Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the US Preventive Services Task Force and for an American College of Physicians clinical practice guideline


CRD summary
This review concluded that evidence for treatment benefit in chronic kidney disease was strongest for angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and in patients with albuminuria combined with diabetes or cardiovascular disease. The conclusions represent the evidence presented, but the trials were very variable and further research is required before stronger conclusions can be drawn.

Authors' objectives
To investigate the benefits and harms of screening, monitoring and treatment of chronic kidney disease stages 1 to 3 in adults.

Searching
MEDLINE was searched for studies published from 1985 to November 2011 in English; search strategies were reported. Reference lists of relevant reviews and included studies and articles suggested by experts were searched. Grey literature (conference abstracts, unpublished trial data, government documents and scientific information packets from pharmaceutical companies) were searched.

Study selection
Randomised controlled trials (RCTs) or controlled trials with at least one-year follow-up that investigated the impact of a systematic screening regimen for chronic kidney disease stages 1 to 3 and feasible for use in the primary care setting were eligible for inclusion. Trials needed to compare screening to no screening, usual care or an alternative screening regimen in unselected adults (18 years and over). Regimens for monitoring worsening renal function or kidney damage and treatment were evaluated in RCTs of adults with stages 1 to 3 chronic kidney disease. Comparators for treatment regimens included placebo, usual care, no treatment, other active treatment and different dose levels or treatment thresholds of the same active treatments using different regimens. Where no RCTs were available, evidence from observational studies was used.

The included studies evaluated a range of treatment regimens that included angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), beta-blockers, calcium channel blockers (CCBs), thiazide diuretics and statins. Study populations and regimens investigate varied considerably across studies. Definitions of chronic kidney disease and clinical outcomes measured were inconsistent between trials.

As a minimum one reviewer selected and a second reviewer screened 10% of studies and those where the initial reviewer was uncertain.

Assessment of study quality
Study quality was rated by one reviewer as good, fair or poor based on allocation concealment, blinding methods, how incomplete data were addressed and whether reasons for drop-outs/attrition were reported. The assessment was checked by a second reviewer.

Data extraction
Data were extracted for all-cause mortality, cardiovascular mortality, myocardial infarction (any, fatal, non-fatal), stroke (any, fatal, non-fatal), congestive heart failure (hospitalisation, death), composite vascular outcomes, composite renal outcomes, end-stage renal disease (progression to kidney transplant, dialysis), quality of life, physical function and activities of daily living. Relative risks (RR) and 95% confidence intervals (CI) were calculated.

Data were extracted by one reviewer and checked by a second reviewer.
Methods of synthesis
Pooled relative risks with 95% CI were calculated using a random-effects model where clinical heterogeneity of patient populations, interventions and outcomes was considered minimal (not defined). Heterogeneity was investigated using the I² statistic. Strength of the evidence was evaluated based on the risk of bias, consistency, directness and precision of the two primary outcomes and rated as high (further research unlikely to change the confidence in the result), moderate (further research may change the result or confidence in it), low (further research was likely to have an important impact) or insufficient (unavailable/does not permit conclusion).

Results of the review
One hundred and ten trials met the inclusion criteria. The level of evidence was low or insufficient for the vast majority of studies for the two primary outcomes (mortality and end-stage renal disease); overall the quality of the RCTs was considered fair to good. No RCTs were identified that investigated the impact of screening or monitoring regimens; indirect evidence was presented in the main Agency for Healthcare Research and Quality (AHRQ) report (see Other Publications of Related Interest).

Compared to placebo or no treatment, ACE inhibitors were associated with a reduced risk of end-stage renal disease (RR 0.65, CI, 0.49 to 0.88; seven trials) and composite renal outcomes (three RCTs not pooled), but not mortality (18 RCTs), myocardial infarction, stroke and other vascular outcomes. Results were mixed for composite vascular outcomes.

Compared to placebo, ARBs were associated with a reduced risk of end-stage renal disease in patients with macroalbuminuria (RR 0.77, CI, 0.66 to 0.90; three trials), but not mortality (four RCTs), myocardial infarction, congested heart failure complications and any other clinical vascular or renal outcome.

There was no statistically significant difference between ARBs and ACE inhibitors for any of the outcomes reported.

Compared to placebo, beta-blockers reduced all-cause mortality (RR 0.73, CI, 0.65 to 0.82; five RCTs), cardiovascular mortality (RR 0.76 CI, 0.64 to 0.90; three trials) and congestive heart failure complications overall in patients with an impaired estimated glomerular filtration rate, but not for any specific category of glomerular filtration rate.

Compared to controls, statin resulted in a significantly reduced risk for mortality (RR 0.81, CI, 0.71 to 0.94; 10 trials), but not end-stage renal disease, myocardial infarction, stroke and most reported composite vascular outcomes.

Compared to a usual regimen, strict blood pressure control (seven RCTs), a low protein diet (six RCTs) and intensive multicomponent treatments (five RCTs) did not show any statistically significant benefits in the outcomes measured.

Results for regimens investigated in one or two RCTs (CCBs, thiazide diuretic, strict glycaemic control), some treatment combinations and a range of subgroup analyses were presented; further comparisons were reported in the full AHRQ report (see Other Publications of Related Interest). Few RCTs reported on harms (details in the paper and report).

Authors’ conclusions
The role of chronic kidney disease screening or monitoring in improving clinical outcomes is uncertain. Evidence for chronic kidney disease treatment benefit was strongest for angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and in patients with albuminuria combined with diabetes or cardiovascular disease.

CRD commentary
The review addressed a series of clear review questions supported by appropriate inclusion criteria. Several relevant sources were searched. Attempts were made to identify unpublished studies. Only studies published in English were included, so language bias could not be ruled out. Some attempts were made to reduce selection bias and data extraction and study quality assessment were conducted in duplicate. The quality of RCTs was assessed using appropriate criteria. The identification of supporting observational studies was not systematic.

The authors highlighted that many of the studies were post hoc analyses of subgroups and this may have limited the reliability and generalisability of the results. The analyses seemed appropriate.

This was a generally well-conducted review and the conclusions represent the evidence presented but (as indicated by
the evidence was very heterogeneous and further research is required before stronger conclusions can be drawn.

**Implications of the review for practice and research**

**Practice:** The authors did not state implications for practice.

**Research:** The authors suggested that future studies should compare chronic kidney disease screening and monitoring with usual care on important clinical outcomes. Refined modelling of chronic kidney disease screening and monitoring was warranted. Large-scale treatment RCTs should define chronic kidney disease according to current criteria. Trials should measure longer-term vascular and renal outcomes. Trials should report outcomes by chronic kidney disease stage, albuminuria, estimated glomerular filtration rate categories and subcategories and important patient characteristics. Judicious use of administrative data sets may also be informative.

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