Screening for, Monitoring, and Treatment of Chronic Kidney Disease Stages 1 to 3: A Systematic Review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline

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Background: Screening and monitoring for chronic kidney disease (CKD) could lead to earlier interventions that improve clinical outcomes.

Purpose: To summarize evidence about the benefits and harms of screening for and monitoring and treatment of CKD stages 1 to 3 in adults.

Data Sources: MEDLINE (1985 through November 2011), reference lists, and expert suggestions.

Study Selection: English-language, randomized, controlled trials that evaluated screening for or monitoring or treatment of CKD and that reported clinical outcomes.

Data Extraction: Two reviewers assessed study characteristics and rated quality and strength of evidence.

Data Synthesis: No trials evaluated screening or monitoring, and 110 evaluated treatments. Angiotensin-converting enzyme inhibitors (relative risk, 0.65 [95% CI, 0.49 to 0.88]) and angiotensin II–receptor blockers (relative risk, 0.77 [CI, 0.66 to 0.90]) reduced end-stage renal disease versus placebo, primarily in patients with diabetes who have macroalbuminuria. Angiotensin-converting enzyme inhibitors reduced mortality versus placebo (relative risk, 0.79 [CI, 0.66 to 0.96]) in patients with microalbuminuria and cardiovascular disease or high-risk diabetes. Statins and β-blockers reduced mortality and cardiovascular events versus placebo or control in patients with impaired estimated glomerular filtration rate and either hyperlipidemia or congestive heart failure, respectively. Risks for mortality, end-stage renal disease, or other clinical outcomes did not significantly differ between strict and usual blood pressure control. The strength of evidence was rated high for angiotensin II–receptor blockers and statins, moderate for angiotensin-converting enzyme inhibitors and β-blockers, and low for strict blood pressure control.

Limitations: Evidence about outcomes was sometimes scant and derived from post hoc analyses of subgroups of patients enrolled in trials. Few trials reported or systematically collected information about adverse events. Selective reporting and publication bias were possible.

Conclusion: The role of CKD screening or monitoring in improving clinical outcomes is uncertain. Evidence for CKD treatment benefit is strongest for angiotensin-converting enzyme inhibitors and angiotensin II–receptor blockers, and in patients with albuminuria combined with diabetes or cardiovascular disease.

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Chronic kidney disease (CKD) is defined as kidney dysfunction (glomerular filtration rate [GFR] <60 mL/min per 1.73 m^2) or kidney damage (usually reflected by albuminuria) that persists for at least 3 months (**Figure 1**) (1).

Eleven percent of U.S. adults aged 20 years or older have CKD, of whom 95% have early disease (stages 1 to 3) (2). Prevalence of CKD stages 1 to 3 increases markedly with older age and is strongly associated with medical conditions, such as diabetes, hypertension, and cardiovascular disease (CVD). Chronic kidney disease is usually asymptomatic until advanced, and progression varies. However, CKD stages 1 to 3, as well as reduced GFR and albuminuria independently, increase the risk for many adverse health outcomes, including CVD, end-stage renal disease (ESRD), and mortality (3, 4).

Strategies that are proposed to prevent CKD-associated complications include screening selected patients for CKD, monitoring patients with CKD stages 1 to 3 for changes in kidney function or damage, and treating patients with CKD stages 1 to 3 for their CKD, or, more often, for its associated conditions and cardiovascular risk factors.

Because the effects of these interventions are uncertain, we conducted this systematic review to evaluate the evidence about the clinical benefits and harms of screening for and monitoring and treatment of CKD stages 1 to 3. This report was intended to provide an evidence base to guide recommendations on CKD from the U.S. Preventive

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Services Task Force and the American College of Physicians Clinical Guidelines Committee.

Methods

We followed a protocol developed with stakeholder input. The **Appendix Figure** (available at www.annals.org) shows the analytic framework and key questions we used to guide this review. The full technical report, which incorporated peer review and public comments, is available on the Agency for Healthcare Research and Quality (AHRQ) Web site (5).

Data Sources

We searched MEDLINE to identify randomized, controlled trials (RCTs) published from 1985 to 25 November 2011. We manually reviewed reference lists of relevant articles and articles suggested by experts. For complete search strategies, see **Appendix 1** (available at www.annals.org).

Study Selection

We applied separate eligibility criteria for CKD screening, monitoring, and treatment (**Appendix 2**, available at www.annals.org). Trained reviewers examined titles, abstracts, and full articles for eligibility. A second reviewer evaluated a 10% sample of abstracts. When discrepancies were identified, all abstracts initially reviewed by 1 reviewer were reviewed by a second reviewer. Randomized, controlled trials that included participants who at least approximated the definitions for CKD stages 1 to 3 were considered to be eligible for the questions about CKD monitoring and treatment. Only English-language studies were included.

Data Extraction and Quality Assessment

For each article, a first reviewer extracted details on study design, participant characteristics, outcomes, and adverse events and rated study quality. A second reviewer checked the extracted data for accuracy. A priori, we selected mortality and ESRD as our primary efficacy outcomes, followed by clinical cardiovascular events (for example, myocardial infarction [MI], stroke, and congestive heart failure [CHF]), and composite vascular and renal outcomes that included these outcomes. Biochemical outcomes, such as halving of GFR, doubling of serum creatinine, and conversion from microalbuminuria to macroalbuminuria, were considered secondary and are reported in **Supplements 1**, **2**, and **3** (available at www.annals.org). By using criteria developed by the Cochrane Collaboration (6), we rated individual RCT quality as good, fair, or poor on the basis of the adequacy of allocation concealment (7), blinding, reporting of reasons for attrition, and how analyses accounted for incomplete data. By using methods developed by the AHRQ and the Effective Health Care Program (8), we evaluated overall strength of evidence for mortality and ESRD outcomes for each treatment comparison on the basis of the criteria of risk for bias, consistency, directness, and precision (**Appendix Table 1**, available at www.annals.org). We resolved discrepancies in quality and strength of evidence ratings by discussion and consensus.

Figure 1. **Definition of CKD.**

CKD is defined as decreased kidney function and/or kidney damage persisting for at least 3 mo. Kidney dysfunction is indicated by a glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2. Kidney damage is most frequently manifested as increased urinary albumin excretion (e.g., urinary albumin–creatinine ratio >30 g/g). CKD is categorized into 5 stages:

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

CKD = chronic kidney disease; GFR = glomerular filtration rate.

Data Synthesis and Analysis

We pooled results if clinical heterogeneity of patient populations, interventions, and outcomes was minimal. Data were analyzed in Review Manager 5.0 (Cochrane Collaboration, Oxford, United Kingdom). Random-effects models were used to generate pooled estimates of relative risks (RRs) and 95% CI. Statistical heterogeneity was summarized by using the I^2 statistic (9). When there were few RCTs for a given treatment and no overlap of reported outcomes, we synthesized the data qualitatively.

Role of the Funding Source

This review was funded by the AHRQ, and the American College of Physicians Clinical Guidelines Committee provided support for manuscript preparation. Staff at the AHRQ and a technical expert panel, including members of the American College of Physicians Clinical Guidelines Committee and U.S. Preventive Services Task Force and others, helped to develop and refine the scope, and assisted with review of draft manuscripts. The AHRQ granted copyright assertion before the manuscript could be submitted for publication, although the authors are solely responsible for the content and decision to submit it for publication.

Results

Our literature search for RCTs of CKD screening yielded 335 references; 321 were excluded after review of the title and abstract, and the remainder were excluded after review of the full text. Our search for RCTs of monitoring of CKD stages 1 to 3 yielded 920 references, with 901 excluded after review of the title and abstract, and the remainder excluded after review of the full text. Our MEDLINE search for RCTs of treatment of CKD stages 1 to 3 yielded 5291 references, with 4187 excluded after review of the title and abstract and 1012 excluded after review of the full text, leaving 92 eligible trials. Eighteen

additional eligible RCTs of CKD treatment were initially identified from trial or systematic review reference lists or by technical expert panel members or reviewers, for a total of 110 eligible RCTs of treatment of CKD stages 1 to 3 (**Figure 2**).

In asymptomatic adults, what evidence is there that systematic CKD screening improves clinical outcomes or is associated with harms?

We found no RCTs of CKD screening in adults who were asymptomatic with or without recognized risk factors for CKD incidence, progression, or complications.

In adults with CKD stages 1 to 3, what evidence is there that systematic monitoring for worsening kidney function and/or kidney damage improves clinical outcomes or is associated with harms?

We found no RCTs of monitoring adults with CKD stages 1 to 3 for worsening kidney function or damage.

Among adults with CKD stages 1 to 3, what evidence is there that treatment improves clinical outcomes?

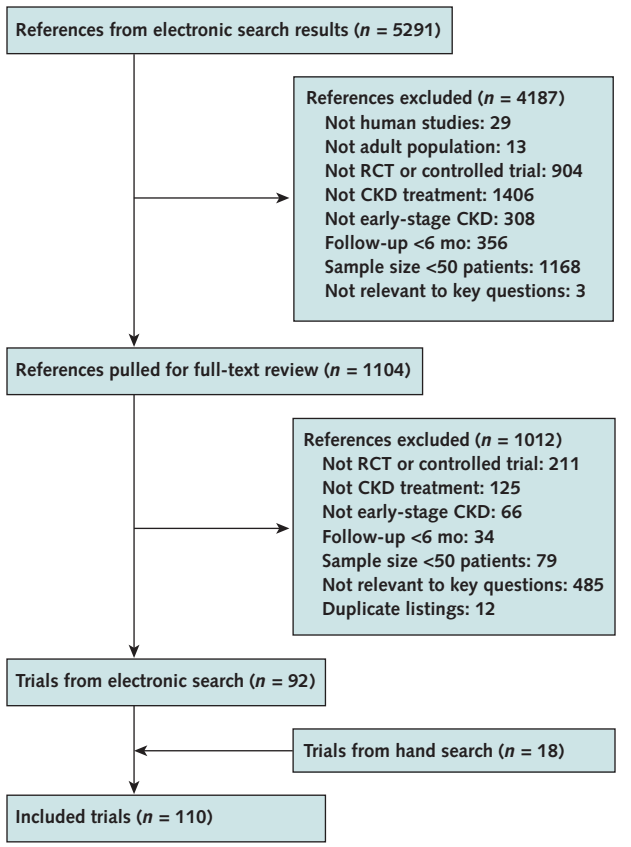
See the **Table** for a summary of our findings.

ACE Inhibitors. Nineteen eligible RCTs randomly assigned patients with CKD to treatment with ACE inhibitors versus placebo (10–29) or no treatment (30). Nearly all trials defined CKD on the basis of albuminuria (10–25), including 1 subgroup analysis from a larger trial (16, 30). Three studies were subgroup analyses of patients with impaired estimated GFR from larger trials (20, 26, 27).

We found moderate-strength evidence that patients with CKD stages 1 to 3 who were assigned to treatment with an ACE inhibitor had no reduced risk for mortality versus placebo or no treatment (RR, 0.91 [CI, 0.79 to 1.05]; 18 trials) (10–24, 26, 27, 29). Although mortality was reduced in RCTs comprising participants with microalbuminuria (RR, 0.79 [CI, 0.66 to 0.96]; 10 trials) (10, 12–14, 16, 18, 19, 21, 24, 29), these results were driven by 1 trial comprising patients with CVD or high-risk diabetes that included 97% of the deaths in the microalbuminuria subgroup (83). However, in that trial, there was no apparent difference in treatment effect between participants with microalbuminuria (RR, 0.77 [CI, 0.64 to 0.93]) and participants overall (RR, 0.76 [CI, 0.63 to 0.92]). By comparison, risk for mortality was not reduced with an ACE inhibitor versus placebo in trials restricted to patients with impaired estimated GFR (RR, 0.94 [CI, 0.70 to 1.26]; 4 trials) (20, 24, 26, 27), including 3 subgroup analyses (20, 26, 27).

We found moderate-strength evidence that ACE inhibitors reduced risk for ESRD versus placebo in patients with CKD stages 1 to 3 (RR, 0.65 [CI, 0.49 to 0.88]; 7 trials) (12, 15–17, 22–24, 30) although this benefit seemed to be driven by 3 trials limited to participants with macroalbuminuria, most of whom also had diabetes and hypertension (RR, 0.60 [CI, 0.43 to 0.83]) (15, 22, 23). In contrast, risk for ESRD was not statistically significantly reduced in trials comprising persons with CKD defined by microalbuminuria or impaired GFR only, in whom few ESRD events occurred ($P = 0.48$ for interaction with trials limited to participants with macroalbuminuria). Although patients with CKD stages 1 to 3 assigned to treatment with ACE inhibitors versus placebo had no statistically significant reduction in risk for MI, stroke, or other vascular outcomes and results were mixed for composite vascular outcomes, all 3 trials reporting composite renal outcomes found a reduced risk for this outcome (15, 22, 24).

Figure 2. **Summary of evidence search and selection.**



CKD = chronic kidney disease; RCT = randomized, controlled trial.

Angiotensin II–Receptor Blockers. Among 5 eligible RCTs that compared angiotensin II–receptor blockers (ARBs) with placebo (31–35), we found high-strength evidence that patients with CKD stages 1 to 3 assigned to treatment with ARBs had no reduced risk for mortality (RR, 1.04 [CI, 0.92 to 1.18]; 4 trials) (31–33, 35). Results seemed to be similar in subgroups with or without albuminuria ($P = 0.26$ for interaction). We also found high-strength evidence that ARBs reduced risk for ESRD in patients with CKD stages 1 to 3 (RR, 0.77 [CI, 0.66 to

0.90]; 3 trials) (31, 32, 35). However, because 99% of ESRD events occurred in patients with macroalbuminuria, most of whom also had diabetes and hypertension (31, 32, 35), we could not determine whether ARBs reduced risk for ESRD in patients with microalbuminuria or impaired GFR only and without diabetes or hypertension. In addition, risk for cardiovascular mortality, MI, CHF complications, or any other clinical vascular or renal outcome did not significantly differ between ARBs and placebo. The 1 trial that reported results stratified by CKD status found no statistically significant difference between ARBs and placebo for risk for mortality or any clinical vascular or renal outcomes in patients with CKD overall (35). However, for the 1 reported composite renal outcome, participants with albuminuria had a greater reduction in risk with ARBs versus placebo than those with no albuminuria ($P = 0.01$ for interaction). For all other clinical outcomes, this trial reported no statistically significant difference in treatment effect between subgroups of patients with and without reduced estimated GFR and albuminuria, although ESRD events were rare.

ACE Inhibitors Versus ARBs. Among 7 eligible RCTs that randomly assigned patients with CKD stages 1 to 3 to treatment with ACE inhibitors versus ARBs (10, 36–41), we found low-strength evidence that risk for mortality did not differ between treatment groups (RR, 1.04 [CI, 0.37 to 2.95]; 5 trials) (10, 37, 39–41). There was also no statistically significant difference between ACE inhibitors and ARBs for risk for any other reported clinical vascular or renal outcome, although few events occurred and CIs around risk estimates were wide for both mortality and all of these outcomes. No study reported ESRD outcomes.

ACE Inhibitor Plus ARB Combinations Versus ACE Inhibitor or ARB Monotherapy. Among 6 eligible RCTs that assigned patients with CKD stages 1 to 3 to treatment with ACE inhibitor plus ARB combinations versus ACE inhibitor or ARB monotherapy (35–38, 42–44), including 2 subgroup analyses (35, 36, 43), we found moderate-strength evidence that there was no statistically significant difference in risk for mortality (35–37, 42, 43) and low-strength evidence that there was no statistically significant difference in risk for ESRD (35, 36, 44). In 1 trial, combination therapy increased risk for the single reported composite renal outcome versus ACE inhibitors overall, with no significant difference in treatment effect between subgroups of patients with and without reduced estimated GFR or albuminuria ($P \geq 0.27$ for interaction by CKD status) (35, 36). In a second trial, combination therapy versus ACE inhibitors reduced risk for 1 reported composite vascular outcome, although treatment benefit was similar in subgroups with and without CKD ($P = 0.23$ for interaction) (43).

β-Blockers. Five eligible RCTs randomly assigned patients with CHF to treatment with β-blockers versus placebo and reported subgroup results in participants with impaired estimated GFR (Castagno D, McMurray J. Personal communication) (45–48). Nearly all patients were receiving an ACE inhibitor or ARB at baseline. We found moderate-strength evidence that patients with CKD stages 1 to 3 assigned to treatment with β-blockers had a reduced risk for all-cause mortality (RR, 0.73 [CI, 0.65 to 0.82]; 5 trials). Risk was also reduced for CVD mortality (RR, 0.76 [CI, 0.64 to 0.90]; 3 trials) and CHF complications. The RR between β-blocker and placebo groups did not differ by estimated GFR category for any clinical outcome in 4 trials ($P > 0.2$ for interaction or reported as not significant), (Castagno D, McMurray J. Personal communication) (46–48) but suggested greater risk reduction in participants with lower estimated GFR ($P < 0.05$ for interaction) for 4 of 9 reported clinical outcomes in 1 trial (45). No study reported renal outcomes.

Calcium-Channel Blockers. Two eligible trials randomly assigned mostly hypertensive patients with albuminuria to treatment with calcium-channel blockers versus placebo (14, 32), with virtually all clinical outcomes reported in 1 trial (32). We found low-strength evidence that calcium-channel blockers did not reduce risk for mortality (RR, 0.90 [CI, 0.69 to 1.19]; 2 trials) or ESRD (RR, 1.03 [CI, 0.81 to 1.32]; 1 trial). Although calcium-channel blockers reduced risk for MI (RR, 0.58 [CI, 0.37 to 0.92]), risk was not reduced for stroke, CHF, or composite vascular outcomes.

Thiazide Diuretics. One eligible trial randomly assigned patients with systolic hypertension to treatment with thiazide diuretics versus placebo and reported subgroup results in participants with serum creatinine levels of 119.34 μmol/L or greater (≥1.35 mg/dL) (49). We found low-strength evidence that patients with increased creatinine levels assigned to treatment with thiazide diuretics had no reduction in mortality (RR, 1.17 [CI, 0.74 to 1.85]). However, the thiazide diuretic group had a reduced risk for stroke (RR, 0.49 [CI, 0.24 to 0.99]) and for 1 of 2 reported composite vascular outcomes. In results reported only for 1 composite vascular outcome, the RR between thiazide diuretic and placebo groups did not differ between subgroups with and without increased creatinine ($P = 0.96$ for trend). No renal outcomes were reported.

Strict Versus Standard Blood Pressure Control. In 7 eligible trials (50–57), 6 comprised entirely (50–52, 56) or mostly (54, 55, 57) of patients with hypertension, study participants with CKD stages 1 to 3 were randomly assigned to different targets for treatment of blood pressure. Targets and medications that were used varied among trials, but the strict control target was usually approximately 10 to 15 mm Hg less than the standard control target. In trials reporting follow-up systolic and diastolic blood pressure results, mean achieved blood pressure ranged from 128 to 133 mm Hg for systolic blood pressure and 75 to 81 mm Hg for diastolic blood pressure in the strict control group versus 134 to 141 mm Hg for systolic blood pressure and 81 to 87 mm Hg for diastolic blood pressure in the standard control group (50, 51, 53, 54). The difference in

Table. **Summary of Evidence: Benefits of Treatment of CKD Stages 1 to 3**

Intervention	Studies	Study Quality	Results*	Strength of Evidence†
ACE inhibitor vs. placebo or no treatment	19 RCTs (10–30), including 4 subgroup analyses (16, 20, 26, 27, 30)	Mostly fair	Mortality: No reduced risk overall (RR, 0.91 [95% CI, 0.79–1.05]; 18 trials), but reduced risk in patients with microalbuminuria (RR, 0.79 [CI, 0.66–0.96]; 10 trials). ESRD: Reduced risk overall (RR, 0.65 [CI, 0.49–0.88]; 7 trials), with possible variability in treatment benefit by CKD subgroup, including for patients with macroalbuminuria (RR, 0.60 [CI, 0.43–0.83]; 3 trials), with few ESRD events in RCTs of patients with microalbuminuria (RR, 0.88 [CI, 0.27–2.88]) or impaired estimated GFR only (RR, 0.94 [CI, 0.06–15.01]). Other clinical outcomes: No reduced risk for MI (RR, 0.89 [CI, 0.71–1.12]; 4 trials), stroke (RR, 0.88 [CI, 0.61–1.27]; 5 trials), or CHF complications, and mixed results for composite vascular outcomes. Reduced risk for composite renal outcomes in all 3 RCTs reporting these outcomes.	Mortality: moderate ESRD: moderate
ARB vs. placebo	5 RCTs (31–35), including 1 subgroup analysis (35)	Mostly good	Mortality: No reduced risk (RR, 1.04 [CI, 0.92–1.18]; 4 trials). ESRD: Reduced risk (RR, 0.77 [CI, 0.66–0.90]; 3 trials, of which 2 were limited to patients with diabetes and macroalbuminuria). There were few ESRD events in RCTs of patients with microalbuminuria (RR, 0.93 [CI, 0.13–6.57]) or impaired estimated GFR only (RR, 0.52 [CI, 0.05–5.72]). Other clinical outcomes: Reduced risk for CHF hospitalization in 1 of 2 trials reporting and of the primary composite renal outcome in 1 of 3 trials reporting. No statistically significantly reduced risk for MI or any composite vascular outcomes. No results reported for stroke.	Mortality: high ESRD: high
ACE inhibitor vs. ARB	7 RCTs (10, 36–41)	Mostly fair	Mortality: No reduced risk (RR, 1.04 [CI, 0.37–2.95]; 5 trials). ESRD: No results reported. Other clinical outcomes: No statistically significantly reduced risk for MI, CHF, or composite renal outcome, although few events were reported. No results reported for stroke or composite vascular outcomes.	Mortality: low ESRD: insufficient
ACE inhibitor + ARB vs. ACE inhibitor‡	6 RCTs (35–38, 42–44), including 2 subgroup analyses (35, 36, 43)	Mostly fair	Mortality: No reduced risk (RR, 1.03 [CI, 0.91–1.18]; 3, trials including >99% of events in 1 trial). Also, no reduced risk in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB (RR, 1.02 [CI, 0.93–1.13]). ESRD: No reduced risk (RR, 1.00 [CI, 0.15–6.79]; 1 trial). Also, no reduced risk in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB (RR, 1.19 [CI, 0.77–1.85]). Other clinical outcomes: Reduced risk for composite vascular outcome in 1 RCT reporting this outcome, and in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB. No statistically significantly reduced risk for stroke or CHF (few events).	Mortality: moderate§ ESRD: low
ACE inhibitor + ARB vs. ARB‡	3 RCTs (35–38), including 1 subgroup analysis (35, 36)	2 fair, 1 good	Mortality: No events in 1 trial reporting. No reduced risk in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB (RR, 1.02 [CI, 0.93–1.13]). ESRD: No results reported. No reduced risk in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB (RR, 1.19 [CI, 0.77–1.85]). Other clinical outcomes: Reduced risk for composite vascular outcome in 1 RCT that reported results for ACE inhibitor plus ARB vs. ACE inhibitor or ARB. No results reported for MI, stroke, CHF, or composite renal outcomes.	Mortality: moderate§ ESRD: low
β-blocker vs. placebo	5 RCT subgroup analyses in patients with CHF and low estimated GFR (Castagno D, McMurray J. Personal communication) (45–48)	4 good, 1 fair	Mortality: Reduced risk (RR, 0.73 [CI, 0.65–0.82]; 5 trials). ESRD: No results reported. Other clinical outcomes: Reduced risk for CVD mortality (RR, 0.76 [CI, 0.64–0.90]; 3 trials), CHF hospitalization (RR, 0.69 [CI, 0.56–0.86]; 3 trials), CHF death (RR, 0.58 [CI, 0.36–0.92]; 3 trials), and, in all but 1 trial, of composite vascular outcomes. No results reported for MI, stroke, or composite renal outcomes.	Mortality: moderate ESRD: insufficient
Calcium-channel blocker vs. placebo	2 RCTs, mostly in patients with albuminuria and hypertension (14, 32)	1 good, 1 fair	Mortality: No reduced risk (RR, 0.90 [CI, 0.69–1.19]; 2 trials). ESRD: No reduced risk (RR, 1.03 [CI, 0.81–1.32]). Other clinical outcomes: Reduced risk for MI (RR, 0.58 [CI, 0.37–0.92]; 2 trials), but no statistically significant reduced risk for stroke, or composite vascular or renal outcomes.	Mortality: low ESRD: low
Thiazide diuretic vs. placebo	1 RCT subgroup analysis in patients with systolic hypertension and increased creatinine (49)	Good	Mortality: No reduced risk (RR, 1.17 [CI, 0.74–1.85]). ESRD: No results reported. Other clinical outcomes: Reduced risk for stroke (RR, 0.49 [CI, 0.24–0.99]) and 1 of 2 composite vascular outcomes reported. No results reported for MI or composite renal outcomes.	Mortality: low ESRD: insufficient

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Table—Continued

Intervention	Studies	Study Quality	Results*	Strength of Evidence†
Strict vs. usual blood pressure control	7 RCTs (50–57), including 2 subgroup analyses (52, 56)	Mostly fair	Mortality: No reduced risk (RR, 0.86 [CI, 0.68–1.09]; 4 trials). ESRD: No reduced risk (RR, 1.03 [CI, 0.77–1.38]; 3 trials). Other clinical outcomes: No statistically significantly reduced risk for MI, stroke, or reported composite vascular or renal outcomes.	Mortality: low ESRD: low
Statin vs. placebo or control	14 RCTs in patients with hyperlipidemia (21, 58–69), including 12 subgroup analyses (58–64, 66–69)	Mostly good	Mortality: Reduced risk (RR, 0.81 [CI, 0.71–0.94]; 10 trials). ESRD: No reduced risk (RR, 0.98 [CI, 0.62–1.56]; 2 trials). Other clinical outcomes: Reduced risk for MI (RR, 0.73 [CI, 0.54–0.98]; 3 trials), stroke (RR, 0.61 [CI, 0.41–0.91]; 7 trials), and most reported composite vascular outcomes. No statistically significantly reduced risk for composite renal outcome in 1 trial reporting.	Mortality: high ESRD: low
Low-protein diet vs. usual diet	6 RCTs (57, 70–74), of which 5 also included patients with CKD stages 4 and 5 (57, 71–74)	Fair	Mortality: No reduced risk (RR, 0.58 [CI, 0.29–1.16]; 4 trials). ESRD: No reduced risk (RR, 1.62 [CI, 0.62–4.21]; 3 trials). Other clinical outcomes: No statistically significantly reduced risk for MI or stroke (few outcomes reported). Reduced risk for composite renal outcome in 1 trial reporting.	Mortality: low ESRD: low
Strict vs. usual glycemic control	2 RCTs in patients with diabetes and microalbuminuria (75, 76)	Good	Mortality: 1 trial reported 1 death, but did not report the assigned treatment group. ESRD: No results reported. Other clinical outcomes: 1 trial reported 1 episode of acute renal failure, but did not report assigned treatment group. No other clinical outcomes reported.	Mortality: insufficient ESRD: insufficient
Intensive multicomponent treatment vs. usual care	5 RCTs mostly in patients with hypertension and diabetes (77–82)	Mostly fair	Mortality: No reduced risk (RR, 0.91 [CI, 0.67–1.24]; 5 trials). ESRD: No reduced risk (RR, 0.47 [CI, 0.10–2.20]; 3 trials). Other clinical outcomes: No statistically significantly reduced risk for MI, stroke, CHF complications, or 1 reported composite renal outcome. Significantly reduced risk for composite vascular outcomes in 1 of 3 trials reporting.	Mortality: low ESRD: low

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MI = myocardial infarction; RCT = randomized, controlled trial; RR = relative risk.

* For many treatment comparisons, not all trials reported results for all outcomes.

† Strength of evidence was rated using the following grades: 1) High confidence indicated 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 confidence denoted that further research may change our confidence in the estimate of effect and may change the estimate; 3) low confidence indicated 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 that there is low confidence that the evidence reflects the true effect; and 4) insufficient, indicating that the evidence was unavailable or did not permit a conclusion.

‡ Included 1 RCT that assigned participants to ACE inhibitor plus ARB vs. ACE inhibitor vs. ARB but reported results only for ACE inhibitor plus ARB vs. the combined monotherapy treatment groups.

§ Strength of evidence for ACE inhibitor plus ARB vs. ACE inhibitor and strength of evidence for ACE inhibitor plus ARB vs. ARB both took into account results from 1 RCT that assigned participants to treatment with an ACE inhibitor plus ARB vs. ACE inhibitor vs. ARB, but that only reported results for ACE inhibitor plus ARB vs. the combined monotherapy treatment groups.

achieved mean arterial pressure between treatment groups ranged from 4 to 9 mm Hg (50, 51, 53–55, 57). However, we found low-strength evidence that strict control did not reduce risk for mortality (RR, 0.86 [CI, 0.68 to 1.09]; 4 trials) (50–53) or ESRD (RR, 1.03 [CI, 0.77 to 1.38]; 3 trials) (50, 51, 53). In addition, risk for MI, stroke, or any reported composite vascular or renal outcome did not significantly differ between treatment groups. In 1 trial comprising patients with low estimated GFR in which there was no statistically significant between-group difference in risk for any of the 3 composite renal outcomes overall, a post hoc analysis reported that the strict control group had a reduced risk for 1 composite renal outcome in the subgroup with baseline protein–creatinine ratios greater than 0.22 (adjusted hazard ratio, 0.74 [CI, 0.56 to 0.99]; $P = 0.09$ for unadjusted interaction versus subgroup with protein–creatinine ratio ≤0.22) (56).

Statins. Among 14 eligible RCTs that compared statins with placebo (21, 58–65, 69), diet (66), or usual care (67, 68), all but 2 (21, 65) were subgroup analyses in participants with impaired estimated GFR or creatinine clearance from a larger trial. We found moderate-strength evidence that patients with CKD stages 1 to 3 assigned to treatment with statins had reduced risk for mortality compared with control (RR, 0.81 [CI, 0.71 to 0.94]; 10 trials) (21, 58–61, 64–67, 69), and low-strength evidence of no reduced risk for ESRD versus control (RR, 0.98 [CI, 0.62 to 1.56]; 2 trials) (65, 68). In addition, patients with CKD stages 1 to 3 assigned to treatment with statins had reduced risk for MI, stroke, and most reported composite vascular outcomes. However, trials consistently found no statistically significant interaction of CKD on treatment group effect for any of these clinical outcomes (59, 60, 62, 64, 67, 69).

Low-Protein Diet. Six eligible trials randomly assigned patients with CKD stages 1 to 3 to variably defined low-protein diets versus usual diets (57, 70–74). All but 1 study (70) reported results for patients with CKD stages 1 to 3 in combination with those for participants with CKD stages 4 or 5. We found low-strength evidence that low-

protein diets did not reduce risk for mortality (RR, 0.58 [CI, 0.29 to 1.16]; 4 trials) or ESRD (RR, 1.62 [CI, 0.62 to 4.21]; 3 trials), although few events occurred and CIs were wide for both outcomes. Risk for a composite renal outcome was reduced in the low-protein diet group in 1 trial reporting this outcome (73).

Among adults with CKD stages 1 to 3, what evidence is there that treatment is associated with harms?

Few RCTs reported information on study withdrawals. When withdrawals were reported, they were often high and infrequently were reported separately by treatment group. Few trials reported adverse events, and these often seemed to be neither predefined nor systematically collected or reported. Adverse events reported were consistent with those reported in RCTs not limited to patients with CKD, with risk relative to placebo significantly increased for cough with ACE inhibitors, hyperkalemia with ARBs, and hypotension with β-blockers. In 1 large RCT that compared an ACE inhibitor plus ARB combination with an ACE inhibitor alone, combination treatment was associated with a significant increase in risk for cough, hyperkalemia, hypotension, and acute kidney failure requiring dialysis (RR, 1.95 [CI, 1.09 to 3.49]) (35).

DISCUSSION

We found no RCTs of CKD screening or monitoring and, thus, no direct evidence about their benefits or harms. In contrast, we found direct RCT evidence about the benefits of several treatments for patients with CKD stages 1 to 3, including ACE inhibitors, ARBs, β-blockers, and statins. Although CKD increased the absolute risk for adverse clinical vascular and renal events, other than the significantly reduced risk for ESRD with ACE inhibitors or ARBs in patients with macroalbuminuria (most of whom also had diabetes and hypertension), we found little evidence that any relative improvement in clinical outcomes with these treatments versus placebo differed between patients with CKD and those without.

The strongest evidence about the benefits and harms of systematic CKD screening versus usual care or no screening would come from RCTs that report clinical outcomes. We found no such trials. However, other studies have provided indirect evidence about these questions. Clinical and administrative data, primarily from large representative U.S. cohorts, suggest that targeted screening could identify many patients with undiagnosed CKD. First, CKD stages 1 to 3 are common in older patients (2) and in adults with specific illnesses (for example, diabetes, hypertension, and CVD) (84). Second, most persons with CKD stages 1 to 3, even those with diabetes and hypertension, are not clinically recognized (85) and do not have CKD testing in usual care (86, 87), with albuminuria measured less often than serum creatinine. Albuminuria and serum creatinine–derived estimated GFR are widely available in primary care settings, with high sensitivity and specificity for 1-time measures of renal damage or dysfunction (2). However, the risk for false-positive screening is substantial (88, 89), and these measures have unknown sensitivity and specificity for CKD as defined by persistently decreased GFR or albuminuria (90). Further, evidence from CKD treatment trials seems to differ on the basis of whether study participants have macroalbuminuria, microalbuminuria, or impaired estimated GFR, and different CKD screening tests may detect only modestly overlapping groups of patients. Thus, considerations about the potential benefit of CKD screening must be specific to the screening regimen. In that context, modeling studies have incorporated data (including CKD epidemiology, screening test characteristics, and benefits and harms of treatment) to estimate the cost-effectiveness of screening for microalbuminuria (91) or macroalbuminuria (92). These studies have concluded that, compared with usual care, targeting screening for albuminuria in older patients with diabetes or hypertension and treating patients who screen positive with ACE inhibitors or ARBs may be cost-effective. However, these modeling studies may overgeneralize CKD screening benefits. They assume that reductions in mortality risk with ACE inhibitors versus placebo reported in 1 subgroup analysis comprising patients with CKD who have albuminuria and either CVD or high-risk diabetes (16) apply to all patients with albuminuria (for example, including persons with diabetes with no other cardiovascular risk factors and patients with isolated hypertension) (91, 92). Our review did not find evidence to support this assumption.

The strongest evidence about the benefits and harms of systematic monitoring of patients with CKD stages 1 to 3 for worsening renal function or damage versus usual care or no monitoring would come from RCTs that reported clinical outcomes. We found no such trials. However, data from observational studies suggest that targeted CKD monitoring could identify many patients with unrecognized progression who are at increased risk for adverse clinical outcomes. First, several studies have reported that patients with diabetes, hypertension, hyperlipidemia, obesity, smoking, or proteinuria are more likely to have faster progression of kidney damage or dysfunction (93–95). Second, although nearly all patients with diagnosed CKD stages 1 to 3 have serum creatinine levels measured regularly in usual practice, only 30% to 40% are tested annually for albuminuria (86); as a result, albuminuria progression may be unrecognized in many patients. Third, although we are unaware of studies that report the sensitivity and specificity of estimated GFR or albuminuria for identifying persistent progression of CKD stages 1 to 3, and the risk for false-positive identification of CKD progression is unknown, categorically worsening albuminuria in patients with CKD significantly increases risk for mortality and adverse clinical vascular and renal outcomes independent of baseline albuminuria severity (96). Even ac-

counting for RCT evidence that selected treatments improve important clinical outcomes in patients with CKD stages 1 to 3, it is uncertain from all this fragmentary evidence whether modifying treatment of worsened CKD detected by monitoring improves clinical outcomes compared with modifying treatment of worsened CKD detected by usual care. Further, we found no modeling studies that quantitatively estimated the effectiveness of any strategy for monitoring progression of CKD stages 1 to 3 followed by treatment of patients with progression versus a control strategy.

We found no RCTs or prospective observational studies of CKD screening or monitoring that reported harms. However, this does not exclude the possibility of harms associated with these interventions. Potential harms of CKD screening are adverse effects from screening and follow-up tests, including follow-up of false-positive results, psychological effects from labeling asymptomatic individuals as having the disease, medication adverse effects, increased medical visits, and increased health care costs. Potential harms of systematic monitoring of patients with CKD stages 1 to 3 for worsening kidney function or damage are adverse effects from monitoring and follow-up tests, including potentially unnecessary testing, medication adverse effects, and increased medical visits and health care costs.

The strongest RCT evidence of the benefit of treating CKD stages 1 to 3 was reduction in risk for ESRD with ACE inhibitors or ARBs. However, this benefit seemed to be limited to the subgroup of patients with CKD who have macroalbuminuria, most of whom had concomitant diabetes and hypertension. Although we found no evidence that ACE inhibitors or ARBs reduced risk for ESRD versus placebo in patients with microalbuminuria or impaired estimated GFR only, ESRD events were rare in these subgroups, and analyses of these studies had low statistical power to detect a treatment-related difference in risk for progression to ESRD. Whether our finding that ACE inhibitors reduced risk for mortality versus placebo when ARBs did not indicates a true advantage of ACE inhibitors over ARBs in patients with CKD stages 1 to 3 is uncertain. The higher prevalence of CVD in trials that compared ACE inhibitors with placebo than in those that compared ARBs with placebo may contribute to this finding. Unfortunately, the 5 RCTs in patients with CKD stages 1 to 3 that compared ACE inhibitors with ARBs and reported clinical outcomes had little power to identify a difference in risk for mortality or any vascular or renal outcome. Among patients with CKD stages 1 to 3, the relative reduction in risk for mortality and other clinical vascular and renal outcomes associated with treatment with ACE inhibitors, ARBs, β-blockers, thiazide diuretics, and statins seemed to be limited to patients with specific comorbid conditions and did not differ substantially from that found in patients without CKD. This finding suggests that populations evaluated in these trials may have a clinical indication for such treatments (for example, ACE inhibitors in patients with CVD or high-risk diabetes, β-blockers with CHF, and statins with hyperlipidemia), regardless of having CKD or CKD progression.

Additional trials that randomly assigned participants with CKD stages 1 to 3 to more versus less intensive treatment showed no consistent difference in clinical outcomes between treatment groups. Interpretation of trials that compared strict versus standard blood pressure control is complicated by variability in baseline, target, and achieved blood pressures between trials. Similarly, interpretation of trials that compared low-protein with usual diets is complicated by variability in the level of protein prescribed and inclusion of participants with CKD stages 4 to 5 in addition to those with CKD stages 1 to 3. Although neither intensive intervention seemed to reduce the risk for any clinical outcome versus control therapy, given limitations in individual study quality and the few clinical events reported in these trials, future studies are likely to refine these estimates of effect. By comparison, trials that compared ACE inhibitors combined with ARBs versus ACE inhibitors or ARBs alone showed a possibly unfavorable tradeoff between improvement in 1 composite vascular outcome at the cost of increased risk for renal adverse effects, including acute kidney failure requiring dialysis.

This review is limited in part by the available literature, including our inability to identify RCTs that directly evaluated the benefits or harms of CKD screening or monitoring. Inconsistent definitions of CKD and clinical outcomes among treatment trials may limit generalizability of findings across studies. Many RCTs reported few clinical outcomes and even fewer adverse events, limiting our confidence around risk estimates for these outcomes. Because nearly all eligible trials that reported baseline GFR had a mean estimated GFR of 45 mL/min per 1.73 m^2 or greater, results of this review may not apply equally to patients with lower estimated GFRs. Further, many studies were post hoc analyses of subgroups with CKD drawn from RCTs that enrolled more general populations, and many other trials involving the same populations and interventions have not reported results for their subgroups with CKD stages 1 to 3; thus, results of this review may be affected by publication bias. Although the scant attention we paid to biochemical CKD treatment outcomes, such as change in estimated GFR and albuminuria, may also be considered a limitation, our decision to focus the review on clinical outcomes was made a priori. Although these biochemistries are adverse prognostic markers, some trials have reported increases in fatal cardiovascular events (97) and in renal failure requiring dialysis (35), despite improved albuminuria.

Overall, we found no direct evidence about the benefits or harms of screening patients for CKD or for monitoring patients with CKD stages 1 to 3 for CKD progression. Indirect evidence suggested that targeting CKD screening or monitoring may be possible but that the po-

tential benefit of these interventions was uncertain. Evidence for CKD treatment benefit was strongest for ACE inhibitors and ARBs, particularly for reduction in risk for ESRD in patients with macroalbuminuria who also have diabetes and hypertension. Future studies should compare CKD screening and monitoring with usual care on important clinical outcomes. Refined modeling studies of CKD screening and monitoring are warranted. Large-scale treatment RCTs should define CKD according to current criteria. Trials should also be designed a priori to do long-term collection of clinical vascular and renal outcomes and to report outcomes by CKD stage, albuminuria, estimated GFR categories and subcategories (that is, dividing patients with CKD stage 3 into those with estimated GFR <45 and ≥ 45 mL/min per 1.73 m^2), and important patient characteristics. Judicious use of administrative data sets may also be informative.

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Appendix 1: Literature Search Strategies

We developed separate search strategies for the screening, monitoring, and treatment key questions. We searched MEDLINE and developed and tested search strings to identify RCTs or controlled clinical trials. We included studies that enrolled an adult population (aged ≥18 years), were published since 1985, and were written in English. Evidence suggests that for systematic reviews of conventional medicine, which were evaluated in the present review, restriction to include only English-language trials should not bias estimates of the effectiveness of the interventions. Only full articles were included. Details of the major search strategies are provided in **Appendix Table 2**.

To identify systematic reviews related to the 3 topic areas, we completed a search of MEDLINE using the same search strategies as detailed in **Appendix Table 2**, 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 controlled clinical trials that were not identified 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 controlled clinical trials to directly address whether screening or monitoring impact clinical outcomes or harms, we conducted a nonsystematic search for observational studies to identify indirect evidence about the benefits and harms of screening for and monitoring of CKD. All citations were then imported into EndNote X (Thomson Reuters, New York, New York) and Excel (Microsoft, Redmond, Washington) for abstract review and database management.

A broad search of the gray literature was completed by the AHRQ Scientific Resource Center librarian. Gray literature, which, by definition, is not systematically stored or indexed, included abstracts presented at conferences, unpublished trial data, government documents, and scientific information packets from pharmaceutical companies on medications evaluated in this topic.

We conducted the initial searches in March and April 2010. All searches were updated in January 2011 and again in November 2011.

Appendix 2: Trial Eligibility 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. Within the sections for each pair of key questions, inclusion criteria are detailed in the Patients sections and exclusion criteria are detailed in the Study Selection sections.

Key Questions 1 and 2: Benefits and Harms of CKD Screening

Patients

We restricted the review to studies that enrolled adults without known CKD, who did or did not have 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 Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes definitions for CKD stages 1 to 3 were considered eligible.

Study Selection

We sought RCTs or controlled clinical trials that assessed the direct effect of systematic screening for CKD stages 1 to 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 have systematic screening for CKD versus usual care or a comparator intervention, study follow-up duration less than 1 year, and sample size less than 1000 randomly assigned participants.

When no RCTs were identified that evaluated a CKD screening intervention and reported clinical outcomes and harms, indirect evidence was reviewed about its possible benefits and harms. This indirect evidence included observational studies on

CKD prevalence, clinical recognition, accuracy and reliability of CKD screening tests, and RCTs of CKD treatments. Although these observational studies were not identified by a comprehensive literature search, whenever possible, we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs.

Comparators

Studies compared systematic screening for CKD stages 1 to 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. Clinical outcomes were all-cause mortality, cardiovascular mortality, MI (any, fatal, or nonfatal), stroke (any, fatal, or nonfatal), CHF (hospitalization or death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes were progression to stage 4 or 5 kidney disease, doubling of serum creatinine or halving of estimated GFR, and conversion from microalbuminuria to macroalbuminuria. Harms were any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

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 about these questions.

Key Questions 3 and 4: Benefits and Harms of CKD Monitoring

Patients

We restricted the review to studies that enrolled adults with CKD stages 1 to 3 who were systematically monitored for worsening of kidney function or damage. As above, studies whose definitions of CKD stages 1 to 3 at least closely approximated the current Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes definitions were considered eligible.

Study Selection

We sought RCTs or controlled clinical trials that assessed the direct effect of monitoring on clinical outcomes and harms. Examples of tests to monitor for worsening kidney function 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 in a primary care setting. Our exclusion criteria were as follows: nonadult population, population entirely or predominately did not have CKD stages 1 to 3, not an RCT that assigned participants to have systematic monitoring for worsening of kidney function or damage versus usual care or comparator interventions, and sample size of fewer than 50 randomly assigned participants.

When no RCTs were identified that evaluated CKD monitoring interventions and reported clinical outcomes or harms, indirect evidence was reviewed about its possible benefits and harms. This indirect evidence included observational studies on CKD progression, clinical recognition, accuracy and reliability of CKD monitoring tests, and RCTs of CKD treatments. Although these observational studies were not identified by a comprehensive literature search, whenever possible, we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs.

Comparators

Studies compared systematic monitoring of patients with CKD stages 1 to 3 for changes in kidney function 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. Clinical outcomes were all-cause mortality, cardiovascular mortality, MI (any, fatal, or nonfatal), stroke (any, fatal, or nonfatal), CHF (hospitalization or death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes were progression to stage 4 or 5 kidney disease, doubling of serum creatinine or halving of GFR, and conversion from microalbuminuria to macroalbuminuria. Harms were any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Study Designs

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

Key Questions 5 and 6: Benefits and Harms of CKD Treatment

Patients

We restricted the review to studies that enrolled adults with CKD stages 1 to 3. Again, studies whose definitions of CKD stages 1 to 3 at least closely approximated the current Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes definitions were considered eligible.

Interventions

We included studies of both CKD-specific and nonspecific treatments. We attempted to identify studies of ACE inhibitors,

ARBs, calcium-channel blockers, aldosterone antagonists, α-blockers, β-blockers, loop diuretics, thiazide and related diuretics, combination antihypertensive regimens, targeting thresholds of blood pressure control independent of specific antihypertensive agent or agents, insulin, sulfonylureas, thiazolidinediones, biguanides (for example, metformin), targeting thresholds for glycemic control, statins, bile acid sequestrants, cholesterol absorption inhibitors (for example, ezetimibe), anorexiants, lipase inhibitors, low-protein diets, and other diets.

Comparators

These studies compared active treatment of patients with CKD stages 1 to 3 with placebo, usual care or 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. Clinical outcomes were all-cause mortality, cardiovascular mortality, MI (any, fatal, or nonfatal), stroke (any, fatal, or nonfatal), CHF (hospitalization or death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes were progression to stage 4 or 5 kidney disease, doubling of serum creatinine or halving of GFR, and conversion from microalbuminuria to macroalbuminuria. Harms were any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

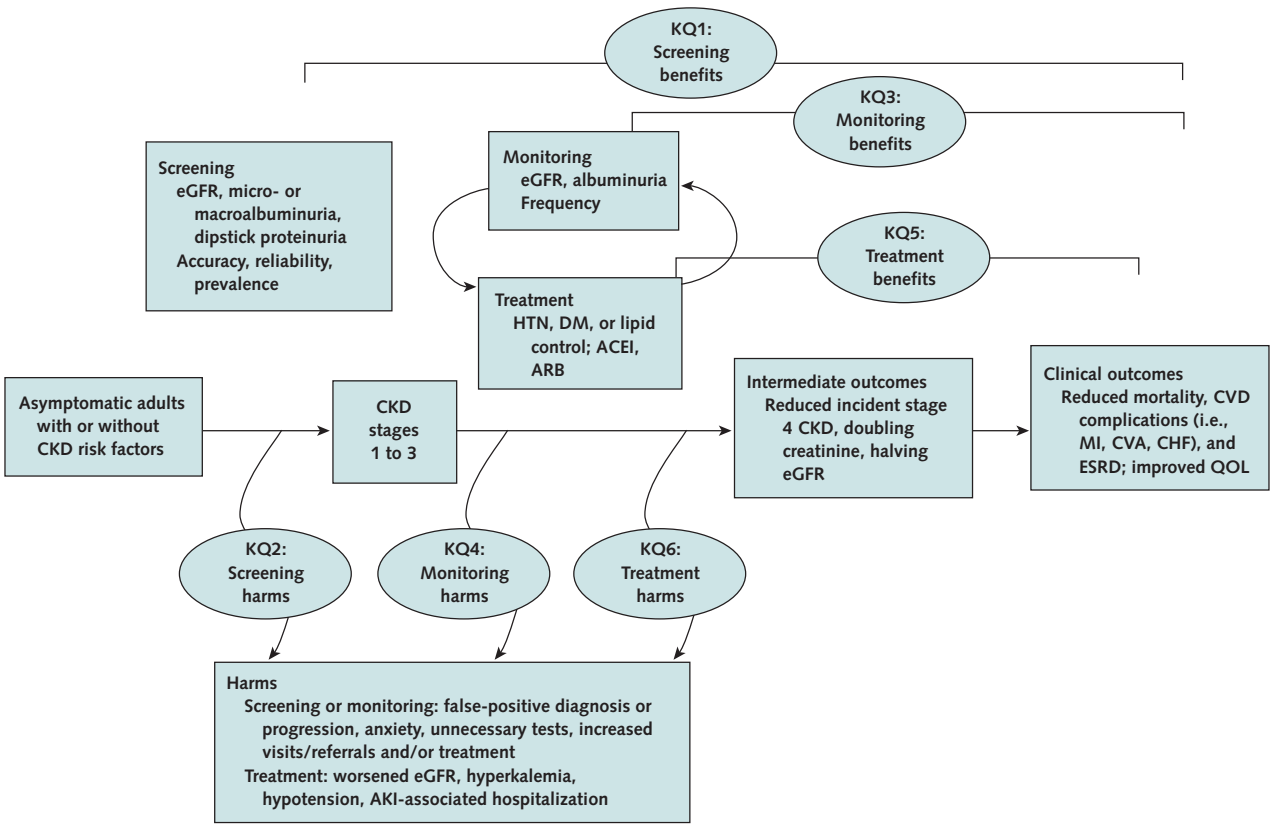
Study Designs

We included only RCTs.

Study Selection

Separate literature searches were completed for the 3 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 or exclusion criteria for the topic area of the search. Titles and abstracts with insufficient information to determine eligibility were pulled for review of the full-text article. If the initial reviewer was uncertain about eligibility, 1 of the physician project leads reviewed the abstract (or article) and made a final decision about inclusion or exclusion. We selected a 10% sample (representing the work of all abstract reviewers) for repeated review. Because of discrepancies between the results of 1 initial reviewer and the second reviewer, all abstracts reviewed by the initial reviewer 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 or 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 technical expert panel and by the public during the comment period were also reviewed for eligibility.

Appendix Figure. **Analytic framework.**



The patient population of interest is asymptomatic adults with or without CKD risk factors. The first and second key questions are related to benefits (KQ1) and harms (KQ2) of screening this population for the presence of CKD stages 1 to 3. The third and fourth key questions are related to benefits (KQ3) and harms (KQ4) associated with monitoring patients with early CKD. The fifth and sixth key questions are related to benefits (KQ5) and harms (KQ6) associated with treatment of patients with early CKD. The framework shows that monitoring may lead to treatment and that treatment may be monitored. The framework also includes intermediate outcomes of treatment that may be associated with the clinical outcomes of interest. ACEI = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II–receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HTN = hypertension; KQ = key question; MI = myocardial infarction; QOL = quality of life.

Appendix Table 1. **Strength of Evidence for Chronic Kidney Disease Treatment**

Comparison (Number of Studies)	Outcome, Control	Studies (Participants), *n (n)*	Risk of Bias Design	Quality	Consistency	Directness	Precision	Strength of Evidence
ACE inhibitor monotherapy studies								
ACE inhibitor vs. placebo (19)	All-cause mortality	18 (14 808)	RCTs	Good	Inconsistent	Direct	Precise	Moderate
	ESRD	7 (7490)	RCTs	Good	Consistent	Direct	Imprecise	Moderate
ACE inhibitor vs. ARB (7)	All-cause mortality	5 (894)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor vs. CCB (6)	All-cause mortality	5 (1307)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	3 (3823)	RCTs	Good	Inconsistent	Direct	Imprecise	Low
ACE inhibitor vs. β-blocker (3)	All-cause mortality	3 (1080)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	3 (1080)	RCTs	Fair	Inconsistent	Direct	Imprecise	Low
ACE inhibitor vs. diuretic (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 vs. placebo (5)	All-cause mortality	4 (5242)	RCTs	Good	Consistent	Direct	Precise	High
	ESRD	3 (4652)	RCTs	Good	Consistent	Direct	Precise	High
ARB vs. CCB (3)	All-cause mortality	2 (1206)	RCTs	Fair	Unknown	Direct	Imprecise	Low
	ESRD	1 (1148)	RCT	Good	Unknown	Direct	Imprecise	Low
ACE inhibitor + ARB vs. other studies								
ACE inhibitor + ARB vs. ACE inhibitor (6)	All-cause mortality	3 (3059)	RCTs	Fair	Consistent	Direct	Precise	Moderate
	ESRD	1 (90)	RCT	Poor	Unknown	Direct	Imprecise	Insufficient
ACE inhibitor + ARB vs. ARB (3)	All-cause mortality	1 (86)	RCTs	Fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + ARB vs. ACE inhibitor or ARB (1)	All-cause mortality	1 (8933)	RCT	Good	Unknown	Direct	Precise	Moderate
	ESRD	1 (8933)	RCT	Good	Unknown	Direct	Imprecise	Low
ACE inhibitor + ARB vs. ACE inhibitor + aldosterone antagonist (1)	All-cause mortality	1 (53)	RCT	Poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + CCB or diuretic vs. other studies								
ACE inhibitor + CCB vs. ACE inhibitor (1)	All-cause mortality	1 (207)	RCT	Poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + CCB vs. CCB (1)	All-cause mortality	1 (207)	RCT	Poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + CCB vs. ACE inhibitor + diuretic (2)	All-cause mortality	1 (332)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + diuretic vs. placebo (1)	All-cause mortality	1 (4519)	RCT (post hoc)	Good	Unknown	Direct	Precise	Low
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor + aldosterone antagonist vs. ACE inhibitor (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ARB vs. ARB studies								
ARB (telmisartan) vs. different ARB (2)	All-cause mortality vs. losartan	1 (860)	RCT	Poor	Inconsistent	Direct	Precise	Low
	All-cause mortality vs. valsartan	1 (857)	RCT	Fair	Inconsistent	Direct	Imprecise	Low
	ESRD vs. losartan	None	NA	NA	NA	NA	NA	Insufficient
	ESRD vs. valsartan	1 (857)	RCTs	Fair	Unknown	Direct	Imprecise	Insufficient

Continued on following page

Appendix Table 1—**Continued**

Comparison (Number of Studies)	Outcome, Control	Studies (Participants), *n (n)*	Risk of Bias Design	Quality	Consistency	Directness	Precision	Strength of Evidence
ARB (high dose) vs. ARB (standard dose) (3)	High vs. standard dose candesartan all-cause mortality	1 (269)	RCT	Good	NA	NA	NA	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
	High vs. standard dose irbesartan all-cause mortality	1 (389)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
	High vs. standard dose telmisartan all-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
Aldosterone antagonist studies								
ACE inhibitor + aldosterone antagonist vs. ACE inhibitor (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
Aldosterone antagonist (+ ACE inhibitor or ARB) vs. placebo (+ ACE inhibitor or ARB) (1)	All-cause mortality	1 (59)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
Miscellaneous BP control vs. other studies								
β-Blocker vs. placebo (5)	All-cause mortality	5 (5858)	RCT (post-hoc)	Good	Consistent	Direct	Precise	Moderate
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
CCB vs. placebo (2)	All-cause mortality	2 (1226)	RCTs	Fair	Unknown	Direct	Imprecise	Low
	ESRD	1 (1136)	RCT	Good	Unknown	Direct	Imprecise	Low
CCB vs. diuretic (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	1 (4129)	RCT (post-hoc)	Good	Unknown	Direct	Imprecise	Low
CCB vs. β-blocker (3)	All-cause mortality	2 (692)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	1 (658)	RCT	Good	Unknown	Direct	Imprecise	Low
Diuretic vs. placebo (1)	All-cause mortality	1 (393)	RCT (post-hoc)	Good	Unknown	Direct	Imprecise	Low
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
ACE inhibitor vs. non–ACE inhibitor (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	1(131)	RCT	Fair	Unknown	Direct	Imprecise	Low
Strict BP control vs. usual BP control (7)	All-cause mortality	4 (1803)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	3 (1506)	RCTs	Fair	Consistent	Direct	Imprecise	Low
Non-BP control interventions section: Antilipid treatment trials								
Statin vs. placebo or control (14)	All-cause mortality	9 (14 096)	RCTs	Good	Consistent	Direct	Precise	High
	ESRD	2 (1689)	RCT	Good	Consistent	Direct	Imprecise	Low
High- vs. low-dose statin (3)	All-cause mortality	2 (3226)	RCT	Good	Inconsistent	Direct	Imprecise	Low
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
Gemfibrozil vs. placebo (1)	All-cause mortality	1 (399)	RCT	Good	Unknown	Direct	Imprecise	Low
	ESRD	1 (399)	RCT	Good	Unknown	Direct	Imprecise	Insufficient
Gemfibrozil vs. low-triglyceride diet (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	1 (57)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient

Continued on following page

Appendix Table 1—Continued

Comparison (Number of Studies)	Outcome, Control	Studies (Participants), *n (n)*	Risk of Bias Design	Quality	Consistency	Directness	Precision	Strength of Evidence
Non-BP control interventions section: Dietary intervention and weight loss								
Low-protein diet vs. usual protein diet (6)	All-cause mortality	4 (1280)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	3 (302)	RCTs	Fair	Consistent	Direct	Imprecise	Low
Low-protein diet vs. other diet (1)	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 vs. low-phosphate diet vs. usual diet (1)	All-cause mortality	1 (98)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	1 (98)	RCT	Fair	Unknown	Direct	Imprecise	Low
Low-triglyceride diet vs. gemfibrozil trials (1)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	1 (57)	RCT	Fair	Unknown	Direct	Imprecise	Insufficient
Non-BP control interventions section: Glycemic control studies								
Intensive vs. standard glycemic control studies (2)	All-cause mortality	None	NA	NA	NA	NA	NA	Insufficient
	ESRD	None	NA	NA	NA	NA	NA	Insufficient
Non-BP control interventions section: Intensive multicomponent intervention studies								
Intensive multicomponent intervention vs. control studies (5)	All-cause mortality	5 (1366)	RCTs	Fair	Consistent	Direct	Imprecise	Low
	ESRD	4 (929)	RCTs	Fair	Inconsistent	Direct	Imprecise	Low

ACE = angiotensin-converting enzyme; ARB= angiotensin II–receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; ESRD = end-stage renal disease; NA = not applicable.

Appendix Table 2. Literature Search Strategies

Screening (Key Questions 1 and 2)

Database: Ovid MEDLINE

Search Strategy

1	exp mass screening/ or screening.tw. or exp early diagnosis/
2	(expression screening or throughput screening or molecular screening or pharmaceutical screening or mutation screening or genetic screening).tw. or exp genetic screening/ or cancer screening.tw. or compound screening.tw. or drug screening.tw. or exp drug evaluation, preclinical/
3	1 not 2
4	(randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5	exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6	3 and 4 and 5
7	exp animals/ not humans.sh.
8	6 not 7
9	limit 8 to english language
10	limit 9 to yr="1985 -Current"
11	limit 10 to "all child (0 to 18 years)"
12	limit 10 to "all adult (19 plus years)"
13	11 not 12
14	10 not 13

Monitoring (Key Questions 3 and 4)

Database: Ovid MEDLINE

Search Strategy

1	monitoring.tw. or exp disease progression/
2	cardiac monitoring.tw. or exp drug monitoring/ or exp environmental monitoring/ or drug monitoring.tw. or exp blood glucose self-monitoring/ or exp blood gas monitoring, transcutaneous/ or exp clinical trials data monitoring committees/ or exp esophageal pH monitoring/ or exp monitoring, immunologic/ or exp uterine monitoring/ or exp monitoring, intraoperative/ or exp radiation monitoring/ or exp monitoring, physiologic/
3	1 not 2
4	(randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5	exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6	3 and 4 and 5
7	exp animals/ not humans.sh.
8	6 not 7
9	limit 8 to english language
10	limit 9 to yr="1985 -Current"
11	limit 10 to "all child (0 to 18 years)"
12	limit 10 to "all adult (19 plus years)"
13	11 not 12
14	10 not 13

Treatment (Key Questions 5 and 6)

Database: Ovid MEDLINE

Search Strategy

1	exp albuminuria/co, de, dh, dt, mo, pc, th or exp proteinuria/co, de, dh, dt, mo, pc, th or exp glomerular filtration rate/ or exp kidney diseases/co, de, dh, dt, mo, pc, th or exp kidney/co, de, dh, dt, mo, pc, th or exp diabetic nephropathies/co, de, dh, dt, mo, pc, th or exp kidney failure, chronic/co, de, dh, dt, mo, pc, th or exp chronic renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency, chronic/co, de, dh, dt, mo, pc, th
2	exp *renal replacement therapy/ or exp renal dialysis/ or exp *kidney neoplasms/ or *nephritis/ or exp *urinary tract infections/ or exp *urolithiasis/ or exp anuria/ or exp diabetes insipidus/ or exp fanconi syndrome/ or exp hepatorenal syndrome/ or exp hydronephrosis/ or exp kidney cortex necrosis/ or exp Kidney Diseases, Cystic/ or kidney papillary necrosis/ or exp nephritis/ or exp renal artery obstruction/ or exp Renal Tubular Transport, Inborn Errors/ or exp Tuberculosis, Renal/ or exp Zellweger syndrome/ or exp AIDS-Associated Nephropathy/ or exp Hyperoxaluria/ or exp Nephrocalcinosis/ or exp Perinephritis/ or exp Renal Osteodystrophy/
3	1 not 2
4	(randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/ or randomized controlled trials as topic/
5	3 and 4
6	exp animals/ not humans.sh.
7	5 not 6
8	limit 7 to english language
9	limit 8 to yr="1985 -Current"
10	limit 9 to "all child (0 to 18 years)"
11	limit 9 to "all adult (19 plus years)"
12	10 not 11
13	9 not 12