

Screening, Monitoring, and Treatment of Stage 1 to 3 Chronic Kidney Disease: A Clinical Practice Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the screening, monitoring, and treatment of adults with stage 1 to 3 chronic kidney disease.

Methods: This guideline is based on a systematic evidence review evaluating the published literature on this topic from 1985 through November 2011 that was identified by using MEDLINE and the Cochrane Database of Systematic Reviews. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline included all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, chronic heart failure, composite vascular outcomes, composite renal outcomes, end-stage renal disease, quality of life, physical function, and activities of daily living. This guideline grades the evidence and recommendations by using ACP's clinical practice guidelines grading system.

Recommendation 1: ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: weak recommendation, low-quality evidence)

Recommendation 2: ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II-receptor blocker. (Grade: weak recommendation, low-quality evidence)

Recommendation 3: ACP recommends that clinicians select pharmacologic therapy that includes either an angiotensin-converting enzyme inhibitor (moderate-quality evidence) or an angiotensin II-receptor blocker (high-quality evidence) in patients with hypertension and stage 1 to 3 chronic kidney disease. (Grade: strong recommendation)

Recommendation 4: ACP recommends that clinicians choose statin therapy to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. (Grade: strong recommendation, moderate-quality evidence)

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Chronic kidney disease (CKD) is nearly always asymptomatic in its early stages (1). The most commonly accepted definition of CKD was developed by Kidney Disease: Improving Global Outcomes (KDIGO) (2) and the Kidney Disease Outcomes Quality Initiative (KDOQI) (3) as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. Criteria for CKD include markers of kidney damage (albuminuria, as indicated by an albumin excretion rate of 30 mg/24 h or greater and an albumin-creatinine ratio of 3 mg/mmol or greater [≥ 30 mg/g]); urine sediment abnormalities; electrolyte and other abnormalities due to tubular disorders; abnormalities detected by histologic examination; structural abnormalities detected by imaging; history of kidney transplantation or presence of kidney damage; or kidney dysfunction that persists for 3 or more months, as shown by structural and functional abnormalities (most often based on increased albuminuria, as indicated by a urinary albumin-creatinine ratio of 3 mg/mmol or greater

[≥ 30 mg/g]) or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for 3 or more months.

Traditionally, CKD is categorized into 5 stages that are based on disease severity defined by GFR (3) (Table 1); stages 1 to 3 are considered to be early-stage CKD. People with early stages of the disease are typically asymptomatic, and the diagnosis is made by using laboratory tests or imaging. In 2013, KDIGO revised CKD staging to consider both 5 stages of GFR as well as 3 categories of albuminuria to define CKD severity (2).

See also:

Print

Summary for Patients. I-28

Web-Only

CME quiz

* This paper, written by Amir Qaseem, MD, PhD, MHA; Robert H. Hopkins Jr., MD; Donna E. Sweet, MD; Melissa Starkey, PhD; and Paul Shekelle, MD, PhD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Paul Shekelle, MD, PhD (Chair); Roger Chou, MD; Molly Cooke, MD; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Nick Fitterman, MD; Mary Ann Forciea, MD; Robert H. Hopkins Jr., MD; Linda L. Humphrey, MD, MPH; Tanveer P. Mir, MD; Douglas K. Owens, MD, MS; Holger J. Schünemann, MD, PhD; Donna E. Sweet, MD; and Timothy Wilt, MD, MPH. Approved by the ACP Board of Regents on 17 November 2012.

Table 1. Definition of CKD Stages Based on GFR*

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

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

* Adapted from reference 3. The Kidney Disease: Improving Global Outcomes Work Group recently updated its definition of CKD progression to include consideration of both GFR and albuminuria stages (2).

Approximately 11.1% (22.4 million) of adults in the United States have stage 1 to 3 CKD, and prevalence appears to be increasing, especially for stage 3 CKD (4, 5). Approximately one half of persons with CKD have either stage 1 or 2 CKD (increased albuminuria with normal GFR), and one half have stage 3 CKD (low GFR, with one third of these individuals having increased albuminuria and two thirds having normal albuminuria) (5). The prevalence of CKD is slightly higher in women than in men (12.6% vs. 9.7%) (6).

Stage 1 to 3 CKD, reduced GFR, and albuminuria are associated with mortality (7, 8), cardiovascular disease (9), fractures (10), bone loss (11), infections (12), cognitive impairment (13), and frailty (14). Treatment of stage 1 to 3 CKD involves treating associated conditions and complications. Many patients with CKD may already be taking medications targeting comorbid conditions, such as hypertension, cardiovascular disease, and diabetes.

This American College of Physicians (ACP) guideline presents available evidence on the screening, monitoring, and treatment of stage 1 to 3 CKD. Clinicians are the target audience. The target patient population for screening is adults, and the target population for treatment is adults with stage 1 to 3 CKD.

METHODS

This guideline is based on a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (15) and conducted by the Minnesota Evidence-based Practice Center (6) that addressed the following key questions:

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 to 3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening

kidney function or kidney damage improves clinical outcomes?

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

5. Among adults with CKD stages 1 to 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 to 3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

The literature search identified randomized, controlled trials and controlled clinical trials published in English from 1985 through November 2011, by using MEDLINE and the Cochrane Database of Systematic Reviews and review of reference lists of relevant articles and articles suggested by experts. Details of the evidence review methods are available in the full AHRQ report (6).

This guideline rates the recommendations by using the ACP's guideline grading system (Table 2) (16).

RISK FACTORS FOR CKD

The major risk factors for CKD include diabetes, hypertension, and cardiovascular disease. Other risk factors include older age; obesity; family history; and African American, Native American, or Hispanic ethnicity. Diabetes is more prevalent in patients with stage 1 to 3 CKD (20%) than in patients without CKD (5%) (17). Hypertension is also more prevalent in patients with CKD (64% in stage 3 and 36% in stage 1) than in patients without CKD (24%) (17). The prevalence of cardiovascular disease increased from 6% in patients without CKD to 36% in those with stage 3 CKD (17).

SCREENING FOR CKD

Benefits of Screening

Direct Evidence

No randomized, controlled trials that compared the effect of systematic CKD screening versus no CKD screening on clinical outcomes were identified.

Indirect Evidence

Prevalence. Among U.S. adults older than 20 years, 11.1% have stage 1 to 3 CKD. Approximately 5% of adults younger than 52 years and without diabetes, hypertension, or obesity have CKD, compared with 68% older than 81 years (17). Most patients with stage 1 to 3 CKD are not clinically recognized to have CKD (18, 19).

Adverse Health Consequences. Although stage 1 to 3 CKD is usually asymptomatic, it is associated with mortality (7, 8), cardiovascular disease (9), fractures (10), bone

loss (11), infections (12), cognitive impairment (13), and frailty (14).

Validity and Reliability of Screening Tests. No population-based studies have tested the sensitivity or specificity of 1-time CKD screening using either estimated GFR or albuminuria or the validity and reliability of repeated screening. Serum creatinine is measured by using a simple blood test. Although no studies have compared GFR estimated from serum creatinine values with direct GFR measurement, estimation is believed to be reasonably accurate (20). There are many sources of variability when measuring urinary albumin loss (21), and the method of collection and measurement of urinary albumin and creatinine has yet to be standardized.

Effect of Treatments on Screen-Detected CKD. There was no randomized trial evidence evaluating the effectiveness of treatment on clinical outcomes of CKD identified through screening.

Harms of Screening

Direct Evidence

No randomized, controlled trials have evaluated the harms of systematic CKD screening.

Indirect Evidence

Expert opinion suggests that the harms of CKD screening include misclassification of patients owing to false-positive test results, adverse effects of unnecessary testing, psychological effects of being labeled with CKD, adverse events associated with pharmacologic treatment changes after CKD diagnosis, and possible financial ramifications of CKD diagnosis.

MONITORING FOR CKD

Benefits of Monitoring

Direct Evidence

No randomized, controlled trials have evaluated clinical outcomes for patients with stage 1 to 3 CKD who were systematically monitored for worsening kidney function versus no CKD monitoring, usual care, or an alternative CKD monitoring regimen.

Indirect Evidence

Frequency of Worsening of Kidney Function or Damage in Patients With Stage 1 to 3 CKD. The mean annual GFR decline in patients with CKD varies widely, ranging from approximately 1 to greater than 10 mL/min/1.73 m² (3). Annual rates of conversion from microalbuminuria to macroalbuminuria range from 2.8% to 9% (22–27). Factors that have been shown to predict faster decline in GFR include diabetes, proteinuria, hypertension, older age, obesity, dyslipidemia, smoking, male sex, and cause of primary kidney disease.

Association of CKD Progression With Adverse Health Consequences. No studies longitudinally assessed the risk for adverse health outcomes in patients with worsening CKD.

Table 2. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) workgroup.

A meta-analysis of prospective cohort studies reported risk for all-cause and cardiovascular mortality for different GFRs and degrees of albuminuria (8). Patients with albuminuria and GFR greater than 60 mL/min/1.73 m² (CKD stage 1 or 2) had a higher mortality risk if they had macroalbuminuria compared with microalbuminuria, although lower GFR within this range was not associated with a higher mortality risk. Mortality risk was increased in patients with a GFR of 45 to 59 mL/min/1.73 m², higher in those with GFR 30 to 44 mL/min/1.73 m², and even higher in those with GFR less than 30 mL/min/1.73 m².

Validity and Reliability of Tests to Monitor CKD Progression. The same tests are used both to screen for CKD and monitor its progression. No studies assessed the accuracy, precision, specificity, or sensitivity of estimating GFR over time or for detecting a change in CKD stage on the basis of GFR category. The lack of consistent reproducibility in albuminuria measurements causes concern about the ability of longitudinal albuminuria measurements to accurately represent CKD progression.

Effect of Treatments on Clinical Outcomes in Patients Whose CKD Has Progressed. Evidence is lacking on whether treatments reduce the risk for adverse clinical outcomes in patients with worsening CKD.

Harms of Monitoring

Direct Evidence

No randomized, controlled trials were identified that compared the adverse effects of systematic monitoring of stage 1 to 3 CKD versus no CKD monitoring, usual care, or an alternative CKD monitoring regimen.

Indirect Evidence

Expert opinion suggests that the harms of monitoring for CKD progression include incorrect reclassification of patients, adverse effects of unnecessary testing, labeling effects, adverse events associated with changes in pharmacologic treatments after testing, and possible financial ramifications of a more advanced CKD diagnosis.

TREATMENT OF CKD

Table 3 summarizes the evidence on treatments for stage 1 to 3 CKD.

Antihypertensive Drugs

Monotherapy

Patients receiving β -blockers or calcium-channel blockers for CKD treatment may have received other concomitant antihypertensive agents.

Angiotensin-Converting Enzyme Inhibitors Versus Placebo. Nineteen studies compared treatment with angiotensin-converting enzyme (ACE) inhibitors with placebo in patients with stage 1 to 3 CKD (23–26, 28–42). Moderate-quality evidence showed that treatment with ACE inhibitors reduced the risk for end-stage renal disease (ESRD) (relative risk [RR], 0.65 [95% CI, 0.49 to 0.88]) compared with placebo in patients with stage 1 to 3 CKD (26–28, 31, 33–35, 38). The risk for ESRD was not reduced in patients with only microalbuminuria or impaired GFR. Moderate-quality evidence showed that treatment with ACE inhibitors did not reduce the risk for all-cause mortality compared with placebo (23–26, 28–39, 41) (Table 3). Pooled data from 10 trials (23–26, 29–31, 35, 36, 39) showed that mortality risk was reduced in patients with microalbuminuria (RR, 0.79 [CI, 0.66 to 0.96]), although most of the data were derived from a large study that showed no difference in mortality between patients with and without microalbuminuria (43). Therapy with ACE inhibitors did not reduce the risk for cardiovascular mortality, myocardial infarction (MI), stroke, or other vascular outcomes.

ACE Inhibitors Versus β -Blockers. Low-quality evidence showed no difference in the risk for ESRD or all-cause mortality, cardiovascular mortality, stroke, or heart failure between patients treated with ACE inhibitor monotherapy compared with β -blocker monotherapy (44–46) (Table 3).

ACE Inhibitors Versus Diuretics. Low-quality evidence showed no difference between ACE inhibitor-treated and diuretic-treated patients in terms of risk for ESRD (47) (Table 3). Evidence was insufficient to determine whether the treatments alter the all-cause mortality risk. There was no statistically significant difference between the 2 treatments in risk for stroke or multiple composite cardiovascular outcomes.

ACE Inhibitors Versus Angiotensin II–Receptor Blockers. End-stage renal disease outcomes were not reported in studies comparing ACE inhibitor monotherapy with angiotensin II–receptor blocker (ARB) monotherapy. Low-quality evidence showed that there was no difference between these 2 monotherapies in risk for all-cause mortality (36, 48–51) (Table 3). There was no statistically significant difference between the 2 treatments for other reported clinical vascular or renal outcomes.

ACE Inhibitors Versus Calcium-Channel Blockers. Low-quality evidence showed that there was no difference in the

risk for ESRD (47, 52, 53) or all-cause mortality (23, 52–56) between ACE inhibitor monotherapy and calcium-channel blocker monotherapy (Table 3). There was also no difference between the 2 treatments in terms of risk for cardiovascular mortality, stroke, congestive heart failure (CHF), or any composite vascular end point.

ACE Inhibitors Versus Non-ACE Inhibitor Antihypertensive Therapy. Low-quality evidence showed that ACE inhibitor monotherapy did not statistically significantly reduce the risk for ESRD compared with non-ACE inhibitor antihypertensive therapy (calcium antagonists, β -blockers, or α -adrenoblockers) (57) (Table 3). Evidence was insufficient that ACE inhibitor therapy compared with non-ACE inhibitor antihypertensive therapy is associated with a reduced risk for all-cause mortality.

ARB Monotherapy Versus Placebo. High-quality evidence showed that treatment with ARBs reduced the risk for ESRD in patients with stage 1 to 3 CKD (RR, 0.77 [CI, 0.66 to 0.90]) compared with placebo (58–60). However, it was not possible to determine whether risk was also reduced in patients with microalbuminuria or impaired GFR who do not have diabetes and hypertension (58–60). High-quality evidence showed that treatment with ARBs did not reduce the risk for all-cause mortality compared with placebo (58–61) (Table 3). Treatment with ARBs did not reduce the risk for cardiovascular mortality, MI, CHF complications, or any other clinical vascular outcome compared with placebo; however, ARB treatment did statistically significantly improve renal outcomes.

ARBs Versus Calcium-Channel Blockers. Low-quality evidence showed that ARB monotherapy did not reduce the risk for ESRD (59) or all-cause mortality (59, 62) compared with calcium-channel blocker monotherapy (Table 3). There was also no statistically significant difference between the 2 treatments in terms of risk for stroke, cardiovascular mortality, CHF, or composite vascular end points.

β -Blockers Monotherapy Versus Placebo. End-stage renal disease outcomes were not reported in studies comparing β -blocker monotherapy with placebo. Moderate-quality evidence showed that treatment of CKD with a β -blocker reduced the risk for all-cause mortality compared with placebo (RR, 0.73 [CI, 0.65 to 0.82]) (63–66). β -Blocker treatment also statistically significantly reduced the risk for cardiovascular mortality (64, 66), CHF hospitalization (65, 66), and CHF death (65, 66).

Calcium-Channel Blockers Versus Placebo. Low-quality evidence showed that treatment with calcium-channel blockers in mostly hypertensive patients with albuminuria did not reduce the risk for ESRD (59) or all-cause mortality (23, 59) compared with placebo, although this treatment did reduce the risk for MI (23, 59) (Table 3). There was no statistically significant reduction in composite renal outcomes.

Calcium-Channel Blockers Versus β -Blockers. Low-quality evidence showed that calcium-channel blocker monotherapy did not statistically significantly reduce the

Table 3. Summary of Evidence for CKD Treatment

Intervention	Outcome	Strength of Evidence From RCTs (Reference)	Result	Other Outcomes	Adverse Events*
ACE inhibitor vs. placebo	Mortality	Moderate (23–26, 28–39, 41, 42)	No reduced risk overall (RR, 0.91 [95% CI, 0.79 to 1.05])	Reduced risk for composite renal outcomes; mortality risk reduced in patients with microalbuminuria	Cough
	ESRD	Moderate (26–28, 31, 33–35, 38)	Reduced risk (RR, 0.65 [CI, 0.49 to 0.88])		
ARB vs. placebo	Mortality	High (58–61)	No reduced risk (RR, 1.04 [CI, 0.92 to 1.18])	Reduced risk for CHF hospitalization (1 of 2 trials reporting) and composite renal outcomes (1 of 3 trials reporting)	Hyperkalemia
	ESRD	High (58–61)	Reduced risk (RR, 0.77 [CI, 0.6 to 0.90])		
ACE inhibitor vs. ARB	Mortality	Low (36, 48–51)	No reduced risk (RR, 1.04 [CI, 0.37 to 2.95])	No reduced risk for other outcomes reported	NR
	ESRD	Insufficient	NA		
ACE inhibitor + ARB vs. ACE inhibitor	Mortality	Moderate (50, 71, 72)	No reduced risk (RR, 1.03 [CI, 0.91 to 1.18])	Reduced risk for composite vascular outcomes	Increased risk for cough, hyperkalemia, hypotension, and acute kidney failure requiring dialysis
	ESRD	Low (70)	No reduced risk (RR, 1.00 [CI, 0.15 to 6.79])		
ACE inhibitor + ARB vs. ARB	Mortality	Moderate† (60)	No reduced risk (RR, 1.02 [CI, 0.93 to 1.13])	Reduced risk for composite vascular outcomes	NR
	ESRD	Low† (60)	No reduced risk (RR, 1.19 [CI, 0.77 to 1.85])		
β-Blocker vs. placebo	Mortality	Moderate (63–66)	Reduced risk (RR, 0.73 [CI, 0.65 to 0.82])	Reduced risk for CVD mortality, CHF hospitalization, CHF death, and composite vascular outcomes	Heart failure, fatigue, bradycardia, dizziness, and hypotension
	ESRD	Insufficient	NA		
Calcium-channel blocker vs. placebo	Mortality	Low (23, 59)	No reduced risk (RR, 0.90 [CI, 0.69 to 1.19])	Reduced risk for MI	Hyperkalemia
	ESRD	Low (59)	No reduced risk (RR, 1.03 [CI, 0.81 to 1.32])		
Thiazide diuretic vs. placebo	Mortality	Low (69)	No reduced risk (RR, 1.17 [CI, 0.74 to 1.85])	Reduced risk for stroke	NR
	ESRD	Insufficient	NA		
Calcium-channel blocker vs. β-blocker	Mortality	Low (46, 67, 68)	No reduced risk (RR, 0.62 [CI, 0.31 to 1.22])	No reduced risk for other outcomes reported	NR
	ESRD	Low (46, 67)	No reduced risk (RR, 1.00 [CI, 0.70 to 1.44])		
Calcium-channel blocker vs. diuretic	Mortality	Insufficient	NA	No reduced risk for other outcomes reported	NR
	ESRD	Low (47)	No reduced risk (RR, 0.90 [CI, 0.67 to 1.21])		
Strict vs. standard blood pressure control	Mortality	Low (46, 75, 76, 78)	No reduced risk (RR, 0.86 [CI, 0.68 to 1.09])	No reduced risk for other outcomes reported	NR
	ESRD	Low (46, 75, 78)	No reduced risk (RR, 1.03 [CI, 0.77 to 1.38])		
Statin vs. control	Mortality	High (29, 79, 81–87)	Reduced risk (RR, 0.81 [CI, 0.71 to 0.94])	Reduced risk for MI, stroke, most composite vascular outcomes reported	NR
	ESRD	Low (79, 80)	No reduced risk (RR, 0.98 [CI, 0.62 to 1.56])		
Low-protein diet vs. usual-protein diet	Mortality	Low (93–96)	No reduced risk (RR, 0.58 [CI, 0.29 to 1.16])	Reduced risk for composite renal outcome (1 trial reporting)	Weight loss, weight gain, hyperkalemia
	ESRD	Low (92–94)	No reduced risk (RR, 1.62 [CI, 0.62 to 4.21])		
Strict vs. usual glycemic control	Mortality	Insufficient	NA	No reduced risk for other outcomes reported	NR
	ESRD	Insufficient	NA		
Intensive multicomponent treatment vs. usual care	Mortality	Low (97–101)	No reduced risk (RR, 0.91 [CI, 0.67 to 1.24])	Reduced risk for composite vascular outcomes (1 of 3 trials reporting)	NR
	ESRD	Low (16, 98–100)	No reduced risk (RR, 0.74 [CI, 0.26 to 2.08])		

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; ESRD = end-stage renal disease; MI = myocardial infarction; NA = not applicable; NR = not reported; RCT = randomized, controlled trial; RR= relative risk. * Adverse events were sparsely reported in the trials included in this study and often similar in control and treatment groups. † Data derived from a study comparing ACE inhibitor plus ARB combination therapy with either ARB or ACE inhibitor monotherapy.

risk for ESRD (46, 67) or all-cause mortality (46, 67, 68) compared with β -blocker monotherapy (Table 3). No statistically significant difference in renal outcomes was reported.

Calcium-Channel Blockers Versus Diuretics. Low-quality evidence showed that calcium-channel blocker monotherapy did not statistically significantly reduce the risk for ESRD compared with diuretic monotherapy (47) (Table 3). Mortality data were not reported. There were no statistically significant differences in renal or vascular outcomes reported.

Thiazide Diuretics Versus Placebo. No renal outcomes were reported for the comparison of thiazide diuretic monotherapy with placebo. Low-quality evidence showed no difference between the 2 groups in risk for all-cause mortality (69) (Table 3). Diuretic monotherapy statistically significantly reduced the risk for stroke and 1 composite vascular outcome.

Combination Therapy Versus Monotherapy

ACE Inhibitors Plus ARBs Versus ACE Inhibitors Alone. Low-quality evidence showed no statistically significant difference in risk for ESRD between treatment with ACE inhibitors plus ARBs compared with ACE inhibitors alone (70) (Table 3). Moderate-quality evidence also showed no statistically significant difference in the risk for all-cause mortality in the combined treatment group compared with monotherapy (50, 71, 72) (Table 3).

ACE Inhibitors Plus ARBs Versus ARBs Alone. There was no evidence directly comparing the risk for ESRD or mortality with ACE inhibitors plus ARBs compared with ARB monotherapy. However, 1 trial (60) compared ACE inhibitor plus ARB combination therapy with either ARB or ACE inhibitor monotherapy (results for monotherapy reported together); moderate-quality evidence showed no reduced risk for ESRD, and low-quality evidence showed no reduced risk for all-cause mortality in the combined treatment group (Table 3).

Other Comparisons. Evidence was insufficient to determine the effect of the following comparisons on ESRD or mortality: ACE inhibitors plus calcium-channel blockers versus ACE inhibitor monotherapy or calcium-channel blocker monotherapy; ACE inhibitors plus diuretics versus ACE inhibitor monotherapy; and ACE inhibitors plus diuretics versus placebo.

Combination Therapy Versus Combination Therapy

Evidence was insufficient to determine the effect of the following comparisons on ESRD or mortality: ACE inhibitor plus ARB versus ACE inhibitor plus aldosterone antagonist; ACE inhibitor plus diuretic versus ACE inhibitor plus calcium-channel blocker; ACE inhibitor plus aldosterone antagonist versus ACE inhibitor plus placebo; and ACE inhibitor and ARB plus aldosterone antagonist versus ACE inhibitor and ARB plus placebo.

Strict Versus Standard Blood Pressure Control

Seven studies (46, 73–78) randomly assigned patients with stage 1 to 3 CKD (mostly with hypertension) to strict versus standard blood pressure targets, and medications varied among studies. The mean achieved blood pressure ranged from 128 to 133 mm Hg systolic and 75 to 81 mm Hg diastolic in the strict-control group versus 134 to 141 mm Hg systolic and 81 to 87 mm Hg diastolic in the standard-control group. Low-quality evidence showed no difference in risk for ESRD (46, 75, 78) or all-cause mortality (46, 75, 77, 78). between strict and standard blood pressure control (Table 3). There was no statistically significant difference between other reported vascular or renal outcomes.

Non-Blood Pressure Control Interventions

Statins Versus Control

Low-quality evidence showed that treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) did not reduce the risk for ESRD in patients with dyslipidemia and stage 1 to 3 CKD (79, 80) (Table 3). Moderate-quality evidence (subgroup analyses) showed that statins reduced the risk for all-cause mortality in patients with dyslipidemia as well as stage 1 to 3 CKD (RR, 0.81 [CI, 0.71 to 0.94]) (29, 79, 81–87). Statins were found to statistically significantly reduce the risk for MI, stroke, and most composite vascular outcomes reported.

Low-quality evidence from 1 trial (88) that reported on mortality in patients with CKD and dyslipidemia treated with high-dose atorvastatin (80 mg/d) versus low-dose atorvastatin (10 mg/d) found no difference in the risk for all-cause mortality (7.0% vs. 7.5%, respectively; RR 0.93 [CI, 0.72 to 1.20]); however, the high-dose atorvastatin group had a decreased risk for CHF hospitalization and composite vascular outcomes. Another study (89) reported no differences between high- and low-dose statin treatment in terms of composite vascular outcomes. No results were reported for ESRD or any renal outcomes.

Gemfibrozil Versus Placebo or Control

Low-quality evidence from a single trial (90) supports no difference in all-cause mortality reduction for treatment with the triglyceride-lowering medication gemfibrozil compared with placebo (RR, 0.91 [CI, 0.52 to 1.62]). No individuals in the study experienced ESRD. Gemfibrozil was found to statistically significantly reduce the risk for the composite outcome of fatal coronary heart disease, nonfatal MI, or stroke compared with placebo. Evidence was insufficient to determine whether treatment with gemfibrozil reduced the risk for ESRD or all-cause mortality compared with a triglyceride-lowering diet (91).

Low-Protein Diet Versus Usual-Protein Diet

Low-quality evidence from 3 trials comparing a low-protein diet with usual diet in patients with stage 1 to 3 CKD (92–94) showed no statistically significant difference

in association with ESRD (Table 3), and data from 4 trials (93–96) showed no statistically significant difference in the risk for all-cause mortality (Table 3).

Intensive Diabetes Control Versus Usual Care

Evidence was insufficient to determine whether intensive glycemic control in patients with type 1 or type 2 diabetes improved the risk for ESRD or all-cause mortality.

Intensive Multicomponent Treatment Versus Usual Care

Low-quality evidence showed no reduced risk in ESRD (97–100) or all-cause mortality (97–101) between the intensive multicomponent treatment and usual care (Table 3).

HARMS OF TREATMENT STRATEGIES FOR STAGE 1 TO 3 CKD

Most of the trials did not report adverse events, and those reported were similar for patients with CKD and other patients treated with the same drugs. The most commonly reported adverse event with ACE inhibitor treatment was cough. Therapy with ARBs was associated with statistically significantly increased hyperkalemia (3.2% vs. 1.3% with placebo; RR, 2.38 [CI, 1.57 to 3.61]). Adverse events associated with β -blocker therapy included heart failure, fatigue, bradycardia, dizziness, and hypotension. One trial (60) reported that ACE inhibitor plus ARB was associated with statistically significantly increased risk for cough, hyperkalemia, hypotension, and acute kidney failure requiring dialysis (RR, 1.95 [CI, 1.09 to 3.49]) compared with ACE inhibitor monotherapy. No adverse events were reported for other therapies included in the review.

SUMMARY

No randomized, controlled trials evaluated the benefits and harms of screening for stage 1 to 3 CKD. Benefit of screening would be derived from the anticipated benefits of treatment. No studies tested the sensitivity and specificity of 1-time screening in the general population using estimated GFR or albuminuria for diagnosis of CKD. There was no evidence evaluating the benefits of early treatment on clinical outcomes of patients with CKD who were identified through screening. Potential harms of screening include labeling, adverse effects of unnecessary tests and treatments, and financial ramifications.

No randomized, controlled trials evaluated the benefits and harms of monitoring patients with stage 1 to 3 CKD for disease progression. Rates of annual GFR decline vary, and lower GFR rates have been associated with increased mortality risk. Because there is considerable individual variability in albuminuria measurements, there are concerns about the accuracy of longitudinal measurement for CKD progression. Also, evidence evaluating the validity and reliability of the monitoring tests is lacking. Potential

harms of monitoring for CKD progression are the same as those for screening.

Many patients, regardless of CKD status, are already taking ACE inhibitors, ARBs, statins, or other drugs to treat existing comorbid conditions. Monotherapy with ACE inhibitors or ARBs statistically significantly reduced the risk for ESRD in patients with CKD, but benefits were limited to patients with macroalbuminuria, and most of these patients also had diabetes and hypertension. No studies showed that treatment with other drug monotherapy statistically significantly reduced the risk for ESRD. Treatment with statins reduced the risk for mortality, MI, and stroke in patients with hyperlipidemia. β -Blocker therapy also reduced the risk for mortality, MI, and CHF, although most of the patients included in the studies were already being treated with ACE inhibitors or ARBs. Calcium-channel blockers, diuretics, a low-protein diet, intensive diabetes control, and intensive multicomponent interventions did not reduce the risk for ESRD or all-cause mortality compared with placebo or control.

None of the combination therapies were shown to have a beneficial effect on reducing the risk for ESRD or all-cause mortality compared with monotherapy. Evidence was insufficient to determine the efficacy of various combination therapies compared with other combination therapies for reducing risk for ESRD or all-cause mortality.

Harms of pharmacologic treatments were not generally reported specifically for patients with patients and were similar to adverse effects experienced by all other patients treated with the same drug (Table 3).

The **Figure** summarizes the recommendations.

RECOMMENDATIONS

Recommendation 1: ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: weak recommendation, low-quality evidence)

Screening is recommended when it improves important clinical outcomes while limiting harms for screened individuals. Screening for CKD does not meet these generally accepted criteria for population-based screening (102). Although prevalence increases with age, CKD has a relatively low prevalence in the general population without risk factors. The accuracy of available screening measures for CKD or its progression is uncertain. No available evidence evaluates the sensitivity and specificity of various screening tests in the general population. Albuminuria and serum creatinine-derived estimated GFR are widely available in primary care settings, with a high sensitivity and high specificity for 1-time measures of renal damage or dysfunction, but the risk for false-positive results is also very high (5, 103, 104).

There was no evidence evaluating the benefits of early treatment in patients identified by screening. In contrast, harms, including false-positive results, disease labeling, and

Figure. Summary of the American College of Physicians guideline on screening, monitoring, and treatment of stage 1 to 3 CKD.



Summary of the American College of Physicians Guideline on Screening, Monitoring, and Treatment of Stage 1 to 3 CKD

Disease/Condition	Stage 1 to 3 CKD
Target Audience	Internists, family physicians, and other clinicians
Target Patient Population	Adults with stage 1 to 3 CKD
Interventions Evaluated	<p>Screening and monitoring tests:</p> <ul style="list-style-type: none"> • Estimated GFR • Microalbuminuria • Proteinuria <p>Treatments:</p> <ul style="list-style-type: none"> • ACE inhibitors • ARBs • β-Blockers • Calcium-channel blockers • Thiazide diuretics • 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors • Low-protein diet • Intensive diabetes control • Intensive multicomponent interventions
Outcomes Evaluated	All-cause mortality, cardiovascular mortality, myocardial infarction, stroke, chronic heart failure, composite vascular outcomes (including but not limited to myocardial infarction, stroke, and hospitalization for heart failure), composite renal outcomes (including but not limited to doubling of serum creatinine, need for dialysis, and reduction of GFR by 50%), ESRD, quality of life, physical function, and activities of daily living
Benefits of Screening, Monitoring, and Treatment	<p>Screening: Early identification of undiagnosed or possibly asymptomatic CKD that may help in reducing mortality and morbidity (such as kidney failure or clinical cardiovascular events) associated with CKD</p> <p>Monitoring: Identification of progression to later stages of CKD that may help in reducing mortality and morbidity (such as kidney failure or clinical cardiovascular events) associated with CKD</p> <p>Treatment: Reduced risk for mortality, ESRD, or other vascular or renal outcomes</p>
Harms of Screening, Monitoring, and Treatment	<p>Screening: False-positive results, disease labeling, unnecessary tests and adverse effects, unnecessary treatments and adverse effects, financial and insurance ramifications</p> <p>Monitoring: Incorrect reclassification of CKD status, unnecessary tests and adverse effects, disease labeling, adverse events associated with change of treatment, financial and insurance ramifications</p> <p>Treatment: Adverse effects vary depending on treatment but may include cough, hyperkalemia, hypotension, heart failure, fatigue, bradycardia, dizziness, and acute kidney failure requiring dialysis</p>
Recommendations	<p><i>Recommendation 1: ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: weak recommendation, low-quality evidence)</i></p> <p><i>Recommendation 2: ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II-receptor blocker. (Grade: weak recommendation, low-quality evidence)</i></p> <p><i>Recommendation 3: ACP recommends that clinicians select pharmacologic therapy that includes either an angiotensin-converting enzyme inhibitor (moderate-quality evidence) or an angiotensin II-receptor blocker (high-quality evidence) in patients with hypertension and stage 1 to 3 chronic kidney disease. (Grade: strong recommendation)</i></p> <p><i>Recommendation 4: ACP recommends that clinicians choose statin therapy to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. (Grade: strong recommendation, moderate-quality evidence)</i></p>
High-Value Care	On the basis of the literature reviewed, ACP found no evidence that screening for CKD in patients without risk factors improves clinical outcomes. In addition, there is no proven additional benefit of screening adults who are already taking ACE inhibitors or ARBs for microalbuminuria. In the absence of any known benefits, ordering screening laboratory studies is not going to have any effect on the clinical outcomes of the patient and will add costs to the health care system due to additional follow-up tests, including follow-up tests as a result of false-positive screens, increased medical visits, and costs of keeping or obtaining health insurance.
Clinical Considerations	<p>Many patients with CKD may already be taking ACE inhibitors, ARBs, or statins to treat existing conditions. Often, these therapies would be indicated regardless of CKD status owing to comorbid conditions.</p> <p>Patients with CKD and macroalbuminuria could benefit from reduced risk for ESRD with ACE inhibitor or ARB monotherapy.</p>

ACE = angiotensin-converting enzyme; ARB = angiotensin II-receptor blocker; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate.

unnecessary testing and treatment, are associated with the screening. Given the potential harms of screening for stage 1 to 3 CKD and unknown benefits, current evidence does not support screening for stage 1 to 3 CKD in adults without risk factors.

Recommendation 2: ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II–receptor blocker. (Grade: weak recommendation, low-quality evidence)

Evidence suggests that treatment with ACE inhibitors (moderate-quality evidence) or ARBs (high-quality evidence) reduces the risk for ESRD. Whether there are additional benefits of testing patients who are already taking ACE inhibitors or ARBs for proteinuria is unknown. Proteinuria is an intermediate marker; there is no evidence that monitoring proteinuria levels in patients taking ACE inhibitors or ARBs is beneficial or that reduced proteinuria levels translate into improved outcomes for patients with CKD.

Recommendation 3: ACP recommends that clinicians select pharmacologic therapy that includes either an angiotensin-converting enzyme inhibitor (moderate-quality evidence) or an angiotensin II–receptor blocker (high-quality evidence) in patients with hypertension and stage 1 to 3 chronic kidney disease. (Grade: strong recommendation)

Evidence showed that treatment with ACE inhibitors (moderate-quality) or ARBs (high-quality) reduces the risk for ESRD in patients with stage 1 to 3 CKD. These medications also reduced composite renal outcomes, the risk for doubling of serum creatinine, and the progression from microalbuminuria to macroalbuminuria. Head-to-head trials revealed no difference in outcomes with ACE inhibitors or ARBs. The harms of ACE inhibitors include cough, angioedema, hyperkalemia, rash, loss of taste, and leukopenia. The harms of ARBs include hyperkalemia, angioedema, and dizziness.

The current evidence did not show any benefit of combination therapy with an ACE inhibitor plus an ARB compared with monotherapy with ACE inhibitors or ARBs. In addition, the risk for adverse effects significantly increased with ACE inhibitor plus ARB combination therapy, including cough, hyperkalemia, hypotension, and acute kidney failure requiring dialysis.

Evidence revealed no difference in ESRD or mortality between strict blood pressure control (128 to 133/75 to 81 mm Hg) and standard control (134 to 141/81 to 87 mm Hg).

Recommendation 4: ACP recommends that clinicians choose statin therapy to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. (Grade: strong recommendation, moderate-quality evidence)

High-quality evidence showed that statins reduced the risk for all-cause mortality. Evidence also showed that statins lower the risk for MI, stroke, and most cardiovascular outcomes in patients with stage 1 to 3 CKD. Patients

included in the studies had mean low-density lipoprotein levels of 142 mg/dL (range, 109 to 192 mg/dL).

Two recently published systematic reviews not included in the AHRQ report also showed benefits of lipid-lowering therapy or statin therapy in patients with CKD (105, 106). One study showed that statin therapy decreased mortality and cardiovascular events in patients with stage 1 to 3 CKD (105), and the other study showed that lipid-lowering therapy (including statins) decreased cardiac death and atherosclerosis-mediated cardiovascular events in patients with CKD (106). Low-quality evidence showed no effect on the risk for ESRD in patients with stage 1 to 3 CKD.

INCONCLUSIVE AREAS OF EVIDENCE

Screening for CKD in Asymptomatic Adults With Risk Factors

Although there are known risk factors for CKD (diabetes, hypertension, and cardiovascular disease), ACP found the current evidence insufficient to evaluate the benefits and harms of screening for CKD in asymptomatic adults with CKD risk factors.

Periodic Monitoring of Patients Diagnosed With Stage 1 to 3 CKD

No randomized, controlled trials evaluated the benefits and harms of monitoring patients with stage 1 to 3 CKD. There is a lack of evidence that modifying treatment when progression occurs improves patient outcomes. Harms also include adverse effects from follow-up tests, unnecessary testing, increased medical visits, and health care costs. Hence, ACP concluded there is no net benefit of routinely monitoring patients with stage 1 to 3 CKD, although individual monitoring could be helpful for some patients on the basis of their risk level. Examples of individual monitoring include 1) GFR to monitor progression of the disease, changes in functioning, or well-being over time; 2) monitoring blood pressure as both a cause and complication of CKD; 3) monitoring proteinuria and serum creatinine; and 4) monitoring pharmacologic medications.

ACP HIGH-VALUE CARE ADVICE

The ACP found no evidence that screening for CKD in adults without risk factors improves clinical outcomes. In addition, there is no proven benefit of screening adults who are already taking ACE inhibitors or ARBs for microalbuminuria. In the absence of evidence that screening improves clinical outcomes, testing will add costs, owing to both the screening test and to additional follow-up tests (including those resulting from false-positive findings), increased medical visits, and costs of keeping or obtaining health insurance.

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Note: Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians’ judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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References

1. Centers for Disease Control and Prevention. National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2010. Atlanta: U.S. Department of Health and Human Services, CDC; 2010. Accessed at www.cdc.gov/diabetes/pubs/factsheets/kidney.htm on October 10, 2013.
2. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1-136.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):S1-266. [PMID: 11904577]
4. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2010;80:17-28. [PMID: 21150873]
5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-12. [PMID: 19414839]
6. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, et al. Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment. Comparative Effectiveness Review No. 37. Prepared by the Minnesota Evidence-based Practice Center under contract no. HHSA 290-2007-10064-I. Rockville, MD: Agency for Healthcare Research and Quality; January 2012. AHRQ publication no. 11(12)-EHC075-EF. Accessed at www.ncbi.nlm.nih.gov/books/NBK84564/ on 9 October 2013.
7. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296-305. [PMID: 15385656]

8. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073-81. [PMID: 20483451]
9. Weiner DE, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis.* 2006;48:392-401. [PMID: 16931212]
10. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, et al; Osteoporotic Fractures Research Group. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med.* 2007;167:1333-9. [PMID: 17242313]
11. Ishani A, Paudel M, Taylor BC, Barrett-Connor E, Jamal S, Canales M, et al; Osteoporotic Fractures in Men (MrOS) Study Group. Renal function and rate of hip bone loss in older men: the Osteoporotic Fractures in Men Study. *Osteoporos Int.* 2008;19:1549-56. [PMID: 18392664]
12. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al; Alberta Kidney Disease Network. CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis.* 2009;54:24-32. [PMID: 19447535]
13. Khatri M, Nickolas T, Moon YP, Paik MC, Rundek T, Elkind MS, et al. CKD associates with cognitive decline. *J Am Soc Nephrol.* 2009;20:2427-32. [PMID: 19729443]
14. Wilhelm-Leen ER, Hall YN, Tamura MK, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med.* 2009;122:664-71.e2. [PMID: 19559169]
15. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, et al. 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. *Ann Intern Med.* 2012;156:570-81. [PMID: 22508734]
16. Barrett BJ, Garg AX, Goeree R, Levin A, Molzahn A, Rigatto C, et al. A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: a randomized controlled trial. *Clin J Am Soc Nephrol.* 2011;6:1241-7. [PMID: 21617090]
17. United States Renal Data System. United States Renal Data System 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases; 2010. Accessed at www.usrds.org/atlas10.aspx on 10 October 2013.
18. Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System. Atlanta: U.S. Department of Health and Human Services. Accessed at www.cdc.gov/ckd on 8 October 2013.
19. Ryan TP, Sloand JA, Winters PC, Corsetti JP, Fisher SG. Chronic kidney disease prevalence and rate of diagnosis. *Am J Med.* 2007;120:981-6. [PMID: 17976426]
20. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-54. [PMID: 16908915]
21. Miller WG, Bruns DE, Hortin GL, Sandberg S, Aakre KM, McQueen MJ, et al; National Kidney Disease Education Program-IFCC Working Group on Standardization of Albumin in Urine. Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem.* 2009;55:24-38. [PMID: 19028824]
22. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR; UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63:225-32. [PMID: 12472787]
23. Crepaldi G, Carta Q, Deferrari G, Mangili R, Navalesi R, Santeusano F, et al. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. The Italian Microalbuminuria Study Group in IDDM. *Diabetes Care.* 1998;21:104-10. [PMID: 9538979]
24. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *Am J Med.* 1995;99:497-504. [PMID: 7485207]

25. O'Hare P, Bilbous R, Mitchell T, O'Callaghan CJ, Viberti GC; **Ace-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects Study Group**. Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension: results of a randomized controlled trial. *Diabetes Care*. 2000;23:1823-9. [PMID: 11128360]
26. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med*. 1993;118:577-81. [PMID: 8452322]
27. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev*. 2006;CD006257. [PMID: 17054288]
28. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*. 1997;349:1857-63. [PMID: 9217756]
29. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al; **Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators**. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110:2809-16. [PMID: 15492322]
30. Bojestig M, Karlberg BE, Lindström T, Nystrom FH. Reduction of ACE activity is insufficient to decrease microalbuminuria in normotensive patients with type 1 diabetes. *Diabetes Care*. 2001;24:919-24. [PMID: 11347755]
31. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al; **HOPE Study Investigators**. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421-6. [PMID: 11466120]
32. Katayama S, Kikkawa R, Isogai S, Sasaki N, Matsuura N, Tajima N, et al. Effect of captopril or imidapril on the progression of diabetic nephropathy in Japanese with type 1 diabetes mellitus: a randomized controlled study (JAPAN-IDDM). *Diabetes Res Clin Pract*. 2002;55:113-21. [PMID: 11796177]
33. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993;329:1456-62. [PMID: 8413456]
34. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J; **DIABHYCAR Study Investigators**. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ*. 2004;328:495. [PMID: 14960504]
35. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med*. 1996;334:939-45. [PMID: 8596594]
36. Muirhead N, Feagan BF, Mahon J, Lewanczuk RZ, Rodger NW, Botteri F, et al. The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. *Current Therapeutic Research*. 1999;60:650-60.
37. Perkovic V, Ninomiya T, Arima H, Gallagher M, Jardine M, Cass A, et al. Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. *J Am Soc Nephrol*. 2007;18:2766-72. [PMID: 17804673]
38. Ruggenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999;354:359-64. [PMID: 10437863]
39. Sano T, Kawamura T, Matsumae H, Sasaki H, Nakayama M, Hara T, et al. Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care*. 1994;17:420-4. [PMID: 8062609]
40. Trevisan R, Tiengo A. Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. North-East Italy Microalbuminuria Study Group. *Am J Hypertens*. 1995;8:876-83. [PMID: 8541002]
41. Solomon SD, Rice MM, K AJ, Jose P, Domanski M, Sabatine M, et al; **Prevention of Events with ACE inhibition (PEACE) Investigators**. Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation*. 2006;114:26-31. [PMID: 16801465]
42. Brugs JJ, Boersma E, Chonchol M, Deckers JW, Bertrand M, Remme WJ, et al; **EUROPA Investigators**. The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial. *J Am Coll Cardiol*. 2007;50:2148-55. [PMID: 18036453]
43. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000;355:253-9. [PMID: 10675071]
44. Hannedouche T, Landais P, Goldfarb B, el Esper N, Fournier A, Godin M, et al. Randomised controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. *BMJ*. 1994;309:833-7. [PMID: 7950612]
45. van Essen GG, Apperloo AJ, Rensma PL, Stegeman CA, Sluiter WJ, de Zeeuw D, et al. Are angiotensin converting enzyme inhibitors superior to beta blockers in retarding progressive renal function decline? *Kidney Int Suppl*. 1997;63:S58-62. [PMID: 9407423]
46. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al; **African American Study of Kidney Disease and Hypertension Study Group**. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-31. [PMID: 12435255]
47. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT Jr, Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165:936-46. [PMID: 15851647]
48. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, et al; **Diabetics Exposed to Telmisartan and Enalapril Study Group**. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004;351:1952-61. [PMID: 15516696]
49. Lacourcière Y, Bélanger A, Godin C, Hallé JP, Ross S, Wright N, et al. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. *Kidney Int*. 2000;58:762-9. [PMID: 10916100]
50. Menne J, Farsang C, Deak L, Klebs S, Meier M, Handrock R, et al. Valsartan in combination with lisinopril versus the respective high dose monotherapies in hypertensive patients with microalbuminuria: the VALERIA trial. *J Hypertens*. 2008;26:1860-7. [PMID: 18698222]
51. Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol*. 2007;18:1889-98. [PMID: 17494885]
52. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al; **African American Study of Kidney Disease and Hypertension (AASK) Study Group**. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285:2719-28. [PMID: 11386927]
53. Zucchelli P, Zuccala A, Gaggi R. Comparison of the effects of ACE inhibitors and calcium channel blockers on the progression of renal failure. *Nephrol Dial Transplant*. 1995;10 Suppl 9:46-51. [PMID: 8643208]
54. Fogari R, Preti P, Zoppi A, Rinaldi A, Corradi L, Pasotti C, et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. *Am J Hypertens*. 2002;15:1042-9. [PMID: 12460699]
55. Marin R, Ruilope LM, Aljama P, Aranda P, Segura J, Diez J; **Investigators of the ESPIRAL Study**. Efecto del tratamiento antihipertensivo Sobre la Progresión de la Insuficiencia Renal en pacientes no diabéticos. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *J Hypertens*. 2001;19:1871-6. [PMID: 11593109]
56. Zucchelli P, Zuccala A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int*. 1992;42:452-8. [PMID: 1405330]
57. Cinotti GA, Zucchelli PC; **Collaborative Study Group**. Effect of lisinopril on the progression of renal insufficiency in mild proteinuric non-diabetic nephropathies. *Nephrol Dial Transplant*. 2001;16:961-6. [PMID: 11328901]
58. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al; **RENAAL Study Investigators**. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-9. [PMID: 11565518]

59. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-60. [PMID: 11565517]
60. Tobe SW, Clase CM, Gao P, McQueen M, Grosshennig A, Wang X, et al; ONTARGET and TRANSCEND Investigators. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. *Circulation*. 2011;123:1098-107. [PMID: 21357827]
61. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870-8. [PMID: 11565519]
62. Ogawa S, Takeuchi K, Mori T, Nako K, Tsubono Y, Ito S. Effects of monotherapy of temocapril or candesartan with dose increments or combination therapy with both drugs on the suppression of diabetic nephropathy. *Hypertens Res*. 2007;30:325-34. [PMID: 17541211]
63. Castagno D, Jhund PS, McMurray JJ, Lewsey JD, Erdmann E, Zannad F, et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. *Eur J Heart Fail*. 2010;12:607-16. [PMID: 20354032]
64. Cohen-Solal A, Kotecha D, van Veldhuisen DJ, Babalis D, Bohm M, Coats AJ, et al; SENIORS Investigators. Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial. *Eur J Heart Fail*. 2009;11:872-80. [PMID: 19648605]
65. Ghali JK, Wikstrand J, Van Veldhuisen DJ, Fagerberg B, Goldstein S, Hjalmarsen A, et al; ERIT-HF Study Group. The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J Card Fail*. 2009;15:310-8. [PMID: 19398079]
66. Wali RK, Iyengar M, Beck GJ, Charyan DM, Chonchol M, Lukas MA, et al. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. *Circ Heart Fail*. 2011;4:18-26. [PMID: 21036889]
67. Wright JT Jr, Kusek JW, Toto RD, Lee JY, Agodoa LY, Kirk KA, et al. Design and baseline characteristics of participants in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Control Clin Trials*. 1996;17(4 Suppl):3S-16S. [PMID: 8889350]
68. Bakris G, Burgess E, Weir M, Davidai G, Koval S; AMADEO Study Investigators. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int*. 2008;74:364-9. [PMID: 18496508]
69. Pahor M, Shorr RI, Somes GW, Cushman WC, Ferrucci L, Bailey JE, et al. Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly program. *Arch Intern Med*. 1998;158:1340-5. [PMID: 9645829]
70. Kanno Y, Takenaka T, Nakamura T, Suzuki H. Add-on angiotensin receptor blocker in patients who have proteinuric chronic kidney diseases and are treated with angiotensin-converting enzyme inhibitors. *Clin J Am Soc Nephrol*. 2006;1:730-7. [PMID: 17699280]
71. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation*. 2009;120:1577-84. [PMID: 19805651]
72. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonist to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol*. 2009;20:2641-50. [PMID: 19926893]
73. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330:877-84. [PMID: 8114857]
74. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. *Am J Kidney Dis*. 1999;34:809-17. [PMID: 10561135]
75. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365:939-46. [PMID: 15766995]
76. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int*. 2002;61:1086-97. [PMID: 11849464]
77. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension*. 1989;13(5 Suppl):180-93. [PMID: 2490833]
78. Toto RD, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA. "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. *Kidney Int*. 1995;48:851-9. [PMID: 7474675]
79. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Sharman JE, Coombes JS. Effects of atorvastatin on arterial stiffness in chronic kidney disease: a randomised controlled trial. *J Atheroscler Thromb*. 2010;17:235-41. [PMID: 20032570]
80. Rahman M, Baimbridge C, Davis BR, Barzilay J, Basile JN, Henriquez MA, et al; ALLHAT Collaborative Research Group. Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Kidney Dis*. 2008;52:412-24. [PMID: 18676075]
81. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindendfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. *Am J Kidney Dis*. 2007;49:373-82. [PMID: 17336698]
82. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al; CARDS Investigators. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis*. 2009;54:810-9. [PMID: 19540640]
83. Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP; ALLIANCE Investigators. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. *Am J Kidney Dis*. 2009;53:741-50. [PMID: 19216014]
84. Lemos PA, Serruys PW, de Feyter P, Mercado NF, Goedhart D, Saia F, et al. Long-term fluvastatin reduces the hazardous effect of renal impairment on four-year atherosclerotic outcomes (a LIPS substudy). *Am J Cardiol*. 2005;95:445-51. [PMID: 15695126]
85. Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y; MEGA Study Group. Pravastatin and cardiovascular risk in moderate chronic kidney disease. *Atherosclerosis*. 2009;206:512-7. [PMID: 19423108]
86. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol*. 2010;55:1266-73. [PMID: 20206456]
87. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*. 2004;110:1557-63. [PMID: 15364796]
88. Shepherd J, Kastelein JJ, Bitner V, Deedwania P, Breazna A, Dobson S, et al; TNT (Treating to New Targets) Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51:1448-54. [PMID: 18402899]
89. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendzus K, Bulbulia R, Rahimi K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658-69. [PMID: 21067805]
90. Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Effect of gemfibrozil on change in renal function in men with moderate chronic renal insufficiency and coronary disease. *Am J Kidney Dis*. 2004;44:832-9. [PMID: 15492949]
91. Samuelsson O, Attman PO, Knight-Gibson C, Kron B, Larsson R, Mulec H, et al. Effect of gemfibrozil on lipoprotein abnormalities in chronic renal insufficiency: a controlled study in human chronic renal disease. *Nephron*. 1997;75:286-94. [PMID: 9069450]
92. Dussol B, Iovanna C, Raccach D, Darmon P, Morange S, Vague P, et al. A randomized trial of low-protein diet in type 1 and in type 2 diabetes mellitus

- patients with incipient and overt nephropathy. *J Ren Nutr.* 2005;15:398-406. [PMID: 16198932]
93. Koya D, Haneda M, Inomata S, Suzuki Y, Suzuki D, Makino H, et al; **Low-Protein Diet Study Group.** Long-term effect of modification of dietary protein intake on the progression of diabetic nephropathy: a randomised controlled trial. *Diabetologia.* 2009;52:2037-45. [PMID: 19652945]
94. Rosman JB, Langer K, Brandl M, Piers-Becht TP, van der Hem GK, ter Wee PM, et al. Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int Suppl.* 1989;27:S96-102. [PMID: 2636680]
95. Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, et al. Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int.* 1997;52:778-91. [PMID: 9291200]
96. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet.* 1991;337:1299-304. [PMID: 1674294]
97. Barrett BJ, Garg AX, Goeree R, Levin A, Molzahn A, Rigatto C, et al. A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: a randomized controlled trial. *Clin J Am Soc Nephrol.* 2011;6:1241-7. [PMID: 21617090]
98. Chan JC, So WY, Yeung CY, Ko GT, Lau IT, Tsang MW, et al; **SURE Study Group.** Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care.* 2009;32:977-82. [PMID: 19460913]
99. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348:383-93. [PMID: 12556541]
100. Joss N, Ferguson C, Brown C, Deighan CJ, Paterson KR, Boulton-Jones JM. Intensified treatment of patients with type 2 diabetes mellitus and overt nephropathy. *QJM.* 2004;97:219-27. [PMID: 15028852]
101. Harris LE, Luft FC, Rudy DW, Kesterson JG, Tierney WM. Effects of multidisciplinary case management in patients with chronic renal insufficiency. *Am J Med.* 1998;105:464-71. [PMID: 9870830]
102. Wilson J, Jungner G. Principles and practice of screening for disease. World Health Organization Chronicle Geneva. 1968;22:473.
103. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 2003;41:1-12. [PMID: 12500213]
104. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med.* 2003;348:2285-93. [PMID: 12788992]
105. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:263-75. [PMID: 22910937]
106. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:251-62. [PMID: 22910936]

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