Systematic Review: Blood Pressure Target in Chronic Kidney Disease and Proteinuria as an Effect Modifier

Ashish Upadhyay, MD; Amy Earley, BS; Shana M. Haynes, DHSc; and Katrin Uhlig, MD, MS

Background: The optimal blood pressure target in patients with chronic kidney disease (CKD) is unclear.

Purpose: To summarize trials comparing lower versus higher blood pressure targets in adult patients with CKD and focus on proteinuria as an effect modifier.

Data Sources: MEDLINE and the Cochrane Central Register of Controlled Trials (July 2001 through January 2011) were searched for reports from randomized, controlled trials with no language restriction.

Study Selection: Authors screened abstracts to identify reports from trials comparing blood pressure targets in adults with CKD that had more than 50 participants per group; at least 1-year follow-up; and outcomes of death, kidney failure, cardiovascular events, change in kidney function, number of antihypertensive agents, and adverse events.

Data Extraction: Reviewers extracted data on study design, methods, sample characteristics, interventions, comparators, outcomes, number of medications, and adverse events and rated study quality and quality of analyses for proteinuria subgroups.

Data Synthesis: Three trials with a total of 2272 participants were included. Overall, trials did not show that a blood pressure target of less than 125/75 to 130/80 mm Hg is more beneficial than a target of less than 140/90 mm Hg. Lower-quality evidence suggests that a low target may be beneficial in subgroups with proteinuria greater than 300 to 1000 mg/d. Participants in the low target groups needed more antihypertensive medications and had a slightly higher rate of adverse events.

Limitations: No study included patients with diabetes. Trial duration may have been too short to detect differences in clinically important outcomes, such as death and kidney failure. Ascertainment and reporting of adverse events was not uniform.

Conclusion: Available evidence is inconclusive but does not prove that a blood pressure target of less than 130/80 mm Hg improves clinical outcomes more than a target of less than 140/90 mm Hg in adults with CKD. Whether a lower target benefits patients with proteinuria greater than 300 to 1000 mg/d requires further study.

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ratio >0.03 g/g or dipstick-positive albuminuria), or elevated urinary protein level [>300 mg/d, or urinary protein–creatinine ratio >0.2 g/g]) (8). Studies had to report at least 1 of the following outcomes: death, kidney failure, clinical cardiovascular events, categorical change in kidney function, rate of change in GFR (GFR slope), and number of antihypertensive agents needed to achieve blood pressure targets. Adverse events of interest were patient withdrawal because of adverse events, decrease in drug dose or discontinuation of therapy, and symptoms related to hypotension. We excluded studies with fewer than 50 participants per group or follow-up shorter than 1 year.

Data Extraction and Quality Assessment

One of the authors extracted data from each article, and another author confirmed the data extraction. We extracted data on study design, methods, sample characteristics, interventions, comparators, outcomes, number of medications, and adverse events.

We graded overall study quality as good, fair, or poor (9–11). Studies were graded by one of the authors, which was confirmed by another author and finalized in a meeting of all authors. Two authors perused the inclusion and exclusion criteria of the trials to assess applicability.

We assessed the quality of the subgroup analyses by baseline proteinuria on the basis of recently proposed criteria for reporting and interpreting subgroup analyses (12, 13). Although we examined published articles and articles on study designs, we did not contact investigators for unpublished answers to our quality questions.

Data Synthesis and Statistical Analysis

Data were summarized in tables and synthesized in narrative form. Given the limited number of trials and the clinical heterogeneity for types of CKD, measures of proteinuria, and outcome definitions, we did not perform quantitative meta-analysis.

Role of the Funding Source

The authors are supported by KDIGO to conduct systematic reviews and provide methods support for developing KDIGO guidelines, including the ongoing guideline on management of blood pressure in CKD. The findings were presented to the KDIGO guideline Work Group, and the manuscript was confidentially shared with the Work Group Chairs, who approved submission but did not provide feedback or comments on the manuscript. The funding source did not participate in the design, conduct, or reporting of the study.

RESULTS

Search Yield

The Figure summarizes the search yield. Eight reports from 3 RCTs with a total of 2272 patients were included in this review (14–21). No articles examined blood pressure targets exclusively in patients with CKD and diabetes.

Trial Characteristics

The 3 RCTs included in this review are the MDRD (Modification of Diet in Renal Disease) Study (14–16), the AASK (African American Study of Kidney Disease and Hypertension) Trial (17, 18), and the REIN-2 (Ramipril Efficacy in Nephropathy 2) trial (19). The MDRD Study and AASK Trial also have reports on posttrial observational follow-up (20, 21). All trials provide subgroup analyses by baseline proteinuria levels. Trial characteristics are summarized in Table 1.

The MDRD Study A included 585 patients with GFRs of 25 to 55 mL/min per 1.73 m² and Study B included 255 patients with GFRs of 13 to 24 mL/min per 1.73 m². Patients with diabetes who required insulin were excluded from the study, and only 3% of patients were classified as having diabetic nephropathy. The trial phase had a 2 × 2 factorial design, and patients were randomly assigned to a low or usual blood pressure target and 1 of 2 types of diet. The use of all antihypertensive agents was allowed, but angiotensin-converting enzyme (ACE) inhibitors, with or without a diuretic, were encouraged as the first-choice agents and calcium-channel blockers, with or without a diuretic, were encouraged as the second-choice

BP = blood pressure; KDIGO = Kidney Disease: Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative.
agents. In the posttrial follow-up observation lasting a mean of 6 years, no specific blood pressure target or antihypertensive agent was recommended.

The AASK Trial included black adults with hypertensive nephrosclerosis. Patients with diabetes were excluded from the study. The trial phase had a 3 × 2 factorial design, and patients were randomly assigned to a low or usual blood pressure target and therapy with 1 of 3 initial antihypertensive agents (ACE inhibitor, \( \beta \)-blocker, or dihydropyridine calcium-channel blocker). The trial protocol allowed the sequential addition of furosemide, doxazosin, clonidine, hydralazine, and minoxidil to achieve the randomized blood pressure target. In the 8- to 12-year posttrial follow-up observation, all patients were assigned the blood pressure target of less than 130/80 mm Hg and were treated with either an ACE inhibitor or an angiotensin-receptor blocker.

The REIN-2 trial included patients with proteinuria greater than 1000 mg/d for at least 3 months. Patients with proteinuria between 1000 and 3000 mg/d were included if their creatinine clearance was less than 45 mL/minute per 1.73 m\(^2\), and patients with proteinuria greater than 3000 mg/d were included if their creatinine clearance was less than 70 mL/minute per 1.73 m\(^2\). Patients with type 1 diabetes mellitus were excluded. All patients were treated with the ACE inhibitor ramipril, 5 mg/d, during the trial. The dihydropyridine calcium-channel blocker felodipine, 5 to 10 mg/d, was an add-on therapy in the group assigned to the low blood pressure target. Antihypertensive agents other than ACE inhibitors, angiotensin-II–receptor blockers, and dihydropyridine calcium-channel blockers were allowed in both groups.

### Quality Assessment

Methodological quality of the 3 trials was graded as good. Quality of the follow-up reports was graded as fair because the original trial interventions were not continued.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDRD Study (n = 840)</th>
<th>AASK Trial (n = 1094)</th>
<th>REIN-2 Trial (n = 338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, y</td>
<td>Trial: 4 (mean, 2.2)</td>
<td>Trial: 4 (median, 3.8)</td>
<td>3 (median, 1.6)</td>
</tr>
<tr>
<td>Posttrial: 7 (mean, 6.2)</td>
<td>Posttrial: 8.8-12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of CKD</td>
<td>Nondiabetic CKD</td>
<td>Hypertensive nephrosclerosis</td>
<td>ND (excluded T1DM)</td>
</tr>
<tr>
<td>Race</td>
<td>White: 85%</td>
<td>Black: 100%</td>
<td>ND (conducted in Europe)</td>
</tr>
<tr>
<td>Applicable CKD stage</td>
<td>3–4</td>
<td>3</td>
<td>3–4</td>
</tr>
<tr>
<td>Inclusion criterion of kidney function (measured GFR or CrCl), mL/min per 1.73 m(^2)</td>
<td>GFR, 13–55</td>
<td>GFR, 20–65</td>
<td>CrCl &lt;70 if proteinuria &gt;3000 mg/d</td>
</tr>
<tr>
<td>Baseline kidney function (measured GFR), mL/min per 1.73 m(^2)</td>
<td>Low BP target: 33</td>
<td>Low BP target: 46</td>
<td>Low BP target: 36</td>
</tr>
<tr>
<td>Baseline proteinuria category</td>
<td>300–1000 mg/d</td>
<td>USUAL BP target: 45</td>
<td>Usual BP target: 34</td>
</tr>
<tr>
<td>Proteinuria exclusion criteria</td>
<td>UPE &gt;10 000 mg/d</td>
<td>UPCR &gt;2.5 g/g</td>
<td>UPE &lt;1000 mg/d if CrCl &lt;45 mL/min per 1.73 m(^2)</td>
</tr>
<tr>
<td>Median UPE: Low BP target: 390 mg/d</td>
<td>Mean UPCR (IQR), by subgroup: UPCR &lt;0.22 g/g</td>
<td>Mean UPCR (IQR), by subgroup: UPCR ≥0.22 g/g</td>
<td>UPE &lt;3000 mg/d if CrCl is 45–70 mL/min per 1.73 m(^2)</td>
</tr>
<tr>
<td>Median UPCR (IQR): Low BP target: 0.08 g/g (0.03–0.36 g/g)</td>
<td>Median UPCR (IQR), by subgroup: UPCR ≥0.22 g/g</td>
<td>Median UPCR (IQR), by subgroup: UPCR ≥0.22 g/g</td>
<td>UPE &lt;3000 mg/d if CrCl is 45–70 mL/min per 1.73 m(^2)</td>
</tr>
<tr>
<td>BP inclusion criteria, mm Hg</td>
<td>MAP ≤125</td>
<td>DBP &lt;95</td>
<td>ND</td>
</tr>
<tr>
<td>Target BP, mm Hg</td>
<td>Low BP target: MAP ≤92 (&lt;125/75)*</td>
<td>Low BP target: MAP &lt;92</td>
<td>Low BP target: &lt;130/80</td>
</tr>
<tr>
<td>Achieved BP, mm Hg</td>
<td>Low BP target: MAP ≤107 (&lt;140/90)*</td>
<td>Low BP target: MAP &lt;102–107</td>
<td>Low BP target: &lt;130/80</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Rate of change in GFR</td>
<td>Rate of change in GFR and composite of ≥50% (or ≥25 mL/min per 1.73 m(^2)) reduction in GFR, ESRD, or death</td>
<td>ESRD</td>
</tr>
<tr>
<td>Study quality</td>
<td>Trial: Good</td>
<td>Posttrial: Fair</td>
<td>Good</td>
</tr>
</tbody>
</table>

AASK = African American Study of Kidney Disease and Hypertension; BP = blood pressure; CKD = chronic kidney disease; CrCl = creatinine clearance; DBP = diastolic blood pressure; ESRD = end-stage renal disease; GFR = glomerular filtration rate; IQR = interquartile range; MAP = mean arterial pressure; MDRD = Modification of Diet in Renal Disease; ND = no data; REIN-2 = Ramipril Efficacy in Nephropathy 2; T1DM = type 1 diabetes mellitus; UPCR = urinary protein–creatinine ratio; UPE = urinary protein excretion.

* In participants aged >61 y, target MAP was ≤98 mm Hg and ≤113 mm Hg for the low and usual target groups, respectively.
and, in the MDRD Study, the choice of agents and blood pressure targets were not defined.

Table 2 shows the quality assessment of the subgroup analyses by baseline proteinuria levels. Published articles reporting results and study design were reviewed for quality assessment (15–22).

**Trial Results**

Table 3 summarizes the trial and follow-up results, and Appendix Table 2 (available at www.annals.org) summarizes the results from the proteinuria subgroup and interaction analyses.

**Clinical Outcomes**

The MDRD Study, AASK Trial, and REIN-2 trial failed to show benefit for clinical outcomes from the low versus usual blood pressure targets. Although the point estimates in the MDRD Study and AASK Trial suggested that the low target might reduce kidney failure, the CIs...
around the estimates were wide and included the possibility of either important benefit or harm. The only statistically significant result was in the MDRD Study follow-up, which showed a 23% reduction (95% CI, 18% to 43%) in the hazard for kidney failure in the group assigned to the low target. Data on deaths and cardiovascular disease outcomes were not informative given the lack of ascertainment or low event rates.

**Proteinuria Subgroups**

The cut points and measures for proteinuria assessment varied across studies. A total of 11 subgroup results were reported; 7 showed benefits for the low blood pressure target in higher proteinuria subgroups (Appendix Table 2). Benefit was seen in subgroups with a urinary protein–creatinine ratio greater than 0.22 g/g in the AASK Trial (considered to correlate with urinary protein excretion >300 mg/d) and urinary protein excretion greater than 1000 mg/d in the MDRD Study. One subgroup analysis in the follow-up report from the AASK Trial showed that the usual blood pressure target was beneficial in patients with a urinary protein–creatinine ratio of 0.22 g/g or less for the composite outcome of a 50% decrease in GFR or kidney failure.

Inconsistencies between interaction tests and subgroup analyses were found within and across studies (Appendix Table 2). In the MDRD Study, overall results for the rate of decrease in GFR were negative, but the low blood pressure target was beneficial in high proteinuria subgroups (>1000 mg/d in MDRD Study A and >3000 mg/d in MDRD Study B). The interaction tests by baseline proteinuria were also positive, suggesting benefit of the low blood pressure target mainly in people with high proteinuria. In the follow-up report from the MDRD Study, however, the result for kidney failure was favorable for the low blood pressure target. Subgroup analysis showed that the low target was beneficial in patients with proteinuria greater than 1000 mg/d, but the interaction test by baseline proteinuria was not statistically significant, suggesting benefit of the low target in all proteinuria levels. In the AASK Trial, the results for the primary composite clinical outcome were negative, whereas the subgroup analysis showed that the low blood pressure target was beneficial in patients with urinary protein–creatinine ratios greater than 0.22 g/g in both the trial and follow-up. For the other composite outcomes, however, subgroup analyses and corresponding interaction tests favored lower blood pressure targets in the high proteinuria group only during follow-up.

**Number of Antihypertensive Agents**

In the MDRD Study, the mean number of antihypertensive agents prescribed per patient for the low and usual blood pressure target groups was 1.9 and 1.5, respectively, in Study A and 2.1 and 1.8 in Study B. In the AASK Trial, the mean number of antihypertensive agents was not reported, but the total number of drug classes used during the trial was 3.0 in the low target group and 2.4 in the usual target group.

**Adverse Events**

In the MDRD Study, participants were asked to report on 24 symptoms attributable to low blood pressure during each follow-up visit. Of the 24 symptoms, only the frequency of “feeling faint” differed significantly between the low and usual blood pressure target groups in both studies (Study A and Study B). “Feeling faint” was reported in 15% of visits per patient in the low target group compared with 12% in the usual target group in Study A \( (P = 0.0012) \) and 18% of visits per patient in the low target group compared with 12% in the usual target group in Study B \( (P = 0.009) \). More patients in the low target group also needed a reduction in antihypertensive medications because of persistent symptoms of hypotension (3.2% vs. 0.7% in the usual target group; \( P = 0.01 \)). The incidence of conditions requiring patient withdrawal from the study, however, did not differ between the groups.

In the AASK Trial, all participants were asked about shortness of breath, syncope, dizziness, and lightheadedness. In addition, the investigators also reported on the incidence of hyperkalemia, angioedema, edema, cough, and sexual dysfunction. Among all adverse events, only cough was more frequent in the low target group than in the usual target group (55% vs. 47%; \( P < 0.05 \)). This is not explained by the greater use of ACE inhibitors in the low target group, because the 3 \( \times 2 \) factorial design ensured similar distribution of drug classes in the 2 groups.

In the REIN-2 trial, 6 of 169 participants in the low target group and 3 of 169 participants in the usual target group had treatment-related adverse events that necessitated withdrawal from the trial. A total of 23% of participants in the low target group and 17% in the usual target group had serious adverse events, but specific events were not reported.

**Discussion**

This systematic review of RCTs in adults with CKD did not find conclusive evidence favoring a blood pressure target of less than 125/75 to 130/80 mm Hg rather than a target of less than 140/90 mm Hg. After a mean 2- to 4-year follow-up, the main trial results did not show benefit for clinical outcomes (14–19). Only the posttrial follow-up report from the MDRD Study showed benefit of the lower target for kidney failure after about a 6-year follow-up (21). Subgroup analyses by baseline proteinuria levels in the MDRD Study and AASK Trial, but not in the REIN-2 trial, suggest benefit for the lower target in patients with proteinuria greater than 1000 mg/d and urinary protein–creatinine ratio greater than 0.22 g/g, respectively (15–21). Treatment to a lower target required, on average, 0.3 to 0.6 additional antihypertensive drugs per patient.
(14, 17, 20). A slightly higher rate of adverse events was suggested in the low target groups (14, 17, 19).

Clinical heterogeneity in study populations and interventions may have resulted in some of the inconsistencies across trials. Trials studied participants with different causes of CKD and used different antihypertensive regimens. Only the AASK Trial had, by design, a balanced use of an ACE inhibitor, a β-blocker, and a calcium-channel blocker in each group. The benefit for kidney failure in the MDRD Study follow-up may have been confounded by the greater use of ACE inhibitors in the low target group than in the usual target group (51% vs. 32%). The lack of any benefit in the higher proteinuria subgroup of the REIN-2 trial was in the setting of all patients receiving an ACE inhibitor and the low target group also receiving the dihydropyridine calcium-channel blocker felodipine.

Trials were graded as good quality, whereas the reports from posttrial follow-up and subgroup analyses were graded as fair quality. Confidence in subgroup findings is enhanced if the purpose and categories for analysis are prespecified in the study design (12, 13, 23–25). The REIN-2 trial was the only study that had prespecified subgroup analysis by baseline proteinuria levels, but it did not report on interaction testing. Cut points and measurement techniques used for proteinuria subgroup analyses varied in all 3 studies. Results were inconsistent between interaction tests and subgroup analyses for the same or different outcomes, both within and across studies. Exploratory subgroup analyses, although important in generating hypotheses for future research, are often underpowered, susceptible to spurious results because of multiple testing, and vulnerable to reporting and publication biases (12, 13).

A major limitation of the evidence base is that the 3 trials excluded people with type 1 diabetes mellitus and included very few patients with diabetic kidney disease. In addition, trial duration may have been too short to detect differences for clinically important outcomes, such as death and kidney failure. We captured delayed effects by including reports from the posttrial follow-up, but these were limited by the possibility of confounding from lack of randomization. We also cannot discount publication bias or selective reporting of some outcomes or subgroup analyses, because we did not contact investigators for unpublished data. Studies with small sample sizes and short follow-up were excluded, but they probably would not have changed our conclusions. Ascertainment and reporting of adverse events were also inconsistent across studies.

To put our findings in the context of the current literature, we conducted a separate MEDLINE search to identify reviews on this topic published between 1 January 2008 and 31 December 2010 (search terms are provided in Appendix Table 3, available at www.annals.org). We believe ours is the only review specifically in patients with CKD and with a detailed analysis of effect modification by baseline proteinuria. The 2009 Cochrane review by Arguedas and colleagues (26) in patients with hypertension included the CKD trials and also found no benefit for a target lower than 140/90 mm Hg to 160/100 mm Hg for mortality or morbidity. The reviews by Rosendorff and Black (27) and Roy and colleagues (28) highlight limited evidence for a low blood pressure target in patients with cardiovascular disease and raise concern about impaired coronary perfusion from aggressive lowering of diastolic blood pressure in patients with coronary artery disease or left ventricular hypertrophy.

In addition to these reviews, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial provides important supplemental information (29). The ACCORD trial compared systolic blood pressure targets of less than 120 mm Hg and less than 140 mm Hg in more than 4000 patients with diabetes at high risk for cardiovascular outcomes. Most participants had normal kidney function, but approximately 40% had micro- or macroalbuminuria. The main result did not show any difference in the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death between the 2 groups, but GFR decreased below 30 mL/min per 1.73 m² more often and more serious adverse events were attributed to antihypertensive treatment in the low target group. Finally, several recent commentaries and editorials have also highlighted the controversies surrounding the topic of blood pressure targets in CKD (30–35).

Future research needs to address the evidence gap for patients with diabetes and CKD. A subgroup analysis of persons with elevated albuminuria in the ACCORD trial would be informative in this regard. For patients without diabetes, the ongoing SPRINT (Systolic Blood Pressure Intervention Trial) (36) and the HALT-CKD (HALT Progression of Polycystic Kidney Disease) study (37) could provide valuable data. SPRINT compares systolic blood pressure targets of less than 120 mm Hg and less than 140 mm Hg in 9000 patients with hypertension and without diabetes; it will be completed by 2018. It is enrolling participants with CKD, cardiovascular diseases, or risk factors for cardiovascular diseases. Similarly, the HALT-PKD study compares the efficacy of blood pressure targets of 95/60 to 110/75 mm Hg and 120/70 to 130/80 mm Hg in patients with autosomal dominant polycystic kidney disease; it will be completed by 2013. Although both SPRINT and the HALT-PKD study excluded participants with heavy proteinuria (urinary albumin–creatinine ratio >0.6 g/g for SPRINT and >0.5 to 1.0 g/g for HALT-PKD), subgroup analysis in the lower proteinuria range should be considered for these trials to better understand the effect modification by proteinuria. For ACCORD, SPRINT, HALT-PKD, and other future trials, the use of well-established albuminuria, proteinuria, and GFR categories will be helpful to harmonize and compare subgroup results across studies (38).

In summary, evidence does not conclusively show that a currently recommended blood pressure target of less than
130/80 mm Hg improves clinical outcomes more than a conventional target of less than 140/90 mm Hg in adults with CKD. A lower target may be beneficial in persons with proteinuria greater than 300 to 1000 mg/d. We suggest that practitioners use discretion in patients with CKD and proteinuria and base the blood pressure target on individualized risk–benefit assessment and the patient’s tolerance and preferences. Treatment to a lower target may require greater vigilance to monitor for and avoid possible symptoms and adverse events from hypotension.

From the Tufts Center for Kidney Disease Guideline Development and Implementation, Tufts Medical Center, and Tufts University School of Medicine, Boston, Massachusetts.

Note: A draft of the KDIGO blood pressure guideline will be available for public review in the next few months. If interested in participating in the review, please register at www.kidney.org/professionals/kdigo/guidelinesignup.cfm.

Disclaimer: The judgments and interpretations in this article are those of the authors and are not those of the KDIGO guideline Work Group.

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References


**Manuscript Processing and Turnaround**

*Annals* sends about half of submitted manuscripts for peer review and publishes about 10% of submitted material. The 2010 processing and notification turnaround time for manuscripts that were rejected without external peer review was within 1 week for more than 95% of submitted manuscripts. The processing and notification turnaround time for manuscripts that were received and rejected after external peer review was within 4 weeks for 50% and within 8 weeks for 98%.
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Appendix Table 1. Search Strategy for Randomized, Controlled Trials of Blood Pressure Targets

1. exp kidney diseases/
2. exp kidney glomerulus/
3. exp kidney function tests/
4. kidney transplantation.mp. or exp Kidney Transplantation/
5. ((kidney or renal) adj transplant$ or recipient$).tw.
6. or/1-5
7. *bone transplantation/ or *heart transplantation/ or *liver transplantation/ or *lung transplantation/ or *pancreas transplantation/ 8. 6 not 7.
9. (Proteinuria$ or albuminuria$).tw. or exp proteinuria/ or exp albuminuria/
10. 8 and 9.
11. exp hypertension/
12. exp hypertension, renal/
13. hypertens$.af.
14. high blood pressure.af.
15. (eleva$ adj6 blood pressure).tw.
16. or/11-15
17. 8 and 16
18. exp Angiotensin-Converting Enzyme Inhibitors/
19. Capoten.tow. or 62571-86-2.m
20. benazepril.tow. or 86541-75-9.m
22. Vasotec.tow. or 84680-54-6.m.
23. (Prinivil or Zestril).tow. or 83915-83-7.m.
24. Monopril.tow. or 98048-97-6.m.
25. Altace.tow. or 87333-19-5.m.
26. perindopril.tow. or perindopril.af. or 82834-16-0.m.
27. (quinapril or Accupril).tow. or 82586-55-8.m.
28. (moexipril or Univasc).tow. or 103775-10-6.m.
29. (trandolapril or Mavik).tow. or 87679-37-6.m.
30. moexipril.af.
31. or/18-30
32. exp Receptors, Angiotensin/
33. (candesartan orlexelat or Atacand).tow. or 139481-59-3.m.
34. (eprosartan or Teveten).tow. or 133040-01-4.m.
35. (olmesartan medoxomil or Benicar).tow. or 144689-24-7.m.
36. (irbesartan or Avapro).tow. or 138402-11-6.m.
37. (eplerenone or acetazolamide).tow. or 59-66-5.m.
38. (valsartan or Diovan).tow. or 137862-53-4.m.
39. or/30-39
40. or/24-32
41. (beta-blocker or Acebutalol).tow. or 37517-30-9.m.
42. Atenolol.tow. or 29122-68-7.m.
43. Bucindolol.tow. or 63695-18-7.m.
44. esmolol.tow. or 84057-94-3.m.
45. metoprolol.tow. or 37350-58-6.m.
46. propranolol.tow. or 13523-86-9.m.
47. carvedilol.tow. or 72956-09-3.m.
48. beta-blocker (or Acebutalol).tow. or 37517-30-9.m.
49. Benazepril.tow. or 80340-01-4.m.
50. (nifedipine or Verapamil).tow. or 144689-24-7.m.
51. (azelnidipine or Benicar).tow. or 144701-48-4.m.
52. exp Losartan/ or losartan.tw. or Cozaar.tw. or 114798-26-4.m.
53. (irbesartan or Avapro).tow. or 138402-11-6.m.
54. (eplerenone or acetazolamide).tow. or 59-66-5.m.
55. (valsartan or Diovan).tow. or 137862-53-4.m.
56. (with or without).tw.
57. or/24-32
58. exp Calcium Channel Blockers/
59. exp calcium antagonist/
60. spironolactone.tw. or 88150-42-9.m.
61. (bendroflumethiazide or Benicar).tw. or 83915-83-7.m.
62. (eplerenone or acetazolamide).tow. or 59-66-5.m.
63. or/61-72
64. exp Calcium Channel Blockers/
65. (amlodipine or Vasotec).tw. or 87333-19-5.m.
66. (furosemide or Lasix).tw. or 72509-76-3.m.
67. (labetalol or Trandate).tow. or 87333-19-5.m.
68. (nifedipine or Adalat).tow. or 87333-19-5.m.
69. (isradipine or Plendil).tow. or 87333-19-5.m.
70. (nifedipine or Adalat).tow. or 87333-19-5.m.
71. (benazepril or Lotensin).tow. or 87333-19-5.m.
72. (telmisartan or Micardis).tow. or 134798-26-4.m.
73. (olmesartan medoxomil or Benicar).tow. or 144689-24-7.m.
74. (candesartan cilexetil or Atacand).tow. or 139481-59-3.m.
75. (irbesartan or Avapro).tow. or 138402-11-6.m.
76. (eplerenone or acetazolamide).tow. or 59-66-5.m.
77. exp Calcium Channel Blockers/
78. spironolactone.tw. or 88150-42-9.m.
79. (furosemide or Lasix).tw. or 72509-76-3.m.
80. (labetalol or Trandate).tow. or 87333-19-5.m.
81. (nifedipine or Adalat).tow. or 87333-19-5.m.
82. (isradipine or Plendil).tow. or 87333-19-5.m.
83. or/61-72
84. (telmisartan or Micardis).tow. or 134798-26-4.m.
85. (olmesartan medoxomil or Benicar).tow. or 144689-24-7.m.
86. (candesartan cilexetil or Atacand).tow. or 139481-59-3.m.
87. (irbesartan or Avapro).tow. or 138402-11-6.m.
88. (eplerenone or acetazolamide).tow. or 59-66-5.m.
89. exp Calcium Channel Blockers/
90. exp calcium antagonist/
91. exp Losartan/ or losartan.tw. or Cozaar.tw. or 114798-26-4.m.
92. or/24-32
93. exp Losartan/ or losartan.tw. or Cozaar.tw. or 114798-26-4.m.
94. (with or without).tw.
95. or/24-32
96. (beta-blocker or Acebutalol).tow. or 37517-30-9.m.
97. (labetalol or Trandate).tow. or 87333-19-5.m.
98. (nifedipine or Adalat).tow. or 87333-19-5.m.
99. (isradipine or Plendil).tow. or 87333-19-5.m.
100. (eplerenone or acetazolamide).tow. or 59-66-5.m.
101. Random Allocation/
102. Double-blind Method/
103. Single-blind Method/
104. clinical trial.pt.
105. Clinical Trials.mp. or exp Clinical Trials/
107. (isradipine or Plendil).tow. or 87333-19-5.m.
108. Placebos/
109. placebo$tw.
110. randomized controlled trial.pt.
111. trial$.tw.
112. (randomized control trial or clinical control trial).sd
113. (latin adj square).tw.
114. Comparative Study.tw. or Comparative Study.pt.
115. exp Evaluation studies/
116. Follow-Up Studies/
117. Prospective Studies/
118. (control$ or prospective$ or volunteer$).tw.
119. Cross-Over Studies/
120. or/98-119
121. 97 and 120
122. Animals/ not humans/
123. 121 not 122
124. (guidelines or meta analysis or practice guideline or “review” or review).mp. [mp—ti, ot, ab, sh, hw, kw, nm]
125. 123 not 124
126. limit 125 to yr = “2002-2009”
127. remove duplicates from 126
### Appendix Table 2. Results of Interaction Tests and Subgroup Analyses by Baseline Proteinuria in Trials of Blood Pressure Targets (Low Versus Usual) in Patients With Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MDRD Study</th>
<th>AASK Study</th>
<th>REIN-2 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria Category</td>
<td>Trial</td>
<td>Observational Follow-up</td>
<td>Proteinuria Category</td>
</tr>
<tr>
<td>≥50% (or 25 mL/min per 1.73 m²) decrease in GFR, kidney failure, or death*</td>
<td>Overall</td>
<td>NS</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>UPCR ≤0.22 g/g</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPCR &gt;0.22 g/g</td>
<td>Favors low target (HR, 0.74 [95% CI, 0.56–0.99]; P = 0.04)</td>
<td>Favors low target (HR, 0.73 [CI, 0.58–0.93]; P = 0.01)</td>
</tr>
<tr>
<td>Kidney failure or death</td>
<td>Overall</td>
<td>NS</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>UPE &lt; 300 mg/d</td>
<td>Favors low target</td>
<td>UPE ≤0.22 g/g</td>
</tr>
<tr>
<td></td>
<td>UPE, 300–1000 mg/d</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;3000 mg/d</td>
<td>Favors low target (HR, 0.61 [CI, 0.45–0.85];†)</td>
<td>Favors low target with increased proteinuria (P = 0.02)</td>
</tr>
<tr>
<td>Interaction test</td>
<td>NS (P = 0.08)</td>
<td>Interaction test</td>
<td>Overall</td>
</tr>
<tr>
<td>50% decrease in GFR or kidney failure‡</td>
<td>Overall</td>
<td>NS</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>UPCR ≤0.22 g/g</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPCR &gt;0.22 g/g</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Interaction test</td>
<td>NS</td>
<td>Interaction test</td>
<td>Overall</td>
</tr>
<tr>
<td>Rate of GFR decline</td>
<td>Overall</td>
<td>NS</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>UPE &lt; 300 mg/d</td>
<td>Favors low target</td>
<td>UPE ≤0.22 g/g</td>
</tr>
<tr>
<td></td>
<td>UPE, 300–1000 mg/d</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;3000 mg/d</td>
<td>Favors low target (HR, 0.93 [CI, 0.35–0.83];†)</td>
<td>Favors low target with increased proteinuria (P = 0.007)</td>
</tr>
<tr>
<td>Interaction test</td>
<td>NS (P = 0.09)</td>
<td>Interaction test</td>
<td>Overall</td>
</tr>
<tr>
<td>Interaction test</td>
<td>Overall</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

AASK = African American Study of Kidney Disease and Hypertension; CVD = cardiovascular disease; GFR = glomerular filtration rate; HR = hazard ratio; MDRD = Modification of Diet in Renal Disease; NS = not significant; REIN-2 = Ramipril Efficacy in Nephropathy 2; SCR = serum creatinine; UPCR = urinary protein–creatinine ratio; UPE = urinary protein excretion.

* Doubling of SCR, kidney failure, or death for observational follow-up study.
† Estimate from a figure. P = no data.
‡ Doubling of SCR or kidney failure for observational follow-up study.
§ Annual GFR decrease of 4.0 vs. 5.0 mL/min per 1.73 m². Estimate from a figure. P = no data.
| Annual GFR decrease of 8.5 vs. 13 mL/min per 1.73 m² in Study A and 5 vs. 7.5 mL/min per 1.73 m² in Study B. Estimates from a figure. P = no data. |
### Appendix Table 3. Search Strategy for Recent Reviews of Blood Pressure Targets in Proteinuria

1. exp Kidney Glomerulus/
2. exp Kidney disease/
3. exp Kidney Function Tests/
4. exp Renal Replacement Therapy/
5. exp Kidney Transplantation/
6. exp kidney, artificial/
7. exp ultrafiltration/
8. exp sorption, detoxification/
9. renal.af. or renal.tw.
10. nephro$.af. or nephro$.tw.
11. kidney.af. or kidney.tw.
13. h?emodialysis.af. or h?emodialysis.tw.
14. (hemofiltr$ or haemofiltr$).af. or (hemofiltr$ or haemofiltr$).tw.
15. or/1-14
16. Animals/ not humans.mp. [mp−ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
17. 15 not 16
18. exp blood pressure/
19. 17 and 18
20. limit 19 to (meta analysis or “review” or “review literature” or review, academic)
21. limit 20 to yr−“2008-2010”