml/min/1.73m^2, higher for 45-59 (CKD stage 3), still higher for 30-44, and higher for GFR <30 ml/min/1.73m^2 (CKD stage 4).

- Within individuals with GFR <60 ml/min/1.73m2 (CKD stage 3):
  - Mortality risk is increased for each lower level of eGFR, lowest for 45-59, higher for 30-44, and higher for GFR <30 ml/min/1.73m2 (CKD stage 4).
  - Mortality risk is lowest in those without albuminuria, higher in those with microalbuminuria, and highest in those with macroalbuminuria.

Are there valid, reliable, and clinically available tests to monitor CKD progression in patients with CKD stages 1-3?

Tests used to monitor CKD progression in patients with CKD stages 1-3, most typically quantitative measures of albuminuria and estimates of GFR calculated from serum creatinine, are derived from simple blood and urine tests that are widely available in primary care settings.

As described earlier in the section on screening, formulas to estimate GFR are automatically reported in many clinical labs from serum creatinine and are highly correlated with direct GFR measurement.[45] Compared to measured GFR, the CKD-EPI formula to estimate GFR has only a small bias at all levels of measured GFR,[46] which represents an improvement in accuracy compared to the MDRD formula, particularly in individuals with GFR ≥60 ml/min/1.73m^2. Both formulas suffer from some imprecision, however, as more than 15 percent of their estimates diverge from measured GFR by at least 30 percent.[5] Still, they appear to perform well for one-time classification of individuals as either having CKD or not. The sensitivity and specificity of estimated GFR <60 mL/min/1.73m^2 for detection of directly measured GFR <60 mL/min/1.73m^2 were 91 percent and 87 percent according to the CKD-EPI equation and 95 percent and 82 percent according to the MDRD Study equation.[5] Unfortunately, we did not identify data regarding the accuracy and precision of these formulas for assessing change in GFR within individuals over time, or their sensitivity and specificity for detecting change in GFR category over time (e.g. a decline from a GFR of 30 to 59 ml/min/1.73m2 to one of <30 ml/min/1.73m^2).

Also as described in the section on screening, inter-assay and intra-assay coefficient of variance for urinary albumin is less than 5 percent.[48,49] However, as is the case for individuals without CKD, intra-individual variation of urinary albumin excretion is high in individuals with CKD. The impact of hydration can be addressed by accounting for urine output (e.g. using urine albumin-to-creatinine ratio), but nonhydration factors that may impact estimates of urinary albumin excretion include body position, exercise, certain medications, fever, and urinary tract infections.[10] As an illustration of this variability, based on NHANES data, among individuals with one-time microalbuminuria and GFR ≥60 ml/min/1.73m^2, only 63 percent had either microalbuminuria or macroalbuminuria on repeat testing two months later.[50] Further, even in a diabetic population with persistent microalbuminuria over a 2 year period, regression of the microalbuminuria to normal occurred in 59 percent patients during a subsequent 6 year evaluation period.[51] This variability makes it more difficult to determine whether longitudinal changes in measured albuminuria represent progression of CKD.

In patients with CKD stages 1-3 whose CKD has progressed, do treatments improve important clinical outcomes?

For monitoring to improve clinical outcomes, changes in CKD status such as the patient reaching a specific threshold or rate of change in kidney function or damage would need to impact patient behavior or provider treatment in ways that improve these outcomes. RCT evidence that certain treatments had differential effects on clinical outcomes between patients with CKD stages 1-3 and those with CKD stage 4, or differential effects between different categories of patients within CKD stages 1-3 might suggest that treatment should be modified when change in CKD status is identified. While RCT data on CKD treatments are reviewed in greater detail elsewhere in this report, there is limited evidence to suggest that some treatments may have such differential effects based on CKD stage. For example, in RCTs comparing ACEI versus placebo treatment, a significant 40 percent reduction in relative risk of ESRD with ACEI is evident in trials comprised of patients with macroalbuminuria. By comparison, in ACEI versus placebo trials comprised of patients with microalbuminuria only, with very low power to detect changes in ESRD events, the pooled effect size suggests no difference between treatments. In a post hoc analysis in CHF patients with CKD, tests for interaction between study participants with GFR of >60, 45 to 60, and 30 to 44 ml/min/1.73m2 suggest that benefit of beta blocker treatment versus placebo may be greater in the lower GFR group for reducing risk of hospitalizations due to CHF (p=.038), of two composite outcomes including all-cause mortality and hospitalization (both p<.05), and may be borderline significant with regard to all-cause mortality (p=.095).

Table 5. Rate of progression from microalbuminuria to macroalbuminuria

Trial	Baseline CKD level	followup Duration	Incidence of Macroalbuminuria
O'Hare, 2000[56] (ATLANTIS)	N=46 100% had microalbuminuria; 100% Insulin Dependent Diabetics GFR (ioexol) mean±SD= 100 ± 23ml/min	2 years	10.9% (5/46) ~5% per year
Strippoli, 2006[52] MICRO HOPE 2000[54]	N=587 100% had microalbuminuria 100% Diabetics	Median 4.5 years	21.6% (127/587) ~5% per year
Crepaldi, 1998[53]	N=34 100% had microalbuminuria 100% Insulin Dependent Diabetics	3 years	20.6% (7/34) ~7% per year
Laffel, 1995[55]	N=70 100% had microalbuminuria; 100% Insulin Dependent Diabetics CrCl (mean±SD)= 80 ± 22 mL/min per $1.73m^2$ at baseline	2 years	18.6% (13/70) ~9% per year
Ravid, 1993[57]	N=45 100% had microalbuminuria 100% Type 2 Diabetics Proteinuria mean±SD= 123 ± 58 mg/24 h	5 years	42.2% (19/45) ~8% per year

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/Kidney Damage?

We found insufficient evidence to address the question regarding whether systematic monitoring of patients with CKD stages 1-3 for worsening kidney function or kidney damage causes adverse effects for patients.

Direct Evidence

We identified no RCTs that compared systematic monitoring of patients with CKD stages 1-3 for worsening kidney function or kidney damage versus no CKD monitoring, versus usual care, or versus an alternative CKD monitoring regimen and evaluated adverse effects for patients.

Indirect Evidence

We considered numerous potential adverse effects of systematic monitoring of patients with CKD stages 1-3 for worsening kidney function or kidney damage (Table 6), but found no literature directly addressing this issue. The primary harms from such monitoring are likely to be incorrect reclassification of patients as having improved or worsened CKD, unnecessary tests and their associated adverse effects (e.g., from phlebotomy or renal biopsies), psychological effects of being labeled with progressive or regressed CKD, adverse events associated with pharmacological treatments initiated or changed following testing that indicates that CKD has worsened or improved, and possible financial and insurance ramifications of a more advanced CKD diagnosis.

Table 6. Potential harms associated with monitoring patients with CKD stages 1-3 for worsening kidney function

A)	Psychological effects of monitoring tests
B)	Adverse physical effects of screening tests (e.g. phlebotomy-associated bruising)
C)	Incorrect reclassification of CKD severity
D)	Unnecessary tests and associated effects, e.g., phlebotomy-associated bruising; pain, bleeding with need for transfusion, and infection associated with renal biopsy
E)	Psychological effects associated with label of worse CKD stage and of further evaluations following diagnosis
F)	Increased visits to primary provider, increased referrals to specialists
G)	Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
H)	Increased costs to patient and health system
I)	increased difficulty obtaining/keeping health insurance coverage

Psychological effects of monitoring.

We did not identify any studies that reported on the psychological effects of monitoring tests for CKD.

Adverse physical effects of monitoring tests and of followup tests to further evaluate monitoring tests.

Phlebotomy required to measure serum creatinine may be associated with a small degree of bruising or discomfort. In a small number of patients, post-screening evaluation will include a renal biopsy, which has an associated risk of pain, bleeding, and infection.

Incorrect reclassification of CKD severity.

We did not identify any studies that reported on the effects of testing that incorrectly reclassifies patients with CKD stage 1-3 as having worse or improved CKD, or even no CKD. Limitations in the precision of formulas that estimate GFR means there is a reasonable likelihood that any one test will suggest that a patient's CKD has changed or remained stable when this isn't the case. However, the small bias, in particular of the CKD-EPI formula, suggests that multiple GFR estimates will cluster accurately around true measured GFR. The high intra-individual variability of albuminuria in the absence of changes in underlying disease means there is at least a modest likelihood that findings of any one quantitative test will be inaccurate, whether it indicates that a patient's albuminuria is improving, stable or worsening. As an example, in one study cited above, more than half of individuals with persistent microalbuminuria during a 2 year period regressed to normal over a subsequent 6 year evaluation period.[51]

Labeling of an individual with more advanced CKD stage.

We did not identify any studies that reported on the effects of labeling an individual with a more advanced CKD stage.

Increased clinic visits to primary and/or specialist providers.

We did not identify any studies that reported on the effect of CKD monitoring tests on subsequent patient visits to primary or specialist providers. However, individuals whose monitoring tests indicate progression of their CKD seem likely to be seen more frequently in primary and specialty clinics. These visits may be for further evaluation to confirm the abnormal monitoring test, or providers may follow and treat these patients under the assumption that they have more severe CKD.

Adverse effects associated with treatment.

We systematically reviewed the RCT evidence on adverse effects of treatments of CKD patients in the Results section for Key Question 6.

Increased costs to patient, healthcare system, and impact on insurance coverage.

These questions were considered outside the scope of this AHRQ review.

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?

ACE Inhibitor Monotherapy Versus Placebo/No Treatment Trials (n=17)

Overview.

In patients with CKD, compared to placebo, we found moderate evidence that ACEI treatment does not reduce risk of all-cause or cardiovascular mortality more than placebo, and low strength of evidence that ACEI treatment does not reduce risk MI or stroke. We found low strength of evidence that ACEIs reduce risk of ESRD compared to placebo in CKD patients studied overall, but moderate strength of evidence that they reduce risk of ESRD in patients with overt proteinuria. There was moderate evidence that ACEIs reduce risk of doubling serum creatinine, and that they reduce progression from microalbuminuria to macroalbuminuria.

Description of studies.

Seventeen trials met all eligibility criteria and randomized participants with CKD (n=10,845, range 52 to 4,912) to an ACEI versus placebo (n=16 trials).[53,55-57,59-70] or no treatment (n=1 trial).[71] Two of the included reports were post-hoc analyses performed within subsets of participants with CKD from larger trial populations that were not originally limited to subjects with CKD.[59,64] Detailed baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 6,721 participants were randomized to ramipril versus placebo (n=7 trials),[56,61,63,64,66,67,69] 1,757 to perindopril versus placebo (n=1 trial),[59] 864 to fosinopril versus placebo (n=1 trial),[60] 665 to captopril versus placebo (n=4 trials)[55,62,65,70] 583 to benazepril versus placebo (n=1 trial),[68] 108 to enalapril versus placebo (n=1 trial),[57] 97 to lisinopril versus placebo (n=1 trial),[53] and 52 to enalapril versus no treatment (n=1 trial).[71] The mean age of subjects was 60 years (range 33 to 70; n=16 trials), and men constituted 66 percent (range 35 to 82; n=15 trials) of all patients randomized. Among the five trials reporting ethnicity, the patients were mostly of white race (77 percent).[55,59,60,65,70] Most trials were conducted in Europe (including North Africa and Israel), three were conducted primarily or partially in the United States, and two were conducted in Japan. Mean or median study duration ranged from 6 months to 5 years. Seven trials had a followup of 3 years or longer and 12 trials had a followup of at least 2 years. Only one trial had a study duration of less than 1 year.[69] One trial was conducted in a subset of individuals who previously had responded to an effort to screen all city residents aged 28 to 75 years for albuminuria.[60]

Renal function.

One of the two post-hoc analyses restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse.[59] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. In 15 of 17 trials, participants were required to have albuminuria or proteinuria. In 10 of these trials, participants

must have been microalbuminuric,[53,55-57,60,63-65,69,71] most commonly with a urinary albumin excretion rate of 20 to 200 µg/minute. In three of the 15 trials, they were required to have overt proteinuria, with minimum thresholds ranging from ≥500 mg/day,[70] to ≥1 but ≤3 g/day,[66] and to >3 g/day.[67] In the last two of the 15 trials, both microalbuminuric and macroalbuminuric participants were allowed,[61,62] with approximately three-quarters of the participants in one of these trials being microalbuminuric,[61] but no similar data reported for the other trial. Among the 15 trials requiring participants to have albuminuria or proteinuria, seven required that participants also have normal creatinine, creatinine clearance or GFR,[53,55,56,60,65,69,71] three allowed some participants with abnormal levels for these renal function measures but mandated a maximally abnormal limit,[61,64,70] and the remaining five trials did not specify an eligibility requirement with respect to these measures.[57,62,63,66,67] Finally, inclusion in two of 17 studies was based strictly on elevated serum creatinine, or reduced creatinine clearance or GFR.[59,68]

Among the 10 trials restricted to microalbuminuric patients, mean baseline urinary albumin excretion rate was reported as 61.0 µg/min (range 53 to 71.5) in five trials[53,55,56,65,69] and as 25.6 mg/24 hour (range 23 to 72) in two trials,[60,71] and mean urinary protein excretion rate was 133 mg/24 hr in one trial.[57] Among the three trials restricted to patients with overt proteinuria, mean urinary protein excretion was 3.0 g/day (range 1.7 to 5.3).[66,67,70] In the two trials that permitted inclusion of both microalbuminuric and macroalbuminuric patients, one reported mean baseline urinary albumin excretion rate of 711 mg/24 hour.[62] One of two trials that did not require albuminuria for inclusion nevertheless had an elevated mean baseline urinary protein excretion rate of 1.8 g/day,[68] while the other did not report baseline albuminuria or proteinuria.[59] In trials reporting, mean baseline serum creatinine was 1.0 mg/dL (range 0.8 to 2.4; n=10 trials),[53,55,57,60-62,66-68,70] mean creatinine clearance was 64.1 ml/min/1.73m^2 (range 43 to 114; n=8 trials),[53,55,62,66-68,70,71] and mean GFR was 68.5 ml/min/1.73m^2 (range 39 to 114; n=5 trials).[53,56,65-67]

Baseline comorbidities.

Twelve of 17 studies were restricted to patients with diabetes, including seven limited to those with type 1 diabetes,[53,55-57,62,63,70] four limited to those with type 2 diabetes,[61,65,69,71] and one analysis that was open to both types of diabetics.[64] Among the five trials that did not report restricting enrollment solely to diabetics,[59,60,66-68] two nevertheless excluded participants with type 1 diabetes,[67,68] and three reported no data on baseline prevalence of diabetes[66-68] Mean glycosylated hemoglobin was 8.2 percent (range 7.1 to 11.7, n=10 trials).[53,55-57,61-63,69-71]

Seven trials excluded participants with hypertension,[53,55-57,60,63,71] including five that mandated that blood pressure be controlled without antihypertensive medications.[55,56,60,71] Four additional trials excluded participants only for severe hypertension.[66-69] In addition, though information on hypertension was not available for all participants from two studies, prevalence was at least 35 percent[69] and 53 percent[59] in these two trials. Prevalence of hypertension across all trials excluding these two with incomplete information was 49.8 percent (n=14 trials). Mean systolic and diastolic blood pressures at baseline were 144 mm Hg (range 126 to 149) and 83 mm Hg (range 74 to 92), respectively.

One trial reported data on prevalence of "cardiovascular disease," at 24 percent.[61] Another trial was comprised entirely of participants with a history of cerebrovascular disease, including 71 percent with ischemic stroke, 10 percent with hemorrhagic stroke, and 7 percent with a stroke of unknown type.[59] Prevalence of specific cardiovascular conditions was reported in few trials, including coronary artery disease (18.5 percent, range 0 to 20, n=2 trials),[55,59] myocardial

infarction (5.1 percent, range 0 to 6, n=3 trials),[55,60,61] and stroke (3.5 percent, range 0.8 to 4; n=2 trials).[60,61] Participants with congestive heart failure were excluded from four trials,[55,60,61,64] and prevalence of CHF was not reported in other trials.

Study quality.

Among the 17 studies, five were rated good quality and 12 were rated fair quality. Allocation concealment was adequate in seven trials and unclear in the remaining studies. All 16 placebo-controlled trials were double blinded. Nine trials reported outcomes assessment by blinded adjudication committees. Analysis by intention-to-treat principle was reported in nine trials. All trials adequately described reasons for study withdrawal except for the two reports that were post hoc subgroup analyses from larger trials. Percentages of study withdrawals ranged from 7 to 32 percent, including nine trials with withdrawal rates greater than 20 percent.[53,55,56,60,62,66-68,70] No data were reported on withdrawals in the two studies that were post hoc analyses of CKD subsets from larger trial populations not limited to CKD.[59,64]

Results.

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1).

All-cause mortality. In trials reporting, patients with CKD randomized to ACEIs did not have a reduced risk of all-cause mortality compared to those assigned placebo (RR 0.99 [95 percent CI 0.83 to 1.18]; n=16 trials, 10,716 patients). Risk of all-cause mortality also was not significantly reduced by ACEI compared to placebo in subgroup analyses restricted to CKD patients with baseline microalbuminuria (RR 0.82 [95 percent CI 0.64 to 1.04]; n=9 trials, 2,654 patients), baseline macroalbuminuria (RR 0.71 [95 percent CI 0.33 to 1.54]; n=3 trials, 761 patients), type 1 diabetes (RR 0.74 [95 percent CI 0.34 to 1.62]; n=7 trials, 990 patients), type 2 diabetes (RR 1.08 [95 percent CI 0.86 to 1.36]; n=3 trials, 5,034 patients), without hypertension (RR 1.87 [95 percent CI 0.65 to 5.37]; n=7 trials, 1,454 patients), or without CHF (RR 1.07 [95 percent CI 0.52 to 2.18]; n=4 trials, 1,192 patients). One post hoc analysis reported no significant difference in relative mortality risk between ACEI and placebo in either patients with or without CKD.[59] Most of the mortality data were derived from few trials as three large trials each reported more than 200 deaths, one trial had 22 deaths, and the remainder had fewer than 10 deaths, including eight trials with either zero or one death.

Cardiovascular mortality. Compared with placebo treatment, trial participants assigned to ACEIs also were not at lower risk for cardiovascular mortality (RR=1.03 [95 percent CI 0.86 to 1.23]).[59-61]

Vascular outcomes (Table 7, Appendix Tables C3-5, and Appendix Figure C1).

Myocardial infarction. Compared to CKD patients randomized to placebo, risk for myocardial infarction was not significantly reduced in those assigned ACEI (2.4 versus 3.1 percent; RR=0.79 [95 percent CI 0.57 to 1.09]; n=3 trials, 5,100 patients).[53,61,69]

Stroke. Compared to CKD patients randomized to placebo, those assigned to ACEI did not have a significant reduction in risk for stroke (6.0 versus 7.2 percent; RR=0.80 [95 percent CI 0.52 to 1.23]; n=4 trials, 7,719 patients).[59-61,66] However, there was evidence of substantial heterogeneity between the trials (I^2=68 percent). Two trials reported significant reductions in risk of stroke in ACEI patients compared to those assigned placebo (0.2 versus 2.3 percent; RR=0.10 [95 percent CI 0.01 to 0.78]; n=864 patients)[60] and (12.5 versus 17.6 percent; RR=0.71 [95 percent CI 0.57 to 0.89]; n=1,757 patients).[59] This latter trial, a post hoc analysis in patients with

cerebrovascular disease, reported a similar relative reduction in stroke risk in patients with or without CKD.[59] A third trial reported no difference in risk of stroke between ACEI and placebo groups (4.8 versus 4.7 percent; RR=1.03 [95 percent CI 0.80 to 1.32]; n=4,912 patients),[61] while there was only one stroke in both treatment groups in the fourth trial.[66]

Other vascular outcomes. Seven trials reported a composite vascular endpoint (Appendix Table C5). Due to variability in these composite outcome definitions, results were not pooled between trials. Two of seven trials reported significant reductions in risk of their defined composite vascular outcome with ACEI treatment compared to placebo (Appendix Figure C1),[59,64] both of which further reported that this ACEI benefit was similar regardless of whether or not patients had microalbuminuria[54] or whether or not they had impaired creatinine clearance.[59] No trials reported a significant increase in risk of the composite vascular outcome in the ACEI group.

Renal Outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1).

End-stage renal disease. In CKD patients overall, ACEIs significantly reduced the risk of ESRD versus placebo (1.7 versus 2.6 percent; RR=0.65 [95 percent CI 0.49 to 0.88]; n=7 trials, 7,490 patients).[57,61,64,66-68,70] In three trials restricted to patients with overt proteinuria at baseline, the reduction in risk of ESRD from ACEIs compared to placebo was 40 percent (12.0 versus 20.7 percent; RR=0.60 [95 percent CI 0.43 to 0.83]; n=861 patients).[66,67,70] By comparison, in trials restricted to CKD patients with microalbuminuria, few participants experienced ESRD, and there was no significant reduction in risk of this outcome between ACEI and placebo groups (0.8 versus 0.9 percent; RR=0.88 [95 percent CI 0.27 to 2.88]; n=1,234 patients).[57,64] Results were similar in two studies that enrolled both participants with microalbuminuria and macroalbuminuria (0.4 versus 0.5 percent; RR=0.93 [95 percent CI 0.42 to 2.03]; n=5,495 patients).[61,68] Nevertheless, the p for interaction was not significant at 0.95.

Other renal outcomes. CKD patients assigned ACEI treatment had a significantly reduced risk compared to placebo for doubling of baseline serum creatinine (RR=0.60 [95 percent CI 0.40 to 0.89]; n=7 trials), and in progression from microalbuminuria to macroalbuminuria (RR=0.38 [95 percent CI 0.18 to 0.84]; n=7 trials). Three trials defined composite renal outcomes (Appendix Table C7) as doubling of serum creatinine or ESRD in one trial,[67] doubling of serum creatinine or need for dialysis in a second trial,[68] and as death, dialysis or renal transplantation in the third trial.[70] In each of these studies, participants randomized to ACEI were about half as likely to reach the composite outcome as participants assigned to placebo, a statistically significant finding in all three trials. In the two trials in which doubling of serum creatinine was part of the composite renal outcome definition, it accounted for 21 percent[67] and 98 percent of the composite events,[68] respectively.

Study withdrawals and adverse events (Appendix Table C8).

Overall study withdrawal rates were comparable in the ACEI and placebo groups, 17.3 percent versus 16.3 percent (RR=1.06 [95 percent CI 0.96 to 1.17]; 12 trials; n=7,336). Patients allocated to an ACEI were more likely to withdraw from treatment due to any or a serious adverse event than patients assigned placebo (20.7 percent versus 18.7 percent; RR=1.12 [95 percent CI 1.02 to 1.23]; 14 trials; n=7,055). Worsening renal insufficiency leading to study withdrawal was reported in three trials, with four events (0.8 percent) in the ACEI group compared to eight (1.7 percent) in the placebo group.[66-68] Specific adverse events were not often reported. Cough was the most commonly reported adverse event and was significantly more

likely in the ACEI group compared to placebo (4.7 percent versus 1.8 percent; RR-2.33 [95 percent CI 1.49 to 3.63]; 10 trials; n-7,361). Hyperkalemia was not significantly increased with use of an ACEI (1.3 percent versus 0.9 percent; RR=1.08 [95 percent CI 0.53 to 2.23]; 8 trials; n=2,758).

Summary of results.

In patients with CKD, compared to placebo, ACEI monotherapy did not significantly reduce risk of all-cause mortality, cardiovascular mortality, or MI. Overall, there was no significant reduction in risk of stroke, though results appeared heterogeneous between trials, with two moderate-sized trials reporting a significant reduction in stroke risk and another one finding no difference. Two of seven trials reporting found a significantly reduced risk in a composite vascular outcome in participants randomized to ACEI. Overall, subjects assigned to ACEIs had a significant 35 percent reduction in risk of ESRD compared to patients assigned to placebo. This risk reduction appeared restricted to studies that enrolled only patients with overt proteinuria. CKD patients assigned to ACEIs had a significant 40 percent reduction in risk of doubling serum creatinine, 62 percent reduction in risk of converting from microalbuminuria to macroalbuminuria, and approximately 50 percent reductions in all composite renal outcomes reported. Overall study withdrawals were not significantly different between ACEI and placebo groups. ACEIs increased risk of cough, but there was little apparent difference from placebo subjects in hyperkalemia. Results were limited in that few trials were of sufficient size to assess mortality or clinical vascular outcomes. This greatly limited the possibilities for exploring observed heterogeneity and evaluations of outcomes within subgroups of CKD patients.

ACE Inhibitor Monotherapy Versus ARB Monotherapy Trials (n=6)

Overview.

In patients with CKD, we found low strength of evidence regarding whether there is a difference between ACEI and ARB treatment for the outcomes of all-cause mortality, cardiovascular mortality, MI, or CHF. We found insufficient evidence regarding whether there is a difference between these treatments for ESRD.

Description of studies.

Six trials met all eligibility criteria and randomized participants (n=4,799, range 90 to 4,046) to ACEI monotherapy versus ARB monotherapy.[65,72-76] Detailed baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 4,046 participants were randomized to ramipril versus ARB (n=1 trial), 353 were randomized to enalapril versus ARB (n=2 trials), 309 were randomized to lisinopril versus ARB (n=2 trials), 91 were randomized to captopril versus ARB (n=1 trial), 4,515 were randomized to telmisartan versus ACEI (n=3 trials), 181 were randomized to valsartan versus ACEI (n=2 trials), and 103 were randomized to losartan versus ACEI (n=1 trial). While five of the six trials maintained the ACEI versus ARB comparison throughout the entire treatment period, in a single partial crossover trial, after 24 weeks patients initially assigned to ACEI were randomized to ACEI plus ARB versus continued ACEI monotherapy, and patients initially assigned to ARB monotherapy were randomized to ARB plus ACEI versus continued ARB monotherapy.[74] By far the largest study, comparing ramipril versus telmisartan, was a post hoc analysis performed within the subset of ONTARGET trial participants with CKD

(n=4,046 out of 25,620).[72] The mean age of subjects was 59 years (range 56 to 61; n=5 trials) and men constituted 62 percent (range 37 to 81; n=5 trials) of all patients evaluated. The ethnicity of patients in the three trials reporting was nearly all white race (96 percent).[65,75,76] Two trials were conducted exclusively in Canada, two exclusively in Europe, one in Turkey, and one trial included sites in the United States, Canada, and Europe, as well as Asia, Africa, and Australia. Mean or median study duration was 1 year in three trials, 2.5 years in one trial, and about 5 years in two trials.

Renal function.

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[72] and a second trial required participants to have microalbuminuria and a GFR $\geq$60 ml/min/1.73m^2, by definition CKD stages 1-2.[65] Otherwise, no trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. Among the six trials, five required participants to be albuminuric, including four restricted to patients with microalbuminuria,[65,73,74,76] and one that allowed subjects to have either microalbuminuria or macroalbuminuria.[75] Among the five trials requiring participants to have albuminuria, two required that they also have normal creatinine or GFR,[65,75] and three allowed some participants with abnormal levels for these renal function measures but mandated a maximally abnormal limit.[73,74,76] One trial determined eligibility based only on impaired GFR.[72] Within trials, measures of baseline renal function were inconsistently reported. The ONTARGET post hoc analysis reported no data on baseline renal function in its CKD population.[72] In other trials, the most commonly reported measure was urinary albumin excretion rate (UAER), with mean UAER 62 µg/min in two trials[65,76] and 260 mg/24 hours in one trial,[74] and median UAER 46 µg/min (ACEI treatment arm) to 60 µg/min (ARB treatment arm) in one trial.[75] The mean GFR was 92 ml/min/1.73m^2 (range 91 to 96, n=3 trials).[65,75,76] In two trials, mean baseline serum creatinine was 1.0 mg/dL in both trials.[74,75] Mean creatinine clearance was 101 ml/min/1.73m^2 (range 97 to 112, n=2 trials).[73,74]

Baseline comorbidities.

The study within the subset of ONTARGET participants with impaired GFR did not report any data on their baseline characteristics,[72] though the main study required subjects to have established atherosclerotic vascular disease or diabetes associated with end-organ damage. In the main study, prevalence of comorbidities included diabetes 37.3 percent, hypertension 68.3 percent, and MI 48.7 percent.[77] Within the five other trials, prevalence of diabetes was 97 percent, including four trials comprised entirely of subjects with type 2 diabetes[65,74-76] and another that excluded type 1 diabetics and had a prevalence of type 2 diabetes of 74 percent.[73] Nearly all study participants were hypertensive at baseline (94 percent; range 33 to 100), including four trials that enrolled only patients with hypertension.[73-76] Five trials excluded patients with severe hypertension,[72-76] and mean baseline systolic and diastolic blood pressure measurements were 151 and 87 mm Hg, respectively. Nearly half the enrollees from one trial had cardiovascular disease,[75] a history of non-MI cardiac disorder was reported in 19 percent of subjects in another trial,[73] and two trials excluded participants with CHF.[73,76] Otherwise, studies reported no data on baseline cardiovascular disease.

Study quality.

Among the six trials, two were rated good quality and four were rated fair quality. Allocation concealment was adequate in three trials[72,73,75] and unclear in the remaining trials. All trials were double blinded except one open-label study.[74] Analysis by the intention-to-treat principle was reported in two trials.[72,75] All trials adequately described reasons for study withdrawals. No data on study withdrawals were reported in one trial.[72] Otherwise, withdrawals were 33 percent in one trial,[75] and ranged between 11 and 14 percent in the other trials.

Results.

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1).

All-cause mortality. There were few deaths in trials reporting this outcome. Between CKD patients assigned to ACEI versus those assigned to ARB, there was no significant difference in risk of all-cause mortality (2.7 versus 2.2 percent; RR 1.04 [95 percent CI 0.37 to 2.95]; n=4 trials, 534 patients). Due to wide confidence intervals around this estimate, results are unable to exclude a meaningful advantage for either ACEI or ARB for this outcome.

Cardiovascular mortality. There were few deaths in trials reporting this outcome. Between CKD patients assigned to ACEI versus those assigned to ARB, there was no significant difference in risk of cardiovascular mortality (1.2 versus 1.0 percent; RR 0.88 [95 percent CI, 0.19 to 4.13]; n=4 trials, 534 patients). Due to wide confidence intervals around this estimate, results are unable to exclude a meaningful advantage for either ACEI or ARB for this outcome.

Vascular outcomes (Table 7, Appendix Tables C3 and C4, and Appendix Figure C1).

Only two trials reported data for cardiovascular outcomes, one of which reported no events.[76] In the other small trial, there were relatively few events.[75]

Myocardial infarction. There was a nonsignificant 38 percent lower risk of MI in the group of CKD patients receiving ACEI compared to the group receiving ARB (3 versus 5.2 percent for MI; RR 0.62 [95 percent CI 0.23 to 1.68]; n=353 patients).

Stroke. No studies of ACEI versus ARB in CKD patients reported results for stroke.

Other vascular outcomes. For patients with CKD, there was a 28 percent lower risk of CHF with ACEI compared to ARB but the result was not significant (3.9 versus 5.2 percent for CHF; RR 0.72 [95 percent CI 0.28 to 1.87]; n=353 patients). No studies of ACEI versus ARB in CKD patients reported results for composite cardiovascular events.

Renal outcomes (Appendix Table C6).

End-stage renal disease. None of the trials reported data for ESRD.

Other renal outcomes. None of the trials reported data for doubling of serum creatinine as an individual endpoint. With regard to progression from microalbuminuria to macroalbuminuria, though this outcome was reported in the ONTARGET trial, results for the number of participants with baseline microalbuminuria were inconsistent throughout the paper, could not be verified, and could not be incorporated in a pooled analysis. In the only other trial that reported this outcome, it occurred in only two participants.[65] The ONTARGET trial reported results for a composite renal outcome, defined as first occurrence of either dialysis, renal transplantation, doubling of baseline serum creatinine, or death.[72] Based on graphical display of the data (risk ratios and number of events in each treatment arm were not reported), there appeared to be no significant difference between ACEI and ARB for reaching this endpoint in either the ONTARGET subgroup with GFR <60 ml/min/1.73m^2 or the subgroup with baseline

microalbuminuria.[72] Further, that the relative reduction in risk of the composite renal outcome between treatment groups in ONTARGET was not significantly different in the CKD subgroup than in ONTARGET participants without CKD (p for interaction 0.84).

Study withdrawals and adverse events (Appendix Table C8).

Overall study withdrawal rates were comparable in the ACEI and ARB groups, 20.2 percent versus 18.1 percent (RR 1.07 [95 percent CI, 0.80 to 1.42]; 5 trials; n=753). Though patients assigned ACEI treatment appeared possibly more likely to withdraw from a study due to an adverse event compared to ARB treatment, 14.4 percent versus 9.7 percent (4 trials, n=534), respectively, this difference was not statistically significant. Renal adverse events were rarely reported. Laboratory abnormalities led to four study discontinuations in the DETAIL trial, two cases of raised serum creatinine levels (both < 2.3mg/dL) in both the ACEI and ARB arms.[75] One subject receiving an ARB in the Muirhead study was withdrawn from treatment due to a decreased GFR and creatinine clearance.[65] Cough was the most commonly reported specific adverse event, and was significantly more likely in participants assigned to ACEI treatment compared to those allocated to ARB treatment (4.7 percent versus 1.8 percent; RR=4.10 [95 percent CI 1.47 to 11.48]; 3 trials; n=284).

Summary of results.

In trials comparing ACEI and ARB treatments individuals with CKD, there were very few vascular events reported, based on which there was no significant difference between treatments for the outcomes of all-cause mortality, cardiovascular mortality, MI, or CHF. No data were reported for stroke, ESRD, or any composite vascular outcome. Results from the CKD subset of the ONTARGET study population, whether defined by GFR <60 ml/min/1.73m^2 or by albuminuria, appeared to show no difference in the risk of the composite renal outcome of doubling creatinine, dialysis, renal transplant, or death. Results were limited by small sample sizes in all but one trial, and by the small number of events among trials reporting them. Because no trial provided followup beyond 5 years, longer term effects of ACEI monotherapy versus ARB monotherapy in CKD patients could not be determined from these trials. Overall study withdrawals were not significantly different between ACEI and ARB treatment groups, though cough was significantly more likely in participants assigned to ACEI.

ACE Inhibitor Monotherapy Versus CCB Monotherapy Trials (n=6)

Overview.

In comparing ACEI versus CCB for treatment of patients with CKD, we found moderate evidence that there is no difference in risk of CHF, and low strength of evidence regarding whether there is a difference in risk of all-cause mortality, cardiovascular mortality, stroke, ESRD, or halving of GFR.

Description of studies.

Six trials met all eligibility criteria and randomized participants (n=4,357, range 88 to 3,049) to ACEI monotherapy versus CCB monotherapy.[53,78-85] Baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 3,137 participants were randomized to lisinopril versus CCB (n=2 trials), 653 were randomized to ramipril versus CCB (n=1 trial), 446 were randomized to

fosinopril versus CCB (n=2 trials), 121 were randomized to captopril versus CCB (n=1 trial), 3,907 were randomized to amlodipine versus ACEI (n=3 trials), and 450 were randomized to nifedipine versus ACEI (n=3 trials). By far the largest eligible study was a post hoc analysis performed in the subset of 3,049 individuals with GFR <60 ml/min/ 1.73m^2 from the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (N= 42,418).[78-80] In the AASK trial, designed as a 3x2 factorial study, besides randomizing 653 participants to ACEI versus CCB, an additional 441 were randomized to beta blocker, and all participants also were randomized to one of two blood pressure target groups.[86,87] The CCB treatment arm was stopped early by recommendation of the data and safety monitoring board, with patients switched to open label medication. The mean age of study participants was 66 years (range 37 to 71; n=6 trials) and men constituted 51 percent (range 48 to 69) of all subjects studied. In the two trials that reported race/ethnicity,[78-80,82] 48 percent of participants were white and 38 percent were African American, including one trial comprised entirely of African American participants.[82] Two trials were conducted primarily in the United States,[78-80,82] three trials were conducted in Italy, and one was performed in Spain. Mean or median study duration ranged from 3 to approximately 5 years.

Renal function.

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[78] and a second trial required participants to have microalbuminuria and a GFR ≥80 ml/min/1.73m^2, by definition CKD stages 1-2.[53] Otherwise, no trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. Among the six trials, two required that participants have microalbuminuria to be included,[53,81] while four determined eligibility based only on impaired creatinine or GFR.[78-80,82-85] Within included participants, there was no single measure of renal function or damage that was reported in every trial. The most commonly reported measure of baseline renal function was serum creatinine, with a mean of 2 mg/dL (range 0.96 to 2.8, n=5 trials)[53,81-85] The mean baseline GFR, reported in three trials, was 50 ml/min/1.73m2 (range 46 to 120),[53,78-80,82] and the mean baseline creatinine clearance concentration was 66 ml/min/1.73m^2 (range 36 to 109, n=3 trials).[53,81,83] Mean proteinuria was 0.94 gm/24 hours (range 1.7 to 1.8, n=3 trials),[82-85] and mean urinary albumin excretion rate was 89 µg/min (range 61 to 97, n=2 trials).[53,81]

Baseline comorbidities.

Thirty percent of study participants had diabetes, which included two trials that restricted enrollment to participants with diabetes[53,81] and three trials that excluded patients with diabetes.[82-85] In two trials reporting data, mean baseline hemoglobin A_{1C} was 7.2.[53,81] Ninety-nine percent of study participants had hypertension, which included five trials that restricted enrollment to participants with hypertension and one small trial that excluded patients with hypertension.[53] Mean baseline systolic and diastolic blood pressure measurements were 149 and 87 mm Hg, respectively. One trial excluded any participants with a history of coronary artery disease,[81] three excluded participants with either recent[53,83] or severe[84,85] cardiovascular events but provided no data on past history of coronary artery disease, while the remaining two trials reported that 29 percent[78-80] and 52 percent[82] of randomized participants, respectively, had a history of coronary artery disease.

Study quality.

Among the six trials, two were rated good quality and four were rated fair quality. Allocation concealment was adequate in three of six trials and three trials were double blinded. Analysis by the intention-to-treat principle was reported in four trials[78-80,82-85] All trials, except the single post hoc analysis, adequately described reasons for study withdrawal. Withdrawals across studies ranged from 0 to 37 percent.

Results.

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1).

All-cause mortality. Risk of all-cause mortality, reported in five studies, was not significantly different in individuals with CKD randomized to ACEI treatment compared to those allocated to CCB therapy (5.4 versus 6.2 percent; RR 0.75 [95 percent CI 0.48 to 1.16]; n=1,307). The estimate of effect was driven primarily by data from the AASK trial, which accounted for 75 percent of the weight and deaths.[82,88] All-cause mortality data for the largest study, ALLHAT, was not available.

Cardiovascular mortality. Cardiovascular mortality was reported in three trials totaling 1,014 patients,[82-85,88] including one small 3-year trial not designed to evaluate the effect of therapy on clinical outcomes. As with all-cause mortality, risk of cardiovascular mortality was not significantly different in individuals with CKD randomized to ACEI treatment compared to those allocated to CCB therapy (RR=0.75 [95 percent CI 0.36 to 1.57]), and the estimate of effect again was driven primarily by data from the AASK trial.

Vascular outcomes (Table 7, Appendix Tables C3-C5, and Appendix Figure C1).

Myocardial infarction. Myocardial infarction was reported in only one small trial (n=64 participants).[53] In this trial, there were no myocardial infarctions in either treatment group; therefore, the relative risk for this outcome between CKD patients randomized to ACEI versus CCB treatment could not be determined.

Stroke. Risk of stroke, reported in three trials,[79,80,83,88] was not significantly different between CKD patients assigned an ACEI versus CCB treatment (RR=1.00 [95 percent CI 0.78 to 1.28]; n=3,943 participants). This estimate was driven mainly by the ALLHAT study, which comprised 88 percent of the weight. There was a 27 percent increased relative risk for stroke in the ACEI group in the AASK trial but this was not statistically significant.[88]

Other vascular outcomes. Based on pooled data from two studies, there was no apparent difference in risk for CHF between CKD patients allocated to ACEI versus CCB treatment (RR=1.09 [95 percent CI 0.91 to 1.32]).[79,88] Two trials reported data on one or more composite cardiovascular outcomes (Appendix Table C5), which, because of their different components, were not pooled.[79,88] There was no statistically significant difference between ACEI and CCB treatment in CKD patients for any composite cardiovascular outcome in any trial. The ALLHAT trial performed additional analyses of clinical outcomes among CKD patients with diabetes.[79] In this subgroup, there was no statistically significant difference between treatment groups in risk of stroke, CHF, or either of two composite vascular endpoints.

Renal outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1).

End-stage renal disease. Overall risk of ESRD, reported in three trials, was not significantly different between CKD patients randomized to ACEI versus CCB treatment (RR=0.82 [95 percent CI 0.57 to 1.19]; n=3,823 patients).[78,82,84,85] However, there was evidence of moderate

heterogeneity (I^2=46 percent), with results suggesting benefit in those assigned to ACEI treatment versus CCB treatment in the AASK (RR=0.73 [95 percent CI 0.48 to 1.11]) and Zucchelli (RR=0.51 [95 percent CI 0.22 to 1.17]) studies, respectively, but not in the ALLHAT study (RR=1.06 [95 percent CI 0.77 to 1.48]), with none of the results from the individual trials achieving statistical significance. Of note, the definitions of ESRD varied slightly between these studies, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis in the ALLHAT study; as need for renal replacement therapy in the AASK study; and as need for dialysis (creatinine clearance below 4 ml/minute) in the Zucchelli study.

Other renal outcomes. Overall risk of 50 percent or greater decline in GFR, reported in two trials, was not significantly different between CKD patients randomized to ACEI treatment versus CCB treatment (RR=1.02 [95 percent CI 0.55 to 1.91], n=3,702).[78,82] However, there was evidence of substantial heterogeneity (I^2=71 percent), and though differences were not statistically significant in either trial, results from the AASK trial appeared to favor ACEI treatment (10.1 percent versus 13.4 percent), while results from the ALLHAT trial appeared worse in the ACEI group (2.3 percent versus 1.6 percent).

Three trials reported data on composite renal outcomes, which, because of their different components, detailed in Appendix Table C7, were not pooled.[78,83,88] In the AASK trial, in which the composite renal outcome included ESRD (i.e., need for renal replacement therapy), death, or reduction from baseline GFR by 50 percent or by 25 mL/min/1.73m^2, CKD patients randomized to ACEI treatment had a nonsignificantly lower risk of this composite outcome than those assigned to CCB treatment (20 versus 26 percent, RR=0.77 [95 percent CI 0.58 to 1.04]).[82] Approximately half of these incident renal events were attributed to halving of GFR (73/143 composite events). In the ALLHAT trial, in which the composite renal outcome included ESRD (death due to kidney disease, dialysis, or renal transplantation), reduction in GFR by 50 percent or by 25 mL/min/1.73 m^2, but did not include all-cause death, the risk of a composite renal event was similar in both treatment groups (7 versus 6 percent, RR=1.16 [95 percent CI 0.89 to 1.53]).[78] Approximately one-third of these incident renal events appeared to be attributed to halving of GFR. In the ESPIRAL trial, in which the composite renal outcome included need for dialysis or doubling of serum creatinine, the risk of a composite renal event was significantly lower in CKD patients allocated to ACEI versus CCB treatment (RR=0.59 [95 percent CI 0.39 to 0.89]).[83] In this trial, it was not reported what proportion of incident cases were due to doubling of serum creatinine.

The ALLHAT trial performed additional analyses of renal outcomes among CKD patients with diabetes, and reported that there were no statistically significant differences in risk of ESRD or the above described composite renal outcome between treatment groups[79]

Study withdrawals and adverse events (Appendix Table C8).

CKD patients randomized to treatment with an ACEI were no more likely to withdraw from treatment (13.3 versus 18.4 percent, p=0.81) or withdraw from treatment due to an adverse event (3.2 versus 4.7 percent, p=0.77) compared to patients assigned to treatment with a CCB. No patient in the AASK trial was reported to have withdrawn from treatment or was lost to followup[86,87] No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.[78-80]

In the AASK trial, adverse events were reported as percentage per patient year. Compared to study participants randomized to CCB, those assigned to ACEI had a significantly higher rate of cough (55 versus 46 percent), angioedema (6 versus 2 percent), and syncope (7 versus 2

percent).[86,87] In contrast, edema was significantly more frequent in the CCB group compared to the ACEI group, 60 versus 46 percent. Hyperkalemia was reported for three ACEI group patients and none in the CCB group. In the ESPIRAL trial, withdrawals due to adverse events occurred in small numbers of CKD patients in both groups, for cough (n=3 in the ACEI group versus n=0 in the CCB group), hyperkalemia (n=6 versus n=0), edema (n=1 versus n=10), and impaired renal function (n=4 versus n=1).[83] In the study by Zucchelli, cough led to study withdrawal in two ACEI patients and severe edema led to study withdrawal in three CCB patients.[84] In the trial by Fogari, two subjects each in the ACEI and CCB groups were withdrawn from treatment due to worsening kidney function.[81]

Summary of results.

In patients with CKD, there was no apparent difference between treatment with ACEI monotherapy and CCB monotherapy for the outcomes of all-cause mortality, cardiovascular mortality, stroke, CHF, any composite vascular endpoint, or ESRD. Relative risk of MI could not be determined. While results for the composite renal outcome indicated significant benefit for ACEI treatment compared to CCB in one trial,[83] there was no between-treatment group difference in the composite renal endpoints reported in two other trials.[78-80,82] Results were limited in that several studies were not designed for and reported no clinical outcomes data, and the modest number of clinical events overall may have limited power to detect differences between treatment groups. Further, no trial provided followup beyond 5 years; therefore, longer term effects of ACE-inhibitor monotherapy versus CCB monotherapy cannot be determined from these data. Withdrawals appeared similar between treatment groups, with cough appearing more common in patients assigned ACEI and edema more common in patients assigned CCB.

ACE Inhibitor Monotherapy Versus Beta Blocker Trials (n=3)

Overview.

In comparing ACEI versus beta blocker treatment in patients with CKD, there was low strength of evidence that there is no difference in risk of all-cause mortality, cardiovascular mortality, stroke, heart failure, and ESRD.

Description of studies.

Three trials met all eligibility criteria and randomized participants (n=1,080, range 100 to 877) to ACEI versus beta blocker monotherapy.[87,89,90] Baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 877 participants were randomized to ramipril versus metoprolol (n=1 trial),[87] 103 were randomized to enalapril versus atenolol (n=1 trial),[89] and 100 were randomized to enalapril versus either atenolol or acebutelol (n=1 trial).[90] The mean age of study participants was 54 years, and men constituted 61 percent of patients studied. In the single trial that reported race/ethnicity, 100 percent of participants self-identified as African American.[87] One trial was conducted in the United States,[87] while two trials were performed in Europe.[89,90] Mean or median study durations were three years or greater in all trials.

Renal function.

No trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. All three trials based eligibility on impairment in GFR (20 to 65

ml/min/1.73m^2),[87] creatinine clearance (30 to 90 ml/min),[89] or creatinine (2.3 to 5.2 mg/dL).[90] None based inclusion on the presence of albuminuria, though one excluded patients with urinary protein-creatinine ratio >2.5,[87] and another excluded participants with nephrotic syndrome.[90] Mean serum creatinine, reported in all three trials, was 2.0 mg/dL (range 1.8 to 3.0). Mean baseline GFR was 47 ml/min/1.73m^2 (range 46 to 53, n=2 trials).[87,89] Urinary protein excretion ranged from 0.5 g/24 hour[87] to 2.2 g/24 hour[90] in two trials. In the third trial, median urinary protein excretion was 3.3 g/24 hour.[89]

Baseline comorbidities.

All three trials excluded individuals with diabetes. Approximately 51 percent of participants had a history of heart disease in one trial,[87,88] patients with coronary artery disease were excluded from one trial,[90] and no data was reported regarding cardiovascular disease in the third trial.[89] While two trials were limited to patients with hypertension,[87,90] more than half of the participants in the third trial were reported to have diastolic blood pressure less than 90 mm Hg off antihypertensive medications.[89] Overall, 96 percent of participants in the three trials had hypertension. Mean baseline systolic and diastolic blood pressure measurements were 152 and 95 mm Hg, respectively.

Study quality.

Among the three trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two trials,[87,90] two trials were double blinded,[87,89] and analysis was performed by intention-to-treat in two trials.[87,90] All trials adequately described reasons for study withdrawal. Percentages of study withdrawals ranged from 0 to 23 percent. The AASK trial reported that no participants withdrew from treatment or were lost to followup.[87]

Results.

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1).

All-cause mortality. For patients with CKD, risk of all-cause mortality between those randomized to ACEI and those assigned beta blocker monotherapy was not significantly different (6.9 versus 9.6 percent; RR=0.71 [95 percent CI, 0.48 to 1.07]; n=3 trials, 1,080 patients). The estimate of effect was driven primarily by data from the AASK trial, which accounted for 94 percent of the weight and 93 percent of deaths.[88]

Cardiovascular mortality. In two trials reporting, there were relatively few cardiovascular deaths, and, though confidence intervals were wide, no difference in risk of cardiovascular mortality between CKD patients assigned to ACEI and those assigned to beta blocker (2.9 versus 2.6 percent; RR 1.08 [95 percent CI, 0.51 to 2.28]).[88,89] As with all-cause mortality, the estimate of effect was again driven primarily by data from the AASK trial.

Vascular outcomes (Table 7, Appendix Tables C3-C5, and Appendix Figure C1).

Myocardial infarction. Two trials reported no data on myocardial infarctions,[87,90] and the third reported that two participants in the ACEI group (4.7 percent) and one in the beta blocker group (2.2 percent) experienced a fatal myocardial infarction.[89]

Stroke. In data derived entirely from the AASK trial, there was no difference for CKD patients allocated to ACEI versus beta blocker treatment groups for the outcomes of stroke (RR=1.01 [95 percent CI 0.58 to 1.78]).[88]

Other vascular outcomes. There were no differences between treatment groups for heart failure (RR=0.92 [95 percent CI 0.51 to 1.66]), or for the composite outcome of coronary artery disease hospitalization or coronary artery disease-related death (4.4 versus 4.1 percent; RR 1.07 [95 percent CI 0.57 to 2.01]) or the composite outcome of first cardiovascular hospitalization or cardiovascular death (14.0 versus 14.7 percent; RR 0.95 [95 percent CI 0.69 to 1.31]).[88]

Renal outcomes. (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1).

End-stage renal disease. In pooled results, among these CKD patients there was no significant reduction in risk of end-stage renal disease with ACEI compared to beta blocker treatment (RR 0.81 [95 percent CI 0.50 to 1.33]; n=3 trials, 1,080 patients). However, the estimate of effect varied substantially between trials, ranging from RR 0.54 [95 percent CI, 0.28 to 1.07])[90] to RR 2.45 [95 percent CI 0.50 to 12.07])[89] in two small trials, with an intermediate result in the largest trial (RR 0.86 [95 percent CI 0.63 to 1.17).[87]

Other renal outcomes. The AASK trial reported that CKD patients assigned ACEI versus beta blocker treatment had a statistically significantly reduced risk of the composite renal outcome of >50 percent reduction in GFR, need for dialysis or transplant, or death (28.9 versus 35.1 percent; RR 0.82 [95 percent CI 0.68 to 1.00]; p=0.048).[87] Results for halving of GFR as an isolated endpoint, doubling of baseline creatinine, or conversion from microalbuminuria to macroalbuminuria were not reported.

Study withdrawals and adverse events (Appendix Table C8).

In results pooled from all three trials, patients assigned to an ACEI were not more likely to withdraw from treatment (3.7 versus 3.1 percent, p=0.76) or withdraw from treatment due to an adverse event (2.2 versus 1.5 percent, p=0.39) compared to patients receiving a beta blocker. No patient in the AASK was reported to have withdrawn from treatment.[87] Hyperkalemia, though uncommon, appeared slightly more frequent in subjects randomized to the ACEI group in all three trials at 2.9 versus 0 percent of patients in two trials,[89,90] and as 0.7 versus 0.2 percent per patient year in the AASK trial.[87] The AASK trial reported significant differences between ACEI and beta blocker subjects in angioedema (6.4 versus 2.7 percent per patient year) and cough (54.9 versus 41.5 percent per patient year).[87]

Summary of results.

In patients with CKD, there was no significant difference between ACEI and beta blocker treatment for risk of all-cause mortality, cardiovascular mortality, stroke, heart failure, or either of two composite vascular endpoints. Overall, there was no difference between ACEI and beta blocker treatment for risk of ESRD, but results were heterogeneous between trials. However, ACEI treatment was associated with a significantly lower risk of the composite renal outcome of >50 percent reduction in GFR, need for dialysis or transplant, or death. With respect to adverse effects, ACEI treatment was associated with a significantly higher rate of cough and angioedema. Results were limited in that only one study, the AASK trial, was designed to evaluate the effect of ACEI and beta blocker treatment on clinical cardiovascular outcomes. The two smaller trials reported few or no events for most vascular endpoints and had very limited power to detect differences in these outcomes between treatment groups. No trial provided mean or median followup beyond 5 years; therefore, longer term effects of ACEI monotherapy versus beta blocker monotherapy cannot be determined from these study results.

ACE Inhibitor Monotherapy Versus Diuretic Trials (n=2)

Overview.

In patients with CKD there was insufficient evidence regarding whether there is a difference in all-cause or cardiovascular mortality risk between those assigned to ACEI and those allocated to diuretic treatment. There was low strength of evidence that there was no difference between ACEI and diuretic for the outcomes of stroke and ESRD, and moderate evidence for an increased risk of CHF in participants randomized to ACEI versus diuretic. Our confidence in these estimates is limited because they are based almost entirely on results reported from a post hoc analysis in a single large trial.

Description of studies.

Two trials met all eligibility criteria and randomized participants (n=4,716, range 570 to 4,146) to ACEI monotherapy versus diuretic monotherapy.[78-80,91] Detailed baseline characteristics are presented in Appendix Tables C1 and C2). One of the included reports was a post-hoc analysis performed within a subset of participants with CKD from the ALLHAT trial, a population that was not originally limited to subjects with CKD.

In one study, from the ALLHAT trial, 4,146 participants were randomized to lisinopril versus chlorthalidone,[78-80] while in the second study, the NESTOR trial, 570 participants were randomized to enalapril versus indapamide.[91] The mean age in these two trials was 70 years (range 60 to 71), and men comprised slightly over half of all patients studied (51 percent; range 49 to 65). The most common race/ethnicity of patients in the two trials was white (61 percent), followed by black (23 percent).[78-80,91] Hispanics comprised 11 percent of participants in the ALLHAT study.[78-80] The NESTOR trial was conducted in Europe,[91] while the ALLHAT study was performed primarily in the United States.[78-80] Study durations were 1 year[91] and 4.9 years, respectively.[78-80]

Renal function.

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse, and reported a mean baseline GFR of 50 ml/min/1.73m^2.[78] The second study, the NESTOR trial, did not base eligibility on CKD stage and neither trial reported baseline distribution of participants by CKD stage. In the NESTOR trial, participants were required to have microalbuminuria for inclusion, and the mean baseline urinary albumin excretion rate was 58 µg/min, the urinary albumin/creatinine ratio was 6.2 mg/g, and the creatinine clearance was 92 ml/min/1.73m2.[91] The two studies excluded subjects with baseline creatinine levels exceeding 1.7 mg/dL[91] and 2 mg/dL,[78-80] respectively.

Baseline comorbidities.

Both studies were limited to patients with hypertension, with mean blood pressures at baseline being 147/83 mm Hg in the ALLHAT study[78-80] and 161/94 mm Hg in the NESTOR trial.[91] In the ALLHAT study, 61 percent of participants reported cardiovascular disease, 31 percent reported coronary artery disease, and 31 percent were diabetic. In the NESTOR trial, however, prevalence of type 2 diabetes was 100 percent (mean hemoglobin A1C 7.6 percent), but no information was reported regarding history of any cardiovascular disease.

Study quality.

Of the two eligible trials, one was rated good quality and one was rated fair quality. Allocation concealment was adequate in the ALLHAT study and unclear in the NESTOR trial. Both trials were double blinded. Analysis by the intention-to-treat principle was reported in ALLHAT. However, the NESTOR trial excluded one randomized participant from analyses who was reported to not have been exposed to study drug.[91] The NESTOR trial reported an 11 percent withdrawal rate and adequately described reasons for study withdrawal. By contrast, the ALLHAT study reported no data regarding withdrawals.

Results.

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1).

Data for all-cause mortality was reported only in the NESTOR trial, in which there were only three total deaths, all of which were cardiovascular. There was one death within subjects assigned to ACEI treatment (0.3 percent) and two deaths in participants within the diuretic group (0.7 percent).

Vascular outcomes (Table 7, Appendix Tables C3-C5, and Appendix Figure C1).

Myocardial infarction. The NESTOR trial reported that within the diuretic group one patient had a fatal MI and two others discontinued treatment after an MI.[91] It was not clear whether this was a complete accounting of all MIs.

Stroke. In the ALLHAT study, among the CKD subgroup evaluated in this post hoc analysis, there was no significant difference between ACEI and diuretic treatment assignment in risk of stroke (6.5 versus 6.0 percent; RR 1.07 [95 percent CI, 0.84 to 1.37]).[78-80]

Other vascular outcomes. In the ALLHAT study, there was a significantly increased risk of heart failure (included fatal, hospitalized, or treated nonhospitalized) in the ACEI treatment group (12.5 versus 9.9 percent; RR 1.26 [95 percent CI, 1.05 to 1.50]).[78-80] In data available only from the ALLHAT study, there was no significant between-treatment difference for the composite vascular outcome of nonfatal MI or coronary heart disease death (RR=0.99 [95 percent CI, 0.83 to 1.17]), or for the composite outcome that included death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, or peripheral arterial disease requiring hospitalization or outpatient revascularization (RR=1.07 [95 percent CI, 0.98 to 1.17]). [78-80] The ALLHAT trial reported additional results within CKD patients with diabetes.[79] In this subgroup, there was no statistically significant difference between treatment groups in risk of stroke or the two composite cardiovascular endpoints described in detail above. However, risk of heart failure was significantly greater in CKD patients with diabetes randomized to ACEI treatment compared to diuretic treatment (RR=1.37 [95 percent CI, 1.05 to 1.79]; n=1,382).

Renal outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1).

End-stage renal disease. The ALLHAT study reported that ACEI and diuretic treatment were comparable in CKD patients regarding the risk of ESRD, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis (RR=0.96 [95 percent CI 0.72 to 1.28]).[78] The ALLHAT trial reported no difference between treatment groups in risk of the incident composite renal outcome defined by ESRD or >50 percent decline in GFR (7 versus 7 percent, RR=1.00 [95 percent CI, 0.80 to 1.27]).[78] The ALLHAT trial also performed additional analyses of renal outcomes among CKD patients with diabetes and reported that there were no

statistically significant differences in reduction in risk of ESRD or the above described composite renal outcome between treatment groups.[79]

Other renal outcomes. The NESTOR trial reported that CKD subjects with microalbuminuria who were assigned to ACEI were less likely than diuretic subjects to convert to macroalbuminuria (6 versus 9 percent; RR 0.69 [95 percent CI, 0.38 to 1.22]),[91] though this result was not statistically significant.

Study withdrawals and adverse events (Appendix Table C8).

No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.[78-80] In the NESTOR trial, CKD patients randomized to ACEI treatment were not more likely to withdraw from treatment, withdraw from treatment due to an adverse event, or withdraw from treatment due to a "medical reason" compared to patients assigned a diuretic.[91]

Summary of results.

Within the two eligible trials of patients with CKD, there was no apparent difference between the ACEI and diuretic monotherapy treatment groups in risk of all-cause or cardiovascular mortality, MI, stroke, ESRD, or other composite clinical vascular or renal outcomes. There was a statistically significantly greater risk of heart failure among CKD patients allocated to ACEI therapy versus diuretic treatment. Results were limited in that one trial was a 1-year bioequivalence study not designed to evaluate the effect of these treatments on clinical events[91] and that the second study was a post hoc subgroup analysis. The large ALLHAT study also did not provide mortality data based on CKD status. Also, since mean followup did not extend beyond 5 years, longer term effects of ACE-inhibitor monotherapy versus diuretic monotherapy cannot be determined from these data. Withdrawals were not significantly different between treatment groups in the one trial reporting, and no adverse events data were available.

Table 7. Pooled clinical and renal outcomes, ACEI monotherapy versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI Events/N (%)	Control Events/N (%)	Relative Risk (95% CI)	I^2 Test for Heterogeneity
ACEI vs. placebo trials (n=17)						
All-cause mortality	16	Fair	608/5398 (11.3)	604/5318 (11.4)	0.99 [0.83-1.18]	25%
Cardiovascular mortality	3	Good	231/3769 (6.1)	222/3764 (5.9)	1.03 [0.86-1.23]	0%
Myocardial infarction, any	3	Fair	62/2535 (2.4)	80/2565 (3.1)	0.79 [0.57-1.09]	0%
Myocardial infarction, fatal	2	Fair	4/378 (1.1)	0/371	4.84 [0.55-2.34]	0%
Myocardial infarction, nonfatal	7	Fair	71/3436 (2.1)	76/3417 (2.2)	0.93 [0.67-1.28]	0%
Stroke	4	Good	232/3868 (6.0)	278/3851 (7.2)	0.80 [0.52-1.23]	68%
Stroke, nonfatal	2	Fair	91/2743 (3.3)	87/2752 (3.2)	0.62 [0.12-3.18]	0%
PREVEND trial composite vascular outcome[a]*	1	Fair	17/431 (3.9)	28/433 (6.5)	0.61 [0.34-1.10]	NA
DIABHYCAR trial composite vascular outcome[b]	1	Good	362/2443 (14.8)	377/2469 (15.3)	0.97 [0.85-1.11]	NA
Micro-HOPE trial composite vascular outcome[c]	1	Good	108/553 (19.5)	155/587 (26.4)	0.74 [0.60-0.92]	NA
ATLANTIS trial composite vascular outcome[d]	1	Fair	16/92 (17.4)	8/46 (17.4)	1.00 [0.46-2.16]	NA
PROGRESS trial composite vascular outcome[e]	1	Good	178/895 (19.9)	222/862 (25.8)	0.77 [0.65-0.92]	NA
REIN, Stratum 1 trial composite vascular outcome[f]	1	Good	2/99 (2.0)	3/87 (3.4)	0.59 [0.10-3.43]	NA
REIN, Stratum 2 trial composite vascular outcome[g]	1	Fair	4/78 (5.1)	3/88 (3.4)	1.50 [0.35-6.51]	NA
End-stage renal disease	7	Good	63/3729 (1.7)	97/3761 (2.6)	0.65 [0.49-0.88]	0%
Doubling of serum creatinine concentration	7	Fair	129/3682 (3.5)	202/3710 (5.5)	0.60 [0.40-0.89]	58%
ACEI versus angiotensin II receptor blocker trials (n=6)						
All-cause mortality	4	Fair	7/257 (2.7)	6/277 (2.2)	1.04 [0.37-2.95]	0%
Cardiovascular mortality	4	Fair	3/257 (1.2)	3/277 (1.0)	0.88 [0.19-4.13]	0%
Myocardial infarction, nonfatal	2	Fair	6/181 (3.3)	9/172 (5.2)	0.62 [0.23-1.68]	NA**
Congestive heart failure	2	Fair	7/181 (3.9)	9/172 (5.2)	0.72 [0.28-1.87]	NA**
ACEI versus calcium channel blocker trials (n=6)						
All-cause mortality	5	Fair	42/774 (5.4)	33/533 (6.2)	0.75 [0.48-1.16]	0%
Cardiovascular mortality	3	Fair	16/625 (2.6)	13/389 (3.3)	0.75 [0.36-1.57]	0%
Congestive heart failure	2	Good	211/1969 (10.7)	182/1733 (10.5)	1.09 [0.91-1.32]	0%
Stroke, any	3	Good	123/2098 (5.9)	111/1845 (6.0)	1.00 [0.78-1.28]	0%
AASK trial composite vascular outcome #1†	1	Good	61/436 (14.0)	23/217 (10.6)	1.32 [0.84-2.07]	NA
AASK trial composite vascular outcome #2†	1	Good	19/436 (4.4)	5/217 (2.3)	1.89 [0.72-5.00]	NA
ALLHAT trial composite vascular outcome #1‡	1	Good	547/1533 (35.7)	537/1516 (35.4)	1.01 [0.92-1.11]	NA
ALLHAT trial composite vascular outcome #2‡	1	Good	184/1533 (12.0)	194/1516 (12.8)	0.94 [0.78-1.13]	NA
End-stage renal disease	3	Good	124/2029 (6.1)	111/1794 (6.2)	0.82 [0.57-1.19]	46%
Halving of GFR	2	Good	80/1969 (4.1)	54/1733 (3.1)	1.02 [0.55-1.91]	71%
AASK trial composite renal outcome¥	1	Good	87/436 (20.0)	56/217 (25.8)	0.77 [0.58-1.04]	NA
ALLHAT trial composite renal outcome§	1	Good	106/1533 (6.9)	90/1516 (5.9)	1.16 [0.89-1.53]	NA

Table 7. Pooled clinical and renal outcomes, ACEI monotherapy versus control treatment trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI Events/N (%)	Control Events/N (%)	Relative Risk (95% CI)	I^2 Test for Heterogeneity
ACEI versus beta blocker trials (n=3)						
All-cause mortality	3	Fair	37/540 (6.9)	52/540 (9.6)	0.71 [0.48-1.07]	0%
Cardiovascular mortality	2	Fair	14/488 (2.9)	13/492 (2.6)	1.08 [0.51-2.28]	0%
AASK trial composite vascular outcome #2†	1	Good	19/436 (4.4)	18/441 (4.1)	1.07 [0.57-2.01]	NA
Stroke	1	Good	23/436 (5.3)	23/441 (5.2)	1.01 [0.58-1.78]	NA
Congestive heart failure	1	Good	20/436 (4.6)	22/441 (5)	0.92 [0.51-1.66]	NA
AASK trial composite vascular outcome #1†	1	Good	61/436 (14)	65/441 (14.7)	0.95 [0.69-1.31]	NA
End-stage renal disease	2	Fair	15/104 (14.4)	19/99 (19.2)	0.97 [0.23-4.13]	66%
AASK trial composite renal outcome¥	1	Good	126/436 (28.9)	155/441 (35.1)	0.82 [0.68-1.00]	NA
ACEI versus diuretics trials (n=2)						
All-cause mortality	1	Fair	1/286 (0.3)	2/284 (0.7)	0.50 [0.05-5.44]	NA
Cardiovascular mortality	1	Fair	1/286 (0.3)	2/284 (0.7)	0.50 [0.05-5.44]	NA
Stroke	1	Good	99/1533 (6.5)	157/2613 (6.0)	1.07 [0.84-1.37]	NA
Congestive heart failure	1	Good	191/1533 (12.5)	259/2613 (9.9)	1.26 [1.05-1.50]	NA
ALLHAT trial composite vascular outcome #1‡	1	Good	547/1533 (35.7)	870/2613 (33.3)	1.07 [0.98-1.17]	NA
ALLHAT trial composite vascular outcome #2‡	1	Good	184/1533 (12.0)	318/2613 (12.2)	0.99 [0.83-1.17]	NA
End-stage renal disease	1	Good	70/1533 (4.6)	124/2613 (4.7)	0.96 [0.72-1.28]	NA
ALLHAT trial composite renal outcome§	1	Good	106/1533 (6.9)	180/2613 (6.9)	1.00 [0.80-1.27]	NA

NA = not applicable; RR = relative risk reduction; ACEI = angiotensin converting enzyme inhibitor
[a]PREVEND = Cardiovascular death and hospitalization for cardiovascular morbidity, defined as hospitalization for documented (1) nonfatal MI or myocardial ischemia, (2) heart failure, (3) PVD, and/or (4) CVA.
[b]DIABHYCAR = Cardiovascular death (including sudden death), nonfatal acute MI, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as dialysis or kidney transplant)
[c]Micro-HOPE = Cardiovascular death, MI, stroke
[d]ATLANTIS = Not clearly defined, noted as "cardiovascular adverse events." Incidences of death, MI and angina/chest pain provided.
[e]PROGRESS = Major cardiovascular events, defined as the composite of nonfatal stroke, nonfatal MI, and cardiovascular death.
[f]REIN, Stratum 1 = Incidence of "non-fatal cardiovascular events" reported but not defined.
[g]REIN, Stratum 2 = Non-fatal cardiovascular events include MI, aortic aneurysm, and uncontrolled HTN.
**Pooling data was not possible for this outcome because only one trial reported events.
† In AASK study, two composite vascular endpoints were defined, as follows: (1) Cardiovascular mortality or first cardiovascular hospitalization; and (2) "Coronary heart disease event" defined as CAD hospitalization (probable MI) and/or fatal coronary heart disease death
‡ In ALLHAT study, two composite vascular endpoints were defined, as follows: (1) Death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease requiring hospitalization or outpatient revascularization; and (2) "Coronary heart disease event" defined as nonfatal MI or fatal coronary heart disease death
¥End stage renal disease (need for renal replacement therapy), reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs, or death.
§End stage renal disease (death due to kidney disease, dialysis, or renal transplantation) or reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs.

ARB Monotherapy Versus Placebo Trials (n=4)

Overview.

In patients with CKD, we found high strength of evidence that, compared with placebo, ARB treatment reduces risk of ESRD or of doubling serum creatinine. These results are based only on data from trials enrolling CKD patients with overt albuminuria. There is insufficient evidence regarding whether ARB treatment reduces risk of these outcomes in CKD patients with microalbuminuria or with impaired GFR only. We found moderate evidence that ARB treatment does not reduce risk of all-cause mortality compared to placebo. We found moderate strength of evidence that ARB treatment reduces risk of progression from microalbuminuria to macroalbuminuria. We found low strength of evidence that ARB treatment does not reduce risk of MI and that ARB treatment does reduce risk of CHF hospitalization compared to placebo. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events in some trials, and the heterogeneity of the study populations.

Description of studies.

Four trials met all eligibility criteria and randomized participants with CKD (n=3,778, range 527 to 1,513) to an ARB versus placebo.[92-95] Detailed baseline characteristics are presented in Appendix Tables C9 and C10.

Among eligible trials, 1,738 participants were randomized to irbesartan versus placebo (n=2 trials), 1,513 participants (n=1 trial) to losartan versus placebo, and 527 participants (n=1 trial) to telmisartan versus placebo. The mean age of subjects was 59.6 years (range 58 to 61.7; n=4 trials), and men constituted 65.9 percent (range 63.2 to 68.5; n=3 trials) of all patients randomized. Three trials reported race/ethnicity, within which 66.5 percent of subjects were white. One trial was conducted in the United States,[94] one in Japan,[92] and two were multi-national.[93,95]

Renal function.

In all four trials, patients were required to have albuminuria or proteinuria. In two of these trials, patients must have been microalbuminuric, with a urinary albumin excretion rate between 20-200 µg/min in one study[93] and a urinary albumin-creatinine ratio between 100-300 mg/g in the second study.[92] In the other two trials patients must have been overtly albuminuric or proteinuric, with either an albumin-creatinine ratio ≥300 mg/g or urinary protein excretion rate ≥0.5 g/day,[95] or a 24 hour urine protein excretion ≥900 mg.[94] In addition to the required albuminuria, two of the trials mandated that participants have a normal serum creatinine,[92,93] by definition CKD stages 1-2. The other two trials required participants to be within a range that included both normal and moderately elevated serum creatinine values (e.g., between 1.0 and 3.0 mg/dL), so that it was not possible to determine CKD stage.[94,95] No trial reported baseline distribution of participants by CKD stage. At baseline, serum creatinine was the measure of renal function most frequently reported, with a mean of 1.7 mg/dL (range 1.2 to 1.9; n=3 trials). Two trials reported urinary albumin excretion rate, with results of 55.5 µg/min (0.08 g/day)[93] and 1.9 g/day,[94] respectively. Median urinary albumin-creatinine ratio reported in one trial was 1,250 mg/g.[95] One trial reported no baseline data on renal function/damage for its participants.[92]

Baseline comorbidities.

All four studies were restricted to subjects with type 2 diabetes, and three further specified exclusion of patients with any nondiabetic kidney disease.[92,93,95] Two trials also were limited to subjects with hypertension,[93,94] while in one trial 93.5 percent of participants had a diagnosis of hypertension.[95] In the fourth trial the prevalence of hypertension was not reported, though patients with severe hypertension (>180/100 mm Hg) were excluded and mean baseline blood pressure was 137/77 mm Hg.[92] Across all four trials mean baseline blood pressures were 153/84 mm Hg (range 137/77 to 159/90 mm Hg). In one trial 28 percent of participants reported a history of cardiovascular disease.[94] However, in the two other trials reporting data,[93,95] cardiovascular disease was uncommon, including myocardial infarction (8.9 percent, range 3 to 11.2, n=2 trials), coronary artery disease (4.5 percent, n=1 trial), stroke (0.9 percent, range 0.1 to 3.1, n=2 trials), and congestive heart failure (CHF) (0 percent, n=1 trial). Another trial excluded patients with an indication for ACEIs or ARBs, possibly indicating an exclusion of patients with CHF.[93] Finally, in one trial no entrance criteria related to cardiovascular disease were listed and no baseline data on cardiovascular disease were reported.[92]

Study quality.

Of the four eligible trials, two were rated good quality and two were rated fair quality. Allocation concealment was adequate in two trials[94,95] and unclear in two trials.[92,93] All trials were double blinded. All but one trial[92] performed analyses using the intention-to-treat principle. All trials adequately described study withdrawal and reasons for withdrawals, with withdrawals ranging from 0.8 to 13.1 percent of randomized participants.

Results.

Mortality (Table 8, Appendix Table C11, and Appendix Figure C2).

Among these CKD patients studied, overall incidence of death ranged in trials reporting, from less than 1 percent of study participants in one trial,[93] to 16.6 percent[94] and 20.7 percent[95] in two other trials. Nevertheless, no individual trial results suggested a difference in risk of death among CKD patients randomized to ARB versus those allocated to placebo. In pooled results, there was no between-treatment difference in mortality risk (RR 0.99 [95 percent CI, 0.85 to 1.17], n=3 trials, 3,251 patients). No trials specifically reported data on cardiovascular mortality.

Vascular outcomes (Table 8, Appendix Tables C11-C13, and Appendix Figure C2).

Myocardial infarction. In the one trial reporting data, among CKD patients there was a 25 percent reduction in risk of MI between ARB and placebo that was not statistically significant (6.7 versus 8.9 percent; RR 0.75 [95 percent CI, 0.53 to 1.06]).[95]

Stroke. No trials reported data on risk of stroke.

Other vascular outcomes. One trial reported a significant reduction in risk of hospitalization for congestive heart failure (11.9 versus 16.7 percent; RR 0.71 [95 percent CI, 0.55 to 0.91]; n=1,513 patients.[95] A second trial reported that CKD patients assigned to ARB had a rate of hospitalization for CHF that was 23 percent lower than placebo, a difference that was not stated to be statistically significant.[94] This study did not report the proportion of patients with one or more CHF hospitalizations, overall or by treatment group. On the other hand, ARB treatment did not significantly reduce risk of composite vascular events (Appendix Table C13) compared to placebo in either of two trials reporting, with RR 0.94 (95 percent CI, 0.81 to 1.08)[95] and RR 0.94 (95 percent CI, 0.77 to 1.15)[94] respectively.

Renal outcomes (Table 8, Appendix Tables C14 and C15, and Appendix Figure C2).

End-stage renal disease. In two trials reporting incident ESRD, subjects with CKD assigned to ARB treatment were 22 percent less likely to progress to ESRD than those allocated to placebo treatment, a statistically significant result (17.2 versus 22.2 percent; RR 0.78 [95 percent CI, 0.67 to 0.91]; n=2,661 patients).[94,95]

Other renal outcomes. In two trials reporting, CKD patients randomized to ARB treatment were significantly less likely to develop a doubling of their baseline serum creatinine (19.5 versus 25.0 percent; RR 0.78 [95 percent CI, 0.68 to 0.91]; n=2,661 patients).[94,95] Risk of conversion from microalbuminuria to macroalbuminuria was 58 percent lower in CKD patients assigned to ARB compared to those allocated to placebo (13.2 versus 31.2 percent; RR 0.42 [95 percent CI, 0.33 to 0.52]; n=2 trials, 1,104 patients).[92,93] One or more composite renal outcomes were reported in two trials (Appendix Table C15),[94,95] with all suggesting that assignment to ARB reduces risk of the composite outcome compared to placebo, though not all differences were statistically significant.

Study withdrawals and adverse events (Appendix Table C16)

Among CKD patients allocated to either ARB or placebo treatment, 5.7 percent withdrew from studies (range 0.8 to 13.1; n=4 trials). One trial reported that patients assigned to ARB treatment had a significantly lower rate of adverse events per 1,000 treatment days than those assigned to placebo.[94] Another trial reported that more than 90 percent of participants had at least one adverse event,[92] but no trials reported data on the proportion of patients with any adverse event by treatment group. This study further reported that 61 percent of all subjects had a serious adverse event and that there was no between-group difference for this outcome. However, again no results were reported by treatment group. A second trial also reported that fewer ARB patients than those assigned placebo had a serious adverse event (15.4 versus 22.9 percent, n=590 participants), and further that ARB patients were not more likely than those assigned to placebo to withdraw from the study due to an adverse event (6.7 versus 8.5 percent).[93] Hyperkalemia necessitating discontinuation of study medication occurred in a significantly higher proportion of patients randomized to ARB treatment than placebo (1.4 versus 0.5 percent; RR 2.97 [95 percent CI, 1.16 to 7.65]; n=2 trials, 2,661 patients). In one study reporting, serum creatinine elevation necessitating discontinuation of study medication appeared similar between treatment groups (ARB 1.5 percent versus placebo 1.2 percent). Another study reported one episode of an early increase in serum creatinine concentration suggestive of renal artery stenosis that necessitated stopping the study medication but did not indicate in which treatment group this adverse event occurred.

Summary of results.

In individuals with CKD, compared with placebo, assignment to ARB treatment was associated with significant reductions in risk of ESRD, of doubling of serum creatinine, of conversion from microalbuminuria to macroalbuminuria, in one of two composite renal outcomes, and in risk of CHF hospitalization. There was no significant difference between treatment groups for the outcomes of all-cause mortality, MI, or any reported composite vascular outcomes. No trials reported results for stroke. Results were limited in that several outcomes were reported in only one trial or not at all, in particular with neither of the studies that enrolled microalbuminuric patients reporting results for MI, stroke, CHF, ESRD, or a composite vascular or renal endpoint. Though withdrawal and adverse event reporting were limited, individuals with

CKD allocated to ARB were significantly more likely to experience hyperkalemia requiring discontinuation of study medication.

ARB Versus CCB Trials (n=4)

Overview.

In patients with CKD, we found low strength of evidence that ARB treatment, relative to CCB, reduces risk of doubling serum creatinine, and low strength of evidence that ARB treatment does not reduce risk of all-cause mortality, stroke, or ESRD. We found insufficient evidence that ARB treatment, compared to CCB, reduces risk of conversion from microalbuminuria to macroalbuminuria. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events in some trials, and the heterogeneity of the study populations.

Description of studies.

Three trials met all eligibility criteria and randomized participants with CKD (n=3,924 patients, range 58 to 2,720) to an ARB versus CCB.[94,96,97] Detailed baseline characteristics are presented in Appendix Tables C9 and C10.

Among eligible trials, one compared candesartan to amlodipine (n=2,720 patients),[96] one compared irbesartan to amlodipine (n=1,146 patients),[94] and one compared candesartan to nifedipine (n=58 patients).[97] In total, there were 2,778 participants randomized to candesartan versus a CCB and 3,866 participants randomized to amlodipine versus an ARB. The mean age of subjects was 63.2 years (range 59 to 65; n = 3 trials), and men constituted 55.4 percent (range 46.6 to 64.3; n = 3 trials) of all patients randomized. Just one trial reported race/ethnicity, in which 72.1 percent of subjects were white.[94] Two other trials were conducted in Japan.[96,97] Median study durations ranged from 1.8 to 3.2 years.

Renal function.

In two trials, the initial study design specified restriction to patients with albuminuria (repeated urinary albumin-creatinine ratio 100-300 mg/g)[97] or proteinuria (urinary protein excretion ≥900 mg/24 hours).[94] In the third study, the current report[96] was a secondary analysis conducted in patients with either GFR <60ml/min/1.73m^2 or a positive dipstick test for proteinuria from among a larger trial population with either serum creatinine >1.3 mg/dL or undefined proteinuria.[97,98] Among the 2,720 participants enrolled in this study, 330 were reported in combined CKD stages 1 or 2, 2,265 were CKD stage 3, and 125 were CKD stage 4. No other study based inclusion on or reported distribution of participants by CKD stage. The only measure of renal function reported in more than one trial was serum creatinine, which ranged from 0.74 to 1.66 mg/dL in two trials reporting,[94,97] and was by definition >1.3 mg/dL in all participants in the third trial.[96] The baseline level of albuminuria differed considerably in two trials reporting, from an albumin-creatinine ratio of 237 mg/g[97] to a 24 hour urinary albumin excretion of 1.9 g.[94] Neither baseline GFR or creatinine clearance was reported in any trials.

Baseline comorbidities.

All three studies included only subjects with hypertension and type 2 diabetes. Mean baseline systolic and diastolic blood pressures was 162/90 mmHg. Two trials excluded subjects with severe hypertension (systolic >200mmHg and/or diastolic >110 or 120 mmHg).[96,97] Trials

provided little information on participant history of cardiovascular disease. In one trial, 28.7 percent of subjects had a history of cardiovascular disease,[94] while in a second trial 4.8 percent of participants had a history of MI.[96] One trial excluded subjects with "severe cerebral or cardiovascular diseases,"[97] while a second trial excluded participants with MI or stroke ≤6 months before screening, coronary angioplasty or bypass≤6 months before screening or currently scheduled, current treatment for class II-IV congestive heart failure or ejection fraction <40 percent, or coronary artery disease requiring beta blocker or calcium channel blocker.[96]

Study quality.

Among the three eligible trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two trials[94] and unclear in two trials.[96,97] One trial was double blinded.[94] Two trials were single blinded, one to the assessors only[96] and one to the patients only.[97] Analysis by the intention-to-treat principle was performed in two trials[94,96] and was unclear in one trial.[97] Two trials adequately described reasons for study withdrawals, with withdrawals ranging from 0.6 to 3.4 percent of randomized participants.[94,97] The third trial did not report any data on withdrawals.[96]

Results.

Mortality (Table 8, Appendix Table C11, and Appendix Figure C2).

All-cause mortality. Results were heterogeneous between these two trials in that one reported no deaths among its 58 participants (and thus, no cardiovascular deaths),[97] while among the 1,146 participants in the other trial, 15.0 percent died in the ARB group versus 14.6 percent in the CCB group.[94] In pooled results, compared to CCB treatment, assignment to ARB therapy did not reduce risk of all-cause mortality among individuals with CKD (14.1 percent for ARB versus 14.2 percent for CCB; RR 1.03 [0.78 to 1.35]; n=2 trials, 1,206 patients).

Vascular outcomes (Table 8, Appendix Tables C11-C13, and Appendix Figure C2).

Myocardial infarction. No trial reported results for MI.

Stroke. One trial reported stroke events, finding no difference in risk of stroke between CKD subjects randomized to ARB compared to those assigned to CCB (RR 1.07 [95 percent CI, 0.70 to 1.64]).[96]

Other vascular outcomes. Two trials reporting a composite vascular outcome as a study endpoint found no significant difference between treatment groups, 0.95 [0.73 to 1.24][96] and 1.06 [0.86 to 1.31],[94] respectively. In one trial that reported results for three composite vascular outcomes stratified by baseline CKD stage, cardiovascular events, cerebrovascular events, and cardiac events, respectively, there was no significant difference in risk of any of these composite outcomes between treatment groups for participants in CKD stages 1 or 2, or for participants in CKD stage 3.[96]

Renal outcomes. (Table 8, Appendix Tables C14 and C15, and Appendix Figure C2).

End-stage renal disease. In the only trial that reported ESRD events, subjects with CKD assigned to ARB treatment were 23 percent less likely to progress to ESRD than those allocated to CCB treatment, though these results were not statistically significant (14.2 percent versus 18.3 percent; RR 0.77 [95 percent CI, 0.59 to 1.01]; n=1,146 patients).[94]

Other renal outcomes. In one trial reporting, CKD patients randomized to ARB treatment were significantly less likely to develop a doubling of their baseline serum creatinine (16.9

versus 25.4 percent, RR 0.67 [95 percent CI, 0.53 to 0.84]; n=1,146 patients).[94] In data based on one small trial, risk of conversion from microalbuminuria to macroalbuminuria was not statistically significantly lower in CKD subjects assigned to ARB treatment (10.0 versus 27.8 percent; RR 0.36 [95 percent CI, 0.11 to 1.18]; n=58 patients).[97] A composite renal outcome was reported in two trials. In one trial, there was a significant reduction in risk among CKD patients assigned to ARB versus CCB (32.6 versus 42.1 percent; RR 0.80 [95 percent CI, 0.68 to 0.93]).[94] In the second trial, there were few renal events and there was no significant difference in risk of this outcome between treatment groups, including 1.2 versus 1.9 percent (p=0.58) for participants with CKD stages 1 or 2, and 1.2 versus 0.8 percent (p=0.31) for participants with CKD stage 3.[96] It appeared that incidence of events included in the composite renal outcome definition in both trials (doubling of creatinine, ESRD) was far higher in the first trial,[94] suggesting that its CKD population had a substantially higher baseline risk for these events, possibly in part associated with a higher baseline level of proteinuria.

Study withdrawals and adverse events (Appendix Table C16).

Few CKD patients allocated to either ARB or CCB treatment withdrew from studies (0.8 versus 0.7 percent, respectively, n=2 trials reporting). One trial reported that ARB subjects had a significantly lower rate of adverse events per 1,000 days than did CCB subjects but did not report the proportion of study participants with adverse events in each treatment group.[94] This study further reported that 61 percent of all subjects had a serious adverse event and that there was no between-group difference for this outcome. However, again no results were reported by treatment group. Hyperkalemia was significantly more frequent among CKD patients allocated to ARB than to CCB (1.9 versus 0.5 percent, $p<0.05$), though this outcome also was reported in only one trial.[94]

Summary of results.

In individuals with CKD, compared with CCB, assignment to ARB treatment was associated with a significant 33 percent reduction in risk of doubling serum creatinine, but no significant difference in risk of all-cause mortality, MI, stroke, ESRD, or at least two defined composite vascular outcomes. Risk for a composite renal outcome including doubling creatinine, ESRD, or death was significantly lower with ARB in one trial that enrolled CKD patients with substantial baseline proteinuria. In another study of CKD patients at lower risk for these renal outcomes, there was no significant reduction in risk. Results were limited in that most outcomes were reported in only one trial or were uncommon. Evaluated CKD study populations appeared heterogeneous with respect to risk of clinical events. However, small sample sizes and few clinical events in some studies, and the limited reported data on baseline vascular disease and renal function/damage, limited evaluation as to whether there are differences in the relative effect of ARB and CCB treatment according to these patient characteristics.

Table 8. Pooled clinical and renal outcomes, ARB monotherapy versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	ARB Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
ARB versus placebo trials (n=4)						
All-cause mortality	3	Good	248/1719 (14.4)	249/1532 (16.3)	0.99 [0.85-1.17]	0%
Myocardial infarction, any	1	Good	50/751 (6.7)	68/762 (8.9)	0.75 [0.53-1.06]	NA
CHF hospitalization	1	Good	89/751 (11.9)	127/762 (16.7)	0.71 [0.55-0.91]	NA
Composite vascular outcome*, RENAAL study	1	Good	247/751 (32.9)	268/762 (35.2)	0.94 [0.81-1.08]	NA
Composite vascular outcome*, IDNT study	1	Good	138/579 (23.8)	144/569 (25.3)	0.94 [0.77-1.15]	NA
End-stage renal disease	2	Good	229/1330 (17.2)	295/1331 (22.2)	0.78 [0.67-0.91]	0%
Doubling of serum creatinine concentration	2	Good	260/1330 (19.5)	333/1331 (25.0)	0.78 [0.68-0.91]	1%
Progression from micro to macroalbuminuria	2	Good	96/729 (13.2)	117/375 (31.2)	0.42 [0.33-0.52]	0%
Composite renal outcome**, RENAAL study	1	Good	327/751 (43.5)	359762 (47.1)	0.92 [0.83-1.03]	NA
Composite renal outcome**, IDNT study	1	Good	189/579 (32.6)	144/569 (39.0)	0.84 [0.72-0.98]	NA
ARB versus CCB trials (n=4)						
All-cause mortality	2	Fair	87/619 (14.1)	93/587 (15.8)	0.92 [0.70-1.20]	NA
Stroke	1	Fair	44/1376 (3.1)	40/1344 (3.0)	1.07 [0.70-1.64]	NA
Composite vascular outcome†, CASE-J study	1	Fair	99/1376 (7.2)	102/1344 (7.6)	0.95 [0.73-1.24]	NA
Composite vascular outcome*, IDNT study	1	Good	138/579 (23.8)	128/567 (22.6)	1.06 [0.86-1.31]	NA
End-stage renal disease	1	Good	82/579 (14.2)	104/567 (18.3)	0.77 [0.59-1.01]	NA
Doubling of serum creatinine concentration	1	Good	98/579 (16.9)	144/567 (25.4)	0.67 [0.53-0.84]	NA
Progression from micro to macroalbuminuria	1	Fair	4/40 (10.0)	5/18 (27.8)	0.36 [0.11-1.18]	NA
Composite renal outcome††, CASE-J study	1	Fair	19/1376 (1.4)	26/1344 (1.9)	0.71 [0.40-1.28]	NA
Composite renal outcome**, IDNT study	1	Good	189/579 (32.6)	233/567 (41.1)	0.80 [0.68- 0.93]	NA

ARB = angiotensin receptor blocker; RR = relative risk; NA = not applicable; CHF = congestive heart failure; CCB = calcium channel blocker
*RENAAL = MI, stroke, first hospitalization from heart failure or unstable angina, coronary or peripheral revascularization, or death from cardiovascular causes.
*IDNT = Death from cardiovascular causes, nonfatal MI, heart failure resulting in hospitalization, stroke resulting in permanent neurological defect, lower limb AKA.
**RENAAL = Time to doubling serum creatinine, incident ESRD (hemodialysis or renal transplant), or death.
**IDNT = Doubling of baseline serum creatinine, incident ESRD (hemodialysis, renal transplant, serum creatinine concentration at least 6.0mg/dl), or death from any cause.
†First cardiovascular event defined as any of the following: sudden death (unexpected death within 24 h without external cause); cerebrovascular event (stroke or transient ischemic attack); cardiac event (heart failure, angina pectoris, or acute myocardial infarction); renal event (included serum creatinine concentration of 4.0 mg/dl or higher, doubling of serum creatinine concentration, or end-stage renal disease); and/or vascular event (dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery).
††Serum creatinine concentration of 4.0 mg/dl or higher, doubling of the serum creatinine concentration or end-stage renal disease.

ACE Inhibitor Plus ARB Therapy Versus ACE Inhibitor Alone Trials (n=6)

Overview.

In patients with CKD, we found moderate strength of evidence that there is no difference between ACEI plus ARB combination therapy versus ACEI monotherapy for the outcome of all-cause mortality. We found insufficient evidence regarding whether there is a difference between these treatments for stroke, CHF, doubling of serum creatinine, progression from microalbuminuria to macroalbuminuria, or ESRD.

Description of studies.

Six trials met eligibility criteria and randomized participants with CKD (N=7,233, range of 54 to 3,988) to combination therapy with an ACEI plus an ARB versus ACEI therapy alone.[72-74,99-101] One of the included reports was a post-hoc analysis performed within a subset of participants with CKD from a larger trial population that was not originally limited to subjects with CKD,[101] while a second report was a post-hoc analysis from a larger trial that evaluated outcomes in multiple participant subgroups, including impaired GFR and albuminuria.[72] Detailed baseline characteristics are presented in Appendix Tables C17 and C18.

The mean age of study subjects was 65 years (range of study means 51-66; n=5 trials), and men constituted 83 percent (range 37 to 88; n=5 trials) of all participants randomized. Among the three trials that reported race/ethnicity, one was entirely comprised of Japanese participants,[100] one reported only that 91 percent of participants were white,[101] and, in third trial, 45 percent of participants were Hispanic, 34 percent were black, and 19 percent were white.[99] Two studies were conducted solely in the United States,[99,101] one study was conducted in Japan[100] one study was conducted in Turkey,[74] and two studies were multinational.[72,73] The mean or median study duration ranged from 30 weeks to 3.1 years. All studies but two[73,99] had followup durations of at least 1 year.

Renal function.

One post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[101] while a second post hoc analysis reported results for a subgroup defined by GFR <60 ml/min/1.73m^2 as well as for a subgroup defined by albuminuria, the latter by definition could have included CKD stages 1-4.[72] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Of the six trials, two required that participants have microalbuminuria,[73,74] two required that participants have macroalbuminuria or overt proteinuria,[99,100] and one reported a post hoc analysis of participants with either microalbuminuria or macroalbuminuria.[72] Among these trials that required participants to have albuminuria or proteinuria, one required that participants also have a normal creatinine,[74] three allowed participants to have abnormal levels for creatinine or creatinine clearance but mandated a maximally abnormal limit,[73,99,101] while one required that participants also had an elevated creatinine between 1.2 and 5 mg/dL.[100]

Overall, four studies reported on some measure of proteinuria at baseline.[72-74,99,100] One reported a mean 24 hour proteinuria of 1.7 g/d,[100] one reported a mean urinary albumin:creatinine ratio of 9.4 mg/mmol,[73] one reported a mean 24 hour albumin excretion rate of 260 mg,[74] and one study reported a mean urinary albumin:creatinine ratio of 907 mg/g.[99] The study by Anand reported only on dipstick proteinuria.[101] Several measures of renal function were reported by the studies, including a mean serum creatinine 1.5 mg/dL (range 1 to 3, n=3

trials),[74,99,100] a mean creatinine clearance of 96 ml/min/1.73m2 (range 65 to 112, n=3 trials),[73,74,99] and a mean eGFR of 50 (range 48 to 51, n=2 trials).[72,101]

Baseline comorbidities.

Two of six trials were restricted to patients with diabetes,[74,99] including one limited to participants with type 2 diabetes.[74] Among the remaining trials, only two report data on diabetes prevalence, with 29 percent[101] and 74 percent[73] of study participants, respectively.

Three trials were restricted to participants with hypertension,[73,74,100] two trials excluded participants with hypertension,[72,99] while prevalence of hypertension in the remaining study was 15 percent.[101] Mean baseline blood pressures was 127/76 mmHg.

Three trials excluded participants with heart failure,[73,99,100] while one included only participants with heart failure.[101] Four trials excluded participants with a recent stroke or ischemic cardiac event. Prevalence of other cardiovascular disease was reported only in that heart failure was attributed to ischemic disease in 36 percent of participants in one trial,[101] and a history of MI or coronary artery procedure was reported in fewer than 10 percent of participants in a second study.[99,100]

Study quality.

Among six eligible trials, two were rated as good quality and four were rated as fair quality. Allocation concealment was adequate in three trials and unclear in the remaining studies. Four trials were double blinded.[72,73,99,101] Two studies were not blinded.[74,100] For the outcomes presented here, only two studies analyzed results according to the intention-to-treat principle.[72,101] All studies adequately described reasons for study withdrawals. Withdrawals ranged from 5 to 24 percent (n=4 trials).

Results.

Mortality (Table 9, Appendix Table C19, and Appendix Figure C3).

All-cause mortality. Overall, there was no significant difference in risk of all-cause mortality between CKD patients randomized to ACEI+ARB versus those allocated to ACEI alone (RR 1.03 [95 percent CI 0.91 to 1.18]). More than 99 percent of events occurred in only one trial.[101]

Cardiovascular mortality. No study reported data for cardiovascular mortality.

Vascular outcomes (Table 9, Appendix Tables C19-C21, and Appendix Figure C3).

Myocardial infarction. No study reported on MI (fatal or nonfatal).

Stroke. Only one study reported on nonfatal stroke,[99] with only two stroke events occurring during the study, one in each study arm.

Other vascular outcomes. Congestive heart failure events were reported only by one study,[99] in which two CHF events occurred in participants randomized to ACEI+ARB versus no events in the ACE monotherapy group. A composite cardiovascular outcome was also only reported in one study.[101] This study had a broad outcome definition for their cardiovascular composite outcome (Appendix Table C21). Combination ACEI+ARB therapy was associated with a modest but statistically significant 11 percent relative risk decrease in CVD events (95 percent CI, 0.80 to 0.98).

Renal outcomes (Table 9, Appendix Table C22, and Appendix Figure C3).

End-stage renal disease. Only one study reported results for ESRD.[100] The risk of ESRD was equivalent in those on combination ACEI+ARB therapy compared to ACEI therapy alone (HR 1.0, 95 percent CI 0.2 to 6.8). This trial reported only four ESRD events, with two occurring in each arm.

Other renal outcomes. One study reported on the outcome of doubling of serum creatinine.[100] In this study, combination ACEI+ARB therapy was associated with a nonsignificant reduction in the risk for doubling of creatinine compared to solitary ACEI therapy (HR 0.07, 95 percent CI 0.0 to 1.13). This outcome occurred in only seven study participants, though all had been assigned to the ACEI monotherapy group. Three trials reported on progression from microalbuminuria to macroalbuminuria.[72-74] Although by far the most events for this outcome were reported in the ONTARGET trial, results reported by this trial for the number of participants with baseline microalbuminuria were inconsistent throughout the paper and could not be incorporated in a pooled analysis. The ONTARGET trial reported results for a composite renal outcome, defined as first occurrence of either dialysis, renal transplantation, doubling of baseline serum creatinine, or death.[72] Based on graphical display of the data (risk ratios and number of events in each treatment arm were not reported), there appeared to be no significant difference between ACEI and ACEI+ARB for reaching this endpoint in either the ONTARGET subgroup with GFR <60 ml/min/1.73m^2 or the subgroup with baseline microalbuminuria.[72] Further, that the relative reduction in risk of the composite renal outcome between treatment groups in ONTARGET was not significantly different in the CKD subgroup than in ONTARGET participants without CKD (p for interaction 0.80).

Study withdrawals and adverse events (Appendix Table C23).

Overall study withdrawals, reported in all four studies, ranged from 6 to 24 percent. Only one study reported on adverse events leading to withdrawal,[73] which was similar in both study arms. Two studies reported on any adverse events[73,99] that appeared to be similar between groups. The most common adverse events reported were hypotension and hyperkalemia. Hyperkalemia was more common in the combination therapy group in one study[101] but not in another.[73]

Summary of results.

In patients with CKD, compared to ACEI monotherapy, assignment to combination ACEI+ARB therapy did not significantly reduce risk of all-cause mortality but was associated with significant reductions in risk of the one composite vascular outcome reported and in risk of progression from microalbuminuria to macroalbuminuria. Results suggested that combination treatment might reduce risk of doubling creatinine, but they did not achieve statistical significance. Too few events were reported for all other outcomes for the results to be clinically meaningful, including for stroke, MI, and ESRD. Reporting on study withdrawals and adverse effects was limited. No trial provided followup beyond 4 years.

Table 9. Pooled clinical and renal outcomes for ACE inhibitor plus ARB versus ACE inhibitor trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI+ARB Events/N (%)	ACEI Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	3	Fair	363/1546 (23.5)	342/1513 (22.6)	1.03 [0.91-1.18]	0%
Stroke, nonfatal	1	Fair	1/26 (3.8)	1/27 (3.7)	1.04 [0.07- 15.75]	NA
CHF	1	Fair	2/26 (7.6)	0/27 (0)	5.19 [0.26- 103.11]	NA
Composite vascular outcome**	1	Good	499/1477 (33.8)	549/1439 (38.2)	0.89 [0.80- 0.98]	NA
End stage renal disease	1	Fair	2/45 (4.4)	2/45 (4.4)	1.00 [0.15- 6.79]	NA
Doubling of serum creatinine	1	Fair	0/45 (0)	7/45 (15.6)	0.07 [0.00-1.13]	NA
Progression to macroalbuminuria	2	Fair	1/139 (0.7)	3/95(3.2)	0.36 [0.04-3.37]	NA

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; RR = relative risk reduction; NA = not applicable
**Death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization

ACE Inhibitor Plus ARB Therapy Versus ARB Alone Trials (n=3)

Overview.

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI+ARB combination therapy versus ARB monotherapy for all-cause mortality, or any other vascular or renal clinical outcome.

Description of studies.

Three trials met eligibility criteria and randomized participants with CKD (n=approximately 4,300) to combination therapy with an ACEI+ARB versus ARB therapy alone.[72-74] Baseline characteristics are presented in Appendix Tables C18 and C24.

Among eligible trials, the mean age of study subjects was 57 years (range of study means 57 to 58; n=2 trials), and men constituted 46 percent (range 37 to 69; n=2 trials) of all participants. Ethnicity was not reported by any study. Two studies were multinational[72,73] and one was conducted in Turkey.[74] The mean or median study duration ranged from 30 weeks to 4.7 years. Two studies had a duration of followup of 1 year or greater.[72,74]

Renal function.

One post hoc analysis reported results for a subgroup defined by GFR <60 ml/min/1.73m^2 as well as for a subgroup defined by albuminuria, the latter by definition could have included CKD stages 1-4.[72] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Of the three trials, two required that participants have microalbuminuria,[73,74] and one reported a post hoc analysis of participants with either microalbuminuria or macroalbuminuria.[72] Of the two trials that required participants to have albuminuria or proteinuria, one required that participants also have a normal creatinine,[74] and one allowed participants to have abnormal levels for creatinine or creatinine clearance but mandated a maximally abnormal limit.[73]

Two studies reported on some measure of proteinuria at baseline.[73,74] One reported a mean urinary albumin:creatinine ratio of 9.4 mg/mmol,[73] and the other reported a mean 24 hour albumin excretion rate of 260 mg.[74] Two studies reported a mean creatinine clearance of 101 ml/min/1.73m2 (range 97 to 112, n=2 trials),[73,74] one reported a mean serum creatinine of 1.0 mg/dL,[74] and one reported a mean eGFR of 50 mL/min/1.73m2.[72]

Baseline comorbidities.

One trial was restricted to patients with type 2 diabetes.[74] In the only other study that reported data, diabetes prevalence was 74 percent.[73] Two trials were restricted to participants with hypertension,[73,74] and one trial excluded participants with hypertension.[72] Mean baseline blood pressures was 152/90 mmHg. One trial excluded participants with heart failure,[73] but otherwise the presence of cardiovascular disease at baseline was not reported in any study.

Study quality.

Among the three trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two studies and unclear the third study. Two studies were double blinded.[72,73] The other study was not blinded.[74] For the outcomes presented here, only one study analyzed results according to the intention-to-treat principle.[72] All studies

adequately described reasons for study withdrawals. Withdrawals ranged from 12 to 14 percent (n=2 trials).

Results.

Mortality (Table 10, Appendix Table C19, and Appendix Figure C4).

Of the three studies, only one reported on mortality during the trial.[73] In this study of 86 patients with CKD there were no deaths.

Vascular outcomes (Table 10, Appendix Tables C19-C20).

Myocardial infarction. No study reported on MI events (fatal or nonfatal).

Stroke. No study reported on stroke events.

Other vascular outcomes. No studies reported on CHF events or any composite cardiovascular outcomes.

Renal outcomes (Table 10, Appendix Table C22, and Appendix Figure C4).

End-stage renal disease. No study reported on ESRD.

Other renal outcomes. No study reported on the outcome of doubling of serum creatinine. With regard to the outcome of progression from microalbuminuria to macroalbuminuria, it was reported that no events occurred in one trial,[74] and only four events in a second trial.[73] Although by far the most events for this outcome were reported in the ONTARGET trial, results reported by this trial for the number of participants with baseline microalbuminuria were impossibly inconsistent throughout the paper and could not be incorporated in a pooled analysis. No study reported on any renal composite outcomes.

Study withdrawals and adverse events (Appendix Table C23).

Overall study withdrawals were reported in only one study at 14 percent. One study reported on adverse events leading to withdrawal,[73] which was similar in both study arms. One study reported on any serious adverse events,[73] which were more common in the combination therapy group (9.3 percent) versus the ARB alone group (2.3 percent). The most common adverse events reported were hypotension, hyperkalemia, and cough. In one study cough was more common in the combination therapy group that in the ARB alone group (4.3 percent versus 0 percent).

Summary of results.

In individuals with CKD, trials comparing ACEI+ARB combination therapy versus ARB alone reported few or no clinical outcomes, including no deaths in one trial reporting this outcome. No trials reported data on MI, stroke, CHF, ESRD, doubling of serum creatinine, or any composite vascular or renal outcome. Though trials reported data for progression from microalbuminuria to macroalbuminuria, all had either few events or errors in reporting that impeded interpretation. Reporting on study withdrawals and adverse effects was limited. No trial provided followup beyond 5 years.

Table 10. Pooled clinical and renal outcomes for ACE inhibitor plus ARB versus ARB trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI+ARB Events/N (%)	ARB Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	1	Fair	0/43 (0)	0/43 (0)	-	NA
Progression to macroalbuminuria	2	Fair	1/139 (0.7)	3/91 (3.3)	0.33 [0.04-3.08]	NA

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; RR = relative risk reduction; NA = not applicable

ACE Inhibitor Plus ARB Versus ACE Inhibitor Plus Aldosterone Antagonist Trial

Overview.

In comparing ACEI plus ARB versus ACEI plus aldosterone antagonist, we found insufficient evidence regarding whether there is a difference between treatments in risk of mortality, or any clinical vascular or renal outcomes.

Description of study.

One trial met all eligibility criteria and randomized 54 participants with CKD and taking an ACEI (lisinopril 80 mg/day) to the addition of either an ARB (losartan) or of an aldosterone antagonist (spironolactone).[99] A third arm of the trial, discussed elsewhere, involved addition of placebo to lisinopril. Detailed baseline characteristics are presented in Appendix Table C25.

The mean age of trial participants was 52 years, and males constituted 49 percent of study subjects. Most patients (55 percent) were Hispanic, with an additional 28 percent black, 15 percent white, and 2 percent Native American. The study duration was 48 weeks.

Renal function.

Patients were included if they had macroalbuminuria, defined as a urinary albumin to creatinine ratio of 300 mg/g or higher despite treatment with an ACEI or ARB for at least 3 months prior to study entry. Females with a serum creatinine greater than 3.0 mg/dl and males with a serum creatinine greater than 4.0 mg/dl were excluded. Baseline renal function for trial participants included mean urine albumin to creatinine ratio of 997.4 mg/g, mean baseline serum creatinine of 1.8 mg/dl, and mean creatinine clearance of 58.0 ml/min.

Baseline comorbidities.

All study participants were required to have hypertension, with a systolic blood pressure on antihypertensive treatment of greater than 130 mm Hg. Mean baseline blood pressure was 134.0/72.5 mm Hg. Trial participants also were required to have diabetes, but with an HbA_{1c} at or below 11 percent. The mean HbA_{1c} at baseline was 7.5 percent. Patients with any history of heart failure, or with a stroke or MI in the past 12 months were excluded. A history of either MI, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty was reported by 7.5 percent of the patients.

Study quality.

The trial was rated fair quality. The method used for treatment allocation was not clearly described. The study was double blinded; however, the analysis was not completed using intention-to-treat principles. From the 54 randomized participants, 35.2 percent withdrew, with reasons for withdrawals adequately explained.

Results.

Mortality (Appendix Table C26 and Appendix Figure C5).

The trial reported one death in the ACEI plus ARB treatment group and no deaths in the ACEI plus aldosterone antagonist group.

Vascular outcomes (Appendix Table C26 and Appendix Figure C5).

Myocardial infarction. The trial reported no MIs in the ACEI plus ARB treatment group and one MI in the ACEI plus aldosterone antagonist group.

Stroke. No stroke events were reported.

Other vascular outcomes. The trial reported two hospitalizations attributed to heart failure in the ACEI plus ARB treatment group. This compared to two hospitalizations attributed to heart failure in the ACEI plus aldosterone antagonist group. No composite vascular outcomes were reported.

Renal outcomes (Appendix Table C27 and Appendix Figure C5).

End-stage renal disease. The trial did not report results for end-stage renal disease.

Other renal outcomes. There was no significant difference between treatment groups in risk of doubling of baseline serum creatinine (RR=1.04 [95 percent CI 0.60 to 1.80]).

Study withdrawals and adverse events (Appendix Table C28).

Withdrawals occurred in 33.3 percent of study participants randomized to the ACEI plus ARB treatment arm versus 37.0 percent of the ACEI plus aldosterone antagonist arm. There were more withdrawals due to adverse events in the ACEI plus aldosterone antagonist group (25.9 percent versus 7.7 percent). Two patients (7.4 percent) in the ACEI plus aldosterone antagonist group and none in the ACEI plus ARB group experienced recurrent hyperkalemia. Similarly, one patient (3.7 percent) in the ACEI plus aldosterone antagonist group and none in the ACEI plus ARB group withdrew from the study because of an increase in serum creatinine.

Summary of results.

In this trial of diabetic, hypertensive CKD patients already on ACEI, there appeared to be no difference between subjects randomized to additional ARB versus additional aldosterone antagonist for the outcome of doubling of baseline creatinine. Few or no results were reported with respect to risk of all-cause mortality, MI, stroke, CHF, or ESRD. Withdrawals due to adverse events appeared possibly were more likely with ACEI combined with aldosterone antagonist. Results were limited in that they are based on only one small trial that reported few clinical endpoints. Further, the withdrawal rate was high and followup duration was less than 1 year.

ACE Inhibitor Plus CCB Versus ACE Inhibitor Monotherapy or CCB Monotherapy Trial

Overview.

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI monotherapy, CCB monotherapy, and ACE+CCB combination therapy for reducing risk of mortality, or any clinical vascular or renal outcome.

Description of study.

We identified one trial that met all eligibility criteria. Patients with CKD were randomized to receive ACEI and CCB combined, ACEI alone, or CCB alone.[81] Detailed baseline characteristics are presented in Appendix Table C29.

After randomization to CCB (amlodipine at 5 to 15 mg/day), ACEI (fosinopril at 10 to 30 mg/day), or the combination, participants began a three month dose titration phase to a goal diastolic blood pressure less than 90 mm Hg for the monotherapy groups and less than 85 mm Hg for the combination therapy group. Patients judged nonresponders or who complained of side effects during the titration phase were withdrawn (n=144 overall, with no data reported by treatment group) and were not entered into the subsequent treatment phase. Study followup during the treatment phase was 4 years.

Renal function.

Study participants were required to have microalbuminuria, defined by UAER 30 to 300 mg/24 hours. For the patients entered in the treatment phase into either the ACEI plus CCB group or the ACEI alone group, the mean baseline serum creatinine was 1.0 mmol/L, mean creatinine clearance was 89.9 mg/min, and mean UAER was 97.9 µg/min. For the patients entered into either the ACEI plus CCB group or the CCB alone group, baseline characteristics were similar. Mean serum creatinine was 1.0 mg/dL, creatinine clearance was 89.3 mg/min, and UAER was 96.6 µg/min.

Baseline comorbidities.

Study participants were required to have hypertension (diastolic blood pressure 90 to 110 mm Hg) and type 2 diabetes (well controlled without insulin). Patients with a history of coronary heart disease, CHF, MI, or stroke were excluded. For patients entered in the treatment phase into either the ACEI plus CCB group or the ACEI alone group, mean baseline blood pressure was 160/99 mm Hg and baseline HbA_{1c} was 7.1 percent. For the patients entered into either the ACEI plus CCB group or the CCB alone group, mean baseline blood pressure was 161/99 mm Hg and HbA_{1c} was 7.0 percent.

Study quality.

The trial was rated fair quality. Concealment of treatment allocation was adequate. This open-label study did not perform analysis according to the intention-to-treat principle. In addition to participants excluded during the dose titration phase, additional participants withdrew during treatment, resulting in 47 percent total withdrawals.

Results.

Mortality (Appendix Tables C30 and C31 and Appendix Figures C6 and C7).

All-cause mortality. The trial reported deaths in few participants, with 2.9 percent, 3.9 percent, and 1.9 percent in ACEI monotherapy, CCB monotherapy, and ACEI+CCB combination groups respectively. There were no significant differences in risk of all-cause mortality between any of these treatment groups.

Cardiovascular mortality. The trial reported cardiovascular deaths in few participants, with 1.9 percent, 1.9 percent, and 1.0 percent in ACEI monotherapy, CCB monotherapy, and ACEI+CCB combination groups respectively. There were no significant differences in risk of all-cause mortality between any of these treatment groups.

Vascular outcomes (Appendix Tables C30 and C31 and Appendix Figures C6 and C7).

Myocardial infarction. There were few events and no difference between the ACEI plus CCB combination compared with either ACEI alone or CCB alone for all-cause MI.

Stroke. There were few events and no difference between the ACEI plus CCB combination compared with either ACEI alone or CCB alone for stroke.

Other vascular outcomes. No other vascular or composite vascular outcomes were reported.

Renal outcomes.

End-stage renal disease. No outcomes were reported for end-stage renal disease.

Other renal outcomes. No other renal or composite renal outcomes were reported.

Study withdrawals and adverse events (Appendix Table C32).

The overall withdrawal rate for the study was 45 percent. Thirty two percent withdrew during the titration period (treatment group not stated). Excluding deaths, an additional 20 percent withdrew during the study period (22 percent CCB, 23 percent ACE, 15 percent ACEI plus CCB). Between 1 and 2 percent of the patients in each group discontinued study medication due to worsening kidney function. Other reported adverse events (also reported for less than 2 percent of the patients in any treatment group) were cough and edema.

Summary.

In one study of patients with CKD, hypertension, and diabetes without a history of cardiovascular disease, few participants died or experienced clinical vascular or renal events. There was no significant difference for any of these outcomes between ACEI plus CCB versus either ACEI monotherapy or CCB monotherapy groups, but wide confidence intervals around all estimates could not exclude large between-group differences. Adverse events were infrequent and risk did not appear significantly different between treatment groups. There were no data on clinical renal outcomes. The study was limited by its exclusion of one-third of randomized participants from the analyses, the large number of additional withdrawals during treatment, the small number of clinical vascular events, and the absence of any reported clinical renal outcomes.

ACE Inhibitor Plus Diuretic Versus ACE Inhibitor Plus CCB Trial

Overview.

In summary, in patients with CKD, we found insufficient evidence regarding whether there is any difference between combination therapy with an ACEI and a diuretic and combination therapy with an ACEI and CCB for risk of mortality or other clinical vascular or renal outcomes.

Description of study.

One trial met all eligibility criteria and randomized 332 patients with CKD to ACEI plus diuretic versus ACEI plus CCB.[102] Detailed baseline characteristics are presented in Appendix Table C33.

Patients randomized to the ACEI plus CCB group received benazepril and amlodipine. Those randomized to the ACEI plus diuretic group received benazepril and hydrochlorothiazide (HCTZ). Doses were titrated to reach a blood pressure target below 130/80 mm Hg, and additional antihypertensives were added as needed other than ACE, ARB, or aldosterone receptor antagonists. The mean age of study participants was 58 years, and men constituted 65 percent of subjects. Patients were mostly white race (60 percent), with blacks comprising another 26 percent of participants. Study followup duration was 12 months.

Renal function.

Study participants were required to have either microalbuminuria or macroalbuminuria (UACR 20 to 500 mg/g), and to have serum creatinine ≤1.3 mg/dl for women and ≤1.5 mg/dl for men. In data available only for the 304 patients who completed followup, the median UACR was 60.6 mg/g, and the median estimated GFR was 90.6 ml/min/1.73m^2.

Baseline comorbidities.

Trial participants were required to have hypertension (mean systolic blood pressure 130 to 179 mm Hg and diastolic blood pressure 80 to 109 mm Hg). Mean baseline blood pressure was 151/88 mm Hg. Individuals with CHF, type 1 diabetes or uncontrolled type 2 diabetes were excluded, as were those with a cardiovascular disease event in the past six months (MI, stroke, transient ischemic attack, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty).

Study quality.

The study was rated fair quality. Treatment allocation concealment was adequate. The study was double blinded. Analysis was not according to the intention-to-treat principle. Withdrawals were 19 percent.

Results.

Mortality (Appendix Table C34 and Appendix Figure C8.

Among 166 patients allocated to ACEI plus diuretic, there were two deaths. Among 166 patients allocated to ACEI plus CCB, there was one death.

Vascular outcomes (Appendix Tables C34 and C35 and Appendix Figure C8).

Myocardial infarction. There were no reports of MI.

Stroke. There were no reports of stroke.

Other vascular outcomes. Three patients in the ACEI plus diuretic group were reported to have undefined "cardiac disorders," and two were reported to have undefined "vascular disorders." In the ACEI plus CCB group, two patients were reported to have "cardiac disorders," and none had a "vascular disorder." There was no significant difference between treatment groups for any of these outcomes.

Renal outcomes (Appendix Table C36 and Appendix Figure C8).

End-stage renal disease. No data were reported for end-stage renal disease.

Other renal outcomes. The risk of progression from microalbuminuria to macroalbuminuria was not significantly different between the ACEI plus diuretic group and the ACEI plus CCB group (4.0 versus 4.6 percent, RR=0.84 [95 percent CI 0.29 to 2.44]).

Study withdrawals and adverse events (Appendix Table C37).

The overall withdrawal rate during the study period was 18.7 percent (21.7 percent in the ACEI plus diuretic group and 15.7 percent in the ACEI plus CCB group). Adverse events resulted in study withdrawal for 10.8 percent of the ACEI plus diuretic group and 5.4 percent of the ACEI plus CCB group, but details were not provided regarding specific adverse events that led to withdrawal. Reported adverse events in the ACEI plus diuretic group and ACEI plus CCB

group, respectively, included edema in 17.5 percent and 7.2 percent, cough in 13.9 percent and 10.3 percent, and dizziness in 9.0 percent and 6.6 percent. Fatigue was reported in 7.8 percent of patient in both groups and headache was reported in 9.6 percent of the ACEI plus diuretic group and 8.4 percent of the ACEI plus CCB group.

Summary.

In one study of patients with CKD defined by albuminuria, hypertension with no recent cardiovascular events, and no heart failure, there was no significant difference between patients allocated to ACEI plus diuretic versus ACEI plus CCB in risk of mortality, or of unspecified "cardiac disorders" or "vascular disorders." However, there were very few events for any of these outcomes, and confidence intervals around risk estimates were wide. No data were reported for MI, stroke, CHF, ESRD, or any transparently defined composite vascular or renal outcome. The risk of progression from microalbuminuria to macroalbuminuria appeared similar between treatment groups, but again confidence intervals were wide. Risk of edema, cough, and dizziness appeared somewhat higher in the ACEI plus CCB group.

ACE Inhibitor Plus Diuretic Versus ACE Inhibitor Monotherapy Trial

Overview.

In patients with CKD, we found low strength of evidence that combination therapy with an ACEI and a diuretic was more effective than ACEI alone in reducing risk of serious cardiovascular events. There was insufficient evidence regarding whether treatments differ for other outcomes.

Description of study.

One trial met all eligibility criteria and randomized 481 patients with CKD to receive either an ACEI and diuretic or a different ACEI alone.[103] Detailed baseline characteristics are presented in Appendix Table C38 for the 457 patients who took at least one dose of study medication and who had albuminuria measured at least once during treatment.

The ACEI plus diuretic group received perindopril and indapamide, while the ACEI monotherapy group received enalapril. Both groups were titrated to achieve a blood pressure goal of less than 140/90 mm Hg. The mean age of subjects was 59 years and 61 percent of study participants were male. Ninety-one percent of the study participants were white. Mean followup duration was 10.7 months.

Renal function.

Study participants were required to have albuminuria (UAER of 20 to 499 µg/min) and to have a serum creatinine less than approximately 1.6 mg/dl. Mean UAER was 92.1µg/min and the mean urine albumin/creatinine ratio was 8.5 mg/mmol.

Baseline comorbidities.

Study participants were required to have type 2 diabetes with HbA_{1c} less than 9 percent in the 3 months prior to the study. Mean baseline HbA_{1c} was 7.2 percent. Participants also were required to have hypertension (systolic blood pressure 140 to 179 mm Hg and diastolic blood pressure less than 110 mm Hg). Mean baseline blood pressure was 158/93 mm Hg.

Study quality.

Study quality was rated fair. Though the study was double blind, allocation concealment was unclear and analysis was not intention-to-treat. Withdrawals were 23 percent and were not adequately described.

Results.

Mortality.

The number of deaths during the study could not be determined.

Vascular outcomes (Appendix Tables C39 and C40 and Appendix Figure C9).

Myocardial infarction. The number of MIs during the study could not be determined.

Stroke. The number of strokes during the study could not be determined.

Other vascular outcomes. The only clinical outcome reported was serious (fatal or requiring prolonged hospitalization) cardiovascular events (defined by ICD9-1975 revision codes for sudden death and many other cardiovascular conditions). There was a significantly reduced risk of achieving the composite vascular outcome in the ACEI plus diuretic group (RR=0.39 [95 percent CI 0.15 to 0.98]).

Renal outcomes.

End-stage renal disease. There were no reports of end-stage renal disease.

Other renal outcomes. There were no other renal outcomes reported.

Study withdrawals and adverse events (Appendix Table C41).

The overall withdrawal rate for the study was 23 percent, including 21 percent in the ACEI plus diuretic group and 25 percent in the ACEI group. Adverse events related to drug treatment were similar for the two groups (14 percent and 15 percent for the ACEI plus diuretic and ACEI groups, respectively) as were withdrawals due to adverse events (8 percent and 9 percent, respectively). Specific adverse events included hyperkalemia in 3.3 percent of the ACEI plus diuretic group and 5.5 percent of the ACEI group and cough in 3.7 percent of the ACEI plus diuretic group and 2.1 percent of the ACEI group.

Summary.

In patients with CKD, hypertension, and type 2 diabetes, a combination of ACEI and diuretic was associated with a significant reduction in risk of serious cardiovascular events compared to treatment with ACEI monotherapy. The risk of adverse events was similar in the two groups. Results were limited because there were no data on mortality or specific cardiovascular or renal outcomes. Further, analysis was not based on intention-to-treat principles and the study withdrawals or dropouts were not adequately described. Mean followup for this study was 10.7 months.

ARB (High Dose) Versus ARB (Standard Dose) Trial

Overview.

We found insufficient evidence regarding whether there is any difference between these three candesartan doses for any clinical vascular or renal outcome in patients with CKD.

Description of study.

One trial met eligibility criteria and randomized 269 participants with CKD to three different doses of candesartan (16 mg/day, 64 mg/day, and 128 mg/day.[20] Detailed baseline characteristics are presented in Appendix Table C42.

Mean age of study participants was 55.3 years and men constituted 80 percent of all study participants. By race/ethnicity, 83 percent of participants were white, 9 percent were Asian, and 4 percent were black. The study was conducted in Canada and followup duration was 30 weeks.

Renal function.

Patients were required to have proteinuria of at least 1 g/day to be included in the trial. By etiology, they were allowed to have untreated primary glomerular disease, diabetic nephropathy, or hypertensive nephrosclerosis. At baseline, mean proteinuria was 2.83 g/day with 57.3 percent of study subjects having 1 to 3 g/day and 42.7 percent at more than 3 g/day proteinuria. Mean GFR was 52.0 ml/min/1.73m^2.

Baseline comorbidities.

All study participants were required to have stable hypertension, with no new antihypertensive medications started less than 6 weeks prior to baseline (at least 3 months for angiotensin converting enzyme inhibitors or angiotensin receptor blockers), and with blood pressure less than 170/100 mm Hg. Mean baseline blood pressure was 133/77 mm Hg. No information was provided on any cardiovascular comorbidities.

Study quality.

The study was rated good quality. The study was double blinded and used adequate concealment methods for treatment allocation. Results were analyzed according to the intention-to-treat principle and withdrawal and dropouts were adequately described. Withdrawals were 14 percent.

Results.

Mortality (Appendix Tables C43).

The study reported that there were no deaths in any of the treatment groups.

Vascular outcomes (Appendix Tables C43, C44, and C48).

Myocardial infarction. There were no reports of myocardial infarction.

Stroke. There were no reports of stroke.

Other vascular outcomes. No other vascular or composite vascular outcomes were reported.

Renal outcomes (Appendix Tables C45 and C49).

End-stage renal disease. There were no reports of end-stage renal disease.

Other renal outcomes. No other renal or composite renal outcomes were reported.

Study withdrawals and adverse events (Appendix Table C46).

Study withdrawals were 20 percent in the 16 mg/day candesartan group, 6.7 percent in the 64 mg/day group, and 15.7 percent in the 128 mg/day group. Study withdrawals due to adverse effects were 12.2 percent in the 16 mg/day group, 5.5 percent in the 64 mg/day group, and 9.0

percent in the 128 mg/day group. The incidence of hyperkalemia was between 3.3 and 4.4 percent for each of the treatment groups.

Summary.

In this single small trial of CKD patients randomized to three different doses of candesartan, there were no deaths in any treatment group and no other data reported for any clinical vascular or renal outcome. Withdrawals and adverse events did not appear higher in the two higher dose candesartan groups compared to the low dose group.

ARB Versus Different ARB Trials (n=2)

Overview.

In patients with CKD, we found a low level of evidence that telmisartan reduces risk of all-cause mortality compared to losartan and insufficient evidence regarding whether there is a difference in risk of all-cause mortality between telmisartan and valsartan. We found insufficient evidence regarding whether telmisartan differs from either losartan or valsartan for risk of cardiovascular mortality, MI, stroke, or ESRD.

Description of studies.

Two trials met all eligibility criteria and randomized 1,745 participants with CKD to treatment comparing two different ARBs.[104,105] Detailed baseline characteristics are presented in Appendix Tables C42 and C47.

One trial randomized 860 participants to telmisartan versus losartan.[104] The second trial randomized 885 participants to telmisartan versus valsartan.[105] The mean age of study participants was 61 years (range 60 to 61) and men constituted 63 percent (range 62 to 64) of all participants studied. Both trials reported race/ethnicity, and 63 percent of participants were white, 30 percent were Asian, and 7 percent were black. Both were multinational studies and followup duration ranged from 10.7 to 12 months.

Renal function.

Both trials required that participants have overt proteinuria, and allowed subjects with either normal or elevated serum creatinine levels, setting an upper abnormal limit. In one trial, participants had to have proteinuria of 900 mg/24 hours or greater and a serum creatinine of 3.0 mg/dl or less.[105] This study reported a mean baseline proteinuria of 2.78 g/day. In the second trial, patients had to have a urine protein-creatinine ratio at least 700 mg/g and a serum creatinine <3.0 mg/dl in women and <3.2 mg/dl in men.[104] At baseline, this study reported a mean urine protein-creatinine ratio of 1,991 mg/g, mean urine albumin-creatinine ratio of 1,394 mg/g, and a mean serum creatinine of 1.55 mg/dl. For both trials considered together, the mean baseline GFR was 53.2 ml/min/1.73m^2 (range 49.6 to 56.6).

Baseline comorbidities.

Both trials were restricted to patients with type 2 diabetes and hypertension. At baseline, mean HbA_{1c} was 7.85 percent and mean blood pressure was 146/81 mm Hg. One trial excluded patients with a history of "clinically significant" heart disease or stroke, which was presumed to exclude patients with a history of coronary artery disease, MI, or congestive heart failure.[104] The second study excluded patients with any history of congestive heart failure and those with a

"recent acute cardiovascular event."[105] It did not report data on prevalence of coronary artery disease, MI, or stroke.

Study quality.

Both trials were rated as fair quality. Allocation concealment was unclear in both studies. Both were double blinded. One study analyzed results according to the intention-to-treat principal and adequately described the 19.1 percent of subjects who withdrew from the study.[105] The second study did not include an intention-to-treat analysis and did not adequately describe the 18.4 percent of participants who withdrew.[104]

Results.

Mortality (Table 11, Appendix Table C43, and Figure C10).

All cause-mortality. Among these patients with CKD, those randomized to telmisartan had a significant 84 percent reduction in risk of all-cause mortality compared to those randomized to losartan (0.5 versus 2.9 percent; RR=0.16 [95 CI, 0.04 to 0.71]).[104] However, the risk of all-cause mortality was higher, although not significantly so, for patients assigned telmisartan versus valsartan (3.5 versus 1.9 percent; RR=1.88 [95 percent CI, 0.81 to 4.39]).[105] Results from these trials were not pooled as the results suggested large differences in the direction of the effect of losartan and valsartan compared to telmisartan. This was reflected in the I^2 of 75 percent.

Cardiovascular mortality. One study reported no significant difference between the telmisartan or valsartan treatment groups for cardiovascular mortality (RR=1.34 [0.47 to 3.82]).[105]

Vascular outcomes (Table 11, Appendix Tables C43, C44, and C48, and Appendix Figure C10).

Myocardial infarction. In one trial reporting, there was no significant difference between telmisartan and valsartan in risk of myocardial infarction (RR=0.36 [0.12 to 1.14]).[105]

Stroke. In the same trial, there was no significant difference between telmisartan and valsartan in the risk of stroke (RR=2.21 [0.77 to 6.29]).[105]

Other vascular outcomes. Again in one trial reporting, there was no significant difference between telmisartan and valsartan in the risk of hospitalization for congestive heart failure (RR=1.17 [0.39 to 3.52]).[105] Both trials defined and reported results for composite vascular endpoints. One reported a borderline statistically significant 40 percent reduction in risk of cardiovascular mortality or cardiovascular morbidity (not defined) in its CKD population assigned to telmisartan versus those assigned to losartan (RR=0.60 [95 percent CI 0.36 to 1.00]).[104] The second trial reported no difference between its participants with CKD allocated to telmisartan versus valsartan for the composite outcome of MI, stroke, hospitalization for CHF or unstable angina, or coronary or peripheral revascularization (RR=0.94 [95 percent CI 0.59 to 1.51]).[105]

Renal outcomes (Table 11, Appendix Tables C45 and C49, and Appendix Figure C10).

End-stage renal disease. In the one trial reporting this outcome, there was no apparent difference in risk for ESRD between CKD patients randomized to telmisartan versus valsartan (RR 0.88 [0.32 to 2.40]).[105]

Other renal outcomes. One trial reported that there was no difference between subjects randomized to telmisartan versus valsartan for doubling of serum creatinine (RR=1.0 [95 percent CI 0.20 to 4.94]).[105] Both trials reported no significant difference between assigned ARBs in risk

of a composite renal outcome defined as doubling of serum creatinine, ESRD, or death. One trial reported a nonsignificant 41 percent reduced risk with telmisartan compared to losartan (RR=0.59 [95 percent CI 0.31 to 1.12]),[104] but the other trial reported a nonsignificant 23 percent increased risk with telmisartan compared to valsartan (RR=1.23 [95 percent CI 0.42 to 1.75]).[105] Neither study reported results for halving of GFR or progression from microalbuminuria to macroalbuminuria.

Study withdrawals and adverse events (Appendix Table C46).

Overall study withdrawals were comparable in the two studies at 18.4 percent[104] and 19.1 percent.[105] There were fewer serious adverse events in the telmisartan group (15.5 percent) than in the losartan group (22.4 percent)[104] but more serious adverse events in the telmisartan group (26.2 percent) than in the valsartan group (23.5 percent).[105] Overall withdrawals for serious adverse events were low (3.2 percent or less in all groups). Similarly, the incidence of hyperkalemia was low in all groups (<2.9 percent).

Summary of results.

In individuals with CKD, type 2 diabetes mellitus, and hypertension, compared to losartan, telmisartan was associated with a significant 84 percent reduction in all-cause mortality and a borderline significant 40 percent reduction in cardiovascular morbidity or cardiovascular mortality. In addition, telmisartan was associated with a nonsignificant 41 percent reduction in risk of the composite endpoint of doubling of serum creatinine, ESRD, or death, and with fewer serious adverse events. However, compared to valsartan, CKD patients randomized to telmisartan appeared to have a nonsignificantly higher risk of all-cause and cardiovascular mortality, stroke, and CHF, but a lower risk of MI. There was little difference in the composite vascular outcome or in any of the adverse event measures recorded. Results were limited by relatively small sample size and number of clinical events, with most outcomes reported only in one trial, and heterogeneity in comparison groups and outcomes that prevented statistical pooling. This resulted in there being low statistical power to determine if even large differences in outcomes between treatment groups were statistically significant. Results also were limited in that there were no studies that directly compared losartan and valsartan. Because no trial was longer than 1 year, it was not possible from these studies to determine the longer term effects of telmisartan versus losartan or valsartan.

Table11. Pooled clinical and renal outcomes, ARB versus different ARB trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intervention Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Telmisartan vs. Different ARB						
All-cause mortality	2	Fair	17/847 (2.0)	21/870 (2.4)	0.59 [0.05-6.88]	88%
Bakris, 2008[104]	1	Fair	2/419 (0.5)	13/441 (2.9)	0.16 [0.04-0.71]	NA
Galle, 2008[105]	1	Fair	15/428 (3.5)	8/429 (1.9)	1.88 [0.81-4.39]	NA
Cardiovascular mortality	1	Fair	8/428 (1.9)	6/429 (1.4)	1.34 [0.47-3.82]	NA
Myocardial infarction	1	Fair	4/428 (0.9)	11/429 (2.6)	0.36 [0.12-1.14]	NA
Stroke	1	Fair	11/428 (2.6)	5/429 (1.2)	2.21 [0.77-6.29]	NA
CHF hospitalization	1	Fair	7/428 (1.6)	6/429 (1.4)	1.17 [0.39-3.52]	NA
Composite vascular† Bakris, 2008[104]	1	Fair	21/419 (5.0)	37/441 (8.4)	0.60 [0.36-1.00]	NA
Composite vascular* Galle, 2008[105]	1	Fair	31/428 (7.2)	33/429 (7.7)	0.94 [0.59-1.51]	NA
End-stage renal disease	1	Fair	7/428 (1.6)	8/429 (1.9)	0.88 [0.32-2.40]	NA
Doubling of serum creatinine	1	Fair	3/428 (0.7)	3/429 (0.7)	1.00 [0.20-4.94]	NA
Composite renal outcome**	1	Fair	14/419 (3.3)	25/441 (5.7)	0.59 [0.31-1.12]	NA
Bakris, 2008[104]	1	Fair	22/428 (5.1)	18/429 (4.1)	1.23 [0.67- 2.25]	NA
Galle, 2008[105]						

RR = relative risk reduction; MI = myocardial infarction; NA = not applicable
†Bakris = Cardiovascular morbidity (not defined) or mortality.
*Galle = Myocardial infarction, stroke, or hospitalization for heart failure or unstable angina, coronary or peripheral revascularization.
**Doubling of serum creatinine concentration, end-stage renal disease (need for long-term dialysis, renal transplantation, or serum creatinine ≥ 6 mg/dl), or death.

ACE Inhibitor Plus Aldosterone Antagonist Versus ACE Inhibitor Plus Placebo Trial

Overview.

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI plus aldosterone antagonist versus ACEI alone for risk of all-cause mortality, MI, stroke, or ESRD.

Description of study.

We identified one trial that met all eligibility criteria and randomized 54 patients with CKD being treated with ACEI to either additional aldosterone antagonist or placebo.[99] Detailed baseline characteristics for this comparison are presented in Appendix Table C50. Data regarding a third treatment arm, the addition of ARB to ACEI are discussed separately.

Mean age of randomized participants was 51 years, and men constituted 46 percent of the subjects. Fifty-four percent of patients were Hispanic, 32 percent were black, 11 percent were non-Hispanic white, and 3 percent were Native American. Mean study followup duration was 11.1 months.

Renal function.

For inclusion, participants were required to have macroalbuminuria (UACR at least 300 mg/g) despite run-in treatment. Women with serum creatinine above 3.0 mg/dL and men with creatinine above 4.0 mg/dL were excluded from the study. Among randomized participants, mean baseline UACR was 1,006 mg/g, mean serum creatinine was 1.6 mg/dL, and mean creatinine clearance was 62 ml/min.

Baseline comorbidities.

All study participants were required to be hypertensive prior to screening but were treated with diet and ACEI during a pre-randomization 3 month run-in period to a target systolic blood pressure of less than 130 mm Hg. Mean blood pressure at randomization was 132/74 mm Hg study participants also were required to have diabetes, and mean HbA_{1c} was 7.8 percent. Patients with a history of heart failure, and those with a stroke or MI within 12 months were excluded from the trial. A history of either MI, CABG, or PTCA was reported by 9.3 percent.

Study quality.

Study quality was rated fair. The trial was double blinded, but allocation concealment was unclear. While the overall study analysis was not by intention-to-treat, this pertained to exclusion from analyses of a single participant randomized into the ACEI plus ARB treatment group that is not the focus of this section of the report. Withdrawals were 30 percent.

Results

Mortality (Appendix Table C51).

There were no deaths during the followup period.

Vascular outcomes (Appendix Tables C51 and C52 and Appendix Figure D11).

Myocardial infarction. Among participants in the ACEI plus aldosterone antagonist group, there was one subject with MI, while in the ACEI plus placebo group, no subjects had an MI.

Stroke. Among participants in the ACEI plus aldosterone antagonist group, there were two subjects with stroke. In the ACEI plus placebo group, one subject had a stroke.

Other vascular outcomes. Among participants in the ACEI plus aldosterone antagonist group, two subjects were hospitalized for heart failure. In the ACEI plus placebo group, no subjects were hospitalized for heart failure. The study did not report results for any composite vascular outcomes.

Renal outcomes.

End-stage renal disease. The study did not report results for ESRD.

Other renal outcomes. The study did not report results for doubling baseline creatinine, halving GFR, or for any composite renal outcome.

Study withdrawals and adverse events (Appendix Table C53).

In the ACEI plus aldosterone antagonist group, withdrawals and withdrawals due to adverse effects occurred in 37 percent and 26 percent of participants respectively, as compared to 22 percent and 7 percent, respectively, in the ACEI plus placebo group. Adverse effects attributing to withdrawal were hyperkalemia (n=2), stroke (n=2), symptomatic hypotension (n=1), gynecomastia (n=1), and increased serum creatinine (n=1) in the ACEI plus aldosterone antagonist group, and stroke (n=1) and increased serum creatinine (n=1) in the ACEI plus placebo group.

Summary.

In this small, short duration study of CKD patients with macroalbuminuria, hypertension and diabetes, but with no history of heart failure and with a low prevalence of other cardiovascular disease, there were no deaths and very few cardiovascular outcomes. Differences in individual cardiovascular outcomes were not statistically significant. Participants in the ACEI plus aldosterone group appeared to be at higher risk for adverse events leading to discontinuation of treatment and study withdrawal. Results were limited by the short study duration, and small number of individual clinical vascular events. Also, no clinical renal outcomes data were reported.

ACE Inhibitor/ARB Plus Aldosterone Antagonist Versus ACE Inhibitor/ARB Plus Placebo Trial

Overview.

In patients with CKD, there was insufficient evidence regarding whether, in comparison to treatment with ACEI or ARB plus placebo, treatment with ACEI or ARB plus aldosterone antagonist reduces mortality or any clinical vascular or renal outcome.

Description of study.

One trial met all eligibility criteria and randomized 59 participants with CKD and taking ACEI or ARB at baseline to the addition of an aldosterone antagonist versus addition of placebo[106] Detailed baseline characteristics are presented in Appendix Table C54.

Participants using an ACEI or ARB in recommended dosages for at least 1 year were randomized to addition of the aldosterone antagonist, spironolactone, 50 mg daily versus

placebo. Mean age in study participants was 52 years and 66 percent of subjects were men. Study followup duration was 1 year.

Renal function.

Eligible participants were required to have albuminuria, defined as either 24 hour urinary albumin excretion greater than 300 mg or UACR greater than 20 mg/mmol. Mean serum creatinine was 98.2 µmol/l, mean UACR was 81 mg/mmol, and mean protein-to-creatinine ratio was 128.5 mg/mmol. The mean estimated GFR was 70.5 ml/min/1.73m^2.

Baseline comorbidities.

All participants had type 2 diabetes. Patients with MI or stroke within the past 3 months or with unstable angina pectoris were excluded. Mean blood pressure was 146/81 mm Hg and mean HbA1c was 8.1 percent.

Study quality.

Study quality was rated fair. Treatment allocation concealment was adequate. The study was double blinded. Analysis was not performed according to the intention to treat principle. Withdrawals were 11.9 percent and were adequately described.

Results

Mortality (Appendix Table C55 and Appendix Figure C12).

There were two deaths in the placebo group due to complications following an MI (RR=0.21 [95 percent CI 0.01 to 4.13]).

Vascular outcomes (Appendix Table C55).

Myocardial infarction. As noted above, there were two fatal MIs in the placebo group.

Stroke. There were no reports of stroke.

Other vascular outcomes. No other vascular outcomes were reported.

Renal outcomes.

End-stage renal disease. There were no reports of end-stage renal disease.

Other renal outcomes. . No other renal outcomes were reported.

Study withdrawals and adverse events (Appendix Table C56).

Of 59 patients randomized, six (17.2 percent) in the aldosterone antagonist group and one (3.3 percent) in the placebo group discontinued treatment as a result of hyperkalemia developed during the first 2 to 12 weeks of treatment. During the rest of the study, two additional patients in the aldosterone antagonist group and one in the placebo group discontinued treatment.

Summary.

In one trial in patients with CKD and diabetes, already on ACEI or ARB, there was no significant difference in risk of all-cause or cardiovascular mortality between those randomized to addition of aldosterone antagonist versus placebo. No data were reported for other vascular or clinical renal outcomes. Results were limited in that they were based on only one small study with low statistical power for clinical events, which do not appear to have been a priori study outcomes.

BB Versus Placebo Trial

Overview.

We found low strength of evidence that in patients with heart failure and CKD who are on optimal medical therapy for their heart failure, treatment with BB significantly reduced risk of all-cause mortality, CHF complications, and MI or cardiac death. These benefits may be greater for patients with eGFR less than 45 ml/min/1.73m^2. We found insufficient evidence in this population regarding whether there is a difference between BB and placebo regarding risk of ESRD.

Description of study.

We identified one trial that met all eligibility criteria and randomized participants with CKD to BB versus placebo.[107] The study was a post hoc subgroup analysis of 1,469 subjects with eGFR ≤60 ml/min/1.73m^2 from the larger MERIT-HF heart failure trial (n=3,991). Detailed baseline characteristics are presented in Appendix Table C57.

All participants in MERIT-HF were required to have been on optimum heart failure therapy consisting of any combination or diuretics and an ACEI, with hydralazine, long acting nitrate, or ARB if an ACEI was not tolerated. Patients then were randomized to the BB, metoprolol XL/CR versus placebo. At baseline, 88 percent of the patients were taking an ACEI and 94 percent were taking diuretics. The mean age of study participants was 68 years and 68 percent of subjects were male. No data were reported on race/ethnicity in this multinational study. Study followup duration was 1 year.

Renal function.

For inclusion in the post hoc analysis, participants were required to have GFR ≤60 ml/min/1.73m2. There were 976 participants with GFR 45 to 60 ml/min/1.73m^2, and 493 with GFR <45 ml/min/1.73m^2. In these two strata combined, mean GFR was 48 ml/min/1.73m^2 and mean serum creatinine was 1.5 mg/dL.

Baseline comorbidities.

All MERIT-HF participants were required to have symptomatic heart failure. Among participants in this post hoc analysis, diabetes was reported for 29 percent, a history of hypertension for 49 percent, and a history of myocardial infarction for 55 percent. Mean baseline blood pressure was 130/77 mm Hg.

Study quality.

Study quality was rated good. Concealment of treatment allocation in this double-blind trial was adequate and analysis was performed according to the intention-to-treat principle. No data on withdrawals were reported for the CKD subgroup.

Results.

Mortality (Appendix Table C58 and Appendix Figure C13).

All-cause mortality. In the patients with CKD and heart failure, there was a significant reduction in the risk of all-cause mortality in those treated with BB versus placebo (8.6 versus 14.3 percent, RR=0.60 [95 percent CI 0.45 to 0.80]). In results stratified by baseline GFR, the

study reported an adjusted HR=0.41 [95 percent CI 0.25 to 0.68] for patients with GFR <45 ml/min/1.73m^2, HR=0.68 [95 percent CI 0.45 to 1.02] for patients with GFR 45 to 60 ml/min/1.73m^2, and HR=0.71 [95 percent CI 0.54 to 0.95] for those with GFR greater than 60 ml/min/1.73m^2, with a test for interaction of p=.095. No mortality data were reported for other patient subgroups.

Vascular outcomes (Appendix Tables C59 and C60 and Appendix Figure C13).

Myocardial infarction. The study did not report results for myocardial infarction as an isolated outcome.

Stroke. The study did not report results for stroke.

Other vascular outcomes. In results in which all participants with GFR ≤60 ml/min/1.73m^2 are pooled, assignment to BB treatment was associated with significant reductions in risks for hospitalization for CHF (12.2 versus 20.0 percent; RR=0.61 [95 percent CI 0.48 to 0.78]) and CHF death (2.0 versus 4.9 percent; RR=0.42 [95 percent CI 0.23 to 0.75]). Similarly, compared to placebo, CKD study participants randomized to BB had significant reductions in risk of the composite vascular outcomes of all cause mortality and hospitalization for CHF (18.5 versus 29.2 percent; RR=0.63 [95 percent CI 0.53 to 0.77]) and cardiac death or nonfatal MI (8.7 versus 14.6 percent; RR=0.60 [95 percent CI 0.45 to 0.80]). In results stratified by baseline GFR (<45, 45-60, and >60 ml/min/1.73m^2), the study consistently reported the numerically lowest HR for each of these outcomes in the patients with GFR <45 ml/min/1.73m^2. The p-value for interaction between baseline GFR stratum and treatment assignment was 0.038 for CHF hospitalization, 0.16 for CHF death, 0.011 for the composite outcome of all cause mortality and CHF hospitalization, and >0.2 for the composite outcome of cardiac death or nonfatal MI. No vascular outcomes data were reported for other patient subgroups.

Renal outcomes.

End-stage renal disease. The study did not report results for ESRD.

Other renal outcomes. The study did not report results for other individual or composite clinical renal outcomes.

Study withdrawals and adverse events (Appendix Table C61).

The study did not report data on withdrawals within the CKD subgroup. Rate of study treatment discontinuation due to adverse events appeared higher in participants with worse GFR, but not worse in those assigned to BB versus placebo. In patients with eGFR 45 to 60 ml/min/1.73m^2, the rate of discontinuations due to adverse events was 13.6 and 13.5 per 100 person years for those assigned BB versus placebo, respectively. In patients with eGFR <45 ml/min/1.73m^2, the rate was 16.9 and 20.8 per 100 person years for those assigned BB versus placebo, respectively. The most commonly reported adverse event resulting in discontinuation was heart failure. Fatigue, bradycardia, dizziness, and hypotension were also reported.

Summary.

In a single post hoc analysis, patients with well controlled heart failure and CKD who were randomized to BB versus placebo had a significantly lower risk of all-cause mortality, hospitalizations for CHF, CHF deaths, and of the composite vascular outcomes of all cause mortality or CHF hospitalization and of cardiac death or nonfatal MI. Analyses stratified by GFR subgroup suggested that the relative benefit of BB versus placebo may be greatest in patients

with eGFR <45 ml/min/1.73m^2, though the statistical test for interaction by GFR strata did not approach statistical significance. Results were limited in that this was a post hoc subgroup analysis, there were no measures of albuminuria available, no clinical renal outcomes and little adverse events data were reported. Because trial followup was only 1 year, longer term effects of BB monotherapy versus placebo in this population cannot be determined from these data.

CCB Versus Placebo Trials (n=2)

Overview.

In patients with CKD, we found low strength of evidence regarding whether treatment with CCB compared to placebo reduces risk of all-cause or cardiovascular mortality, MI, or stroke. We found low strength of evidence that there is no difference between treatments for risk of CHF, ESRD, or doubling of serum creatinine.

Description of studies.

Two trials met all eligibility criteria and randomized 1,226 participants (range 90 to 1,136) with CKD to CCB versus placebo.[53,94,108] Detailed baseline characteristics are presented in Appendix Tables C62 and C63.

The larger trial, IDNT, randomized 1,136 hypertensive, type 2 diabetic individuals to amlodipine versus placebo.[94,108] This trial also included an ARB treatment arm discussed elsewhere in this report. Mean age of study participants was 59 years, 67 percent of all subjects were male and 71 percent of participants were white. The study was multinational and followup duration was 2.6 years.

A second trial randomized 90 normotensive, type 1 diabetic subjects to nifedipine versus placebo,[53] and also included an ACEI treatment arm discussed elsewhere in this report. After randomization, 22 participants were excluded for having UAER outside the 20 to 200 µg/min range and an additional seven for adverse clinical events. Baseline data were only reported on these 61 participants. Within these participants, mean age was 37 years and 70 percent of all subjects were male. No information was reported on race/ethnicity, though the study was conducted in Italy. Followup duration was 3 years.

Renal function.

For inclusion in the IDNT trial, participants were required to have both elevated serum creatinine (1.0 to 3.0 mg/dL for women and 1.2 to 3.0 mg/dL for men) and proteinuria >900 mg/day. At baseline, mean serum creatinine was 1.7 mg/dL, mean proteinuria was 2.9 g/day, and mean albuminuria was 1.9 g/day.

For inclusion in the smaller trial, participants were required to have microalbuminuria, with a UAER of 20 to 200 µg/min, a GFR of 80 ml/min/1.73m^2 or greater, and a serum creatinine <10 percent higher than the upper limit of normal. After randomization, 22 participants were excluded for having UAER outside the 20 to 200 µg/min range. Within participants not withdrawn after baseline, baseline median UAER was 80.2 µg/min, mean serum creatinine was 0.97 mg/dL, mean creatinine clearance was 107.8 mL/min, and mean GFR was 111.8 ml/min/1.73m^2.

Baseline comorbidities.

In the IDNT trial, all participants were required to have hypertension, Mean baseline blood pressure was 159/87 mm Hg. All participants also were required to have diabetes, and mean baseline HbA_{1c} was 8.2 percent. Thirty percent of study subjects had a history of cardiovascular disease.

In the smaller trial, participants with hypertension were excluded and no information on baseline blood pressure was reported. All participants were required to have type 1 diabetes. Baseline HbA_{1c} was not reported, though those with HbA_{1c} 11 percent or greater were excluded. The study did not report any information on the prevalence of cardiovascular disease, though patients with an MI in the prior 3 months were excluded.

Study quality.

Of the two studies, one was rated good quality and one was rated fair quality. The IDNT reported adequate concealment of treatment allocation, while concealment was unclear for the other study. Both trials were double blinded. The IDNT trial performed analyses according to the intention-to-treat principle, but the other study excluded 24 percent of participants after randomization from analyses. Withdrawals ranged from 0.5 percent in the IDNT trial to 32 percent in the other study.

Results.

Mortality (Table 12, Appendix Table C64 and Appendix Figure C14).

All-cause mortality. In the IDNT trial,[94,108] there was a nonsignificant reduction in risk of all-cause mortality (14.6 versus 16.3 percent; RR=0.90 [95 percent CI 0.68 to 1.18]). In the smaller study, only one death occurred, in an individual assigned to the CCB group.[53] In pooled results, risk with CCB treatment was nonsignificantly decreased for all-cause mortality (RR=0.90 [95 percent CI 0.69 to 1.19]).

Cardiovascular mortality. In the IDNT trial,[94,108] there was a nonsignificant reduction in risk of cardiovascular mortality (6.5 versus 8.1 percent; RR 0.81 [95 percent CI 0.53 to 1.22]). In the smaller study, only one cardiovascular death occurred, in an individual assigned to the CCB group.[53] In pooled results, risk with CCB treatment was nonsignificantly decreased for cardiovascular mortality (RR=0.83 [95 percent CI 0.55 to 1.25]).

Vascular outcomes (Table 12, Appendix Tables C64-C66 and Appendix Figure C14).

Myocardial infarction. In the IDNT trial, there was a significant 41 percent reduction in risk of MI in CCB subjects compared to those assigned placebo (4.8 versus 8.1 percent; RR=0.59 [95 percent CI 0.37 to 0.93]). In the smaller study, there was only one MI, which occurred in an individual assigned to the placebo group.

Stroke, In the IDNT trial, participants assigned CCB had a nonsignificant reduction in risk of stroke compared to placebo (2.6 versus 4.6 percent; RR=0.58 [95 percent CI 0.31 to 1.08]).

Other vascular outcomes. In the IDNT trial, in the CCB group compared to the placebo group, there was a nonsignificant increase in risk of CHF (16.4 versus 12.7 percent; RR=1.30 [95 percent CI 0.97 to 1.72]). There was no significant difference between CCB and placebo for either of two composite vascular outcomes. For an outcome that included MI, CHF, neurologic deficit attributed to stroke, or unplanned revascularization, there was a nonsignificant 13 percent reduction in risk in the CCB group (28.4 versus. 32.5 percent; RR=0.87 [95 percent CI 0.73 to 1.04]). For an outcome that included death from cardiovascular causes, nonfatal MI,

hospitalization for CHF, neurologic deficit, or lower limb amputation, there was a nonsignificant 11 percent reduction in risk in the CCB group (22.6 versus 25.3 percent; RR=0.89 [95 percent CI 0.72 to 1.10]).

Renal outcomes (Table 12, Appendix Tables C67 and C68, and Appendix Figure C14).

End-stage renal disease. In results reported only in the IDNT trial, in patients with CKD there was no significant difference between CCB and placebo groups in risk of ESRD (RR=1.03 [95 percent CI 0.81 to 1.32),

Other renal outcomes. In results reported only in the IDNT trial, in patients with CKD there was no significant difference between CCB and placebo groups in risk of doubling of baseline creatinine (RR=1.07 [95 percent CI 0.87 to 1.31), or in the composite renal outcome of doubling of serum creatinine, ESRD, or death (RR=1.05 [95 percent CI 0.91 to 1.21]).[94,108] The smaller of the studies reported a nonsignificant 63 percent reduction in risk of progression from microalbuminuria to macroalbuminuria in the CCB group versus the placebo group (7.7 versus 20.6 percent; RR=0.37 [95 percent CI 0.08 to 1.65]).[53]

Study withdrawals and adverse events (Appendix Table C69).

There were few withdrawals in the larger study, just 0.4 percent of the CCB group and 0.7 percent of the placebo group.[94,108] It was reported that 61 percent of the study participants (including those in an ARB arm) had at least one serious adverse event, but the results were not presented by treatment group. Treatment was discontinued due to adverse events by 9.0 percent of the CCB group and 7.2 percent of the placebo group. Hyperkalemia was reported by 0.5 percent of the CCB group and 0.4 percent of the placebo group. There was one report of an early increase in serum creatinine suggestive of renal artery stenosis, but the group assignment of that patient was not given. In the smaller study, 36.6 percent of the CCB group and 30.6 percent of the placebo group withdrew.[53] Three of the withdrawals from the placebo group were a result of adverse events during the run-in phase; six were from adverse events during the randomized phase.

Summary of results.

In two trials of patients with CKD and diabetes, treatment with CCB as compared to placebo was associated with nonsignificant reductions in risk of all-cause mortality, cardiovascular mortality, MI, stroke, and two different composite vascular outcomes. Risk of congestive heart failure was nonsignificantly higher for patients with CKD. The risk between treatment groups appeared similar for ESRD, doubling of creatinine, and a composite renal outcome, including both of these events as well as death. The rate of withdrawals in the smaller study was high. In both trials, adverse event rates were difficult to interpret due to incomplete reporting. Results were limited in that nearly all were derived from only one trial. The multiple post-randomization exclusions from the smaller trial and its apparent nonsystematic reporting of outcomes lowered our confidence in its reported results. Because the followup of the IDNT trial was 2.6 years, it is not possible to determine from these results the longer term effects of CCB versus placebo in patients with CKD.

Table 12. Pooled clinical and renal outcomes, CCB versus placebo trials

Outcome	Number of Trials Reporting	Quality of the Studies	CCB Events/N (%)	Placebo Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	2	Fair	84/608 (13.8)	93/618 (15.0)	0.90 [0.69-1.19]	0%
Cardiovascular mortality	2	Fair	38/608 (6.3)	46/618 (7.4)	0.83 [0.55-1.25]	0%
Myocardial infarction	2	Fair	27/608 (4.4)	47/618 (7.6)	0.58 [0.37-0.92]	0%
Stroke	1	Good	15/567 (2.6)	26/569 (4.6)	0.58 [0.31-1.08]	NA
Congestive heart failure	1		93/567 (16.4)	72/569 (12.7)	1.30 [0.97-1.72]	NA
Composite vascular*	1	Good	161/567 (28.4)	185/569 (32.5)	0.87 [0.73-1.04]	NA
Lewis (A)[94]			128/567 (22.6)	144/569 (25.3)	0.89 [0.72-1.10]	
Lewis (B)[94]						
End-stage renal disease	1	Good	104/567 (18.3)	101/569 (17.8)	1.03 [0.81-1.32]	NA
Doubling of serum creatinine	1	Good	144/567 (25.4)	135/569 (23.7)	1.07 [0.87-1.31]	NA
Progression to macroalbuminuria	1	Fair	2/26 (7.7)	7/34 (20.6)	0.37 [0.08-0.65]	NA
Composite renal outcome**, Lewis[94]	1	Good	233/567 (41.1)	222/569 (39.0)	1.05 [0.91-1.21]	NA

CCB = calcium channel blocker; RR = relative risk reduction; NA = not applicable
*A = Myocardial infarction, heart failure, permanent neurologic deficit of at least 24-hour duration attributed to stroke, or unplanned (at time of randomization) coronary artery revascularization procedure (all before renal failure, death, or censorship).
*B= Death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle.
**Doubling of baseline serum creatinine concentration, onset of end-stage renal disease (initiation of dialysis, renal transplantation, or serum creatinine concentration ≥ 6.0 mg/dL), or death from any cause

Diuretic Versus Placebo Trial

Overview.

In patients with CKD, we found low strength of evidence that diuretic therapy reduces risk of stroke compared to placebo, and low strength of evidence that there is no difference between treatments in risk of all-cause mortality. We found insufficient evidence regarding whether treatments differ for risk of ESRD.

Description of study.

One trial met all eligibility criteria and randomized CKD patients (n=393) to diuretic versus placebo.[109] Detailed baseline characteristics are presented in Appendix Table C70.

The single eligible study was a subgroup analysis in patients with CKD from within the larger SHEP study (n=4,736), a randomized trial comparing chlorthalidone versus placebo in older patients with hypertension. Mean subject age was 74 years, and men constituted 76 percent of participants. Seventy-six percent of study participants were white, 20 percent were black, and 3 percent were Asian. The study was performed in the United States and followup duration was 5 years.

Renal function.

Participants included in this post hoc analysis were the subgroup from the larger study with a baseline creatinine of 1.35 mg/dL or higher, the level considered to represent the upper threshold of normal in the SHEP trial. Within this subgroup, no measures of baseline renal function were reported.

Baseline comorbidities.

For inclusion in the SHEP trial, participants were required to have isolated systolic hypertension, with a systolic blood pressure of 160 to 219 mm Hg, and a diastolic blood pressure less than 90 mm Hg. Mean baseline blood pressure within patients with CKD was 172/77 mm Hg. A history of myocardial infarction was reported by 5 percent, a history of stroke by 4 percent, and a history of diabetes by 12 percent. Patients were excluded from participation in SHEP for any recent myocardial infarction or stroke or for insulin-treated diabetes.

Study quality.

Study quality was rated as good. Concealment of treatment allocation was adequate and the study was reported to be double blind, though it is not clear whether open-label potassium supplementation for potassium levels <3.5 mmol/L could have compromised blinding. Analysis was performed according to intention-to-treat principles. Study withdrawals were not reported for the CKD subgroup, but were adequately reported for the overall SHEP trial.

Results.

Mortality (Appendix Table C71 and Appendix Figure C15).

The risk of all-cause mortality was nonsignificantly higher in CKD study participants randomized to the diuretic group compared to placebo (17.1 versus 14.7 percent; RR=1.17 [95 percent CI 0.74 to 1.85]).

Vascular outcomes (Appendix Tables C71-C73 and Appendix Figure C15).

Myocardial infarction. The study did not report results for myocardial infarction.

Stroke. In subjects assigned to diuretic, there was a significant 51 percent reduction in the risk of stroke (6.5 versus 12.4 percent; RR=0.49 [0.24 to 0.99]).

Other vascular outcomes. Two composite vascular outcomes were reported (Appendix Table C73), with a significant 37 percent reduction in the risk of any cardiovascular event (16.7 versus 26.6 percent; RR=0.63 [0.43 to 0.93]), and a nonsignificant 38 percent reduction in the risk of fatal or nonfatal coronary heart disease (7.4 versus 11.9 percent; RR 0.62 [95 percent CI 0.34 to 1.16]).

Renal outcomes.

End-stage renal disease. The study did not report on ESRD for the CKD subgroup.

Other renal outcomes. There were two renal deaths in the CKD subgroup, both in participants allocated to diuretic (0.9 percent). No other clinical renal outcomes were reported.

Study withdrawals and adverse events (Appendix Table C74).

Neither study withdrawals nor adverse events data were reported within the CKD subgroup.

Summary.

In this analysis of a subgroup of patients with CKD from a larger trial of older patients with systolic hypertension, diuretic treatment compared to placebo significantly reduced risk of stroke and of one of two composite vascular outcomes. There was no significant difference between treatment groups in all-cause mortality. Results were limited by the small number of patients with CKD, with insufficient statistical power to determine whether large magnitude differences in risk for clinical outcomes were statistically significant. Results also were limited in that this was a post hoc subgroup analysis without confirmation of findings in another study population. Further, results were not reported for several vascular events of interest, including cardiovascular mortality, MI and heart failure, and no clinical renal outcomes were reported.

ACE Inhibitor Versus Non-ACE Inhibitor Antihypertensive Therapy Trial

Overview.

In patients with CKD, we found insufficient evidence that ACEI therapy as compared to non-ACEI antihypertensive therapy is associated with a reduced risk of all-cause mortality, MI, ESRD, or halving of GFR.

Description of study.

We identified one trial that met all eligibility criteria and randomized 131 participants with CKD to ACEI versus non-ACEI hypertension treatment.[110] Detailed baseline characteristics are presented in Appendix Table C75.

Randomized subjects assigned to ACEI were treated with lisinopril or lisinopril in combination with another antihypertensive agent versus a non-ACEI antihypertensive treatment regimen. Prior to randomization, 139 hypertensive patients underwent a run-in period, during which they were to follow a 0.8 g/kg protein and 3-4 g salt intake per day, and non-ACEI antihypertensive agents were used to obtain diastolic blood pressure of 90 mm Hg or less. Only

patients achieving this target on two or fewer drugs, judged compliant, and with stable renal function were eligible to proceed to randomization.

Mean age of randomized study participants was 51 years, and men constituted 66 percent of all subjects. Race/ethnicity of study participants was not reported, though the study was conducted in Italy. Mean followup was 1.9 years.

Renal function.

Participants were required to have creatinine clearance between 20 and 50 ml/min/1.73m^2 and were excluded if they had proteinuria of ≥1 gram/day. Among those enrolled, mean creatinine clearance was 36 ml/min/1.73m^2, mean GFR was 36 ml/min/1.73m^2, mean creatinine was 2.4 mg/dL, and mean proteinuria was 512 mg/day.

Baseline comorbidities.

All study participants had hypertension, with an untreated diastolic blood pressure of ≥95 mm Hg prior to run-in, and a stable treated diastolic blood pressure <90 mm Hg prior to randomization. Patients with malignant hypertension were excluded. Among subjects randomized, mean baseline blood pressure was 142/86 mm Hg. Patients with diabetes, heart failure or another major (undefined) cardiac disease, or a recent history of MI or stroke were excluded from study entry.

Study quality.

Study quality was rated as fair. This study was open-label and concealment of treatment allocation was unclear. Analyses were conducted according to the intention-to-treat principle. No information was reported regarding withdrawals.

Results.

Mortality.

No data were reported on mortality.

Vascular outcomes (Appendix Table C76 and Appendix Figure C16).

Myocardial infarction. The study reported just one myocardial infarction, in a subject assigned to non-ACEI antihypertensive treatment

Stroke. There were no reports of stroke.

Other vascular outcomes. There were no reports of heart failure or any composite vascular outcomes.

Renal outcomes (Appendix Table C77 and Appendix Figure C16).

End-stage renal disease. There was a nonstatistically significant 61 percent reduction in risk of ESRD in those assigned to ACEI treatment as compared to those allocated to non-ACEI treatment (3.0 versus 7.6 percent; RR=0.39 [95 percent CI 0.08 to 1.96].

Other renal outcomes. There was a nonstatistically significant 58 percent reduction in risk of halving of GFR in those assigned to ACEI treatment as compared to those allocated to non-ACEI treatment (4.5 versus 10.6 percent; RR=0.42 [95 percent CI 0.11 to 1.56]). Similarly, There was a nonstatistically significant 59 percent reduction in risk of the composite renal outcome of halving of GFR or need for dialysis in those assigned to ACEI treatment as compared to those allocated to non-ACEI treatment (7.6 versus 18.2 percent; RR=0.41 [95 percent CI 0.15 to

1.10]). However, there were only a small number of events for all these outcomes and none of these differences was clinically significant.

Study withdrawals and adverse events (Appendix Table C79).

No data on study withdrawals were reported. Treatment was discontinued due to adverse events by 6.1 percent of the study participants assigned to the ACEI group and 4.6 percent in the non-ACEI antihypertensive therapy group. There was one incidence of hyperkalemia and one incidence of uncontrolled hypotension in the ACEI group. No hyperkalemia or hypotension events were reported for the non-ACEI antihypertensive therapy group.

Summary of results.

In a single study of patients with hypertension and CKD, antihypertensive treatment with ACEIs in comparison to that without ACEIs was associated with nonsignificant reductions in the risk for MI, ESRD, halving of GFR, and a composite renal outcome including ESRD and GFR. Mortality data and other cardiovascular or renal outcomes were not reported, nor were study withdrawals or serious adverse events. Results were limited by the small sample size, small number of clinical events, and short followup duration.

CCB Versus BB Trials (n=3)

Overview.

In patients with CKD, we found low strength of evidence that treatment with CCB reduces risk of all-cause mortality compared to BB, and low strength of evidence regarding whether there is a difference between treatments in risk of ESRD. We found insufficient evidence regarding whether there are treatment differences in risk of MI, stroke, or doubling of serum creatinine.

Description of studies.

Three trials met all eligibility criteria and randomized participants with CKD (n=12,766, range 34 to 12,074) to CCB versus BB.[86,87,111,112] Detailed baseline characteristics of patients enrolled in the three trials are presented in Appendix Tables C80 and C81.

Among eligible trials, most data were derived from a subgroup analysis reported in a subset of 12,074 patients with undefined "renal dysfunction" from the larger ASCOT-BPLA trial (n=19,257).[112] In this study, participants were randomized to amlodipine versus atenolol. As needed to meet blood pressure targets (<140/90 mm Hg for patients without diabetes and <130/90 mm Hg for patients with diabetes), participants randomized to amlodipine could have had an ACEI added and subjects randomized to atenolol could have had a diuretic added. In the AASK trial, designed as a 3x2 factorial study, besides randomizing 658 participants to amlodipine versus metoprolol, an additional 436 were randomized to an ACEI, and all participants also were randomized to one of two blood pressure target groups as described elsewhere in this report.[86,87] In this trial, the amlodipine treatment arm was stopped early by recommendation of the data and safety monitoring board with patients switched to open label medication. Results presented here compare outcomes including followup until the time blinded amlodipine was discontinued. In the smallest trial,[111] 34 participants were randomized to one of two CCBs (verapamil or diltiazem) versus atenolol. This study also included an additional ACEI treatment arm that is reviewed elsewhere in this report.

The mean age of study participants across all three trials was 55 years (range 55 to 62) and men constituted 60 percent (range 44 to 61, n=2 trials) of all subjects studied. In the two trials that reported race/ethnicity,[86,87,111] 98 percent of participants were African American, including 100 percent of subjects in the AASK trial.[86,87] Two studies were conducted in the United States, and the large subgroup analysis was conducted in Europe. Median study duration ranged from 3 to 5.5 years.

Renal function.

Among eligible trials, one required that participants have impaired GFR (20 to 65 ml/min/1.73m^2)[86,87] and reported a mean baseline GFR of 46 ml/min/1.73m^2, a mean creatinine of 2.0 mg/dL, and mean proteinuria of 0.5 g/day. A second trial required that participants have both impaired creatinine clearance (<70 ml/min) and at least 2 g/day proteinuria, and reported a mean baseline creatinine clearance of 61 ml/min/1.73m^2, a mean creatinine of 1.9 mg/dL, and mean proteinuria of 4.4 g/day.[111] The third study reported no information on the baseline renal function in its "renal dysfunction" subgroup.

Baseline comorbidities.

In all three studies, all participants were required to be hypertensive. In two trials reporting, mean baseline blood pressure was 150/95 mm Hg.[86,87,111] Patients with heart failure were excluded from all three trials, and patients with a history of MI[112] or of any documented coronary artery disease[111] were excluded in two trials. While one trial required that participants be diabetic,[111] a second trial excluded diabetic patients,[86,87] and the third study reported no information on participants' diabetes status.[112]

Study quality.

Study quality was rated good for two trials and fair for one trial. Two of the trials reported adequate treatment allocation concealment.[86,87,112] One study was open-label,[112] a second study was double blind with respect to medication assignment but not to blood pressure target.[86,87] Both reported that endpoint adjudicators were blinded to treatment allocation. The third study provided no information with respect to blinding.[111] Two of the three studies performed analyses according to the intention-to-treat principle. Withdrawals ranged from 0 to 11.5 percent between studies.

Results.

Mortality (Table 13, Appendix Table C82, and Appendix Figure C17).

All-cause mortality. In two trials of CKD patients reporting mortality data, those randomized to CCB versus BB had a nonsignificant 38 percent reduction in risk of all-cause mortality (6.0 versus 9.2 percent; RR=0.62 [95 percent CI, 0.31 to 1.22]; n=692 patients).[86,87,111]

Cardiovascular mortality. One study reported cardiovascular deaths per patient year of followup (CCB 0.9 percent, BB 0.8 percent) but did not report the number and percentage of participants with this outcome by treatment group.[86,87] A second study reported cardiovascular deaths (9.6 percent) but did not report these outcomes by treatment group.[111]

Vascular outcomes (Table 13, Appendix Tables C82-C84, and Appendix Figure C17).

Myocardial infarction. One study reported fatal MI (7.7 percent), but did not report these outcomes by treatment group.[111]

Stroke. One study reported fatal strokes (1.9 percent), but did not report these outcomes by treatment group.[111]

Other vascular outcomes. No trials reported results for heart failure. Two trials reported results for a composite vascular endpoint. One reported that there was no significant difference in the rate of cardiovascular events (cardiovascular mortality or first cardiovascular hospitalization) per patient year (1.7 versus 2.9) between CCB and BB patients, but did not report the number of study participants with these events overall or by treatment group.[86,87] In the second study, though the main ASCOT-LLP study had defined six different composite vascular endpoints, results for the "renal dysfunction" subgroup were only reported for one, defined as cardiovascular mortality, nonfatal MI (symptomatic and silent), unstable angina, chronic stable angina, life threatening arrhythmias, silent nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures, or retinal vascular thromboses.[112] Patients assigned to CCB were significantly less likely to experience this composite outcome than those assigned to BB (14.0 versus 16.0 percent; RR=0.87 [0.80 to 0.95]; n=12,074 patients).

Renal outcomes (Table 13, Appendix Table C85, and Appendix Figure C17).

End-stage renal disease. In one trial of patients with CKD, 9.6 percent of patients were reported to have started dialysis during the trial, but results were not reported by treatment group.[111] In a second trial, there was no significant difference in risk of ESRD between subjects randomized to CCB versus BB (16.6 versus 16.6 percent; RR=1.00 [95 percent CI, 0.70 to 1.44]).[86,87]

Other renal outcomes. In one trial, there was no significant difference between treatment groups for the composite renal outcome of ESRD, death, or at least 50 percent decline in GFR (27.2 versus 26.5 percent; RR=1.02 [95 percent CI, 0.78 to 1.34]). Similarly, there was no significant difference between treatment groups for a composite outcome of ESRD or death (22.5 versus 25.2 percent, RR=0.90 [95 percent CI, 0.67 to 1.20]).[86,87] Doubling of serum creatinine, reported in one small study, was less frequent in the CCB group (11.1 percent versus 31.3 percent; $p<0.05$), a nonsignificant 64 percent reduction in risk (RR=0.36 [95 percent CI 0.08 to 1.59]).[111]

Study withdrawals and adverse events (Appendix Table C86).

One study reported a withdrawal rate of 11.5 percent (six patients), but no withdrawal data were reported by treatment group.[111] Another study reported no withdrawals but noted that 23 patients in the CCB group and 30 in the BB group were no longer active study participants at the end of the study.[87] In the one study reporting withdrawals as a result of serious adverse events, there were no events in either group.[111] Specific adverse events were reported in two studies. In one study, impotence (16.7 percent versus 56.3 percent), insomnia (5.6 percent versus 37.5 percent), lethargy (0 percent versus 81.3 percent), exercise intolerance (0 percent versus 43.8 percent), and dry mouth (5.6 percent versus 81.0 percent) were less frequent in the CCB group than the BB group.[111] The second study reported percentage of patients experiencing the adverse event per patient year of followup. The results were similar for the two groups (hyperkalemia, CCB 0 versus BB 0.2 percent; angioedema, CCB 2.3 versus BB 2.7 percent; shortness of breath, CCB 44.4 versus BB 45.8 percent; syncope, CCB 2.3 versus BB 6.3 percent; dizziness, CCB 46.7 versus BB 47.8 percent; lightheadedness, CCB 48.1 versus BB 47.8 percent; edema, CCB 59.8 versus BB 51.0 percent; cough, CCB 46.3 versus BB 41.5 percent; and sexual dysfunction, CCB 25.7 versus BB 25.2 percent).[87]

Summary.

In patients with CKD and hypertension, there was a nonsignificant 38 percent reduction in all-cause mortality with CCB compared to BB treatment. One of two trials reported a significant reduction in a composite vascular outcome, but this was the only one of six composite vascular endpoints collected in this trial that was reported for patients with renal dysfunction, raising uncertainty regarding whether this risk reduction is a consistent finding within this study. There was no significant difference between CCB and BB treatment groups in risk of ESRD or in risk of the composite renal outcome of ESRD, death, or greater than 50 percent decline in GFR. Both the composite outcome of ESRD or death and the risk of doubling creatinine appeared less likely in patients randomized to CCB, though results were not statistically significant. Results were limited in that most outcomes were not reported by treatment group in more than one study, and by the uncertainty regarding whether the patients in the ASCOT-BPLA study with "renal dysfunction" meet criteria for CKD.

Table 13. Pooled clinical and renal outcomes, CCB versus BB trials

Outcome	Number of Trials Reporting	Quality of the Studies	CCB Events/N (%)	BB Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	2	Fair	14/235 (6.0)	42/457 (9.2)	0.62 [0.31-1.22]	6%
Composite vascular outcome*, Dahlof, 2005[112]	1	Good	825/5893 (14.0)	989/6181 (16.0)	0.87 [0.80-0.95]	NA
End-stage renal disease	1	Good	36/217 (16.6)	73/441 (16.6)	1.00 [0.70-1.44]	NA
Doubling of serum creatinine	1	Fair	1/18 (5.6)	5/16 (31.3)	0.18 [0.02-1.37]	NA
Composite renal outcome**, AASK, Wright, 2002[87]	1	Good	59/217 (27.2)	117/441 (26.5)	1.02 [0.78-1.34]	NA

CCB = calcium channel blocker; BB = beta blocker; RR = relative risk reduction; NA = not applicable
* Cardiovascular mortality, non-fatal MI (symptomatic and silent), unstable angina, chronic stable angina, life threatening arrhythmias, silent non-fatal heart failure, non-fatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thromboses
**GFR event (reduction in GFR by 50% or by 25 ml/min/1.73m^2 from baseline mean), ESRD (dialysis or transplantation), or death

CCB Monotherapy Versus Diuretic Trial

Overview.

In patients with CKD, there was insufficient evidence regarding whether there is a difference between CCB and diuretic treatment for risk of all-cause mortality or ESRD. There was a low strength of evidence that there is no between-treatment difference in risk of stroke or heart failure. Our confidence in these estimates is limited because they are based entirely on results reported from a post hoc analysis from a single large trial.

Description of Study.

One study met all eligibility criteria and randomized 4,129 participants to CCB monotherapy versus diuretic monotherapy.[78-80] Detailed baseline characteristics are presented in Appendix Tables C87 and C88. The eligible study was a post-hoc analysis performed within a subset of participants with CKD from the ALLHAT trial, a study of 23,261 subjects that was not originally limited to individuals with CKD, contained two additional antihypertensive treatment arms and, as part of a factorial design, also randomized participants to pravastatin versus control.

The CCB and diuretic utilized in this trial were amlodipine and chlorthalidone, respectively. The mean age among the 4,129 study participants assigned to CCB versus diuretic was 71 years, and men constituted 47 percent all study subjects. The most common race/ethnicity of trial participants was white non-Hispanic (57 percent), black (25 percent), and Hispanic (12 percent). The ALLHAT trial was performed primarily in the United States. The study duration was 4.9 years.

Renal function.

Patients with a baseline creatinine level >2 mg/dL were excluded from the main ALLHAT trial. Inclusion in the post-hoc analysis was limited to ALLHAT participants with a GFR <60 ml/min/ 1.73m^2. Within subjects in the CKD subgroup, mean baseline GFR was 50 ml/min/1.73m^2. No baseline data on albuminuria was reported.

Baseline comorbidities.

Enrollment was limited to patients with hypertension, with the mean blood pressure at baseline 147/83 mm Hg. Thirty-four percent of participants reported diabetes at baseline, 60 percent reported cardiovascular disease, and 30 percent reported coronary artery disease.

Study quality.

Study quality was rated as good. Allocation concealment was adequate. The trial was double blinded and analysis by the intention-to-treat principle was reported. No data regarding withdrawals was reported.

Results.

Mortality.

Neither all-cause mortality nor cardiovascular mortality data were reported.

Vascular outcomes (Appendix Tables C89 and C90 and Appendix Figure C18).

Myocardial infarction. No data were reported for risk of MI as an isolated outcome.

Stroke. In patients with CKD, there was no significant difference between those assigned CCB versus diuretic treatment for risk of stroke (6.6 versus 6.0 percent; RR=1.10 [95 percent CI, 0.86 to 1.40]). Among patients with diabetes, there was no statistically significant difference between treatment groups for risk of stroke

Other vascular outcomes. Similarly, in this CKD subgroup, there was no significant difference between those assigned CCB versus diuretic treatment for CHF (11.5 versus 9.9 percent; RR=1.16 [95 percent CI, 0.97 to 1.39]). There also was no significant between-treatment difference for the composite vascular outcome of nonfatal MI or coronary heart disease death (RR=1.05 [95 percent CI, 0.89 to 1.24]), or for the composite vascular outcome that included death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, or peripheral arterial disease requiring hospitalization or outpatient revascularization (RR=1.06 [95 percent CI, 0.98 to 1.16]).

The ALLHAT trial reported additional results for CKD patients with diabetes. In this subgroup, risk of CHF was significantly greater in patients randomized to CCB treatment compared to diuretic treatment (RR=1.46 [95 percent CI, 1.12, 1.89]; n=1,387). There was no statistically significant difference between treatment groups for risk of the composite cardiovascular endpoint of nonfatal MI or coronary heart disease death. For the more comprehensive composite cardiovascular endpoint described above, risk of occurrence was significantly greater in patients randomized to CCB treatment compared to diuretic treatment (RR=1.20 [95 percent CI, 1.05, 1.36]; n=1,387).

Renal outcomes (Appendix Tables C91 and C92 and Appendix Figure C18).

End-stage renal disease. In CKD patients, CCB and diuretic treatments were comparable in CKD patients regarding the risk of ESRD, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis (RR=0.90 [95 percent CI 0.67 to 1.21]). Results were similar in diabetics with CKD.

Other renal outcomes. In CKD patients, there was no statistically significant difference between CCB and diuretic treatment groups in risk of the composite renal outcome defined by ESRD or ≥50 percent decline in GFR (6 versus 7 percent, RR=0.86 [95 percent CI, 0.67 to 1.10]). Results were similar in diabetics with CKD.

Study withdrawals and adverse events.

No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.

Summary.

Within the one eligible trial of patients with CKD, there was no apparent difference between the CCB and diuretic monotherapy treatment groups in risk of stroke, ESRD, or other composite clinical vascular or renal outcomes. Results were limited in that the study was a post hoc subgroup analysis. The ALLHAT study also did not report results for risk of mortality or risk of MI in the subgroup of CKD patients. In addition, mean followup did not extend beyond 5 years, so longer term effects of CCB monotherapy versus diuretic monotherapy cannot be determined from these data.

Strict Versus Standard Blood Pressure Target Treatment Trials (n=6)

Overview.

In patients with CKD, we found a low strength of evidence regarding whether antihypertensive treatment targeting stricter blood pressure targets reduces risk of all-cause and cardiovascular mortality compared to treatment targeting standard blood pressure control targets. We found a low strength of evidence regarding whether there was a difference between treatments for risk of ESRD. We found insufficient evidence regarding whether there was a difference between treatments for the outcomes of fatal MI or fatal stroke.

Description of studies.

Six trials met all eligibility criteria and randomized participants with CKD (n=2,520, range 77 to 1,094) to treatment aimed to reach different target blood pressures, i.e. "strict" versus "standard" blood pressure targets.[87,113-118] One study was not limited to individuals with CKD but presented subgroup results for the approximately 3 percent of participants whose baseline creatinine was >1.7 mg/dL.[117] Detailed baseline characteristics are presented in Appendix Tables C93 and C94.

In general, studies established blood pressure targets for their strict control group about 10-15 mm Hg lower than for their standard control group, though there was variability between trials in the absolute blood pressure targets selected. The most common treatment target, used in three trials, was a mean arterial blood pressure (MAP) of ≤92 mm Hg versus a MAP of 100 to 107.[87,114,116] Two trials set diastolic blood pressure (DBP) targets, <90 mm Hg for the strict target versus >90 mm Hg for the standard target in one trial,[117] and 65 to 80 mm Hg for the strict target versus 85 to 95 mm Hg for the standard target in the second trial.[115] The most recent trial compared treatment to achieve blood pressure <130/80 mm Hg versus a DBP target of <90 mm Hg.[113] The specific antihypertensive agents utilized to achieve these blood pressure targets varied between trials. The oldest trial, published in 1989,[117] used diuretics, adrenergic receptor blockers, and vasodilators, while all three trials published in the 1990s used ACEIs with or without diuretics as first-line treatment.[114-116] A trial published in 2002, structured as a 3 x 2 factorial design, assigned participants to initial treatment with either an ACEI, beta blocker or calcium channel blocker.[87] Finally, the most recent trial, published in 2005,[113] titrated all participants with an ACEI prior to randomization and then used a long-acting CCB to compare strict versus standard blood pressure control.

The mean age of study subjects was 53 years (range of study means 37 to 56; n=5 trials), and men constituted 63 percent (range 47 to 75; n=6 trials) of all patients evaluated. Among five trials reporting race/ethnicity, three were predominately[115,117] or entirely[87] comprised of blacks/African Americans. In two other trials, more than 85 percent of participants were white.[114,116] All trials were conducted in the United States, except for one performed in Italy.[113] Mean or median study duration ranged from 19 months to 5 years, with all but one trial having a followup duration of at least 2 years.

Renal function.

Among the six trials, two required that participants have proteinuria to be included,[113,114] while three based eligibility on the presence of impaired GFR or elevation in serum creatinine.[87,115,116] With the exception of one trial,[117] the subgroup analysis that was restricted to participants with baseline creatinine >1.7 mg/dL, measures of baseline renal function were

reported in all studies. Mean GFR was 43 ml/min/1.73m^2 (range 35 to 63), mean serum creatinine was 2.0 mg/dL (range 1.3 to 2.7), and mean proteinuria was 1.0 gm/day (range 0.36 to 2.85). Creatinine clearance, reported in only two trials, averaged 46.2 ml/min/1.73m^2.[113,116]

Baseline comorbidities.

In five trials reporting data, approximately 95 percent of study participants had a history of hypertension. In the sixth trial, though information on history of hypertension was not reported, approximately two-thirds of subjects were receiving blood pressure lowering drugs at baseline.[113] Mean blood pressures at baseline were 142/89 mm Hg (MAP 106 mm Hg). Overall, few study participants had diabetes, though among individual trials one included only patients with type 1 diabetes,[114] two excluded all diabetic patients,[87,115] one had about 15 percent diabetic patients[117] and two studies provided no information regarding whether participants had a history of diabetes.[113,116] While only one trial reported baseline prevalence of cardiovascular disease, at 36 percent,[115] several reported exclusions of such participants, including exclusion of all subjects with recent MI or stroke,[113,115] exclusion of all participants with a history of any past MI or stroke,[114] and exclusion of any participants with clinical or overt heart failure.[87,113] One further trial documented enrollment of individuals with cardiovascular disease, but did not report baseline prevalence.[117]

Study quality.

Among the six trials, study quality was rated as good in one trial and as fair in five trials. Allocation concealment was adequate in three trials and unclear in the remaining studies. Three trials were not blinded,[87,113,117] one was double blinded,[115] and blinding was unclear for two trials.[114,116] For the outcomes presented here, four of six trials analyzed results according to the intention-to-treat principal.[87,114-116] Three trials adequately described reasons for study withdrawal.[87,113,116] Percentages of study withdrawals ranged from 0 to 16 percent (n=4 trials).

Results

Mortality (Table 14, Appendix Table C95, and Appendix Figure C19).

All-cause mortality. Compared to standard blood pressure control, there was no significant reduction in risk of all-cause mortality with strict blood pressure control (RR 0.86 [95 percent CI, 0.68 to 1.09]; n=4 trials, 1,803 patients). These results were driven almost entirely by two trials that, though they each reported a 12 to 15 percent relative reduction in mortality with strict compared to standard blood pressure control, differed markedly in other respects. In the trial by Shulman, 35 percent of participants assigned strict blood pressure control versus 41 percent assigned standard control died during a 5 year followup period, compared to 6.9 percent versus 7.8 percent, respectively, in an approximately 4 year followup period, in the trial by Wright.[87,117] Other differences between these trials included the substantially higher baseline blood pressure, most of which had been untreated, among participants in the Shulman trial,[117] and lower blood pressure targets for both treatment groups, and use of ACEIs and BB only in the trial by Wright.[87]

Cardiovascular mortality. Compared to standard blood pressure control, there was no significant reduction in risk of cardiovascular mortality with strict blood pressure control (RR 0.83 [95 percent CI, 0.54 to 1.26]). Nearly all the weight contributing to this pooled estimate was derived from one trial, in which 20.1 percent versus 23.9 percent of participants experienced a

cardiovascular death (RR 0.84 [95 percent CI, 0.55 to 1.29]),[117] while fewer than 1 percent of participants died due to cardiovascular causes in the only other trial reporting this outcome.[113]

Vascular outcomes (Table 14, Appendix Tables C95-C97, and Appendix Figure C19).

Myocardial infarction. Incidence of fatal MI was reported in few trials and among these trials occurred in less than 5 percent of participants in all treatment groups. Based on these very limited data, there was no significant difference in risk of fatal MI (RR 1.01 [95 percent CI, 0.06 to 15.95]; n=1 trial, 335 patients) between the strict and standard blood pressure control groups. However, the 95 percent CI estimating risk for this outcome is wide and cannot exclude either a clinically important benefit or harm.

Stroke. Similar findings were reported for stroke. As with MI, there was no evidence of reduced risk of fatal stroke (RR 1.09 [95 percent CI, 0.34 to 3.47]; n=2 trials, 632 patients) between the strict and standard blood pressure control groups. Again, the 95 percent CI estimating risk is wide and cannot exclude either a clinically important benefit or harm.

Other vascular outcomes. Only one trial reported a composite vascular endpoint, in this case, a composite of cardiovascular mortality and first cardiovascular hospitalization. Incidence appeared similar between participants assigned to strict versus standard blood pressure control (2.3 percent versus 2.7 percent per patient year, respectively).

Renal outcomes (Table 14, Appendix Tables C98 and C99, and Appendix Figure C19).

End-stage renal disease. Though five trials reported outcomes for ESRD, results were reported separately by treatment group in only three trials. Among these trials, there was no significant reduction in risk for ESRD between strict and standard blood pressure control (16.8 percent versus 16.6 percent; RR 1.03 [95 percent CI, 0.77 to 1.38], n=3 trials, 1,506 patients).

Other renal outcomes. No trials comparing strict versus standard blood pressure targets reported results separately by treatment group for the individual outcomes of doubling of serum creatinine, halving of GFR, or progression from microalbuminuria to macroalbuminuria. Assignment to a strict blood pressure target group did not appear to decrease risk of experiencing any of several study-defined composite renal outcomes (Appendix Table C99), including ESRD, or death (RR 0.91 [95 percent CI, 0.73 to 1.13]);[87] halving of GFR, ESRD, or death (RR 1.06 [95 percent CI, 0.89 to 1.27]);[87] or 50 percent decline in GFR, doubled serum creatinine, ESRD, or death (RR 1.43 [95 percent CI, 0.63 to 3.23]).[115]

Study withdrawals and adverse events (Appendix Table C100).

Overall study withdrawals, reported in four trials, ranged from 0 to 16 percent, with results appearing similar between treatment groups in two trials reporting these data. In the only trial to report serious adverse events and withdrawals due to serious adverse events, incidence of these outcomes appeared possibly more frequent in the strict blood pressure control group.[113] Specific adverse events also were infrequently reported, with cough[87] and postural hypotension[114] each being significantly more frequent in the strict blood pressure target group compared to the standard blood pressure target group in one trial.

Summary of results.

In individuals with CKD, compared with targeting standard blood pressure control, assignment to targeting strict control was associated with 14 percent and 17 percent relative reductions in risk of all-cause mortality and cardiovascular mortality, respectively, which were

not statistically significant. There were no significant differences between treatment groups for the outcomes of MI, stroke, ESRD, or, in individual trials, for several composite renal outcomes. Findings for the mortality and ESRD outcomes were driven mostly by a single trial conducted more than 20 years ago that may have limited generalizability to current patient populations and available antihypertensive treatment options. Results for MI and stroke in particular were limited by small sample sizes and could not exclude either clinically meaningful benefits or harms. Overall results were further limited by heterogeneity in patient populations (i.e., baseline level of renal function, comorbidities), and heterogeneity in blood pressure targets. Reporting on study withdrawals and adverse effects was limited. Finally, no trial provided followup beyond 5 years; therefore, longer term effects of different blood pressure targets cannot be determined from these studies.

Table 14. Pooled clinical and renal outcomes, strict versus standard blood pressure target treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	Strict BP Events/N (%)	Usual BP Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	4	Fair	96/908 (10.6)	103/895 (11.5)	0.86 [0.68-1.09]	0%
Cardiovascular mortality	2	Fair	33/326 (10.1)	35/306 (11.4)	0.83 [0.54-1.26]	0%
Fatal MI	1	Fair	1/167 (0.6)	1/168 (0.6)	1.01 [0.06-15.95]	NA
Stroke, fatal	2	Fair	6/326 (1.8)	5/306 (1.6)	1.09 [0.34-3.47]	0%
End-stage renal disease	3	Fair	126/749 (16.8)	126/757 (16.6)	1.03 [0.77-1.38]	22%
Composite renal outcome*, Wright A[87]	1	Good	173/540 (32.0)	167/554 (30.1)	1.06 [0.89-1.27]	NA
Composite renal outcome*, Wright B[87]	1	Good	118/540 (21.9)	133/554 (24.0)	0.91 [0.73-1.13]	NA
Composite renal outcome**, Toto A[115]	1	Fair	12/42 (28.6)	7/35 (20.0)	1.43 [0.63-3.23]	NA
Composite renal outcome**, Toto B[115]	1	Fair	4/42 (9.5)	5/35 (14.3)	0.67 [0.19-2.29]	NA

BP = blood pressure; RR = relative risk reduction; MI = myocardial infarction; NA = not applicable
* (A) 50% or 25 mL/min reduction in GFR, ESRD (dialysis or transplantation), or death; (B) ESRD or death; ** (A) 50% decline in GFR, doubled serum creatinine, ESRD, or death; (B) 50% decline in GFR or doubled serum creatinine.

Low Protein Diet Versus Usual Protein Diet Trials (n=6)

Overview.

In patients with CKD, we found a low level of evidence that compared to usual protein diets, those with low protein reduce risk of all-cause mortality, or increase risk of ESRD. We also found a low level of evidence regarding whether these treatments differ regarding risk of doubling creatinine or halving GFR. We found insufficient evidence regarding whether these treatments differ regarding risk of fatal MI or fatal stroke.

Description of studies.

Six trials met all eligibility criteria and randomized 1,480 (range 63 to 585) participants with CKD to a low protein diet (typically 0.6 or 0.8 g protein per kg of ideal/lean body weight per day) versus a usual diet (typical protein intake less than 1.3 g/kg/day).[116,118-126] Detailed baseline characteristics are presented in Appendix Tables C101 and C102.

Mean participant age was 52 years (range 49 to 58; n=5 trials), and men constituted 59 percent (range 54 to 83; n=5 trials) of all study participants. In the one trial reporting ethnicity, 85 percent of participants were white. One study was conducted in the United States.[116,118,121,122] Of the remaining studies, two were conducted in Italy[123,124] and one each was conducted in Japan,[119] France,[120] and the United Kingdom.[125,126] Followup periods ranged from 2 to 3.5 years.

Renal function.

Two of the six eligible trials required that participants have albuminuria, with some limitation in the severity of their renal function. In one of these studies, all subjects had to have macroalbuminuria (UAER >200 µg/min) or proteinuria (urine protein excretion rate, i.e. urine protein excretion rate (UPER), >1 g/day) and serum creatinine <2.0 mg/dl.[119] In the second study, patients were required to have UAER >30 mg/day (i.e., at least microalbuminuria) and GFR of at least 15 ml/min (i.e. CKD stages 1-4).[120] The remaining four trials required that participants have either an elevated serum creatinine or a reduced GFR or creatinine clearance, and three also imposed limits on UPER. Thresholds for eligibility in these trials included creatinine 1.2 to 7.0 mg/dl in women and 1.4 to 7.0 mg/dl in men, with UPER less than 10 g/day;[122] creatinine 1.35 to 7.0 mg/dl in women and 1.5 to 7.0 mg/dl in men, with GFR <60 ml/min, and UPER <3 g/day;[124] creatinine clearance 15 to 70 ml/min and UPER <3 g/day;[123] and GFR 10 to 60 ml/min[125,126] Among all six eligible trials, baseline mean UPER ranged from 0.28 g/day/1.73m^2 to 1.5 g/day (n=3 trials), mean UAER was reported in only one trial (366 mg/day), mean serum creatinine was 1.7 mg/dl (range 1.1 to 1.9, n=3 trials), and mean GFR was 45 ml/min/1.73m^2 (range 39 to 86, n=3 trials).

Baseline comorbidities.

Two trials enrolled only patients with diabetes,[119,120] two trials excluded patients with diabetes,[123,124] and two trials did not report baseline prevalence of diabetes[122,125,126] Among two trials reporting,[119,122] mean blood pressure was 132/80 mm Hg. One trial excluded all patients with CHF,[119] another trial excluded patients with either class III or IV CHF,[122] and two trials excluded participants with a recent MI[119,124] or stroke.[119] However, no additional information on baseline cardiovascular morbidity was reported in any trial.

Study quality.

Study quality was rated as fair in all six trials. Allocation concealment was adequate in three studies and unclear in three studies. One trial reported that measures of GFR were blinded,[122] but the other trials were not reported as blinded. Five trials did not perform analyses using intention-to-treat principles, and it was unclear in one study.[122] Withdrawals were adequately described in all but two studies.[123,125,126] Study withdrawals ranged from 2 to 25 percent.

Results.

Mortality (Table 15, Appendix Table C103, and Appendix Figure C20).

All-cause mortality. In the CKD patients studied in eligible trials, low protein diets were associated with a nonsignificant 42 percent reduction in risk of all-cause mortality compared to usual protein diets (1.9 versus 3.3 percent; RR=0.58 [95 percent CI, 0.29 to 1.16]; n=4 trials).[119,122,124,126] All individual trials suggested a lower mortality risk with low protein diets, but the difference was not statistically significant in any trial.

Cardiovascular mortality. Only one trial reported cardiovascular mortality, in which there were four such events (1.4 percent) in the low protein diet group and five cardiovascular deaths (1.7 percent) in the usual protein diet group.[122]

Vascular outcomes (Table 15, Appendix Tables C103 and C104, and Appendix Figure C20).

Myocardial infarction. One trial reported a single fatal MI (2.0 percent) in the usual protein diet group and none in the low protein diet group.[119]

Stroke. One trial reported two nonfatal strokes (0.7 percent) in the low protein diet group and none in the usual protein diet group.[122]

Other vascular outcomes. No other cardiovascular events were reported in any trial.

Renal outcomes (Table 15, Appendix Table C105, and Appendix Figure C20).

End-stage renal disease. In three trials reporting, none of which had more than 10 cases of ESRD, low protein diets were associated with a nonstatistically significant 62 percent increase in risk of ESRD compared to usual protein diets (7.1 versus 4.1 percent; RR=1.62 [95 percent CI 0.62 to 4.21]; n=302 patients).[119,120,126] One additional trial reported that 12 participants (2.1 percent) developed ESRD, but did not report this result separately for the two treatment groups.[122]

Other renal outcomes. One trial reported no significant difference between low and usual protein diet groups in risk of doubling of plasma creatinine (RR=0.93 [95 percent CI 0.53 to 1.64]),[119] while a second trial reported no significant difference between these groups in risk of halving GFR (RR=0.71 [95 percent CI 0.44 to 1.17]).[123] One trial reported a significant 37 percent lower risk of the composite renal outcome of dialysis or doubling of plasma creatinine concentration in CKD subjects randomized to low protein diet versus usual protein diet (11.7 versus 18.6 percent; RR=0.63 [95 percent CI 0.40 to 0.99]).[124] A second trial reported that 60 patients reached a study stopping point due to "rapidly declining glomerular filtration rate."[122] Though it did not report this result separately for the two treatment groups, it did report that there was no significant difference in this outcome between the two groups. No other clinical renal events were reported in any trial.

Withdrawals and adverse events (Appendix Table C106).

Withdrawals were reported in 10.0 percent of randomized participants (range 1.9 to 27.7, n=6 trials). In the four trials that reported withdrawals by treatment group, withdrawals were 13.5 percent and 15.4 percent in low protein diet subjects and usual protein diet subjects, respectively. No data were reported on serious adverse events or withdrawals due to serious adverse events. One trial reported that 2.0 and 2.1 percent of participants in low protein diet and usual protein diet groups, respectively, stopped the trial due to a "serious medical condition."[122] In the low protein diet group, these conditions were pregnancy (n=1), stroke (n=2), acute renal failure (n=1), diabetes necessitating insulin (n=1), and cancer (n=1). In the usual protein diet group, these conditions were diabetes necessitating insulin (n=3), cardiomyopathy (n=1), cancer (n=1), and severe liver disease (n=1). In the same trial, additional outcomes reported as adverse events in the low protein diet group were weight loss (29 percent), weight gain (25 percent), and hyperkalemia (10 percent). Additional outcomes reported as adverse events in the usual protein diet group were weight loss (18 percent), weight gain (40 percent), and hyperkalemia (17 percent).

Summary.

In six trials conducted in patients with CKD, low protein diets were associated with a nonsignificant 42 percent reduction in all cause mortality compared to usual protein diets. In one trial reporting, the small number of cardiovascular deaths appeared similar in both diet intervention groups. No other vascular outcome was reported in more than two cases in any trial. In three trials reporting, all with fewer than 10 cases of ESRD, low protein diets were associated with a nonsignificant 62 percent increase in risk of ESRD compared to usual protein diets. One trial reported a significant 37 percent lower risk of the composite renal outcome of dialysis or doubling of plasma creatinine concentration in CKD subjects randomized to low protein diet versus usual protein diet. Withdrawals ranged widely between trials but did not appear greater in the low protein diet group in any trial. Results were limited by small sample sizes, few trials reporting clinical vascular or renal outcomes, and almost no events in the trials that reported these outcomes. Judging applicability was limited because of the variability in renal function reported between trials and scant data reported on comorbid conditions. Trials did not systematically report adverse events.

Other Dietary Intervention Trials (n=3)

Overview.

In patients with CKD, we found a low level of evidence that, compared to a low protein diet, the CR-LIPE diet reduced risk of mortality, ESRD, and doubling of serum creatinine. There was a low level of evidence that diets altering phosphate intake impacted risk of ESRD and insufficient evidence regarding whether it impacted risk of mortality. There was insufficient evidence regarding whether a low triglyceride diet and pharmacological treatment to lower triglycerides differ regarding risk of mortality or ESRD.

Description of studies.

Three trials met all eligibility criteria and randomized participants with CKD to a diet intervention versus a control treatment group. Detailed baseline characteristics are presented in Appendix Tables C101 and C102.

Among the three trials, one randomized 191 participants to a carbohydrate restricted, low-iron-available, polyphenol-enriched diet (CR-LIPE) versus a low protein diet.[127] Mean age of study participants was 60 years and 53 percent of study participants were men. The study was conducted in the United States. followup duration was 3.9 years.

A second trial randomized 57 participants to a triglyceride lowering diet versus gemfibrozil, a triglyceride lowering medication.[128] Mean age of study participants was 51 years and 75 percent of study subjects were men. The study was conducted in Sweden. Followup duration was 1 year.

The third trial randomized 98 participants to either a low protein-low phosphate diet, a low phosphate diet with phosphate binders, or an unrestricted diet.[129] Mean age of study participants was 45 years and 66 percent of study subjects were men. The study was conducted in the United Kingdom. followup duration was 1.6 years.

Renal function.

For inclusion in the CR-LIPE versus low protein diet trial, participants were required to have GFR 15 to 75 ml/min and UPER 0.35 to 12 g/day. Baseline renal function was reported as mean GFR 63 ml/min, mean UPER 2.47 g/day, and mean creatinine 1.84 mg/dl.[127] For inclusion in the triglyceride lowering diet versus gemfibrozil trial, participants were required to have a GFR of 10 to 70 ml/min/1.73m^2. Baseline renal function was reported as mean GFR of 35.5 ml/min/1.73m^2, mean serum creatinine of 2.4 mg/dl, and mean UAER of 0.95 g/day.[128] For inclusion in the low protein low phosphate diet, low phosphate diet, or unrestricted diet trial, participants were required to have a serum creatinine between 1.7 and 10.2 mg/dl. At baseline, mean serum creatinine was 4.5 mg/dl, mean UPER was 3.15 g/day, and mean creatinine clearance was 26.8 ml/min/1.73m2.[129]

Baseline comorbidities.

For inclusion in the CR-LIPE versus low protein trial, participants were required to be diabetic.[127] No additional information was reported on comorbid conditions. For inclusion in the triglyceride lowering diet versus gemfibrozil trial, participants were required to be nondiabetic. No additional information was reported on comorbid conditions.[128] For the third trial, no information was reported on comorbid conditions.[129]

Study quality.

All three trials were rated as fair quality. Allocation concealment was adequate in one trial[129] and unclear in the other two studies. One study reported that study personnel were blinded to the aims of the study, but it was unclear if the outcome assessment was blinded.[127] The remaining two studies were unblinded. None of the studies analyzed by the intention-to-treat principle. Withdrawals ranged from 5.3 to 15.8 percent, and reasons for withdrawals were adequately explained in two of the three trials.[127,128]

Results.

Mortality (Table 15, Appendix Table C103, Appendix Figure C20).

In one trial, all-cause mortality was 8.0 percent in CKD subjects randomized to the CR-LIPE diet compared to 15.4 percent in the low-protein diet group.[127] In a second trial, risk of all-cause mortality was not significantly different between treatment groups, at 3.0 percent, 13.3 percent,

and 3.1 percent in the low protein-low phosphate, low phosphate-phosphate binding, and control diet groups.[129] The third trial did not report mortality data.

Vascular outcomes.

Myocardial infarction. No data were reported for MI.

Stroke. No studies reported on stroke.

Other vascular outcomes. No heart failure or composite vascular outcomes were reported.

Renal outcomes (Table 15, Appendix Table C105, and Appendix Figure C20).

End-stage renal disease. In one trial, ESRD occurred in 10.0 percent of CKD subjects allocated to the CR-LIPE diet versus 18.7 percent assigned to the low protein diet group.[127] In a second trial, ESRD occurred in 51.5 percent, 46.7 percent, and 46.9 percent of the low protein-low phosphate diet group, low phosphate-phosphate binding group, and control diet group, respectively.[129] In the trial that compared a low triglyceride diet versus gemfibrozil, progression to ESRD was reported for 3.4 percent and 7.1 percent of these treatment groups, respectively.[128]

Other renal outcomes. In one study, participants randomized to a CR-LIPE diet appeared less likely than those assigned to a low protein diet to experience either a doubling in creatinine (20.9 versus 39.2 percent), or the composite renal outcome of renal replacement therapy or death (19.8 versus 39.2 percent, $p<0.05$).[127]

Withdrawals and adverse events (Appendix Table C106).

In the trial comparing the CR-LIPE diet and low protein diet, withdrawals by treatment group were 9.0 percent and 13.2 percent respectively.[127] In the trial comparing a low triglyceride diet to gemfibrozil, no withdrawals were reported in the diet group compared to 21.4 percent withdrawals in the gemfibrozil group, with all attributed to mild gastrointestinal symptoms.[128] In the third trial, 5.3 percent of the participants withdrew, but no data were reported according to treatment group.[129] No other adverse events data were reported from any trial.

Summary of results.

In one trial, CKD patients randomized to a carbohydrate-restricted, low iron available, polyphenol-enriched diet (CR-LIPE) appeared to have lower all-cause mortality, lower risk of ESRD, and lower risk of the composite endpoint of ESRD or death compared to participants assigned to a low protein diet. In a second trial, study participants allocated to a low phosphate-phosphate binding diet appeared to have a higher risk of all-cause mortality than did patients assigned to either a low protein-low phosphate diet or to a control diet. There was no apparent difference between these three diet groups in risk of ESRD. In the third trial, results suggested that CKD patients randomized to a low triglyceride diet may have a lower risk of ESRD and fewer gastrointestinal side effects than patients assigned to gemfibrozil. Results were limited in that all trials were small, reported few clinical outcomes, and did not conduct their analyses according to an intention-to-treat principle.

Table 15. Pooled clinical and renal outcomes for dietary intervention trials

Outcome	Number of Trials Reporting	Quality of the Studies	Low Protein Diet Events /N (%)	Usual Protein Diet Events/N (%)	RR [95% CI]*	I^2 test for Heterogeneity
Low Protein Diet versus Usual Protein Diet (N=6)						
All-cause mortality	4	Fair	12/642 (1.9)	21/638 (3.3)	0.58 [0.29-1.16]	0%
Cardiovascular death	1	Fair	4/291 (1.4)	5/294 (1.7)	0.81 [0.22-2.98]	NA
Myocardial infarction, fatal	1	Fair	0/47 (0)	1/41 (2.4)	0.29 [0.01-6.97]	NA
Stroke, nonfatal	1	Fair	2/291 (0.7)	0/294 (0)	5.05 [0.24-104.76]	NA
End-stage renal disease	3	Fair	11/154 (7.1)	6/148 (4.1)	1.62 [0.62-4.21]	0%
Doubling of serum creatinine	1	Fair	16/47 (34.0)	15/41 (36.6)	0.93 [0.53-1.64]	NA
Halving of GFR**	1	Fair	18/63 (28.6)	26/65 (40.0)	0.71 [0.44-1.17]	NA
Composite renal outcome†	1	Fair	27/230 (11.7)	42/226 (18.6)	0.63 [0.40-0.99]	NA
Low Protein/Low Phosphate Diet versus Low Phosphate Diet (N=1)						
All-cause mortality	1	Fair	1/31 (3.2)	4/29 (13.8)	0.23 [0.03-1.97]	NA
End-stage renal disease	1	Fair	17/31 (54.8)	14/29 (48.3)	1.14 [0.69-1.86]	NA
Low Protein/Low Phosphate Diet versus Usual Diet (N=1)						
All-cause mortality	1	Fair	1/31 (3.2)	1/29 (3.4)	0.94 [0.06-14.27]	NA
End-stage renal disease	1	Fair	17/31 (54.8)	15/29 (51.7)	1.06 [0.66-1.70]	NA
Low Protein versus Other Diet††						
All-cause mortality	1	Fair	14/79 (17.7)	8/91 (8.8)	2.02 [0.89-4.55]	NA
End-stage renal disease	1	Fair	17/79 (21.5)	10/91 (11.0)	1.96 [0.95-4.03]	NA
Doubling of serum creatinine	1	Fair	31/79 (39.2)	19/91 (20.9)	1.88 [1.16-3.05]	NA
Composite renal outcome§	1	Fair	31/79 (39.2)	18/91 (19.8)	1.98 [1.21-3.26]	NA
Low Triglyceride Diet versus Gemfibrozil (N=1)						
End-stage renal disease	1	Fair	1/29 (3.4)	2/28 (7.1)	0.48 [0.05-5.03]	NA

*RR = relative risk reduction; **GFR = reported as halving of creatinine clearance; NA = not applicable
†Need for dialysis or doubling of baseline plasma creatinine concentration.
††50% carbohydrate restricted, low-iron-available, polyphenol-enriched diet.
§Renal replacement therapy or death.

Glycemic Control Trials (n=2)

Overview.

In diabetic patients with CKD, we found a low strength of evidence that intensive diabetes control reduces risk of conversion from microalbuminuria to macroalbuminuria, and insufficient evidence regarding whether there is a difference between treatments in risk of mortality, MI, stroke, or ESRD.

Description of studies.

Two trials met all eligibility criteria and randomized participants with diabetes and CKD to intensive versus standard glycemic control.[130,131] Detailed baseline characteristics are presented in Appendix Tables C107 and C108.

In the first study, conducted in 70 patients, those assigned intensive diabetes control (treatment targets HbA_{1c} ≤7.5percent, fasting blood glucose 72 to 108 mg/dL, and 2 hour postprandial blood glucose ≤180 mg/dL) were treated using insulin by continuous infusion or multiple daily injections. Frequent visits and medication adjustment were made as needed, and 24 hour/day consultation was available. Participants assigned to conventional therapy (no glycemic targets) generally were treated using two daily insulin injections, adjusted only for symptoms, along with conventional education about diet, exercise, and blood glucose monitoring. Standard control patients were seen every 3 months. No changes were made to the usual diabetic diet of participants in either treatment group, and all patients were treated to keep their blood pressure <160/95 mm Hg.[131] Mean age was 37 years, 73 percent of participants were male, and no data was reported on ethnicity.

In the second study, a subgroup analysis within 491 patients with microalbuminuria from a larger diabetes treatment trial (n=1,791), trial participants allocated to the intensive control group were started on maximal doses of oral therapy, and insulin was added as needed to achieve a target HbA_{1c} <6 percent.[130] Participants assigned to standard control were started on one-half of maximal doses of oral therapy and insulin was added as needed to achieve a target HbA_{1c} <9 percent. No data on age, gender, or ethnicity was reported for the subgroup with microalbuminuria.

Renal function.

Both trials were restricted to participants with microalbuminuria. In one study this was defined as UAER between 30 and 200 μg/min.[131] In the second trial, in which subgroup results were reported for conversion from microalbuminuria to macroalbuminuria, no definition of microalbuminuria was reported. Participants in this second trial further were restricted to those with serum creatinine ≤1.6 mg/dl.[130] Participant mean baseline GFR was 116.7 ml/min/1.73m^2 and mean UAER was 47.9 μg/min.

Baseline comorbidities.

Both trials were restricted to participants with diabetes. The first trial enrolled patients with baseline blood pressure <160/95 mm Hg and no evidence of diabetic macrovascular complications.[131] Participant mean HbA_{1c} was 10.1 percent. The second trial enrolled individuals with type 2 diabetes who had HbA_{1c} >7.5 percent, despite maximal doses of oral agents or on insulin.[130] In this second trial, no baseline characteristics were reported for the subgroup of

participants with microalbuminuria, though overall study excluded patients with a cardiovascular event during the previous 6 months, advanced CHF, or severe angina.

Results.

Mortality (Appendix Table C109).

During median followup durations of about 5 years, neither trial reported results comparing intensive versus standard glycemic control within their CKD population for the outcome of mortality. One trial reported that one CKD patient died (2.7 percent) but did not report the group assignment of the patient.[131]

Vascular outcomes.

Myocardial infarction. Neither trial reported on MI.

Stroke. Neither trial reported stroke outcomes.

Other vascular outcomes. Neither trial reported any composite vascular outcomes.

Renal outcomes (Table 16, Appendix Table C110).

End-stage renal disease. There were no reports of ESRD.

Other renal outcomes. One trial reported that one patient experienced acute renal failure (2.7 percent) but did not report the group assignment of the patient.[131] In data from both trials, compared to conventional treatment, participants allocated to intensive diabetes treatment had a nonsignificant 31 percent relative reduction in risk of conversion from microalbuminuria to macroalbuminuria (8.7 versus 12.8 percent; 0.69 [95 percent CI, 0.42 to 1.12]; n=561 patients). Neither study reported on any other renal outcomes.

Study withdrawals and adverse events (Appendix Table C112).

Only one of the two trials reported study withdrawals,[131] with 13.9 percent versus 8.8 percent in the intensive versus conventional treatment groups, respectively. While it further noted that 4.3 percent (three of 70) of study participants withdrew due to serious adverse events, including one death, one leukemia, and one acute renal failure, it did not report these outcomes by treatment group. In one trial, neither incidence of severe hypoglycemia or diabetic ketoacidosis appeared to differ between CKD patients assigned to the two treatment groups.[130] In the second trial, risk of hypoglycemia was not reported for the CKD subgroup, but in the larger overall study population frequency of hypoglycemic events and frequency of severe hypoglycemic events was significantly greater in the intensive control group ($p<0.001$).[131]

Summary.

In diabetic individuals with CKD, compared with conventional treatment, assignment to intensive diabetes treatment was associated with an approximately 31 percent relative reduction in risk of conversion from microalbuminuria to macroalbuminuria that was not statistically significant. There were no data regarding the relative risk between these treatment strategies for all-cause or cardiovascular mortality, MI, stroke, ESRD, doubling of serum creatinine, halving of GFR, or any composite vascular or renal endpoint. Reporting on withdrawals and adverse effects associated with these treatment regimens in CKD patients was limited. Results were limited by the small number of trials, few outcomes reported, the heterogeneity of patient populations, and the heterogeneity in intensity of treatment regimens.

Table 16. Pooled clinical and renal outcomes, glycemic control trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intensive Treatment Events/N (%)	Conventional Treatment Events/N (%)	Relative Risk [95% CI]	I^2 test for Heterogeneity
Intensive treatment versus conventional treatment trials (n=2)						
Progression from micro- to macroalbuminuria	2	Good	25/287	35/274	0.69 [0.42-1.12]	0%

HMG-CoA Reductase Inhibitors (Statins) Versus Control Trials (n=11)

Overview.

In patients with CKD defined by impaired GFR, in comparison to control treatment, there is a high level of evidence that statins reduce risk of all-cause mortality, but a low level of evidence that they reduce risk of MI, stroke, or CHF hospitalization. There is a low level of evidence that there is no difference between statins and control treatment for risk of ESRD. There is insufficient evidence regarding whether there is a difference between statins and control treatment in CKD patients regarding risk of doubling of serum creatinine, halving of GFR, or progression from microalbuminuria to macroalbuminuria.

Description of studies.

Eleven trials met all eligibility criteria and randomized participants with CKD (n=14,193, range 310 to 2,978) to statin therapy versus control.[60,80,132-140] One study, the CARE trial, was reported both by itself[139] and as part of a pooled subject-level meta-analysis of three trials of pravastatin versus placebo.[140] All but one study[60] were post hoc analyses performed within subsets of participants with CKD from larger trial populations not originally limited to subjects with CKD. Detailed baseline characteristics are presented in Appendix Tables C113 and C114.

Among eligible trials, 9,890 participants were randomized to pravastatin versus control, including 5,355 versus placebo (n=2 trials),[60,140] 2,978 versus diet (n=1 trial),[133] and 1,557 versus usual care (n=1 trial).[80] In addition, 1,635 participants were randomized to rosuvastatin versus placebo (n=1 trial),[137] and 1,549 participants were randomized to atorvastatin versus control, including 970 versus placebo (n=1 trial)[134] and 579 versus usual care (n=1 trial).[135] There also were several smaller studies, in which 505 participants were randomized to simvastatin versus placebo (n=1 trial),[136] 310 participants were randomized to fluvastatin versus placebo (n=1 trial),[138] and 304 participants were randomized to lovastatin versus placebo (n=1 trial).[132] The mean age of subjects was 64 years (range 51 to 71; n=11 trials), and men constituted 58 percent (range 24 to 82; n=11 trials) of all patients randomized. Among the five trials that reported race/ethnicity, 82 percent of participants were white. The majority of trials were multinational.[80,134,136-138,140] Mean or median study duration ranged from 2.7 to 5.4 years, with most trials having a followup of at least 4 years.

Renal function.

All studies except one were post hoc analyses from large statin trials, performed in subsets of participants with decreased GFR or creatinine clearance from the larger trial populations. Most of these analyses defined impaired GFR or creatinine clearance as <60 ml/min/1.73m^2,[80,132-135,140] (i.e., CKD stage 3 or worse) or at least provided data for patients under this threshold.[136] No other trials based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Instead, individual studies defined impairment as GFR <51 ml/min/1.73m^2,[137] and creatinine clearance of <55.9 ml/min[138] and <75 ml/min.[139] In trials reporting, mean baseline serum creatinine was 1.3 mg/dL (range 1.0 to 1.5, n=9 trials), mean GFR was 53 ml/min/1.73m^2 (range 50 to 55; n=9 trials), and mean creatinine clearance was 59 ml/min (range 47 to 61; n=2 trials). Most of the larger trials on which the post hoc analyses were based excluded at least some patients with impaired renal function, with exclusion thresholds ranging from creatinine >1.5 to 1.8 mg/dL,[133,134,138,140] >2.5 mg/dL,[137,139] to >4.5 mg/dL.[140] One trial excluded participants with creatinine clearance less than 60 percent of the age-based normal.[60] Just one trial required

participants to have microalbuminuria for inclusion,[60] and this was also the only trial to report mean baseline urinary albumin excretion (23 mg/24 hrs).

Baseline comorbidities.

One trial was restricted to patients with diabetes,[134] and the mean prevalence of diabetes among 11 trials reporting was 22 percent (range 2 to 100). One trial was restricted to patients with hypertension,[80] while hypertensive patients were excluded from one trial.[60] The mean prevalence of hypertension was 49 percent among nine trials reporting. Mean systolic blood pressure was 136 mm Hg (range 131 to 146; n=10 trials) and mean diastolic blood pressure was 80 mm Hg (range 75 to 84; n=9 trials). Six trials were restricted to patients with coronary artery disease (secondary prevention studies),[135-140] including one restricted to patients with a history of myocardial infarction,[139] while patients with coronary artery disease were excluded from four trials (primary prevention studies).[132-134,140] The mean prevalence of coronary artery disease was 46 percent in 12 trials reporting. One trial was restricted to patients with CHF,[137] while patients with CHF were excluded from one trial.[60] The mean prevalence of CHF in four trials reporting was 39 percent. Mean baseline total cholesterol and low density lipoprotein (LDL) cholesterol were 228 mg/dL (range 200 to 265) and 150 mg/dL (range 120 to 192), respectively (n=11 trials).

Study quality.

Study quality was rated as good in seven trials and as fair in four trials. The method of allocation concealment was adequate in eight trials[80,133-137,139,140] but was unclear in three studies.[80,136,140] Eight trials were double blinded, of which seven explicitly stated that outcomes were adjudicated by blinded assessors.[60,132,134,136-138,140] Three trials were open label studies,[80,133,135] though one stated that outcomes were adjudicated by blinded assessors.[80] Analysis was by intention to treat in ten studies[60,80,132-135,137-140] and not by intention to treat in one study.[136] None of the post hoc analyses reported the number of withdrawals within the subgroup of participants with impaired GFR. Only the trial that enrolled participants on the basis of microalbuminuria reported withdrawals (23 percent).[60]

Results.

Mortality (Table 17, Appendix Table C115, and Appendix Figure C22).

All-Cause Mortality. In CKD patients assigned to statins versus control, there was a significant 15 percent reduction in all-cause mortality (8.7 versus 10.2 percent; RR 0.85 [95 percent CI, 0.76 to 0.96]; n=7 trials, 10,697 patients).[60,133-136,138,140] However, in three trials that limited entry to patients with coronary artery disease, the 11 percent reduced all-cause mortality among patients randomized to statin treatment was not statistically significant (12.8 versus 14.3 percent; RR 0.89 [95 percent CI, 0.68 to 1.15]; n=1,394 patients).[135,136,138] Similarly, in two trials that limited enrollment to patients without coronary artery disease, the 32 percent relative reduction in all-cause mortality was not statistically significant (2.2 versus 3.2 percent; RR 0.68 [95 percent CI, 0.36 to 1.26]; n=2,948 patients).[133,134]

Cardiovascular Mortality. In the four trials reporting data for cardiovascular mortality, there were few events (2.4 versus 3.4 percent for statin and control groups, respectively), with a nonsignificant 29 percent relative risk reduction in this outcome in participants randomized to statin treatment versus control (RR 0.71; [95 percent CI, 0.43 to 1.71]; n=2,057 patients).[60,132,135,138] There also was no significant difference in risk of cardiovascular mortality

between subjects assigned to statin versus control groups in two trials limited to patients with coronary artery disease (4.6 versus 6.6 percent; RR 0.69 [95 percent CI, 0.40 to 1.19]; n=889 patients)[135,138] or in one trial limited to patients without coronary artery disease (0 versus 0.6 percent).[132]

Vascular outcomes (Table 17, Appendix Tables C115-C117, and Appendix Figure C22).

Myocardial infarction. In patients with CKD, assignment to statin treatment versus control was associated with a significant 28 percent reduction in risk of MI (RR 0.72 [95 percent CI, 0.54 to 0.98]; n=2 trials, 2,015 patients).[132,139] In one secondary prevention trial, there was no statistically significant reduction in risk of MI between treatment groups (RR 0.74 [95 percent CI, 0.55 to 1.01]; n=1,911 patients).[139] Similarly, in one primary prevention trial with few events, there was no significant reduction in risk of MI between treatment groups (RR 0.37 [95 percent CI, 0.07 to 1.78]; n=304 patients).[132] Nonfatal MI was reported in just one secondary prevention trial, and there was no significant reduction in risk of this outcome in statin subjects compared to those assigned to control (5.9 versus 9.9 percent; RR 0.60 [95 percent CI, 0.34 to 1.07]).[135]

Stroke. In patients with CKD, assignment to statin treatment versus control did not significantly reduce the risk of stroke (1.7 versus 3.0 percent; RR 0.61 [95 percent CI, 0.37 to 1.02]; n=5 trials, 7,102 patients).[60,133-135,139] Results were similar in two secondary prevention trials (3.5 versus 5.0 percent; RR 0.71 [95 percent CI, 0.48 to 1.05]; n=2,290 patients).[135,139] However, in two primary prevention trials, risk of stroke was significantly lower in statin patients than in those allocated to control (0.7 versus 2.2 percent; RR 0.33 [95 percent CI, 0.18 to 0.60]; n=3,948 patients).[133,134]

Other vascular outcomes. In two trials reporting data, including one with fewer than 0.5 percent clinical events in either treatment group,[60] risk of hospitalization due to CHF in individuals with CKD was not significantly different between those who were randomized to statin treatment versus control (RR 0.71 [95 percent CI, 0.38 to 1.32]; n=1,443 patients).[60,135] Nearly all trials reported multiple composite cardiovascular outcomes. For every composite cardiovascular outcome for every trial, the risk of the composite outcome was numerically lower (RR range 0.42 to 0.99) in study participants with CKD assigned to the statin group versus those allocated to control. This difference was statistically significant in the majority of comparisons. Because the definition of the composite cardiovascular outcomes varied between trials, no pooled risk estimate was calculated

Renal outcomes (Table 17, Appendix Tables C118 and C119, and Appendix Figure C22).

End-stage renal disease. Only one trial reported results for ESRD.[80] In this trial of individuals with CKD with and without coronary artery disease there was no difference in risk of ESRD between study participants with CKD allocated to statin versus control treatment (4.1 versus 4.0 percent; RR 1.05 [95 percent CI, 0.64 to 1.73; n=1,557 patients).

Other renal outcomes. Similarly, this study reported no difference between treatment groups in the risk of experiencing the composite renal outcome of ESRD or ≥50 percent decline in renal function (6.4 versus 6.7 percent, RR 0.97 [95 percent CI, 0.66 to 1.43).[80] No trials comparing statin versus control treatment reported results for other renal outcomes.

Study withdrawals and adverse effects (Appendix Table C120).

One trial provided data on withdrawals within patients with CKD, reporting 20 percent in the statin subjects and 26 percent in the placebo subjects.[60] However, the study included within these

totals, 5 percent and 8 percent in each group withdrawn for "other medical reasons," which in part were comprised of subjects reaching study endpoints (i.e., cardiovascular mortality or hospitalization). A second trial reported no withdrawals among 1,711 subjects in both treatment groups.[139] No other post hoc analyses reported information on withdrawals for CKD patients.

Only four trials reported any data on adverse events within study participants with CKD. All reported incidence of elevated creatine kinase, with two trials reporting only one control patient with creatine kinase exceeding ten times the upper limit of normal,[132,135] one trial reporting 0.7 and 0.3 percent of statin and control subjects, respectively, with creatine kinase levels exceeding three times the upper limit of normal,[139] and one trial reporting that 2.6 percent of participants in both treatment groups had a creatine kinase level greater than 500 IU.[133] In three trials reporting, rhabdomyolysis occurred in zero of 1,275 statin subjects and four of 1,319 (0.3 percent) control group subjects.[132,135,139] Three trials reported incidence of abnormal liver function tests.[133,135,139] In all, the incidence was low, and in two trials that reported results for both statin and control groups,[133,139] there was no difference between these groups.

Summary.

In individuals with CKD, statin treatment, as compared to control, was associated with significant reductions in risk of all-cause mortality (15 percent) and MI (28 percent). Results appear to favor statin in both patients with and without a history of coronary artery disease, though they did not achieve statistical significance. Similarly, results were statistically nonsignificant but in favor of statin versus control for risk of stroke and risk of hospitalization due to congestive heart failure. Risk for most composite vascular outcomes was significantly lower in CKD patients assigned statin treatment. In results available from only one trial, there was no difference between statin and control treatment groups regarding risk of ESRD or a composite outcome of ESRD or GFR decline by at least 50 percent. There were no data reported in any trial for doubling of baseline creatinine, halving baseline GFR, or conversion from microalbuminuria to macroalbuminuria.

While the magnitude of effect sizes favoring statins for many vascular outcomes, if real, seemed large enough to be clinically meaningful, results were limited by small sample sizes, in particular for analyses evaluating results in separate primary and secondary prevention subgroups. Results also were limited because, with one exception, studies were post hoc subgroup analyses from large statin trials that were not originally designed to evaluate CKD patients and renal outcomes. Consequently, there are almost no data on any renal outcome or on any vascular or renal outcome as a function of baseline albuminuria. Because most trials excluded patients with moderate and/or severely impaired renal function, available results may not be generalizable to these populations. Another limitation was that though composite vascular endpoints were reported in nearly all trials, the variability in their definitions prevented statistical pooling. Finally, few studies provided data on withdrawals or adverse events, so there was little information available regarding the relative tolerability and safety of statins versus control treatments in this population.

High Versus Low-Dose HMG-CoA Reductase Inhibitors Trial

Overview.

In patients with CKD, there is a low level of evidence that there is no difference in risk of mortality between treatment with high versus low dose statin. There is a low level of evidence

that high dose statin reduces risk of hospitalization secondary to CHF more than does low dose statin. There is insufficient evidence regarding whether there are differences between high and low dose statin for MI, stroke, ESRD, or any other clinical renal outcomes.

Description of study.

One trial met all eligibility criteria and randomized participants with CKD to high versus low dose HMG-CoA reductase inhibitor treatment.[141] This study was a post hoc analysis in 3,107 individuals with GFR <60 ml/min/1.73m^2 from among the 10,003 enrolled in the TNT trial. Detailed baseline characteristics are presented in Appendix Tables C113 and C114.

Patients were randomized to atorvastatin 10 mg daily versus atorvastatin 80 mg daily. The mean age of participants in this post hoc analysis was 66 years, and men constituted 68 percent of patients. Ninety-five percent of study participants were white. Median followup for this multinational study was five years.

Renal function.

Study participants were required to have GFR <60 ml/min/1.73m^2 (i.e., CKD stage 3 or worse), but did not otherwise report participant distribution by CKD stage. Mean GFR was 53 ml/min/1.73m^2. No other measures of renal function were reported.

Baseline comorbidities.

All participants in the TNT trial had coronary artery disease and hyperlipidemia while off cholesterol medications. Additional comorbid conditions included hypertension (63 percent) and diabetes (18 percent). Mean baseline systolic blood pressure was 133 mm Hg, and mean diastolic blood pressure was 78 mm Hg. After all participants completed an 8 week open-label run-in of atorvastatin 10 mg daily, and only those with LDL cholesterol less than 130 mg/dL were considered for enrollment, mean baseline total cholesterol and LDL cholesterol were 176 mg/dL and 96 mg/dL, respectively.

Study Quality.

Study quality was rated as fair. Concealment of allocation to treatment assignment was unclear. The study was double blinded, and outcome adjudication was performed by a blinded endpoint committee. Only 0.4 percent of CKD participants withdrew from the trial.

Results.

Mortality (Table 17, Appendix Table C115, and Appendix Figure C22).

In participants with CKD, there was no significant difference between low and high dose statin groups regarding risk of all-cause mortality (7.0 versus 7.5 percent; RR 0.93 [95 percent CI, 0.72 to 1.20]).

Vascular outcomes (Table 17, Appendix Tables C115-C117, and Appendix Figure C22).

Myocardial infarction. No results were reported for MI.

Stroke. No results were reported for stroke.

Other vascular outcomes Risk for hospitalization due to CHF (3.1 versus 5.5 percent; RR 0.55 [95 percent CI, 0.39 to 0.77]) and for all of the five defined composite vascular outcomes was significantly lower in CKD patients assigned to high dose statin as compared to low dose statin.

Renal outcomes.

End-stage renal disease. No results were reported for ESRD.

Other renal outcomes. No results were reported for doubling of serum creatinine, halving of GFR, progression from microalbuminuria to macroalbuminuria, or for any composite renal outcome.

Withdrawals and adverse effects (Appendix Table C120).

Less than 0.5 percent of participants with CKD withdrew from the study in both high and low dose statin groups. Treatment related adverse effects (8.7 versus 5.2 percent) and treatment discontinuations attributed to adverse effects (4.2 versus 1.9 percent) both were more common in study participants assigned high dose statins. Liver function abnormalities occurred in 1.4 versus 0.1 percent of patients on high versus low dose statin, respectively.

Summary.

In individuals with CKD defined by reduced GFR, high dose statin did not reduce all-cause mortality but significantly reduced risk of hospitalization attributed to CHF and risk of all defined composite vascular endpoints. There were no data reported for the individual outcomes of MI, stroke, ESRD, doubling of serum creatinine, halving of GFR, progression from microalbuminuria to macroalbuminuria, or for any composite renal outcome. Results were limited because they were based on a single post hoc analysis, there were no data comparing treatment results in patients with albuminuria, and results were not reported for many vascular outcomes or any renal outcomes of clinical interest.

HMG-CoA Reductase Inhibitor Versus Bile Acid Sequestrant Trial

Overview.

In patients with CKD, there is a low level of evidence that statin treatment reduces risk of conversion from microalbuminuria to macroalbuminuria compared to treatment with a bile acid sequestrant. There is insufficient evidence regarding whether there is any difference between these treatments for the outcomes of mortality, MI, stroke, CHF, ESRD, doubling of serum creatinine, or halving of GFR.

Description of Study.

One trial met all eligibility criteria and randomized 86 participants with CKD to an HMG-CoA reductase inhibitor versus a bile acid sequestrant.[142] Detailed baseline characteristics are presented in Appendix Tables C113 and C114.

Participants were randomized to simvastatin versus cholestyramine. The mean age of subjects was 62 years. No data on gender or race/ethnicity was reported. Followup duration for this study, based in a single site in Italy, was 4 years.

Renal function.

The study did not base eligibility on CKD stage or report baseline distribution of participants by CKD stage. All participants were required to have microalbuminuria (urine albumin-to-creatinine ratio between 30 and 300 µg/mg) and at least a small measurable decline in GFR in the past 3 years. Mean GFR was 91 ml/min/1.73m2. Mean urine albumin/creatinine ratio was 83 µg/mg

Baseline comorbidities.

Eligible patients had treated hypertension and type 2 diabetes. Mean systolic blood pressure was 131 mm Hg and mean diastolic blood pressure was 76 mm Hg. No information on other comorbid conditions was reported.

Study quality.

Study quality was rated as fair. Though the adequacy of treatment allocation concealment was unclear, the study was double blind and analysis was conducted using the intention-to-treat principle. Withdrawals were adequately described and five percent of participants withdrew from the study.

Results.

Mortality.

No information on mortality was reported.

Vascular outcomes (Appendix Table C115).

Myocardial infarction. The study reported that one participant experienced an MI, but did not indicate this patient's treatment group.

Stroke. No stroke outcomes were reported.

Other vascular outcomes. No information on CHF or any other vascular outcome was reported.

Renal outcomes (Appendix Table C118).

End-stage renal disease. No results were reported for ESRD.

Other renal outcomes. The study reported that conversion from microalbuminuria to macroalbuminuria occurred in 4 percent of participants randomized to simvastatin versus 15 percent of those assigned to cholestyramine ($p<0.01$), but did not provide results for the number of participants experiencing these events in each treatment group or the denominators on which these calculations were derived. No results were reported for other renal outcomes.

Withdrawals and adverse effects (Appendix Table C120).

Withdrawals, all due to adverse effects, were reported in 2.3 percent (n=1) versus 7.0 percent (n=3) of CKD patients allocated to simvastatin and cholestyramine treatment, respectively. The study reported that these adverse effects included renal cancer (n=2), and three- to four-fold increase of liver function tests above baseline levels (n=1), but did not indicate any patient's treatment group.

Summary.

In patients with CKD defined by microalbuminuria, hypertension and diabetes, simvastatin significantly reduced risk of conversion to macroalbuminuria as compared to cholestyramine. There were no between-treatment group data for the endpoints of mortality, MI, stroke, CHF, ESRD, doubling of serum creatinine, halving of GFR, or for any composite vascular or renal outcome. Results were limited because they were based on a single small trial, and there were no between-treatment results for any vascular outcome or any other renal outcomes of clinical interest.

Gemfibrozil Versus Placebo or Control Trials (n=2)

Overview.

In CKD patients defined by impaired GFR, we found a low level of evidence that there is no difference between gemfibrozil and placebo for risk of mortality. There was insufficient evidence regarding whether gemfibrozil and a low triglyceride diet differ for risk of mortality. There was insufficient evidence regarding whether gemfibrozil differs from either placebo or a low triglyceride diet for risk of MI, stroke, CHF, ESRD, doubling of serum creatinine, or halving of GFR. There is insufficient evidence regarding whether, in CKD patients defined by albuminuria, gemfibrozil differs from placebo or a low triglyceride diet for any clinical outcome.

Description of studies.

Two trials met all eligibility criteria and randomized participants with CKD to gemfibrozil versus a control treatment.[128,140,143] The largest of the two trials involved a post hoc analysis involving 470 participants with GFR <60 ml/min/1.73m^2 from the larger (n=2,531) VA-HIT trial. Detailed baseline characteristics are presented in Appendix Tables C113 and C114.

Participants in the post hoc VA-HIT trial analysis, were randomized to gemfibrozil versus placebo. The mean age of participants in this analysis was 67 years, all participants were male U.S. veterans, and 91 percent of study participants were white. Followup for this multinational study was 5.3 years.[140,143] The second study randomized 57 nondiabetic patients to gemfibrozil versus a low triglyceride diet. The mean age of study participants was 51 years, and men constituted 75 percent of study participants. No data on race/ethnicity were reported. Followup for this single-site Swedish study was 1 year.[128]

Renal function.

In the VA-HIT post hoc analysis, participants were required to have GFR <60 ml/min/1.73m^2 (CKD stage 3 or worse).[140,143] All participants in the larger VA-HIT study had been required to have baseline serum creatinine ≤2.0 mg/dL. Mean GFR was 52 ml/min/1.73m^2. Mean creatinine clearance was 60 ml/min/1.73m^2. The second study did not base eligibility on CKD stage. The second study enrolled patients with impaired GFR (10 to 70 ml/min/1.73m^2).[128] Mean GFR was 36 ml/min/1.73m^2 and mean albuminuria was 0.95 g/24 hours. Mean serum creatinine was 2.4 mg/dL. Neither study reported baseline distribution of participants by CKD stage

Baseline comorbidities.

All participants in the VA-HIT trial had coronary heart disease, LDL cholesterol ≤140 mg/dL, and HDL cholesterol ≤40 mg/dL. Additional comorbid conditions included hypertension (67 percent) and diabetes (30 percent). Mean baseline systolic blood pressure was 134 mm Hg, and mean diastolic blood pressure was 77 mm Hg. Mean total and LDL cholesterol were 176 mg/dL and 111 mg/dL, respectively. The second study excluded individuals with diabetes.[128] Mean baseline systolic blood pressure was 137 mm Hg, and mean diastolic blood pressure was 84 mm Hg. Mean total and LDL cholesterol were 244 mg/dL and 170 mg/dL, respectively. No other comorbidity data were reported.

Study quality. Study quality of the VA-HIT post hoc analysis was rated as good.

The adequacy of treatment allocation concealment in the first study was clear. The study was double blinded, including outcome adjudication by a blinded endpoint committee. Analysis was

performed using the intention-to-treat principle. No study participants were reported as lost to followup.[140,143] Study quality of the second study was rated as fair. The adequacy of treatment allocation concealment in the second study was unclear. The study was open label, and analysis was not performed using the intention-to-treat principle. Withdrawals were adequately described, and 11 percent of study participants withdrew from the study.[128]

Results.

Mortality (Table 17, Appendix Table C115, and Appendix Figure C22).

In the VA-HIT study, there was no significant difference in risk of all-cause mortality between CKD patients assigned to gemfibrozil versus placebo (10.0 versus 11.0 percent; RR 0.91 [95 percent CI, 0.52 to 1.62], n=399 patients).[140,143] The gemfibrozil versus low triglyceride diet trial did not report results for mortality.[128]

Vascular outcomes (Table 17, Appendix Table C116 and C117, and Appendix Figure C22).

Myocardial infarction. No between-treatment results were reported for MI for either study.[128,140,143]

Stroke. No between-treatment results were reported for stroke for either study.[128,140,143]

Other vascular outcomes. In patients with CKD within the VA-HIT study, no between-treatment results were reported for the primary composite vascular outcome. For a second composite vascular outcome that included fatal CHD, nonfatal MI, and stroke, risk was significantly lower in participants assigned to gemfibrozil versus placebo (24.0 versus 32.9 percent; RR 0.73 [95 percent CI, 0.54 to 0.97], n=470 patients).[140,143] The gemfibrozil versus low triglyceride diet trial did not report results for any vascular outcome.[128]

Renal outcomes (Table 17, Appendix Table C118, and Appendix Figure C22).

End-stage renal disease. In the VA-HIT study, no patient in either the gemfibrozil or placebo treatment groups experienced ESRD.[140,143] In the gemfibrozil versus low triglyceride diet trial, two of 28 (7.1 percent) CKD participants randomized to gemfibrozil and one of 29 (3.4 percent) allocated to diet developed ESRD.[128]

Other renal outcomes. Neither study reported results for doubling of serum creatinine, halving of GFR, or for any composite renal outcome.

Withdrawals and side effects (Appendix Table C120).

The VA-HIT trial reported no withdrawals and no cases of rhabdomyolysis or elevation of creatine kinase more than three times the upper limit of normal in either treatment group. The gemfibrozil versus low triglyceride diet trial reported withdrawals in 21.4 percent of gemfibrozil participants, all of which were attributed to "mild gastrointestinal symptoms," while there were no withdrawals or gastrointestinal side effects reported in the diet group.

Summary.

In male veterans with CKD defined by impaired GFR, coronary artery disease, LDL≤140 mg/dL and HDL ≤40 mg/dL, gemfibrozil did not reduce all-cause mortality compared to placebo. In the one composite vascular endpoint reported of the two the study defined, gemfibrozil significantly reduced risk of fatal CHD, nonfatal MI, or stroke. In both studies, too few (or no) patients developed ESRD to effectively compare risk between gemfibrozil and either placebo or low triglyceride diet. The gemfibrozil versus diet study suggested an increased risk of

gastrointestinal side effects with gemfibrozil, but the VA-HIT CKD study reported no information on the incidence of adverse gastrointestinal symptoms. Results were limited because they were based on small studies, with few reported outcomes and small numbers of clinical events. Results from the VA-HIT study were limited because they were a post hoc analysis from a larger trial not designed to look at CKD patients or renal outcomes. Studies are limited in that they do not also report results based on baseline albuminuria.

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
HMG-CoA reductase inhibitors versus placebo (N=11)						
All-cause mortality	**7**	**Good**	**458/5284 (8.7)**	**553/5413 (10.2)**	**0.85 [0.76-0.96]**	**0%**
All-cause mortality; non-CAD patients	*2*	*Good*	*43/1953 (2.2)*	*64/1995 (3.2)*	*0.68 [0.36-1.26]*	*61%*
All-cause mortality; CAD patients	*3*	*Fair*	*87/681 (12.8)*	*102/713 (14.3)*	*0.89 [0.68-1.15]*	*0%*
All-cause mortality; CAD and non-CAD patients	*2*	*Fair*	*328/2650 (12.4)*	*387/2705 (14.3)*	*0.87 [0.76-0.99]*	*0%*
Cardiovascular mortality	**4**	**Fair**	**24/1014 (2.4)**	**35/1043 (3.4)**	**0.71 [0.43-1.17]**	**0%**
Cardiovascular mortality; non-CAD patients	*1*	*Fair*	*0/145*	*1/159 (0.6)*	*0.37 [0.01-8.90]*	*NA*
Cardiovascular mortality; CAD patients	*2*	*Fair*	*20/436 (4.6)*	*30/453 (6.6)*	*0.69 [0.40-1.19]*	*0%*
Cardiovascular mortality; CAD and non-CAD patients	*1*	*Fair*	*4/433 (0.9)*	*4/431 (0.9)*	*1.00 [0.28-3.95]*	*NA*
Myocardial infarction, any	**2**	**Fair**	**67/989 (6.8)**	**96/1026 (9.4)**	**0.72 [0.54-0.98]**	**0%**
Myocardial infarction, any; non-CAD patients	*1*	*Fair*	*2/145 (1.4)*	*6/159 (3.8)*	*0.37 [0.07-1.78]*	*NA*
Myocardial infarction, any; CAD patients	*1*	*Good*	*65/844 (7.7)*	*90/867 (10.4)*	*0.74 [0.55-1.01]*	*NA*
Myocardial infarction, nonfatal	**1**	**Good**	**17/286 (5.9)**	**29/293 (9.9)**	**0.60 [0.34-1.07]**	**NA**
Stroke, any	**5**	**Good**	**61/3516 (1.7)**	**106/3586 (3.0)**	**0.60 [0.37-1.02]**	**53%**
Stroke; non-CAD patients	*2*	*Good*	*14/1953 (0.7)*	*44/1995 (2.2)*	*0.33 [0.18-0.60]*	*0%*
Stroke; CAD patients	*2*	*Good*	*40/1130 (3.5)*	*58/1160 (5.0)*	*0.71 [0.48-1.05]*	*0%*
Stroke; CAD and non-CAD patients	*1*	*Fair*	*7/433 (1.6)*	*4/431 (0.9)*	*1.74 [0.51-5.91]*	*NA*
CHF hospitalization	**2**	**Fair**	**16/719 (2.2)**	**23/724 (3.2)**	**0.71 [0.38-1.32]**	**0%**
CHF hospitalization; CAD patients	*1*	*Good*	*15/286 (5.2)*	*22/293 (7.5)*	*0.70 [0.37-1.32]*	*NA*
CHF hospitalization; CAD and non-CAD patients	*1*	*Fair*	*1/433 (0.2)*	*1/431 (0.2)*	*1.00 [0.06-15.86]*	*NA*
Composite vascular outcomes						
Composite vascular outcome*; Kendrick[132] (AFCAPS), definition B[a]	1	Fair	8/145 (5.5)	21/159 (13.2)	0.42 [0.19-0.91]	NA
Composite vascular outcome; Kendrick[132] (AFCAPS), definition C[a]	1	Fair	7/145 (4.8)	18/159 (11.3)	0.43 [0.18-0.99]	NA
Composite vascular outcome; Nakamura[133] (MEGA), definition A[b]	1	Good	21/1471 (1.2)	40/1507 (5.7)	0.54 [0.32-0.91]	NA
Composite vascular outcome; Nakamura[133] (MEGA), definition B[b]	1	Good	25/1471 (3.7)	60/1507 (8.7)	0.43 [0.27-0.68]	NA
Composite vascular outcome; Nakamura[133] (MEGA), definition C[b]	1	Good	33/1471 (4.9)	71/1507 (10.3)	0.48 [0.32-0.72]	NA
Composite vascular outcome; Colhoun[134] (CARDS), definition A[c]	1	Good	25/482 (5.2)	42/488 (8.6)	0.63 [0.39-1.02]	NA
Composite vascular outcome; Colhoun[134] (CARDS), definition A-albuminuric patients[c]	1	Good	24/276 (8.7)	38/275 (13.8)	0.60 [0.37-0.97]	NA
Composite vascular outcome; Colhoun[134] (CARDS), definition B[c]	1	Good	18/482 (3.7)	27/488 (5.5)	0.67 [0.38-1.21]	NA

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Composite vascular outcome; Koren[135] (ALLIANCE), definition A[d]	1	Good	78/286 (27.3)	105/293 (35.8)	0.76 [0.60-0.97]	NA
Composite vascular outcome; Koren[135] (ALLIANCE), definition B[d]	1	Good	73/286 (25.5)	85/293 (29.0)	0.88 [0.67-1.15]	NA
Composite vascular outcome; Koren[135] (ALLIANCE), definition C[d]	1	Good	32/286 (11.2)	54/293 (18.4)	0.61 [0.40-0.91]	NA
Composite vascular outcome; Chonchol[136] (4S), definition A[e]	1	Fair	53/245 (21.6)	77/260 (29.6)	0.73 [0.54-0.99]	NA
Composite vascular outcome; Kjekhus[137] (CORONA), definition A[f]	1	Good	288/791 (15.8)	309/844 (16.3)	0.99 [0.88-1.13]	NA
Composite vascular outcome; Lemos[138] (LIPS), definition A[g]	1	Fair	23/150 (15.3)	47/160 (29.4);	0.52 [0.33-0.82]	NA
Composite vascular outcome; Lemos[138] (LIPS), definition B[g]	1	Fair	7/150 (4.7)	13/160 (8.1)	0.57 [0.24-1.40]	NA
Composite vascular outcome; Lemos[138] (LIPS), definition C[g]	1	Fair	7/150 (4.7)	13/160 (8.1)	0.57 [0.24-1.40]	NA
Composite vascular outcome; Asselbergs[60] (PREVD), definition A[h]	1	Fair	21/433 (4.8)	24/431 (5.6)	0.87 [0.49-1.54]	NA
Composite vascular outcome; Asselbergs[60] (PREVD), definition B[h]	1	Fair	8/433 (1.8)	15/431 (3.5)	0.53 [0.23-1.24]	NA
Composite vascular outcome; Tonelli[140] (WOSCOPS/ CARE/ LIPID), definition A[i]	1	Good	492/2217 (22.2)	647/2274 (28.5)	0.78 [0.70-0.86]	NA
Composite vascular outcome; Tonelli[140] (WOSCOPS/ CARE/ LIPID), definition B[i]	1	Good	573/2217 (25.9)	730/2274 (32.1)	0.81 [0.73-0.88]	NA
Composite vascular outcome; Tonelli[139] (CARE), definition A[j]	1	Good	89/844 (10.5)	126/867 (14.5)	0.73 [0.56-0.94]	NA
Composite vascular outcome; Tonelli[139] (CARE), definition B[j]	1	Good	171/844 (20.3)	237/867 (27.0)	0.74 [0.62-0.88]	NA
End-stage renal disease	**1**	**Good**	**32/779 (4.1)**	**31/778 (4.0)**	**1.03 [0.64-1.67]**	**NA**
Composite renal outcome (ALLHAT)[k]	1	Good	50/779 (6.4)	52/778 (6.7)	0.96 [0.66-1.40]	NA
High versus low-dose HMG-CoA reductase inhibitors (n=1)						
All-cause mortality	1	Fair	112/1602 (7.0)	113/1505 (7.5)	0.93 [0.72-1.20]	NA
CHF hospitalization	1	Fair	49/1602 (3.1)	84/1505 (5.6)	0.55 [0.39-0.77]	NA
Composite vascular outcome; Shepard[141] (TNT), definition A[l]	1	Fair	149/1602 (9.3)	202/1505 (13.4)	0.69 [0.57-0.85]	NA
Composite vascular outcome; Shepard[141] (TNT), definition B[l]	1	Fair	489/1602 (30.5)	574/1505 (38.1)	0.80 [0.73-0.88]	NA
Composite vascular outcome; Shepard[141] (TNT), definition C[l]	1	Fair	110/1602 (6.9)	157/1505 (10.4)	0.66 [0.52-0.83]	NA

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Composite vascular outcome; Shepard[141] (TNT), definition D[l]	1	Fair	356/1602 (22.2)	431/1505 (28.6)	0.78 [0.69-0.88]	NA
Composite vascular outcome; Shepard[141] (TNT), definition E[l]	1	Fair	74/1602 (4.6)	104/1505 (6.9)	0.67 [0.50-0.89]	NA
Gemfibrozil versus placebo trials (n=1)						
All-cause mortality	1	Good	20/199 (10)	22/200 (11.0)	0.91 [0.52-1.62]	NA
Composite vascular outcome; Tonelli[143] (VA-HIT), definition B[m]	1	Good	58/242 (24.0)	75/228 (32.9)	0.73 [0.54-0.97]	NA
End-stage renal disease	2	Fair	2/227 (0.9)	1/229 (0.4)	2.07 [0.20-21.58]	NA

CHF = congestive heart failure; NA = not applicable; RR = relative risk reduction
[a](B)Fatal and nonfatal cardiovascular events; (C) Fatal and nonfatal coronary events
[b](A)First occurrence of a CHD event, including fatal and nonfatal MI, angina pectoris, cardiac/sudden death, and coronary revascularization. Additional composite endpoints included; (B)first CHD event or ischemic stroke; (C) total CVD events, which was not defined
[c](A) Major cardiovascular disease, including acute CHD event (MI, including silent MI, unstable angina, acute CHD death, or resuscitated cardiac arrest), stroke, coronary revascularization, or death; (B) acute CHD event as defined above
[d](A) First primary cardiovascular event, including cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, or unstable angina requiring hospitalization; (B) All-cause mortality, peripheral revascularization, hospitalization for CHF, or stroke; (C) Nonfatal MI or cardiac death
[e](A) Major coronary event, including coronary death, nonfatal MI, resuscitated cardiac arrest, ECG confirmed silent MI
[f](A) Cardiovascular death, nonfatal MI, or nonfatal stroke
[g](A) Adverse coronary atherosclerotic events, which included cardiac death, nonfatal MI, and all surgical or percutaneous coronary interventions not caused by restenosis after an index percutaneous coronary intervention; (B) Cardiac death or MI; (C) All-cause mortality or MI
[h]A) Cardiovascular mortality or hospitalization for any of the following: nonfatal MI, myocardial ischemia, CHF, PVD or stroke; (B) Hospitalization for nonfatal MI or myocardial ischemia
[i]A) Cardiovascular mortality or hospitalization for any of the following: nonfatal MI, myocardial ischemia, CHF, PVD or stroke; (B) Hospitalization for nonfatal MI or myocardial ischemia
[j]A) Death from coronary disease (including fatal MI, sudden death, death during a coronary intervention, and death from other coronary causes) or a symptomatic nonfatal biochemically confirmed myocardial infarction; (B) Major coronary events, defined as fatal coronary disease, nonfatal MI, CABG, or coronary angioplasty
[k](A) ESRD (start of long-term dialysis, death due to kidney disease, or kidney transplantation) or ≥50% decline in GFR; and (B) ESRD or ≥50% decline in GFR
[l](A) Major cardiovascular events, which included CHD death, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, and stroke; (B) Any cardiovascular event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, documented angina, stroke, TIA, CABG, or CHF hospitalization); (C) Major coronary event (defined as CHD death, nonfatal nonprocedure-related MI, or resuscitation from cardiac arrest); (D) Any coronary event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, or documented angina); and (E) Cerebrovascular event (stroke or TIA
[m](B) Major cardiovascular event, which included fatal CHD, nonfatal MI, and stroke

Intensive Multi-Component Intervention Trials (n=4)

Overview.

In patients with CKD, we found a low strength of evidence regarding whether intensive, multi-component treatment and conventional treatment differ for risk of all-cause mortality, cardiovascular mortality, ESRD, or progression from microalbuminuria to macroalbuminuria. We found insufficient evidence regarding whether these treatments differ for risk of MI or stroke.

Description of studies.

Five reports of four unique trials met all eligibility criteria and randomized participants with CKD (n=892 patients, range 90 to 437) to an intensive multi-component treatment intervention versus usual care.[144-148] Detailed baseline characteristics are presented in Appendix Tables C121 and C122.

In all eligible trials, the intensive treatment arm was implemented by a multidisciplinary research team, comprised of at least a physician, a nurse, and a dietitian. In three of these trials, conducted entirely in patients with diabetes, the research team met with the patients at least every three months and directly intervened in their care, treating them to achieve explicit targets for blood pressure (systolic <130 to 140 mm Hg, diastolic <80 to 85 mm Hg), diabetes (HbA1c targets ranged from <6.5 to <8 percent), and lipid control (cholesterol <154 to 193 mg/dL, LDL <100 mg/dL, HDL >42 mg/dL, triglycerides <66 to 75 mg/dL).[144,145,147] The interventions were introduced in a stepwise fashion, including behavior modification and pharmacologic therapy, as necessary. In the fourth trial, the research team implementing the intensive treatment arm met with patients every 3 to 6 months and utilized a mix of direct intervention and letters sent with management recommendations to the patients' primary care providers.[148] In this latter trial, while improved blood pressure control was a stated aim, no explicit blood pressure target was reported, and the study did not discuss management of diabetes or lipids. An emphasis was placed on improving medication compliance and decreasing nephrotoxic drug exposure. In three trials, ACEIs or ARBs were to be initiated in all intensive treatment group participants,[144,145,148] and although the fourth trial did not state that these medications were mandated, it reported ACEI use in 95 percent of enrolled participants at followup.[147] Within the intensive treatment intervention groups, dietary recommendations in three trials included low protein,[144,147,148] with low potassium recommended in two trials.[144,148] Low fat[145] and low sodium[147] each were part of diet recommendations in one trial.

By comparison with the intensive intervention arms, all study participants assigned to control treatment groups were managed by their primary physician. In two trials, their management was left entirely to the discretion of their primary physician.[144,148] However, in two other trials their doctors were to target explicit goals for blood pressure, diabetes, and lipid control, aiming either for the same thresholds being used for treatment of the intensive treatment group,[147] or following national guidelines that were modestly less strict than the thresholds targeted for the intensive treatment group.[145]

The mean age of subjects was 65 years (range 55 to 68; n=4 trials) and men constituted 52 percent (range 34 to 74; n=4 trials) of all patients randomized. In the only trial that reported data on ethnicity/race, 80 percent of participants were African American.[148] Two trials were conducted in Europe (including Scotland and Denmark),[145,147] one was conducted primarily in

the United States,[148] and one was conducted in China.[144] Mean or median study durations ranged from 2 to 7.8 years.

Renal function.

No study based eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Among the four eligible trials, two based participant eligibility on presence of albuminuria,[145,147] while two others determined eligibility based on impaired creatinine clearance and/or elevated serum creatinine.[144,148] In trials reporting these data, mean baseline creatinine clearance was 37.6 mL/min (range 34 to 55, n=2 trials),[147,148] mean baseline serum creatinine was 1.8 (range 0.9 to 2.1, n=2 trials),[145,148] and urinary albumin excretion rate ranged from a mean of 73.5 mg/24 hours in one trial[145] to a median of 755 mg/24 hours in a second trial.[147] In addition, one trial reported a baseline mean GFR of 117 ml/min/1.73m^2,[145] and another reported a mean albumin-to-creatinine ratio of 79 mg/mmol.[147]

Baseline comorbidities.

Hypertension prevalence was reported in three trials, within which 98 percent of participants had a diagnosis of hypertension.[144,147,148] Mean systolic and diastolic blood pressure measurements were 147 and 82 mm Hg, respectively (n=4 trials). Three trials were comprised entirely of type 2 diabetic patients,[144,145,147] with the fourth trial including 44 percent diabetic participants.[148] In the two diabetic trials reporting, mean baseline HbA_{1C} was 8.3 percent (range 7.9 to 8.6).[145,147] The prevalence of other comorbidities included coronary artery disease 35 percent (range 16 to 48, n=3 trials), CHF 30 percent (range 7 to 40, n=2 trials), MI 26 percent (range 2 to 37, n=2 trials), and stroke 16 percent (range 3 to 20, n=3 trials).

Study quality.

Among the four eligible trials, study quality was rated as good for one trial and as fair for three trials. Allocation concealment was adequate in three trials and unclear in the remaining study. All of these intensive multi-component intervention trials were open-label. Analysis by the intention-to-treat principle was performed in two trials. Reasons for study withdrawal were adequately described in all reports, and 2.6 percent (range 0 to 17) of randomized participants withdrew from trials overall.

Results.

Mortality (Table 18, Appendix Table C123, and Appendix Figure C23).

All-cause mortality. Compared to control treatment, assignment of CKD patients to an intensive, multi-component intervention did not significantly reduce risk of all-cause mortality (19.5 percent versus 23.3 percent; RR 0.86 [95 percent CI, 0.67 to 1.10]; n=4 trials, 892 patients).

Cardiovascular mortality. Assignment to the multi-component treatment group was not associated with a significant difference in risk of cardiovascular mortality compared to control treatment (RR 1.07 [95 percent CI, 0.47 to 2.43]; n=2 trials).

Vascular outcomes (Table 18, Appendix Tables C123-C125, and Appendix Figure C23).

Myocardial infarction. Compared to control treatment, allocation of patients with CKD to intensive, multicomponent treatment was not associated with a significant reduction in MI (RR 0.97 [95 percent CI, 0.25 to 3.78]), fatal MI (RR 1.83 [95 percent CI, 0.17 to 19.47]) or nonfatal

MI (RR 0.50 [95 percent CI, 0.16 to 1.59]). However, each of these outcomes was reported only in one trial with a small sample size and few events.

Stroke. Compared to control treatment, allocation of patients with CKD to intensive, multi-component treatment was not associated with a significant reduction in fatal stroke (RR 0.31 [95 percent CI, 0.01 to 7.31]). In contrast, participants assigned to intensive, multicomponent treatment had a significantly lower risk of nonfatal stroke (3.8 percent versus 13.8 percent; RR 0.27 [95 percent CI, 0.08 to 0.94]). Again, this outcome was reported only in one trial with a small sample size and few events.

Other vascular outcomes. Two trials reported a composite vascular endpoint as a main outcome,[144,145] with a significant reduction in risk associated with intensive, multicomponent treatment in one of these trials (RR 0.54 [95 percent CI, 0.34 to 0.86], n=160 patients).[145]

Renal outcomes. (Table 18, Appendix Tables C126 and C127, and Appendix Figure C23).

End-stage renal disease. In three trials reporting, compared to control treatment, assignment of CKD patients to an intensive, multicomponent intervention was associated with a 53 percent relative reduction in risk of ESRD that was not statistically significant (6.9 versus 9.4 percent, RR 0.47 [95 percent CI 0.10 to 2.20]; n=3 trials, 455 patients). More than 80 percent of ESRD events occurred in one trial[144] and there was substantial heterogeneity between trials (I^2=43 percent).

Other renal outcomes. In the single trial reporting, intensive multicomponent treatment significantly reduced risk of progression of CKD patients from microalbuminuria to macroalbuminuria compared to conventional treatment (20.0 versus 38.8 percent, RR 0.52 [95 percent CI, 0.31 to 0.87]; n=160 patients).[145] A composite renal outcome was reported in only one trial, and risk appeared no different between treatment groups (23.1 versus 23.8 percent).[144]

Study withdrawals and adverse events (Appendix Table C128).

CKD patients allocated to intensive multicomponent treatment were no more likely to have withdrawn from treatment than those assigned to control treatment (0.9 versus 0.8 percent; n=3 trials, 687 patients). Adverse events data were only reported in one trial.[145] In this trial, risk of major hypoglycemic events that impaired consciousness and required help from another person was not higher in the intensive, multicomponent treatment group as compared to the conventionally treated group (6.3 versus 15.0 percent, p=0.12). In this trial, there also was no between-group difference in the proportion of patients with at least one minor hypoglycemic event (48.8 versus 52.5 percent, p=0.50).

Summary of results.

In individuals with CKD, compared with usual care, assignment to intensive, multicomponent intervention was not associated with a significant reduction in risk of all-cause mortality. Further, there was no significant association between treatment groups and risk of MI, fatal stroke, and ESRD. In data from single trials only, there was a significantly reduced risk with intensive, multicomponent treatment for the outcomes of nonfatal stroke, a composite vascular endpoint, and conversion from microalbuminuria to macroalbuminuria. Results for all outcomes, with the possible exception of all-cause mortality, were limited by small sample sizes and few events and could not exclude either clinically meaningful benefits or harms. Overall results were further limited by heterogeneity in patient populations and in treatment protocols, including those for both the intensive intervention groups and the usual care groups. Reporting

on study withdrawals and adverse effects was limited. Finally, no trial provided followup beyond 5 years; therefore, longer term effects of intensive, multi-component interventions cannot be determined from these studies.

Table 18. Pooled clinical and renal outcomes for INT versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intensive Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
INT versus control treatment trials (N=4)						
All-cause mortality	4	Fair	85/437 (19.5)	106/455 (23.3)	0.86 [0.67-1.10]	0%
Cardiovascular mortality	2	Fair	11/127 (8.7)	10/123 (8.1)	1.07 [0.47-2.43]	0%
Myocardial infarction, any	1	Good	4/104 (3.8)	4/101 (4.0)	0.97 [0.25-3.78]	NA
Myocardial infarction, fatal	1	Fair	2/47 (4.25)	1/43 (2.3)	1.83 [0.17-19.47]	NA
Myocardial infarction, nonfatal	1	Fair	4/80 (5.0)	4/80 (10.0)	0.50 [0.16-1.59]	NA
Stroke, nonfatal	1	Fair	3/80 (3.8)	11/80 (13.8)	0.27 [0.08-0.94]	NA
Stroke, fatal	1	Fair	0/47 (0)	1/43(2.3)	0.31 [0.01-7.31]	NA
CHF hospitalization	1	Good	13/104(12.5)	15/101(14.8)	0.84 [0.42-1.68]	NA
Composite vascular outcome* Chan, 2009[144]	1	Good	4/104 (3.8)	4/101 (4.0)	0.97 [0.25-3.78]	NA
Composite vascular outcome* Gaede (A), 2003[145]	1	Fair	19/80 (23.8)	35/80 (43.8)	0.54 [0.34-0.86]	NA
End-stage renal disease	3	Fair	16/231 (6.9)	21/224 (9.4)	0.47 [0.10-2.20]	43%
Progression from micro to macroalbuminuria	1	Fair	16/80 (20.0)	31/80 (38.8)	0.52 [0.31-0.87]	NA
Composite renal outcome**, Chan, 2009[144]	1	Good	24/104(23.1)	24/101 (23.8)	0.97 [0.59-1.59]	NA

INT = Intensive Multi-Component Intervention; RR = relative risk reduction; CI = confidence interval; CHF = congestive heart failure; NA = not applicable
* Chan = Hospitalization for heart failure, hospitalization for angina, hospitalization for arrhythmia, MI, coronary revascularization (PTCA/CABG), other revascularization, CVA or transient ischemic attack, and lower limb amputation.
*Gaede = (A) death from cardiovascular causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation as a result of ischemia, or surgery for peripheral atherosclerotic artery disease.
**ESRD (defined as the need for dialysis, or plasma creatinine level ≥500 μmol/l) or death.

Strength of Evidence for Key Question 5

The strength of evidence for Key Question 5 is presented in Table 19.

Table 19. Strength of evidence for key question 5

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
ACEI Monotherapy Studies							
ACEI versus placebo (n=17)	All-cause mortality	16; 10,720	RCTs/good	Consistent	Direct	Precise	Moderate
	ESRD	7; 7490	RCTs/good	Consistent	Direct	Precise	Moderate
ACEI versus ARB (n=6)	All-cause mortality	4; 534	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient
ACEI versus CCB (n=6)	All-cause mortality	5; 1307	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 3823	RCTs/good	Inconsistent	Direct	Imprecise	Low
ACEI versus beta blocker (n=3)	All-cause mortality	3; 1080	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	2; 203	RCTs/fair	Inconsistent	Direct	Imprecise	Low
ACEI versus diuretic (n=2)	All-cause mortality	1; 570	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	1; 4146	RCT/good	Unknown	Direct	Imprecise	Low
ARB Monotherapy Studies							
ARB versus placebo (n=4)	All-cause mortality	3; 3251	RCTs/good	Consistent	Direct	Precise	Moderate
	ESRD	2; 2661	RCTs/good	Consistent	Direct	Precise	High
ARB versus CCB (n=3)	All-cause mortality	2; 1206	RCTs/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 1148	RCT/good	Unknown	Direct	Imprecise	Low
ACEI+ARB versus Other Studies							
ACEI+ARB versus ACE (n=6)	All-cause mortality	4; 20,137	RCTs/fair	Consistent	Direct	Precise	Moderate
	ESRD	1; 90	RCT/poor	Unknown	Direct	Imprecise	Insufficient
ACEI+ARB versus ARB (n=3)	All-cause mortality	2; 17,130	RCTs/fair	Unknown	Direct	Precise	Low
	ESRD	none	-	-	-	-	Insufficient
ACEI+ARB versus ACEI+aldosterone antagonist (n=1)	All-cause mortality	1; 53	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB or diuretic versus Other Studies							
ACEI+CCB versus ACE (n=1)	All-cause mortality	1; 207	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB versus CCB (n=1)	All-cause mortality	1; 207	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB versus ACEI+ diuretic (n=1)	All-cause mortality	1; 332	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+ aldosterone antagonist versus ACE (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
ARB versus ARB Studies							
Telmisartan versus other ARB (n=2)	All-cause mortality, versus losartan	1; 860	RCT/poor	Inconsistent	Direct	Precise	Low
	All-cause mortality, versus valsartan	1; 857	RCT/fair	Inconsistent	Direct	Imprecise	Low
	ESRD	1; 857	RCTs/fair	Unknown	Direct	Imprecise	Insufficient
ARB (High Dose) versus ARB (Standard Dose)	All-cause mortality	1; 269	RCT/good	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Aldosterone antagonist studies							
ACEI+ Aldosterone antagonist versus ACEI (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Aldosterone antagonist (+ACE/ ARB) versus placebo (+ACE/ ARB) (n=1)	All-cause mortality	1; 59	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Miscellaneous Blood pressure Control versus Other Studies							
Beta blocker versus placebo (n=1)	All-cause mortality	1; 1469	RCT/good (post-hoc)	Unknown	Direct	Precise	Low
	ESRD	none	-	-	-	-	Insufficient
CCB versus placebo (n=2)	All-cause mortality	2; 1226	RCTs/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 1136	RCT/good	Unknown	Direct	Imprecise	Low
CCB versus diuretic (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 4129	RCT/good (post-hoc)	Unknown	Direct	Imprecise	Low
CCB versus beta blocker (n=3)	All-cause mortality	2; 692	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	1; 658	RCT/good	Unknown	Direct	Imprecise	Low
Diuretic versus placebo (n=1)	All-cause mortality	1; 393	RCT/good (post-hoc)	Unknown	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient
ACEI versus non-ACE (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1;	RCT/fair	Unknown	Direct	Imprecise	Low
Strict BP control versus Usual BP control (n=6)	All-cause mortality	4; 1803	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 1506	RCTs/fair	Consistent	Direct	Imprecise	Low
Non-Blood Pressure Control Interventions Section: Anti-lipid treatment trials							
HMG-CoA Reductase Inhibitors versus control (n=11)	All-cause mortality	7; 10,697	RCTs/good	Consistent	Direct	Precise	High
	ESRD	1; 1557	RCT/good	Unknown	Direct	Imprecise	Low
High versus low-dose HMG-CoA Reductase Inhibitors (n=1)	All-cause mortality	1; 3107	RCT/good	Unknown	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
Gemfibrozil versus Placebo (n=1)	All-cause mortality	1; 399	RCT/good	Unknown	Direct	Imprecise	Low
	ESRD	1; 399	RCT/good	Unknown	Direct	Imprecise	Insufficient
Gemfibrozil versus Low triglyceride diet (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 57	RCT/fair	Unknown	Direct	Imprecise	Insufficient
Non-Blood Pressure Control Interventions Section: Dietary Intervention and Weight Loss							
Low protein diet versus usual protein diet (n=6)	All-cause mortality	5; 1340	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	4; 362	RCTs/fair	Consistent	Direct	Imprecise	Low
Low protein diet versus other diet (n=2)	All-cause mortality	1; 170	RCT/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 170	RCT/fair	Unknown	Direct	Imprecise	Low
Low protein-low phosphate diet versus low phosphate diet (n=1)	All-cause mortality	1; 60	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	1; 60	RCT/fair	Unknown	Direct	Imprecise	Low
Low triglyceride diet versus gemfibrozil trials (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 57	RCT/fair	Unknown	Direct	Imprecise	Insufficient
Non-Blood Pressure Control Interventions Section: Glycemic Control Studies							
Intensive versus standard glycemic control studies (n=2)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Non-Blood Pressure Control Interventions Section: Intensive Multi-Component Intervention Studies							
Intensive multi-component intervention versus control studies (n=4)	All-cause mortality	4; 892	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 455	RCTs/fair	Inconsistent	Direct	Imprecise	Low

ACEI = Angiotensin-converting Enzyme inhibitor; ARB= angiotensin II receptor blocker ; BP = blood pressure; CCB = calcium channel blocker; ESRD = End-stage renal disease

Summary and Discussion

Clinical Implications

Is Screening for CKD of Benefit to Patients?

No direct RCT evidence addresses the potential benefits of CKD screening. Such a trial would face enormous and possibly insurmountable logistical challenges. Therefore, decisions regarding whether CKD screening is worthwhile will need to be informed by indirect evidence. Providers who look for CKD will find it. This is in part because CKD is common, and in part because CKD screening tests, also used to define CKD if abnormal results persistent, are quite sensitive. However, knowledge of a patient's CKD status, while it facilitates risk stratification, cannot directly benefit the patient unless it leads to a change in his or her treatment that is itself of benefit.

Will Identification of CKD from Screening Change Treatment?

In subgroups of CKD patients, RCTs of BB (patients with systolic CHF, nearly all on ACEI or ARB) and statins (patients with hyperlipidemia) have reported significant reductions in MI and mortality. However, we found insufficient evidence that higher doses produce better outcomes than lower doses. Therefore, benefits are not likely to be gained from screening for CKD in patients already receiving these treatments for these conditions. Regarding patients with systolic CHF currently treated with ACEI or ARB but not on BB, mortality risk is significantly reduced with BB treatment compared to placebo, whether or not GFR is impaired. Along similar lines, most statin trials were comprised of patients with coronary artery disease, who therefore already had an indication for statins whether or not they had CKD. In the primary prevention trials (mean LDL range 117 to 155 mg/dl), data are limited by the small number of cardiovascular events. However, in most of these post hoc primary prevention studies, risk appears reduced for CKD patients allocated to statins, with no significant difference in relative risk reduction between the patients with and without CKD. A CKD diagnosis would mark these patients at higher absolute risk for cardiovascular events, and might be used to inform a decision regarding whether to treat with statins.

RCTs have reported a significantly reduced risk of ESRD but not of mortality or cardiovascular events in CKD patients treated with ACEI or ARB versus placebo. This result appears driven by studies that restricted entry to patients with overt proteinuria. ESRD has not been reduced in trials that enrolled patients with microalbuminuria. This finding is not a surprise, given that such progression is relatively infrequent and the median time to ESRD in these patients far exceeds the followup duration of all studies reviewed. Even pooling all microalbuminuria RCTs, our analyses had very low statistical power to detect a between-group difference in ESRD of 40 percent as observed in the proteinuria RCTs. Most patients in these proteinuria RCTs had both diabetes and hypertension. Screening patients with these diagnoses for proteinuria could identify those in whom ACEI or ARB would be protective. While ACEI and ARB reduced risk of surrogate renal outcomes in CKD patients without proteinuria, mortality and clinical vascular outcomes were not reduced. In the case of such patients, whether benefits of long-term treatment with ACEI or ARB would outweigh harms remains unknown.

We evaluated multiple patient subgroups to investigate whether there were patient characteristics that were not automatic indications for the treatments reviewed in this report, but for which treatment significantly improved clinical outcomes in CKD patients. No trials reported stratified analyses by such patient characteristics, and studies restricted by co-morbid condition (e.g., limited to diabetics) either reported few clinical outcomes or did not find significant reductions in risk of clinical events.

Altogether, RCT data do not provide clear guidance regarding whether screening for CKD beyond these limited circumstances is beneficial. In great part, this is a function of the heterogeneity in trial populations and outcomes, and limitations in events and in reporting. New, well-designed trials would have a high likelihood of impacting conclusions about treatment efficacy, especially in patient subgroups. Updated modeling studies may be the most efficient strategy to address this question.

Will Results from Monitoring Patients with CKD Stages 1-3 for Worsening Kidney Function and/or Damage Change Treatment?

Providers who test patients with CKD stages 1-3 for worsening kidney function and/or damage will find changes in these measures. This is virtually guaranteed by the tests' imprecision and high intra-individual variability. Rationale offered for monitoring has included predicting the interval until the onset of ESRD and evaluating the effect of interventions to slow GFR decline.[10] Another possible rationale would be evidence that, within patients with CKD stages 1-3, certain treatments do not improve clinical outcomes when damage is less or function is better but do improve these outcomes when damage or function is worse.

With regard to forecasting ESRD, most patients with CKD stages 1-3 never progress to ESRD, and those that do progress to ESRD do so over many years. How much benefit patients perceive from predictions estimating onset of ESRD perhaps 20 years in the future remains unclear. With regard to monitoring to evaluate treatment interventions, we identified no RCT that assigned patients with CKD stages 1-3 to systematic monitoring versus another intervention, or that as part of trial protocol implemented treatment changes based on followup GFR or albuminuria results and evaluated clinical outcomes. Even in the absence of such trials, providers wishing to start a treatment such as ACEI or ARB to decrease albuminuria and GFR decline may not need to retest these CKD measures to guide treatment. Almost all of the trials included in this review prescribed ACEI and ARB treatments at a fixed dose throughout the trial. Less often, the initial dose was adjusted or another agent was added to achieve a specific blood pressure target. Studies have shown greater reductions in albuminuria with higher doses of these medications,[20] but it has not been established that their impact on potential monitoring measures such as albuminuria severity is independent of their blood pressure lowering effects.[15] Consequently, the point when such test results would warrant a change in treatment remains unknown, as does the question of whether monitoring patients with CKD stages 1-3 for worsening kidney function and/or damage would benefit the patient.

Do Treatments for Patients with CKD Stages 1-3 Improve Patient Outcomes?

As discussed above, ACEI and ARB significantly reduce risk of ESRD in patients with proteinuria. BB significantly reduced risk of mortality, MI, and CHF complications in patients with CKD and stable CHF already being treated with ACEI or ARB as tolerated. Statins

significantly reduce risk of mortality and MI in patients with CKD and hyperlipidemia. To date, no treatments other than ACEI and ARB have been found to reduce risk of ESRD. In trials involving head-to-head comparisons of active treatments and combination treatments, there was little direct evidence for the superiority of one active treatment over another. Insufficient data addresses whether treatments shown in RCTs to improve outcomes in CKD stage 1-3 patients do so in subgroups in which these treatments might not otherwise be clinically indicated, or would be indicated for just one of multiple options (e.g., no CHF or hypertension for ACEI or ARB).

Future Research

Given the absence of direct evidence regarding the benefits and harms of screening for CKD, a number of research directions could be considered. The most direct would be to conduct a large-scale RCT of CKD screening plus treatment for confirmed diagnoses versus usual care. Current knowledge is sufficient to decide on many of the parameters for such a trial, such as the risk groups to target for screening, the screening tests, the timing of the confirmatory tests, and at least some aspects of treatment. However, such an RCT likely would require tens of thousands of participants followed for a dozen or more years to have adequate power to evaluate final clinical outcomes such as mortality, cardiovascular events (e.g., MI), and ESRD. Such a study is not likely to be feasible. Alternatively, research could seek to refine published modeling studies of CKD screening. Previous modeling studies evaluating proteinuria screening[21] and microalbuminuria screening,[22,23] have taken into account an exhaustive set of factors and concluded that such screening is not likely to be cost-effective unless targeted to populations with an increased prevalence of CKD, including individuals with diabetes, hypertension, and older age. These models could be expanded to evaluate the impact of incorporating estimated GFR into the screening along with measurement of urinary albumin excretion. Additional screening-related research could determine the actual rather than assumed proportion of individuals with abnormal one-time screens for impaired GFR and/or micro- and macroalbuminuria who go on to meet CKD criteria based on persistent abnormalities for at least three months. This research should further seek to quantify the impact of various patient factors on these persistence rates, including the level of GFR and albuminuria at screening, diabetes, hypertension, age, and gender. Research in large screened cohorts, such as the National Kidney Foundation's KEEP, should be conducted to try to quantify harms associated with CKD screening. In addition, modeling studies that don't take potential harms into account may give biased results.

As with screening, the most direct way to address the absence of direct evidence regarding the benefits and harms of monitoring patients with CKD stages 1-3 for progression would be to conduct a large-scale RCT of CKD monitoring plus treatment modification for confirmed progression versus usual care. This likely would be more difficult to conduct than a screening trial. Challenges would include distinguishing the monitoring arm from usual care given that the vast majority of early stage CKD patients receive annual estimated GFR measures and, within a year of documented CKD stage 1-2 diagnosis, approximately 60 percent of patients have received either ACEI or ARB and 50 percent have received a statin.[1] While monitoring could be targeted to CKD patients predicted to have the highest rate of progression, a CKD severity threshold or progression rate would need to be established based on which the patient's treatment regimen would be changed. A modeling study could be developed, but estimating the effect of treatment changes in response to monitoring findings might require prior studies to determine whether treatments have differential effects on clinical outcomes for patients with recent declines in their CKD severity as compared to those whose CKD has remained stable.

Many RCTs have contributed data to help address the question regarding whether treatments of CKD patients improve clinically relevant outcomes, including mortality, and clinical vascular and renal outcomes. However, the vast majority of these trials either did not collect many of these outcomes, are small and/or included too few participants with these outcomes to draw meaningful conclusions, or have methodological flaws including high withdrawal rates and exclusions of randomized participants from analyses. Post hoc analyses of completed large trials

may still continue to be an efficient means for providing partial information regarding the efficacy of different interventions on clinical vascular and renal outcomes. Where data allow, investigators of completed trials could reanalyze results after categorizing participants by CKD stage and albuminuria category as proposed by KDIGO. There may be some large trials for which a merger with Medicare data would be a feasible means of identifying incident ESRD cases over a long followup period. Nevertheless, many studies will remain constrained by their original designs and collected data. Future RCTs should follow standardized methods to address these issues. Studies of treatments other than ACEI or ARB, and involving combinations of ACEI or ARB with an additional agent should be considered. However, for proposed trials comparing active treatments or comparing combination and monotherapy, targeting clinical vascular outcomes and, even more so, ESRD as an endpoint, estimated sample size likely would be very high.

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List of Acronyms/Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers
ACP	American College of Physicians
ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
BB	Beta blocker
CCB	Calcium channel blocker
CCT	Controlled clinical trial
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EPC	Evidence-based Policy Center
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HCTZ	Hydrochlorothiazide
KDIGO	Kidney Disease: Inspiring Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
LDL	Low density lipoprotein
MAP	Mean arterial blood pressure
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
RCT	Randomized controlled trial
RR	Relative risk
TEP	Technical expert panel
UACR	Urinary albumin-creatinine ratio
UAER	Urinary albumin excretion rate
UPER	Urine protein excretion rate
USPSTF	United States Preventive Services Task Force
USRDS	U.S. Renal Data System