Chapter 3: Blood pressure management in CKD ND patients without diabetes mellitus

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INTRODUCTION

This chapter addresses the management of BP in adult CKD patients (specifically non-dialysis-dependent CKD [CKD ND]) without diabetes mellitus. There is overlap with BP management in the elderly (defined as persons >65 years of age or as persons with CKD and aging-related co-morbid conditions). In the elderly in particular and to a lesser extent in younger CKD patients, these co-morbid conditions may require modifications in the approach to BP management.

In this chapter we consider two primary adverse outcomes related to high BP: progression of kidney disease and development of CVD.[137,138] The data are sufficient to provide recommendations on BP targets[139] and the use of ACE-Is or ARBs, although there is evidence of heterogeneity in both areas according to the urine albumin level.[96,140–142] We therefore divided the target populations on the basis of urine albumin level.

We did not find sufficient data to suggest any differences according to CKD stage, so our recommendations are not stage-specific. It is not possible to recommend specific regimens or BP targets for all the various causes of CKD. Although there are strong observational data, there is no evidence from RCTs to indicate that the treatment approach should differ substantially for the patient with glomerular disease and high urine albumin levels compared to the patient with severe renovascular disease. Although we would have preferred to give a target range (lowest to highest) for BP rather than a single target for highest acceptable BP, there are insufficient data based on RCTs to recommend a target for lowest BP level. The recommendations and suggestions in this chapter therefore emphasize an approach based on highest acceptable BP and severity of albuminuria, but the interventions should be implemented cautiously and with subsequent surveillance for adverse effects.

We also recognize that BP agents other than those recommended or suggested below, such as diuretics, may be necessary for BP control, especially as CKD progresses and volume retention becomes more of an issue. However, few RCTs addressing hard cardiovascular or kidney outcomes have randomized patients to a diuretic versus another agent on top of an ACE-I or ARB. Therefore, in contrast to the 2004 KDOQI guideline,[1] we do not provide a guideline statement regarding diuretic use as a preferred second-line agent. The use of diuretics and other BP agents are discussed in more detail below and in Chapter 2.

3.1: We recommend that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. ***(1B)***

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- High BP is a risk factor for CVD and development and progression of CKD.
- Lowering BP in the general population reduces cardiovascular risk.
- Lowering BP in CKD patients reduces the rate of CKD progression.
- CKD is a major risk factor for CVD.

Most recent BP guidelines have suggested a target BP of <140/90 mm Hg for all individuals who are not at high risk for CVD.[1,143] This is based on several lines of evidence, including observational data suggesting that high BP is a risk factor for CVD,[144] observational data suggesting that high BP is a risk factor for development and progression of CKD,[145–148] RCTs of BP agents in the general population showing a benefit of a lower target BP,[149,150] and RCTs in the general population demonstrating that the treatment of BP reduces CVD outcomes.[151]

Several previous guidelines for kidney disease have recommended a BP target of <130/80 mm Hg for all patients with CKD, irrespective of the level of urine protein.[1,143] These recommendations are primarily based on observational data in the general population showing that the presence of CKD, irrespective of the level of urine protein, is associated with high risk of CVD.[152,153] In addition, data from the MDRD study, which randomized patients to a mean arterial pressure (MAP) of <92 mm Hg (equivalent to 125/75 mm Hg) versus 107 mm Hg (equivalent to 140/90 mm Hg) showed that tight BP control reduced progression of kidney disease in patients with >1 g of urine protein per 24 hours.[142]

Since the publication of previous guidelines, several events have resulted in more caution about advocating a BP target of ≤130/80 mm Hg in CKD patients without albuminuria. RCTs in CKD populations have shown that data from the general population cannot necessarily be extrapolated to the CKD population.[26,27] Moreover, particularly in RCTs related to anemia, the RCT findings may be inconsistent with observational data.[154,155] Guideline agencies[156,157] are now requiring more rigorous data, in particular from RCTs, as a basis for recommendations. Several manuscripts have recently emphasized that tight BP control may have adverse effects,[22,158] particularly in the elderly and those with CAD and low diastolic BP.[40] Furthermore, less tight control (i.e., control involving the use of fewer drugs) may improve adherence and reduce costs of treatment, a benefit particularly relevant in resource-poor environments.

Finally, several recent RCTs have not shown a benefit of lower BP targets in patients without proteinuria. For instance, the African American Study of Kidney Disease and Hypertension (AASK) randomized participants to treatment to a MAP of either ≤92 mm Hg or 102 to 107 mm Hg.[140] During the long-term follow-up of participants, there was a benefit associated with the lower BP target among patients with a urine protein/creatinine ratio (PCR) of >220 mg/g (>22 mg/mmol), but not among those with a PCR ≤220 mg/g (≤22 mg/mmol). In fact, in some analyses, there was a trend toward worse outcomes in those targeted to low BP when the urine PCR was ≤220 mg/g (≤22 mg/mmol). Similarly, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[159] no benefit was found with regard to the primary composite outcome with a systolic BP target <120 mm Hg versus a target of <140 mm Hg.

We therefore propose that targets currently recommended in the general population be extrapolated to those with CKD who do not have elevated urinary albumin or protein levels. Results of subgroup analyses of CKD patients included in RCTs assessing target BPs are consistent with the primary results of these trials[160] (Supplementary Table 1 online). This move towards a more conservative target is consistent with other guidelines.[161] We have graded this recommendation as 1B, given that this BP target is currently considered the standard of care for the general population.

3.2: We suggest that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. *(2D)*

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- Urine albumin level of 30 to 300 mg per 24 hours (microalbuminuria) is a risk factor for CVD and CKD progression.
- RCTs suggest that a BP ≤130/80 mm Hg may reduce progression of CKD.

Patients with microalbuminuria are at high risk for progression of CKD as well as development of CVD.[18,153,162–165] RCT data suggest that BP control is particularly important in CKD patients with high urine albumin levels.

Short-term follow-up data from the MDRD study[142] showed an interaction of BP target with level of urine protein, with a definitive benefit for kidney outcomes in patients with >1 g of urine protein per 24 hours and GFR of 25–55 m/min per 1.73 m^2 (in MDRD Study A), with a trend toward a benefit with lower protein levels. Long-term follow-up showed a benefit of a low target BP and no interaction with the urine protein level, suggesting that the benefit may extend to all protein levels. In subgroup analyses, the benefit was statistically significant in those with urine protein excretion of >0.3 g per 24 hours[166] (H Tighiouart, personal communication). However, there may have been insufficient statistical power to detect the interaction; hence, the risk reduction may have been greater in those with higher urine protein levels. Long-term follow-up data from the MDRD study also showed a benefit with regard to kidney outcomes with a lower target BP in specific groups, such as patients with polycystic kidney disease and non-glomerular diseases, that frequently have low urine albumin levels. Long-term follow-up in the AASK study demonstrated a benefit of lower target BPs in patients with a PCR >220 mg/g (>22 mg/mmol).[140] It is unclear whether this PCR cutoff can be translated into an albumin-level cutoff, as this conversion is likely to be dependent on the type of kidney disease, and the ratio of glomerular albuminuria to tubular proteinuria. In the Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) study,[14] a lower BP target was of benefit in reducing the risk of kidney outcomes, particularly in children with higher urine protein levels ($P = 0.06$ for interaction of treatment target with urine protein level).

There have been no BP target trials involving CKD patients focused on hard CVD outcomes. Subgroup analyses from the Hypertension Optimal Treatment (HOT) trial[167] did not show a benefit for CVD outcomes in association with a lower diastolic BP target in CKD patients, although the statistical power to detect a difference was limited ($n = 470$ for those with a creatinine level >1.5 mg/dl [133 μmol/l]). Furthermore, albuminuria data were not available.

Because patients with CKD and microalbuminuria are at high risk, and given that the evidence does not support using different BP targets in non-diabetics and diabetics (see Chapter 4), the Work Group suggests

a BP target of ≤130/80 mm Hg. This ensures consistency among recommendations between persons with diabetes and those without diabetes and facilitates implementation into clinical practice.

3.3: We suggest that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. ***(2C)***

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- Albuminuria is a major risk factor for CVD and CKD progression.
- RCTs show that BP ≤130/80 mm Hg may reduce progression of CKD in patients with urine albumin excretion >300 mg per 24 hours ('macroalbuminuria').

Patients with macroalbuminuria are at very high risk for both progression of CKD and development of CVD.[18,162,163] Observational data suggest that hypertension is a risk factor for CVD and progression of CKD in patients with macroalbuminuria.[168] As noted above, short-term follow-up data from the MDRD study[142] showed an interaction of BP target with the level of urine protein, with a definitive benefit in patients with a urine protein level >1 g per 24 hours (in Study A) and a trend toward a benefit with lower protein levels; long-term follow-up data showed a benefit of a lower target BP. In subgroup analyses, a benefit was noted in patients with urine protein excretion >0.3 g per 24 hours[166] (H. Tighiouart, personal communication). Long-term follow-up data from AASK also showed a benefit of a lower target BP in patients with PCR >220 mg/g (>22 mg/mmol),[140] and the ESCAPE trial[14] showed a benefit in the entire population with a borderline interaction of treatment target and urine protein level.

In summary, we believe there is sufficient evidence to suggest a BP target of ≤130/80 mm Hg for kidney protection in those with macroalbuminuria. We have graded this suggestion 2C, for the following reasons. The reported benefits in the AASK and the MDRD study are based on *post hoc* and subgroup analyses. Furthermore, in both the MDRD study and AASK, MAP was targeted rather than systolic and diastolic BP, and a specific MAP may translate into different systolic and diastolic BP, depending on the individual patient. Additionally, in the MDRD study, a higher MAP was targeted in patients over the age of 60 years.[169] The Ramipril Efficacy in Nephropathy 2 (REIN-2) study did not show a benefit of tight BP control, although admittedly this was a short-term study with relatively few outcomes and it is unclear whether the use of a dihydropyridine calcium-channel blocker (felodipine) in the low-target arm may have confounded the results[170] (See Supplementary Tables 2–4 online). We also do not believe that this recommendation should in any way hinder trials from randomizing patients with CKD and urine protein excretion <1 g per 24 hours to various BP targets, as there is sufficient equipoise and uncertainty to endorse these trials. One such trial that will evaluate this question is Systolic Blood Pressure Intervention Trial (SPRINT) which is funded by National Institutes of Health (NIH).[171,172] It will evaluate cardiovascular and kidney outcomes in patients randomized to a systolic BP of <140 mm Hg versus <120 mm Hg. There is a CKD component for patients with GFR 20–60 ml/min/1.73 m^2. Patients with diabetes and those with 24-hour urine protein excretion of >1 g per 24 hours are excluded from this study.

3.4: We suggest that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. ***(2D)***

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- Urine albumin excretion of 30 to 300 mg per 24 hours (microalbuminuria) is a risk factor for CVD and CKD progression.
- ACE-Is and ARBs have been shown to reduce urine albumin levels.
- RCTs suggest that ACE-Is or ARBs may help reduce progression of CKD and possibly CVD in patients with urine albumin excretion of 30 to 300 mg per 24 hours.

As mentioned above, patients with microalbuminuria are at high risk for both progression of CKD and development of CVD.[18,162–165] Here, we describe the trial data which either focused on kidney disease or CVD outcomes. Some trials focused on both.[173–176]

Kidney disease. In AASK, a study of patients with a PCR <220 mg/g (<22 mg/mmol), the ACE-I ramipril decreased the urine protein level. It remains to be determined whether this translates into a clinically important benefit.[177] In *post hoc* analyses of the Heart Outcomes Prevention Evaluation (HOPE), which was an RCT involving patients with diabetes or vascular disease and at least one other CVD risk factor, ramipril prevented progression of proteinuria or development of new-onset microalbuminuria, independent of diabetes status.[174] In a *post hoc* analysis of Candesartan

Antihypertensive Survival Evaluation in Japan (CASE J), which was an RCT comparing the ARB candesartan with the calcium-channel blocker amlodipine,[178] candesartan reduced progression of CKD 4 (see Supplementary Table 5 online). In subgroup analyses of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND), an RCT that included patients with vascular disease or diabetes, in patients with microalbuminuria (defined as an ACR >3.4 mg/mol [>34 mg/g]), the ARB telmisartan decreased the risk of the composite kidney outcome (doubling of SCr level, dialysis, or death) in comparison with placebo.[179] There was an interaction whereby telmisartan benefited patients with microalbuminuria but was associated with harm in those without microalbuminuria ($P=0.006$ for interaction). Finally, in patients with diabetes, ACE-Is and ARBs have been shown to prevent the development of macroalbuminuria in subjects with microalbuminuria,[180,181] and we have not found evidence of substantive differences between diabetics and non-diabetics with respect to either BP target or agent.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large RCT examining the effects of the ACE-I lisinopril, the thiazide chlorthalidone, and the dihydropyridine calcium-channel blocker amlodipine in individuals >55 years of age with hypertension and at least one other CVD risk factor. Lisinopril did not show a benefit for doubling of creatinine or kidney failure when compared with chlorthalidone in the entire cohort or among patients with CKD at baseline[175] (see Supplementary Table 6 online). ALLHAT, however, did not permit the use of an ACE-I with a diuretic—a combination that is frequently required in clinical practice to achieve adequate BP control.[182–184] In addition, the diuretic arm in ALLHAT achieved better BP control making comparison of agents more difficult to interpret. Unfortunately, albuminuria or proteinuria status was not measured in the enrolled subjects, but assuming that ALLHAT was consistent with other trials of high-risk individuals recruited from the general population (e.g., HOPE or TRANSCEND), the median level of proteinuria was most likely below the microalbuminuria cutoff.

CVD. There have been few RCTs of BP agents that have focused on CVD outcomes in CKD patients without diabetes mellitus (Supplementary Tables 7–32 online). Most of the data are taken from subgroup analyses of patients with CKD from general population studies (Supplementary Tables 1, 5–6, 33–36 online). HOPE showed a benefit for CVD outcomes in patients randomized to ramipril.[185] This benefit extended to those with a creatinine level >1.4 mg/dl (124 mmol/l) or a creatinine clearance <65 ml/min (1.1 ml/sec) in non-diabetic individuals,[173] as well as those with microalbuminuria.[185] In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which included patients with a history of cerebrovascular disease, the ACE-I perindopril, as compared with placebo, decreased the rate of recurrent stroke in those with CKD.[186] Although the level of urine albumin was not specified in PROGRESS, it seems reasonable to assume that CVD protection would extend to those with microalbuminuria. In patients with stable coronary disease in the Prevention of Events with Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) trial, the ACE-I trandolapril, as compared with placebo, reduced mortality in those with a GFR <60 ml/min/1.73 m^2, although trandolapril did not have a benefit in those with a GFR ≥ 60 ml/min/1.73 m^2.[187] However, the effect of trandolapril therapy on outcomes was not significantly modified by the level of albuminuria.[188] In the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), there was no modification of benefit by level of kidney function, and perindopril (versus placebo) decreased the risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest in patients with a GFR <75 ml/min/1.73 m^2 as well as those with a GFR >75 ml/min/1.73 m^2.[189] ALLHAT, however, did not show a benefit of lisinopril over chlorthalidone with respect to CVD outcomes in the subgroup of patients with CKD.[176]

The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) included CKD patients with urine albumin levels of 15 mg to 300 mg per 24 hours. Patients were randomized to the ACE-I fosinopril or placebo. Fosinopril decreased albumin excretion by 26% and showed a trend toward reducing the risk of CVD outcomes (hazard ratio [HR] versus placebo 0.60; 95% CI 0.33–1.10).[190] Similarly, in the CASE J trial, candesartan reduced the rate of CVD outcomes, as compared with amlodipine, in CKD 4 patients[178] (Supplementary Table 5 online).

The Work Group suggests ACE-Is or ARBs as the preferred class of BP-modifying agent in CKD patients with microalbuminuria. This recommendation is based on observational data and subgroup and *post hoc* analyses, hence the grade of 2D.

3.5: We recommend that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with BP-lowering drugs is indicated. *(1B)*

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

RATIONALE

- Urine albumin excretion >300 mg per 24 hours ('macroalbuminuria') is a risk factor for CVD and for CKD progression.
- In RCTs involving patients with CKD and urine albumin excretion >300 mg per 24 hours, ARBs or ACE-Is reduce

the risks of 'hard' outcomes such as the doubling of SCr level, kidney failure, or death.

Patients with macroalbuminuria are at very high risk for both progression of CKD and development of CVD.[18,162,163]

Kidney disease. Several trials have demonstrated a benefit, in patients with macroalbuminuria, of ACE-Is or ARBs over either placebo or other agents, in reducing the risk of macroalbuminuria, doubling of creatinine levels, and development of kidney failure (See Supplementary Tables 7–12 online).

These trials include RCTs in patients with CKD of various causes, primarily glomerulonephritis,[191] African-Americans with hypertension,[177] and patients with advanced CKD (a GFR of 20–70 ml/min/1.73 m^2).[192] A meta-analysis of individual patient data from 11 RCTs compared antihypertensive regimens including ACE-Is to regimens without ACE-Is in 1860 patients with predominantly non-diabetic CKD. In adjusted analyses, ACE-Is were associated with a HR of 0.69 for kidney failure (95% CI 0.51–0.94) and 0.70 for the combined outcome of doubling of the baseline SCr concentration or kidney failure (95% CI 0.55–0.88). Patients with greater urinary protein excretion at baseline benefited more from ACE-I therapy ($P = 0.03$ for kidney failure and $P = 0.001$ for the combined outcome).[141]

The Work Group did not find heterogeneity with regard to the benefit of ACE-Is according to CKD stage; therefore, the guideline statements are not divided on this basis. Furthermore, few RCTs with hard CVD or kidney-disease outcomes randomized patients to a diuretic or another agent in addition to an ACE-I or ARB; therefore, we have not included any guideline statements to support this practice. In fact, one RCT in individuals predominantly without CKD showed that the risk of doubling of the creatinine level was higher with an ACE-I–hydrochlorothiazide combination than with ACE-I–amlodipine.[101] The clinical importance of this end point remains to be determined,[193] as it may reflect a reversible hemodynamic effect. Finally, there is only limited quality evidence evaluating either differences in ACE-I versus ARB, or comparison of ACE-I plus ARB versus either ACE-I or ARB with regard to hard clinical outcomes (Supplementary Tables 13–15 online).

CVD. Only a few RCTs of BP agents have focused on CVD outcomes in subjects with CKD (Supplementary Tables 7–32 online); therefore, most of the data are from subgroup analyses of CKD patients from general population studies. Several analyses have shown a benefit of ACE-Is or ARBs over placebo or another agent, and although most of these studies were performed in patients with urine albumin levels below the macroalbuminuria cutoff, there is no obvious reason why the benefit would not extend to individuals with macroalbuminuria (Supplementary Tables 7–12 online).

In summary, the data in support of the use of ACE-Is or ARBs are reasonably strong for preventing progression of CKD and less so for CVD protection. Notably, they show no harm of either class of drugs with regard to CVD. Taken together, the data on both drug classes support a grade 1B recommendation for ACE-Is or ARBs as a preferred agent in CKD patients with albumin excretion > 300 mg per 24 hours or its equivalent.

RESEARCH RECOMMENDATIONS

- Large RCTs of BP targets are needed in CKD patients without diabetes (stratified by GFR and albuminuria) that are powered for clinical outcomes including kidney failure, CVD events and mortality.
- Large RCTs of BP agents are needed in CKD patients without diabetes (stratified by GFR and albuminuria) that are powered for clinical outcomes including kidney failure, CVD events and mortality.
- Subgroup analyses in new, large-scale RCTs as described above by specific causes of CKD are needed.
- Studies are needed to examine how intermediate outcomes for CKD and CVD (i.e., doubling of creatinine level, change in urine protein level, and development or regression of left ventricular hypertrophy) track with clinical outcomes to assess their validity as prognostic tools and possible surrogate outcomes going forward.
- Development of prediction tools for clinical outcomes in patients with CKD and testing in clinical trials for exploration of treatment heterogeneity are encouraged.
- Development of prediction tools for the adverse outcomes of ACE-Is and ARBs is encouraged.
- Cost-effectiveness analyses of lower BP targets in CKD patients without diabetes as stratified by GFR and albuminuria should be conducted.

DISCLAIMER

SUPPLEMENTARY MATERIAL

Supplementary Table 1. General population RCTs comparing BP targets in CKD subgroups.

Supplementary Table 2. Evidence profile of RCTs examining the effect of blood pressure target in patients with CKD without DM.

Supplementary Table 3. RCTs examining the effect of blood pressure targets in patients with CKD without DM [categorical outcomes].
Supplementary Table 4. RCTs examining the effect of blood pressure targets in patients with CKD without DM [continuous outcomes].
Supplementary Table 5. General population RCTs comparing ARB versus CCB in CKD subgroups with and without DM.
Supplementary Table 6. General population RCTs comparing ACEI or ARB versus control (active or placebo) in CKD subgroups with and without DM.
Supplementary Table 7. Evidence profile of RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM.
Supplementary Table 8. RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM [categorical outcomes].
Supplementary Table 9. RCTs examining the effect of ACEI or ARB versus placebo in patients with CKD without DM [continuous outcomes].
Supplementary Table 10. Evidence profile of RCTs examining the effect of ACEI or ARB versus CCB in patients with CKD without DM.
Supplementary Table 11. RCTs examining the effect of ACEI or ARB versus CCB in patients with CKD without DM [categorical outcomes].
Supplementary Table 12. RCTs examining the effect of ACEI or ARB versus CCB in patients with CKD without DM [continuous outcomes].
Supplementary Table 13. Evidence profile of RCTs examining the effect of ACEI versus ARB in patients with CKD without DM.
Supplementary Table 14. RCTs examining the effect of ACEI versus ARB in patient with CKD without DM [categorical outcomes].
Supplementary Table 15. RCTs examining the effect of ACEI versus ARB in patient with CKD without DM [continuous outcomes].
Supplementary Table 16. Evidence profile of RCTs examining the effect of high versus low dose ACEI in patients with CKD without DM.
Supplementary Table 17. RCTs examining the effect of high dose ACEI versus low dose ACEI in patient with CKD without DM [categorical outcomes].
Supplementary Table 18. RCTs examining the effect of high dose ACEI versus low dose ACEI in patient with CKD without DM [continuous outcomes].
Supplementary Table 19. Evidence profile of RCTs examining the effect of high versus low dose ARB in patients with CKD without DM.
Supplementary Table 20. RCTs examining the effect of high dose ARB versus low dose ARB in patient with CKD without DM [categorical outcomes].
Supplementary Table 21. RCTs examining the effect of high dose ARB versus low dose ARB in patient with CKD without DM [continuous outcomes].
Supplementary Table 22. RCTs examining the effect of ACEI versus β-blocker in patients with CKD without DM [categorical outcomes].
Supplementary Table 23. RCTs examining the effect of ACEI versus β-blocker in patients with CKD without DM [continuous outcomes].
Supplementary Table 24. RCTs examining the effect of ACEI + CCB versus ACEI in patients with CKD without DM [categorical outcomes].
Supplementary Table 25. RCTs examining the effect of ACEI + CCB versus ACEI in patients with CKD without DM [continuous outcomes].
Supplementary Table 26. RCTs examining the effect of ACEI + CCB versus CCB in patients with CKD without DM [categorical outcomes].
Supplementary Table 27. RCTs examining the effect of ACE + CCB versus CCB in patients with CKD without DM [continuous outcomes].
Supplementary Table 28. RCTs examining the effect of CCB versus CCB in patients with CKD without DM [categorical outcomes].
Supplementary Table 29. RCTs examining the effect of CCB versus CCB in patients with CKD without DM [categorical outcomes].
Supplementary Table 30. RCTs examining the effect of β-blocker versus CCB in patients with CKD without DM [categorical outcomes].
Supplementary Table 31. RCTs examining the effect of β-blocker versus CCB in patients with CKD without DM [continuous outcomes].
Supplementary Table 32. RCTs examining the effect of central-acting agent versus CCB in patients with CKD without DM [continuous outcomes].
Supplementary Table 33. General population RCTs comparing ACEI + diuretic versus placebo in CKD with DM subgroups [categorical outcomes].
Supplementary Table 34. General population RCTs comparing ACEI + diuretic versus placebo in CKD with DM subgroups [continuous outcomes].
Supplementary Table 35. General population RCTs comparing ARB or (ACE + ARB) versus ACE in CKD subgroups with and without DM.
Supplementary Table 36. General population RCTs comparing CCB versus active control in CKD subgroups with and without DM.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php