Cardiovascular effects of blood pressure lowering in patients with chronic kidney disease

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GUIDELINES

Chronic kidney disease not requiring dialysis

a. We recommend that blood pressure targets in people with chronic kidney disease (CKD) should be determined on an individual basis taking into account a range of patient factors (1C) including baseline risk, albuminuria level, tolerability and starting blood pressure levels.

b. We suggest that most people with CKD should be treated to similar targets as the general population, such that most blood pressure readings are below 140/90 (2D). We suggest that most blood pressure readings should be below 130/80 in individuals with CKD and macroalbuminuria (2B).

c. We recommend that lifestyle modification (weight loss, salt restriction, exercise etc) be incorporated in blood pressure lowering regimens for all people with CKD (1C).

d. We suggest that:
   • Angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) should be used in most people with CKD who require blood pressure lowering (particularly those with albuminuria), due to the volume of evidence showing benefits for cardiovascular as well as renal outcomes (2B).
   • Diuretics, calcium channel blockers and beta blockers may also be used to lower blood pressure in people with CKD requiring treatment (2B).
   • Other agents should be used with caution as there are no trial data demonstrating a benefit in people with CKD (2D).

e. We suggest that blood pressure lowering agents may also be used where tolerated in people with CKD who have blood pressure levels in the normal range and are at high risk of cardiovascular events (2C).

f. We recommend that a combination of two or more of ACE inhibitors, ARB and renin inhibitors should not be used to prevent cardiovascular or renal events in people with CKD, as the combination provides no additional proven benefit, while increasing the risk of adverse outcomes (1B).

Chronic kidney disease requiring dialysis

g. We recommend that blood pressure should be lowered in individuals with CKD receiving dialysis who have suboptimal blood pressure levels (1C), and in the absence of specific data, suggest a similar target to the general population where possible (2D).

h. We suggest that reducing ideal weight be used as the initial strategy to lower blood pressure in people with CKD requiring dialysis (2C).

UNGRADED SUGGESTIONS FOR CLINICAL CARE
There is little evidence about the efficacy in preventing CVD of different combinations of BP lowering drugs in people with CKD. If BP targets are not met, the choice of a second agent should be based on individual patient factors, tolerability, and side effects (ungraded).

The choice of blood pressure lowering agent should be made on the grounds of individual patient variables, co-morbidities, tolerability and side-effect profiles (ungraded).

IMPLEMENTATION AND AUDIT

Blood pressure levels achieved in people with different levels of CKD should be monitored.

BACKGROUND

Blood pressure and cardiovascular risk in patients with evidence of kidney disease

Individuals with CKD are at significantly increased risk for cardiovascular events. Blood pressure is an important determinant of cardiovascular risk in the general population in which interventions that lower BP have been clearly shown to prevent cardiovascular events. Blood pressure levels are commonly elevated in people with CKD raising the possibility that BP lowering may offer significant benefit in this group. The objective of this guideline is to evaluate the evidence of different BP lowering regimens in preventing CVD in patients with CKD.

There are three main questions:
1. What is the evidence that BP lowering is effective at reducing cardiovascular risk in patients with CKD?
2. What is the evidence for different treatment regimens in terms of their efficacy at reducing CVD risk in patients with evidence of kidney disease?
3. What BP target should clinicians aim for in treating patients?

SEARCH STRATEGY

Databases searched: MeSH terms and text words for chronic kidney disease, end-stage kidney disease and renal replacement therapy were combined with MeSH terms and text words for blood pressure, ACE inhibitors, antihypertensive agents, angiotensin II Type 1 receptor blockers, calcium channel blockers, diuretics and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 19 September 2007 and updated search 23 February 2011 and April 2013.

WHAT IS THE EVIDENCE?

1. Effects of blood pressure lowering agents in patients with chronic kidney disease (KDOQI defined stage 3 and 4)

1.1 Angiotensin-converting enzyme inhibitor based compared to placebo-based regimens

EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA): EUROPA examined the effects of perindopril versus placebo in more than 12,000 patients with stable coronary heart disease without heart failure. The primary endpoint was a composite outcome of CVD death, nonfatal MI, or resuscitated cardiac arrest. During a mean follow-up of 4.2 years there were 1085 CVD events. In patients with relatively preserved renal function (estimated glomerular filtration rate (eGFR) > 75), perindopril was associated with a RRR of 23% (HR 0.77 95% CI: 0.64 - 0.93) compared with the placebo group. In those individuals with lower renal function (eGFR < 75), the RRR, compared with placebo, was similar (0.84, 95% CI: 0.72 - 0.98; P for heterogeneity in the cardio protective effect of perindopril based on renal function = 0.47). [1]

Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND-IT): 864 subjects from the PREVEND cohort were randomised in a factorial design to receive an ACEi (fosinopril) and/or a statin (pravastatin) or placebo. The mean follow-up was 46 months and the primary
end-point was CVD mortality and hospitalization for CVD morbidity of which there were 45 events overall. There was a non-significant reduction in the primary end-point in subjects randomised to fosinopril (HR 0.60, 95% CI: 0.33 to 1.10; P = 0.098). The main limitation of this study was insufficient power to detect differences in the primary outcome.[2]

Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial: 8290 patients with stable coronary artery disease were randomised to either ACEi (trandolapril) or placebo. After a median follow-up of 4.8 years, trandolapril therapy was associated with a 27% reduction in mortality (HR 0.73, 95% CI: 0.54 - 1.00) in patients with eGFR < 60 mL/min compared with a non-significant reduction of 6% (HR 0.94, 95% CI: 0.78 - 1.13) with eGFR > 60. The treatment effects on cardiovascular outcomes were consistent in patients with and without CKD.[3] As with the other studies, this study was also not powered to examine treatment effects by level of renal function. Furthermore, the heterogeneity in the treatment effects on all-cause mortality are contradicted by those of EUROPA, PROGRESS, and ADVANCE [1, 4, 5] that found no evidence of a treatment effect according to level of renal function.

Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS): PROGRESS was a randomised trial in 6105 individuals with a previous history of stroke. In a sub-study among 1757 individuals with stage 3 or greater CKD, active therapy reduced the risk of recurrent stroke in patients with CKD by 35% (95% CI: 0.50 - 0.83) irrespective of baseline systolic blood pressure (SBP) (< 140, 140 - 159, > 160 mmHg) with no evidence to suggest an adverse effect among individuals with low BP [5]. Furthermore, in contrast to the PEACE study which suggested a beneficial effect of treatment with an ACEi only in individuals with glomerular filtration rate (GFR) < 60 mL/min, the administration of a perindopril-based BP-lowering regimen produced similar reductions in the risk for major CVD events at all levels of baseline kidney function: RR 0.74, 95% CI: 0.63 - 0.86 for creatinine clearance > 60 mL/min vs RR 0.70, 95% CI: 0.58 - 0.86 for creatinine clearance < 60 mL/min. [5]

Heart Outcomes and Prevention Evaluation (HOPE): A post-hoc analysis of the HOPE study. A total of 980 patients with mild renal insufficiency (serum creatinine > 124 µmol/L) and 8307 patients with normal renal function (serum creatinine concentration < 124µmol/L) were randomised to ACEi (ramipril) or placebo. The primary outcome was a composite of CVD death, MI or stroke. Ramipril reduced the incidence of the primary outcome similarly in patients with and without renal insufficiency: HR 0.80, 95% CI: 0.59 - 1.09) and 0.79 (0.70 – 0.88); p for heterogeneity between the two groups > 0.2. [6]

Action in Diabetes and Vascular disease: preterAx and diamicroN-mr Controlled Evaluation (ADVANCE) study: The ADVANCE trial examined the effects of a fixed combination of perindopril (4 mg/day) with indapamide (1.25 mg/day) on major macrovascular and microvascular events in 11,140 patients with type 2 diabetes. A post-hoc analysis of the ADVANCE trial in patients with no CKD, Kidney Disease Outcome Quality Initiative defined (KDOQI) stage 1 or 2 CKD, and stage 3 or greater CKD showed that a fixed combination of perindopril with indapamide produced similar reductions in the risk for major macrovascular events, irrespective of the stage of CKD: no CKD HR 1.03, 95% CI: 0.84 - 1.25; CKD 1 or 2 HR 0.89 (0.70 – 1.13); CKD ≥ 0.87 (95% CI 0.68 – 1.10). [4]

1.2 Angiotensin receptor blocker-based regimens compared to controls

Irbesartan Diabetic Nephropathy Trial (IDNT): 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomised to an angiotensin-II receptor blocker (irbesartan) or a CCB (amlodipine) or placebo. The primary outcome of the IDNT main trial was a composite endpoint of serum creatinine doubling, chronic dialysis, renal transplantation, or death and the secondary outcome was cardiovascular events. After a mean follow-up of 2.6 years, with respect to the incidence of the 410 cardiovascular events, there was no clear evidence of a benefit of either treatment on reducing the incidence of a cardiovascular event (irbesartan vs placebo RR 0.91, 95% CI: 0.72 - 1.14; amlodipine vs placebo RR 0.88, 95% CI: 0.69 - 1.11); nor was there evidence of superiority of either treatment on the incidence of cardiovascular events: irbesartan vs amlodipine RR 1.03, 95% CI: 0.81 - 1.32. [7]

Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study (RENAAL): The findings of the IDNT study are supported by those from the RENAAL study which showed that losartan provided superior nephroprotection compared to those patients receiving conventional antihypertensive treatment (including CCB and diuretics) [8]. In RENAAL, 1513 patients were randomised to either losartan or placebo in addition to conventional antihypertensive treatment. Based on 515 cardiovascular events, there was no difference between the two groups with respect to the secondary cardiovascular outcome which was a composite of cardiovascular morbidity and mortality (32.9% in the losartan group vs 35.2% in the placebo group; relative risk reduction 10%, P = 0.26).
Valsartan in Heart-Failure Trial (Val-HEFT): The Val-HEFT trial tested the benefit risk ratio of valsartan 320 mg/day on top of an ACEi regimen in 5010 patients with symptomatic heart failure. The study had two primary endpoints: all-cause mortality and the first morbid event, which was defined as death, sudden death with resuscitation, hospitalization for heart failure, or the administration of intravenous inotropic or vasodilator agents for 4 hours or more without hospitalisation. A post-hoc analysis assessed the benefits of valsartan versus placebo in patients with CKD defined as an eGFR < 60 mL/min/1.73m2 versus those without CKD. The benefit of valsartan 320 mg/day on the risk for a morbid event in 2890 patients with CKD did not differ from patients without CKD; HR 0.86, 95% CI: 0.74 - 0.99 and HR 0.91 (0.73 - 1.12) respectively, P for interaction 0.23 [9].

1.3 Calcium channel blockers compared to placebo

Irbesartan Diabetic Nephropathy Trial (IDNT): As described above, this trial also compared a group of participants randomised to amlodipine based therapy compared to placebo. Based on a total of 410 cardiovascular events, there was no clear evidence of a benefit on reducing the incidence of a cardiovascular event (RR 0.88, 95% CI: 0.69 - 1.11) [7].

1.4 Different blood pressure lowering targets

Hypertension Optimal Treatment (HOT): In this study, 18,790 patients were randomised to one of three diastolic blood pressure (DBP) target groups: < 90, < 85, < 90 mmHg. Antihypertensive therapy with felodipine (CCB) was given to all patients. Additional therapy and dose increments were prescribed to reach the target DBP. Angiotensin-converting enzyme inhibitors of B-blockers or diuretics were added to the BP-lowering regimen when necessary to achieve target DBP level. Of the 18,597 patients at baseline with serum creatinine values, 470 subjects had a serum creatinine value > 1.5 mg/dl and 2821 patients had a creatinine clearance < 60 mL/min. The incidence of major CVD events in patients with a serum creatinine > 1.5 mg/dl was very similar in the three DBP target groups (26.5, 26.7 and 27.9 per 1000 patient years). However, as there were only 45 major CVD events in this sub-group, the analysis did not have sufficient power to detect a significant difference between groups. Similarly, in individuals with creatinine clearance < 60 mL/min, although CVD event rates tended to be higher in the group with the highest DBP target level (< 90 mmHg), there was no statistical evidence that CVD event rates were lower in the lowest DBP target groups [10]. But again, as there were only 165 major CVD events in this subgroup, the analysis probably did not have sufficient power to detect a difference in event rates between the three groups.

African American Study of Kidney disease and hypertension (AASK) trial: 1094 African Americans with reduced GFR (between 20 and 65 mL/min/1.73m2) were randomised using a factorial design to two separate BP-lowering comparisons: therapy based on a B-blocker (metoprolol) vs an ACEi (ramipril) vs a CCB (amlodipine); as well as either a usual BP (140/90 mmHg) or low BP treatment goal (125/75 mmHg). The primary outcome of the trial was the differences in renal outcomes between BP goals. After a mean follow-up of 4.1 years there were 202 cardiovascular events with no evidence to suggest superiority of the low vs usual BP goal; HR 1.06, 95% CI: 0.76 - 1.49,[11] The main limitation of this study was insufficient power to detect differences in cardiovascular endpoints.

1.5 Head to head comparisons

Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)

ALLHAT recruited 33,327 persons with hypertension who were 55 years of age or older with 1 or more risk factors for chronic heart disease (CHD) and who were stratified into 3 baseline GFR groups: normal or increased (90 mL/min per 1.73 m2; N = 8126 patients), mild reduction (60 to 89 mL/min per 1.73 m2; N = 18 109 patients), and moderate or severe reduction (< 60 mL/min per 1.73 m2; N = 5662 patients) [12]. Patients were randomly assigned to diuretic (chlorthalidone), CCB (amlodipine), or ACEi (lisinopril) to achieve a BP target of < 140/99mmHg. The primary outcome was fatal CHD or nonfatal MI. Combined CVD was defined as a composite of the primary outcome and peripheral arterial disease. After 6 years follow-up there were 8887 CVD events. There was no evidence of a statistically significant difference in risk for CHD, combined CVD or stroke between the chlorthalidone and amlodipine groups in either the overall population or in the subgroup of study participants with baseline GFR < 60 mL/min. In the overall population, participants randomised to lisinopril had a similar risk for CHD, a 10% higher risk of combined CVD and a 15% greater risk of stroke compared to those assigned to chlorthalidone. Lisinopril was similar to chlorthalidone in preventing CHD but was less effective in
reducing stroke, combined CVD events, and heart failure. Patients assigned to either amlodipine or lisinopril were at statistically significant increased risk of stroke compared to those receiving chlorthalidone. In none of the above analyses was there any evidence of a treatment effect by baseline GFR function.

Overall, neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke or combined CVD and chlorthalidone is superior to both for preventing heart failure. A limitation of this trial is that the magnitude of BP reduction achieved was higher in the chlorthalidone arm than in either the amlodipine or lisinopril arms by 2.3 mmHg at 2 years follow-up (the differences in BP reduction decreased over the following 4 years and were non-significant) which may have accounted in part for the more beneficial effects of chlorthalidone. These data are, however, consistent with the IDNT trial in which the secondary composite endpoint of CVD outcome was not statistically significantly different among the amlodipine, irbesartan or placebo groups (although the trial was underpowered to adequately assess this outcome).

Irbesartan Diabetic Nephropathy Trial (IDNT): This trial, summarized above found no difference between the effects of an irbesartan vs amlodipine based regimen for cardiovascular events, RR 1.03, 95% CI: 0.81 - 1.32 [7].

African American Study of Sidney disease and hypertension (AASK) trial: As described above, this study also had an arm comparing therapy based on a B-blocker (metoprolol) vs an ACEi (ramipril) vs a CCB (amlodipine) After a mean follow-up of 4 years there were 202 cardiovascular events with no evidence to suggest superiority of any of the three randomised treatments: ramipril vs metoprolol HR 1.05 (0.72 – 1.53); amlodipine vs metoprolol HR 0.71, 95% CI: 0.43 - 1.16; ramipril vs amlodipine HR 1.49, 95% CI: 0.90 - 2.45 [11]. The main limitation of this study was insufficient power to detect differences in cardiovascular endpoints.

ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET): ONTARGET[13] examined the effects of ramipril versus telmisartan versus the combination of ramipril and telmisartan in more than 25,000 patients at high cardiovascular risk. The primary endpoint was a composite outcome of CVD death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. During a mean follow-up of 56 months 1412 cardiovascular events occurred. In the overall population no improvements in cardiovascular (or renal) events were observed with dual RAAS therapy versus single RAAS therapy. In individuals with lower renal function (eGFR < 60) there were also no improvements in cardiovascular events: the RRR, compared with single RAAS therapy was 0.99, 95% CI: 0.88 – 1.12.

2. Effects of blood pressure lowering agents in patients receiving dialysis

Meta-analysis of blood pressure lowering agents on cardiovascular events and mortality in patients receiving dialysis

Most trials evaluating the cardiovascular protective effects of BP-lowering agents systematically excluded dialysis patients. Furthermore, the first trials conducted specifically among patients on dialysis reported conflicting results. Therefore, a meta-analysis was conducted including all randomised controlled trials evaluating the benefits and risks of BP-lowering drugs in patients on dialysis. A total of 8 trials which reported on 1679 patients with 495 cardiovascular outcomes were included in this meta-analysis [14]. Of these trials, three assessed the effects of an ARB, two assessed an ACEi, two a β blocker, and one a CCB. Treatment with BP-lowering drugs was associated with a 29% lower risk of cardiovascular events compared with control regimens (RR 0.71, 95% CI: 0.55–0.92; P = 0.009). Furthermore, BP-lowering therapies significantly decreased the risk for all-cause mortality by 20% (RR 0.80; 95% CI: 0.66 - 0.96, P = 0.014) and cardiovascular mortality by 29% (RR 0.71; 95% CI: 0.50 - 0.99, P = 0.044) compared with control regimens. The effects appeared to be consistent across a range of patient characteristics, and were irrespective of the drug class assessed. Blood pressure-lowering drugs appeared to be well tolerated; a low proportion of patients ceased medication which did not differ between treatment groups.

3. Effects of blood pressure lowering agents in renal transplant recipients

Study on Evaluation of Candesartan cilexetil after REnal Transplantation (SECRET): The only prospective long-term study on the cardiovascular efficacy and safety of BP-lowering drugs in renal transplant recipients is the SECRET trial [15]. The trial recruited normotensive and hypertensive
subjects with a renal allograft transplantation within 1 to 10 years prior to enrolment and a creatinine clearance ≥ 25 mL/min. The primary endpoint was the composite of all-cause mortality, cardiovascular mortality or renal graft failure. Subjects were randomly assigned to candesartan cilexetil 16 mg/day or placebo. The trial was powered to detect a difference in event rate of 26% which required the recruitment of 350 subjects per treatment arm. The trial was prematurely terminated due to a lower than expected event rate. At the time of termination 502 subjects were enrolled. A total of 26 primary events were recorded which were equally distributed among the two treatment groups. Systolic and diastolic BP as well as proteinuria were better controlled in the candesartan cilexetil group. The obvious limitation of this study is the early termination and the insufficient power to detect clinically important differences between the treatment groups.

SUMMARY OF EVIDENCE

Randomised controlled trials in CKD populations evaluating the benefit risk ratio of BP-lowering regimens on cardiovascular outcomes are lacking. Recommendations in this guideline are therefore based on a synthesis of the best available evidence.

a. Evidence from large randomised-controlled trials indicates that BP-lowering in individuals with impaired renal function reduces the risk of cardiovascular mortality and morbidity and total death.

b. There is limited evidence that lower BP targets in patients with renal impairment are at reduced risk of CVD. As a result it would seem reasonable to extrapolate BP targets from high-risk patients with normal renal function, and to incorporate likely benefits for kidney function, where evidence of benefit exists for a lower target (namely less than 130/80 mmHg) in people with albuminuria or proteinuria.

c. There is evidence that ACEi are efficacious at reducing BP and subsequent CVD and all-cause mortality in patients with mild, moderate and severe renal impairment. There is currently little evidence about the comparative effectiveness of other agents in preventing cardiovascular mortality and morbidity in this patient population. Post-hoc analyses of angiotensin-converting enzyme inhibitors (ACEi) trials have shown that the treatment effects of ACEi on cardiovascular outcomes are consistent in patients with and without CKD. Angiotensin-converting enzyme inhibitors appear therefore a reasonable first choice for prevention of CVD in this population.

d. The evidence about the cardiovascular protective effects of angiotensin receptor blockers (ARBs) in CKD patients is scarce. However, they have been shown to confer renal protection in patients with diabetic nephropathy and are therefore a sensible alternative if ACEi are not tolerated in this population.

e. Head to head studies have reported similar cardiovascular outcomes with different classes of agents in people with CKD, although the power to detect meaningful differences is limited. ACEi, ARBs, calcium channel blockers (CCB) and diuretics are therefore all reasonable choices for people with CKD. Renin angiotensin system blockade with ACEi or ARBs is likely to have renal benefits in people with proteinuria and should therefore be preferred in this population (see separate guideline).

f. There is little evidence about the efficacy in preventing CVD of different combinations of BP lowering drugs in people with CKD. If BP targets are not met, the choice of a second agent should be based on individual patient factors, tolerability, and side effects.

WHAT DO THE OTHER GUIDELINES SAY?

INTERNATIONAL GUIDELINES:

Kidney Disease Outcomes Quality Initiative 2003 [16]: The blood pressure goal for all CKD patients to prevent renal and cardiovascular disease is less than 130/80 mmHg. The guideline recommends ACEi or ARBs as “preferred agents” for diabetic kidney disease and for patients with non-diabetic kidney disease with a spot protein: creatinine ratio ≥ 200 mg/g. The guideline indicates “no preferred agent” in patients with non-diabetic kidney disease with a spot protein: creatinine ratio < 200 mg/g or in the transplant recipient population. Diuretic regimens should however be included in the BP
management in most CKD patients. The choice of other BP lowering agents should be made on the basis of cardiovascular specific indications, patient characteristics and side-effects profiles.

**UK Renal Association [17]:** The guideline recommends BP lowering amongst patients with CKD to ≤ 130/80 mmHg. Angiotensin-converting enzyme inhibitor and ARBs should be part of the BP lowering regimen of patients with CKD and urinary protein excretion > 1g/day, unless there is a specific contraindication.

**Canadian Society of Nephrology [18]:** According the CKD management guideline ACEi and ARBs should be included in the antihypertensive regimen in patients with diabetes mellitus and CKD. For patients with proteinuric CKD (urinary albumin: creatinine ratio ≥ 30 mg/g) antihypertensive therapy should include an ACEi or ARB. In patients with non-proteinuric CKD antihypertensive therapy can include either an ACEi, ARB, diuretic, or calcium channel blocker. Blood pressure target in this population irrespective of the presence of proteinuria is less than ≤ 130/80 mmHg.

**European Best Practice Guidelines:** No recommendation.

**SUGGESTIONS FOR FUTURE RESEARCH**

1. Studies determining the optimal BP goal for protection against cardiovascular events should be conducted.

2. Studies determining the comparative efficacy and safety of ARB, CCB, β-blockers and diuretics on cardiovascular outcomes in patients with CKD on top of ACEi-based regimens could be considered.

3. Well designed and sufficiently powered randomised controlled trials are required to determine the cardiovascular benefits and tolerability of BP-lowering agents in patients receiving maintenance dialysis and in renal transplant recipients.

**CONFLICT OF INTEREST**

Rachel Huxley has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

Toshiharu Ninomiya has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

Vlado Perkovic has a Level IIb conflict of interest according to the conflict of interest statement set down by CARI.

Hiddo Lambers Heerspink has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.
REFERENCES


17. UK Renal Association, CLINICAL PRACTICE GUIDELINES: Cardiovascular Disease in CKD. 2010.

## APPENDICES

### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugts et al 2007 (EUROPA) [1]</td>
<td>12,056</td>
<td>Sub-group analysis of a randomised double blind placebo controlled trial.</td>
<td>Patients with stable coronary artery disease without heart failure. Exclusion criteria included serum Cr &gt;1.7 mg/dL. ACE Perindopril vs. placebo. Primary outcome: Composite of CV death, non-fatal MI and resuscitated cardiac arrest.</td>
<td>4.2 yr</td>
<td>Adjusted HR for baseline eGFR (ml/min/1.73m²) and clinical outcomes:</td>
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<td>4.2 yr</td>
<td>Primary endpoint – placebo group (overall rate 9.9%)</td>
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<td>4.2 yr</td>
<td>&lt;45: 1.59 (95%CI 0.88,2.86)</td>
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<td>45-59: 1.31 (95%CI 0.97-1.76)</td>
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<td>60-74: 1.13 (95%CI 0.88,1.46)</td>
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<td>Primary endpoint – perindopril group (overall rate 8.0%)</td>
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<td>4.2 yr</td>
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<td>4.2 yr</td>
<td>&lt;90: 0.71 (95%CI: 0.49,1.02)</td>
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Limitations: Unplanned sub group analysis. Excluded elevated serum Cr. Renal function based on single serum Cr determination at baseline.
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<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
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</thead>
</table>
| Asselbergs et al 2004 (PREVEND IT) [2] | 864 | Double blind placebo controlled randomised trial.                          | Individuals participating in the PREVEND population based observational study with persistent microalbuminuria, blood pressure <160/100 mm Hg, no antihypertensive use, total cholesterol <8.0 mmol/L and no lipid lowering medication. ACE Fosinopril vs. placebo or Pravastatin vs. placebo. Primary outcome: composite of CV death and CV hospitalisation. | 3.8 years         | RR for all-cause mortality in fosinopril group compared to placebo:  
  • 1.26 (95%CI 0.34, 4.64). Placebo rate 0.9%.  
  MD for SDB and DBP mm Hg: fosinopril vs. placebo:  
  • SBP: -4.00 (95%CI -6.40, -1.60)  
  • DBP: -2.00 (95%CI -3.20, -0.80)  
  HR for primary endpoint in fosinopril vs. placebo  
  • 0.60 (95%CI: 0.33, 1.10). Placebo rate 6.5%.  
  Limitations: Lower than anticipated event rate. No data available as to the event rate in microalbuminuric subjects from the general population. |
| Solomon et al 2006 (PEACE) [3]        | 8290 | Sub group analysis of double blind placebo controlled randomised trial.     | Patients (≥50 years) with chronic stable coronary disease. Exclusion included serum Cr >2.0 mg/dL.  
  ACE Trandolapril vs. placebo  
  Primary outcome: composite of CV death and nonfatal MI. | 4.8 years         | Adjusted HR for outcomes according to eGFR (ml/min/1.73m²).  
  • All-cause mortality – placebo group (overall rate 8.1%)  
    o <45: 2.23 (95%CI 1.36-3.65)  
    o 45-59: 1.28 (95%CI 0.951.73)  
    o 60-74: 1.04 (95%CI 0.80,1.34)  
    o ≥75: 1.00  
  • All-cause mortality – trandolapril group (overall rate 7.2%)  
    o <45: 2.17 (95%CI 1.21,3.89)  
    o 45-59: 1.08 (95%CI 0.87,1.49)  
    o 60-74: 1.02 (95%CI 0.78,1.33)  
    o ≥75: 1.00  
  • CV death, MI, revascularisation – placebo group (overall rate 23%)  
    o <45: 1.78 (95%CI 1.20,2.64)  
    o 45-59: 1.21 (95%CI 0.99,1.46)  
    o 60-74: 1.06 (95%CI 0.99,1.23)  
    o ≥75: 1.00  
  • CV death, MI, revascularisation – trandolapril group (overall rate 22%)  
    o <45: 1.40 (95%CI 0.93,2.10)  
    o 45-59: 1.14 (95%CI 0.94,1.38)  
    o 60-74: 0.94 (95%CI 0.81,1.09)  
    o ≥75: 1.00  
  All-cause mortality treatment effect HR for trandolapril vs. placebo:  
  • <60: 0.73 (95%CI: 0.54,1.00)  
  • ≥60: 0.94 (95%CI: 0.78,1.13)  
  Limitations: Unplanned sub group analysis. Excluded elevated serum Cr. Renal function based on single serum Cr determination at baseline. Small number of low eGFR. No albuminuria. |
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</table>
| Perkovic et al (2007) [5] (PROGRES) | 6,071 | Sub group analysis of double blind placebo controlled randomised trial. | Patients with history of cerebrovascular disease. No exclusion on basis of renal function. Serum Cr measured through study. Perindopril (with and without indapamide) vs. placebo. Primary outcome: major cardiovascular events. | 3.8 years | Adjusted HR associated with CKD:  
  - Major cardiovascular events: 1.29 (95% CI: 1.11,1.49)  
  - All-cause mortality: 1.43 (95%CI: 1.18,1.73)  
  All-cause mortality RR for perindopril and placebo treatment according to CrCl (ml/min):  
    - No CKD: 1.03 (95% CI 0.84,1.25)  
    - Stage 1 or 2: 0.89 (95%CI 0.70,1.13)  
    - Stage ≥3: 0.87 (95%CI 0.68,1.10)  
  Limitations: Unplanned sub group analysis. Multiple laboratories used for serum creatinine. Limited number of CrCl <30 ml/min. No albuminuria. |
| Mann et al 2001 [6] (HOPE) | 8,307 | Sub group analysis of double blind placebo controlled randomised trial. | Patients with cardiovascular disease or diabetes mellitus combined with other risk factors. Exclusion included serum Cr >2.3mg/dL or dipstick proteinuria >1+. ACE ramipril vs placebo. Primary outcome: incidence of CV death, MI or stroke. | 4.5 years | Adjusted (centre effect only) HR for treatment effect and renal insufficiency at baseline:  
  - All-cause mortality – placebo group overall rate 17.8%  
    - No CKD: 0.80 (95%CI 0.67,0.96)  
    - ≥65: 0.90 (95%CI 0.76,1.07)  
  - Major CV event – placebo group overall rate 22.2%  
    - No CKD: 0.75 (95%CI 0.64,0.89)  
    - ≥65: 0.80 (95%CI 0.70,0.92)  
  Limitations: Unplanned sub group analysis. Excluded elevated serum Cr. Renal function based on single serum Cr determination at baseline. Small number of low CrCl. |
| Lambers Heerspink et al. 2010 [4] sub-study (ADVANCE) | 10,640 | Sub group analysis of double blind placebo controlled randomised trial. | Patients with Type 2 diabetes and evidence of elevated CKD risk. Albuminuria status known. ACE+DIU (perindopril, indapamide) vs. placebo. Primary outcome: incidence of major vascular events. | 4.3 years | Treatment effect HRs for perindopril plus indapamide vs. placebo according to CKD status:  
  - Major vascular events – placebo group overall rate 9.3%  
    - No CKD: 1.03 (95% CI 0.84,1.25)  
    - Stage 1 or 2: 0.89 (95%CI 0.70,1.13)  
    - Stage ≥3: 0.87 (95%CI 0.68,1.10)  
  - All-cause mortality – placebo group overall rate 8.5%  
    - No CKD: 0.91 (95%CI 0.73,1.13)  
    - Stage 1 or 2: 0.90 (95%CI 0.70,1.10)  
    - Stage ≥3: 0.87 (95%CI 0.67,1.10)  
  Limitations: Unplanned sub group analysis. eGFR and albuminuria based on determination at baseline. |
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| Berl et al 2003 [7] (IDNT) | 1,715 | Double blind placebo controlled randomised trial. Multi-centre (International) | Patients with hypertension and nephropathy due to Type 2 diabetes. ARB irbesartan or amlodipine vs. placebo. Primary outcomes: Composite of serum creatinine doubling, chronic dialysis, renal transplantation, or death. | 2.6 years | Treatment effect HRs cardiovascular composite  
  - Irbesartan vs placebo (placebo rate 33%)  
    - 0.90 (95%CI 0.74,1.10)  
  - Amlodipine vs placebo (placebo rate 33%)  
    - 1.00 (95%CI 0.83,1.21)  
  - Irbesartan vs amlodipine (amlodipine rate 19%)  
    - 0.90 (95%CI 0.74,1.10)  
  Treatment effect HRs MI  
  - Irbesartan vs placebo (placebo rate 8%)  
    - 0.90 (95%CI 0.60,1.33)  
  - Amlodipine vs placebo (placebo rate 8%)  
    - 0.58 (95%CI 0.37,0.92)  
  - Irbesartan vs amlodipine (amlodipine rate 5%)  
    - 1.54 (95%CI 0.9,2.54)  
  Limitations: Cardiovascular events secondary outcomes. Early termination. |
| Brenner et al 2001 [8] (RENAAL) | 1513  | Double blind placebo controlled randomised trial. Multi-centre (International) | Patients with Type 2 diabetes and nephropathy. ARB losartan vs. placebo. Primary outcomes: Composite of time to serum creatinine doubling, ESRD, or death. | 3.4 years | All-cause mortality RR’s losartan vs. placebo:  
  - 1.03 (95%CI: 0.85, 1.26). Placebo rate 20.3%.  
  Cardiovascular composite RR’s losartan vs. placebo:  
  - 0.94 (95%CI: 0.815, 1.08). Placebo rate 35%.  
  Limitations: Cardiovascular events secondary outcomes. Early termination. |
| Anand et al 2009 [9] (Val-HeFT) | 5,010 | eGFR ml/min/1.73 m²  
  - <60 (2916)  
  - 60 (2086)  
  - <60 plus proteinuria (289)  
  - >60 plus proteinuria (116) | Patients with NYHA Class II-IV heart failure and LVEF<40% at least 3 months prior. Excluded if serum creatinine >221µmol/L Valsartan 40mg bd titrated to 160mg bd  
  Primary outcome: mortality and composite of mortality and morbidity. | 1.9 years | Mortality associated with dip stick positive proteinuria:  
  - HRadj 1.28 (1.01,1.62)  
  Mortality associated in those with dip stick positive proteinuria and low and high eGFR ml/min/1.73 m²:  
  - <60: HRadj 1.26 (0.96,1.66)  
  - >60: HRadj 1.37 (0.83,2.26) P=0.94  
  The beneficial effects of valsartan on mortality did not differ between those with low and high eGFR ml/min/1.73 m²:  
  - <60: HRadj 1.01 (0.85,1.20)  
  - >60: HRadj 0.91 (0.69,1.25)  
  Limitations: Excluded severe CKD. Relied on dip stick analysis for proteinuria. Potential for residual confounding associated with sub group analysis. |
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| Ruilope et al 2001 [10] (HOT) | 18,790  | Sub group analysis of a randomised controlled trial. | Patients with hypertension. Serum creatinine measured at baseline and final visit. DBP targets: ≤90mm vs. ≤85mm vs. ≤80mm. | 3.8 years          | Adjusted RR associated with CKD( CrCl <60 vs. >60 ml/min):  • Major cardiovascular events: 1.58 (95% CI: 1.29, 1.95). Rate in >60 group 3.2%  • All-cause mortality: 1.65 (95%CI: 1.34, 2.03). Rate in >60 group 1.2%.  
No significant differences in event rates between DBP target groups.
Limitations: subgroup analysis. Assessments made on the basis of baseline measure of serum Cr. Low event rates.                                                                 |
<p>| Norris et al 2006 [11] (AASK) | 1,094   | Sub group analysis of a randomised controlled trial. | African Americans with hypertension and eGFR of 20 to 65 ml/min/1.73m². Aim was to limit to BP caused CKD. ACEi vs. βblocker vs. CCB Primary outcome: Renal function. | 4.1 years          | Adjusted HR’s for CV deaths (event rate 2.9%).  • Low vs. usual BP goal: 0.98 (95%CI 0.48,2.01)  • Ramipril vs. metoprolol: 1.06 (95%CI 0.47,2.39)  • Amlodipine vs. metoprolol: 1.18 (95%CI 0.46,3.04)  • Ramipril vs. amlodipine: 0.90 (95%CI 0.35,2.30) Adjusted HR’s for CV composite outcomes (event rate 14%).  • Low vs. usual BP goal: 0.84 (95%CI 0.61,1.61)  • Ramipril vs. metoprolol: 0.98 (95%CI 0.69,1.39)  • Amlodipine vs. metoprolol: 0.77 (95%CI 0.48,1.24)  • Ramipril vs. amlodipine: 1.27 (95%CI 0.78,2.06) Limitations: CV secondary outcomes. CV event rates low. Limited to African Americans. CV events not monitored after ESRD.                                                                 |
| Rahman et al 2005 [12] ALLHAT | 33,357  | Sub group analysis of a randomised controlled trial. | Patients aged &gt;55 years with hypertension and at least 1 additional risk factor for coronary heart disease (CHD). ACE Lisinopril vs. DIU Chlorthalidone vs. CCB Amlodipine Primary outcome: Composite of fatal CHD or nonfatal MI. | 4.9 years          | Adjusted HR’s across baseline eGFR (ml/min/1.73m²) groups compared to eGFR ≥90:  • CHD (control event rate 6.7%):  o &lt;60: 1.38 (95%CI 1.20,1.59)  o 60-89: 1.09 (95% CI 0.97,1.23)  • Combined CVD (control event rate 22.3%):  o &lt;60: 1.35 (95%CI 1.24,1.46)  o 60-89: 1.08 (95% CI 1.01,1.15) Unadjusted HRs for amlodipine/chlorthalidone comparison for non-fatal MI and fatal CHD:  • &lt;60: 1.06 (95%CI 0.89, 1.27) (chlorthalidone event rate 6.2%)  • 60-89: 0.98 (95% CI 0.87,1.10)  • ≥90: 0.90 (95% CI 0.73,1.10) Unadjusted HRs for lisinopril/chlorthalidone comparison for non-fatal MI and fatal CHD:  • &lt;60: 1.00 (95%CI 0.84, 1.20) (chlorthalidone event rate 6.2%)  • 60-89: 0.97 (95% CI 0.86,1.09)  • ≥90: 1.04 (95% CI 0.86,1.27) Limitations: Post hoc subgroup analysis. Lack of proteinuria data. High CVD risk group and not just hypertension. Participants treated with multiple drugs.                                                                 |</p>
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<td>Yusuf et al.</td>
<td>25,620</td>
<td>Randomised controlled trial</td>
<td>Participants ≥ 55 years of age, with atherosclerotic vascular disease or with diabetes with end-organ damage. Participants were randomised into three groups. (ONTARGET Study) Primary outcomes: composite of dialysis, doubling of serum creatinine, and death.</td>
<td>56 months (median)</td>
<td>● The primary outcome (death from cardiovascular causes) occurred in 16.5% (1412) patients in the ramipril group as compared with 16.7% (1423) patients in the telmisartan group (relative risk, 1.01: 95%CI: 0.94 to 1.09)&lt;br&gt;● The primary outcome occurred in 16.3% (1386) patients in the telmisartan/ramipril group (RR 0.99; 95%CI: 0.92 to 1.07), however there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, P &lt; 0.001), syncope (0.3% vs. 0.2%, P=0.03) and renal dysfunction (13.5% vs. 10.2%, P&lt;0.001) as compared with the ramipril group.&lt;br&gt;● The telmisartan monotherapy group had lower rates of cough (1.1% vs. 4.2%, P&lt;0.001) and angioedema (0.1% vs. 0.3%, P=0.01) and higher rate of hypotensive symptoms (2.6% vs. 1.7%, P&lt;0.001) as compared with the ramipril group.</td>
</tr>
<tr>
<td>Lambers Heerspink et al 2009 [14]</td>
<td>8 trials (1679 patients)</td>
<td>Systematic review and met-analysis of randomised controlled trials</td>
<td>Randomised controlled trials that assessed effects of agents that lower blood pressure on CV events in adult patients on maintenance dialysis. Outcomes: All cardiovascular events, all-cause mortality.</td>
<td></td>
<td>All cardiovascular events (control rate 34%):&lt;br&gt;● RR 0.71 (95%CI 0.55,0.92)&lt;br&gt;All-cause mortality (control rate 34%):&lt;br&gt;● RR 0.80 (95%CI 0.66-0.96).&lt;br&gt;CV mortality:&lt;br&gt;● RR 0.71 (95%CI 0.50, 0.99) (control rate 26%)&lt;br&gt;Limitsations: Small number and sample size of available studies.</td>
</tr>
<tr>
<td>Philip et al 2010 [15]</td>
<td>502</td>
<td>Double blind placebo controlled randomised trial. Multi-centre (Europe)</td>
<td>Kidney transplant patients with CrCl ≥25 ml/min. Exclusion included treatment with an ACEi or an ARB. ARB candesartan vs. placebo. Primary outcome: composite of all-cause mortality, CV morbidity and all-cause graft failure.</td>
<td>21.4 (mean)</td>
<td>At termination there were 13 primary outcome events in both arms (5.1% in treatment and 5.3% in control – P=0.763).&lt;br&gt;Limitations: Trial terminated as there were too few events to allow assessment of primary outcome.</td>
</tr>
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<td>Study ID (author, year)</td>
<td>Method of allocation concealment *</td>
<td>Blinding (participants)</td>
<td>Blinding (investigators)</td>
<td>Blinding (outcome assessors)</td>
<td>Intention-to-treat analysis †</td>
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<td>Brugts et al 2007 (EUROPA) [1]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Asselbergs et al 2004 (PREVEND IT) [2]</td>
<td>Block randomisation, third party</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Solomon et al 2006 (PEACE) [3]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Perkovic et al (2007) [5] (PROGRESS)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Mann et al 2001 [6] (HOPE)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Lambers Heerspink et al. 2010 [4] sub-study (ADVANCE)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Berl et al 2003 [7] (IDNT)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Brenner et al 2001 [8] (RENAAL)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Anand et al 2009 [9] (Val-HeFT)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>unclear</td>
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<tr>
<td>Ruilope et al 2001 [10] (HOT)</td>
<td>Central</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Norris et al 2006[11] (AASK)</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Rahman et al (2005) [12]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Yusuf et el. The ONTARGET Investigators (2008)[13]</td>
<td>Central</td>
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<td>Philip et al (2010) [15]</td>
<td>Not stated</td>
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<td>Yes</td>
<td>Unclear</td>
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