Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: anti-hypertensive agents

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GUIDELINES

Non-diabetic Kidney Disease

a. We recommend that either angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) should be used as first line therapy (1B)

b. We recommend that combination therapy with both ACEI and ARBs should be avoided (1C)

Blood pressure targets

c. We recommend BP ≤140/90 (1B)

d. We recommend BP ≤130/80 in people with micro or macroalbuminuria (UACR >3.5mg/mmol in women; UACR >2.5mg/mmol in men) (1B)

Diabetic Kidney Disease - Type I and Type II Diabetes

a. We recommend that either ACEI or ARBs should be used as first line therapy (1A)

b. We recommend that combination therapy with both ACEI and ARBs should be avoided (1C)

c. β-Blockers, calcium channel blockers and thiazide diuretics are all appropriate second line therapy (1B)

Blood pressure targets

d. We recommend a blood pressure target of ≤130/80 in all people with diabetes (1B)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

There are no ungraded statements.

IMPLEMENTATION AND AUDIT

Kidney Check Australia Taskforce (KCAT) education programs should incorporate these updated guidelines. Audits of primary health care providers, similar to the BEACH study, should be commissioned to evaluate awareness of these guidelines.

Relevant education programs (KCAT) and guidelines (Heart Foundation) should incorporate these recommendations. Audits of primary health care providers should be commissioned to evaluate awareness of these guidelines and use (type and dose) of anti-hypertensive agents.

Relevant education programs (KCAT) and guidelines (Diabetes Australia) should incorporate these recommendations. Audits of primary health care providers should be commissioned to evaluate awareness of these guidelines and to monitor relevant key performance indicators, including blood pressure targets, and cardiovascular and renal outcomes.

BACKGROUND

Chronic kidney disease (CKD) represents a major, rapidly growing, public health burden worldwide. In Australia, CKD affects approximately 1 in 7 (or more than 2 million) adults over the age of 25, and contributes to nearly 10% of all deaths and over 1.1 million hospitalisations annually. [1, 2] Several studies, in various populations [3-22], have demonstrated that:

- CKD is a potent, independent cardiovascular (CV) risk factor, with CV events occurring between 10 to 100 times more frequently in the CKD population, and
- CKD has a multiplicative impact on other chronic diseases.

CKD is expensive. In 2000-01, the estimated total recurrent health expenditure on CKD in Australia was $647 million. [23] A recent analysis of the health economic impact of end-stage kidney disease (ESKD) in Australia estimated that, at the end of 2007, hospital dialysis cost around $189 million per year. [24]

Taken together, CKD is a significant contributor of morbidity and mortality, and represents a major expense to the health care system. Early intervention with appropriate medical therapies is essential to address this public health burden and may reduce the progression of CKD and CV risk by up to 50%. [25] The objective of this guideline is to review currently available evidence in this regard and provide appropriate clinical recommendations. Recommendations in other guidelines, and the evidence underpinning these recommendations, have also been reviewed.

The effect of specific anti-hypertensive agents on CKD progression has been discussed in detail in several, previously published, KHA-CARI Guidelines:
(http://www.cari.org.au/ckd_prevent_list_published.php)

- ACE inhibitor and angiotensin II antagonist combination treatment,
- ACE inhibitor treatment in diabetic nephropathy,
- Angiotensin II antagonists,
- Antihypertensive therapy in diabetic nephropathy,
- Blood pressure control: role of specific anti-hypertensives,
- Blood pressure control: targets, and
- Reducing proteinuria.

They are briefly discussed here in the context of recent clinical updates.

The updated KHA-CARI guidelines are reasonably consistent with other existing guidelines in making the following recommendations:

1. In patients with diabetes, ACEI / ARBs should be used as first line therapy.
2. In patients without diabetes, ACEI / ARBs should be used as first line therapy in patients with proteinuric kidney disease. The threshold level of proteinuria above which ACEI / ARBs are recommended has been variably defined as follows:
   - KHA-CARI: protein $\geq$ 0.5 g/d
   - NICE:[26]
     - in patients without hypertension, urine ACR > 70 mg/mmol, PCR > 100 mg/mmol or protein > 1 g/d, or
     - in patients with hypertension, urine ACR $\geq$ 30 mg/mmol, PCR $\geq$ 50 mg/mmol or protein $\geq$ 0.5 g/d
   - KDOQI: urine PCR $\geq$ 200 mg/g (KDOQI), regardless of hypertension[27]
   - CSN: urine ACR $\geq$ 30 mg/mmol[28]
   - National Vascular Disease Guidelines: urine ACR >35 mg/mmol in females and >25 mg/mmol in males[29]

These updated guidelines focus specifically on patients with early CKD (stages 1-3) and synthesise the results of available randomised controlled trials (RCTs) examining renal and cardiovascular outcomes.

Importantly, new evidence reviewed in this updated guideline has led to an upward revision of the recommended BP targets. These new targets are in line with those recommended by the NHMRC-endorsed National Vascular Disease Prevention Alliance Guidelines on Management of Absolute Cardiovascular Risk [29].

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for ACE inhibitors, angiotensin II antagonists, renin angiotensin system inhibition, calcium channel blockers, β blockers and target blood pressure. The updated search was carried out in Medline (2005 – August 2009) and the Cochrane library. No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 2005 - 20011 were also searched for trials. A search update was conducted in Medline (2009 – May 2012) using the same MeSH terms and text words.

Date of search/es: October 2009 and May 2012.

WHAT IS THE EVIDENCE?

Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptor blockers (ARB)

Abundant literature exists to recommend the preferential use of ACEIs and ARBs in retarding the progression of CKD, particularly diabetic kidney disease. Renoprotective benefits have also been demonstrated in children with CKD treated with ACEI[30]. More recent trials support the efficacy of ARBs in reducing proteinuria in diabetic patients with CKD [31],[32-34] One recent trial [35] also examined the effect of supramaximal therapy with candesartan (up to 128 mg/day) in 269 patients over a 30-week period. The investigators found that treatment led to further reductions in proteinuria, compared to standard doses, but was associated with early withdrawal due to hyperkalaemia in 11 patients.

Casas et al.[36] recently published a meta-analysis evaluating the effect of renin-angiotensin-aldosterone system (RAAS) blockade on renal outcomes. Sixty one RCTs (39 485 patients), comparing the effects of ACEI / ARBs with other antihypertensive drugs on GFR, were analysed, demonstrating no significant benefit. By comparison, 13 trials (37089 patients) were included that compared the effects of ACE / ARBs on the occurrence of end-stage kidney disease. A small reduction in favour of ACE / ARBs was found (RR 0.87), in the absence of any significant blood pressure lowering effect. However, no significant benefit was seen in patients with diabetes (4 RCTs, 14 437 patients).

Another meta-analysis by Balamuthusamy et al. [37] examined the role of RAS blockade in improving CV outcomes in patients with CKD. Twenty five trials, including 45,758 patients, were analysed. In comparison to control therapy, RAS blockade was associated with a reduction in CV risk in non-diabetic (RR 0.56, 95% CI 0.47-0.67, $P < 0.001$) but not diabetic patients when compared to control therapy. There was a significant reduction in heart failure in diabetic patients when compared to placebo (RR 0.78, 95% CI 0.66-0.92, $P < 0.05$) and compared to control (RR0.63, 95% CI 0.47-0.86, $P<0.05$). There was no difference in heart failure in non-diabetic patients (RR 0.95, 95% CI 0.56-1.62, $P < 0.05$) with RAS blockade, compared to control therapy (there were no placebo trials).

Sharma et al[38] reported the results of a meta-analysis of 2177 participants enrolled in 4 RCTs reporting the effect of ACEI or ARB in people with early (stage 1 to 3) CKD who did not have diabetes mellitus. Three of these trials compared ACEI (ramipril, benazepril or trandolapril) with placebo and 1 trial compared ACEI (perindopril or trandolapril) with ARB therapy (losartan or candesartan). Two of the studies were sub-groups of larger RCTs[39, 40]. The proportion of patients with stage 3a CKD varied between 39% and 88% in different studies, whilst the proportion with stage 3b CKD varied between 12% and 61%. Two studies included patients with diabetes mellitus (<30% of total sample) [40, 41]. Two studies were rated as having a low risk of bias, 1 study a moderate-to-high risk of bias and 1 study

(comparing ACEI with ARB) a high risk of bias. Analysis of 2 studies involving 1906 participants found that ACEi compared with placebo had no impact on all-cause mortality (RR 1.80, 95% CI 0.17-19.27, p=0.63) or cardiovascular events (RR 0.87, 95% CI 0.66-1.14, p=0.31) in people with stage 3 CKD. Statistically significant heterogeneity was identified for all-cause mortality (I^2 = 81%, P = 0.02), but not for cardiovascular events (I^2 = 0%, P = 0.49). When renal outcomes were considered, one study assessed as having a low risk of bias reported no difference in the risk of ESKD among those with an eGFR > 45 mL/min/1.73 m^2 treated with ACEi versus placebo (RR 1.00, 95% CI 0.09 to 1.11, P = 0.99), whilst another study rates as having a moderate risk of bias demonstrated a statistically significant reduction in the doubling of serum creatinine among the ACEi group versus placebo (RR 0.51, 95% CI 0.34-0.77) and a decrease in urinary protein of 29% in the ACEi group compared with an increase by 9% in the placebo group at 36 months (statistical significance not reported). The latter study also found no difference in adverse events between the ACEI and placebo groups (RR 1.09, 95% CI 0.70-1.68). The only study comparing ACEI with ARB[42], rated as having a high risk of bias, reported no difference in blood pressure, proteinuria or creatinine clearance between the 2 groups (all-cause mortality, cardiovascular events, ESKD and adverse events were not reported). There were no studies comparing ARB with placebo or ACEI+ARB with placebo that were identified. The authors concluded that "there is currently insufficient evidence to determine the effectiveness of ACEi or ARB treatment for patients with stage 1 to 3 CKD who do not have diabetes mellitus." A critical limitation of this systematic review was that it excluded a large number of RCTs (93 in total), mainly because the studies did not report sub-group outcomes in patients with early (stages 1-3 CKD). The review also excluded trials in patients with single specific renal diagnoses.

Strippoli et al[43] conducted a meta-analysis of 49 RCTs (12,067 participants) comparing ACEI or ARB with placebo or each other in patients with diabetic kidney disease (38 compared ACEI with placebo, 4 compared ARB with placebo, 7 compared ACEI with ARB). Trial methodological quality was generally suboptimal. Although no significant difference was observed in the risk of all-cause mortality for ACEI versus placebo (RR 0.91, 95% CI 0.71-1.17) or ARB versus placebo (RR 0.99, 95% CI 0.85-1.17), a subgroup analysis of RCTs which used ACEI at the maximum tolerable dose compared with placebo/no treatment demonstrated a significant reduction in the risk of all-cause mortality (5 studies, 2034 patients; RR 0.78, 95% CI 0.61-0.98) but not in RCTs using ≤half the maximum tolerable dose of ACEI (4 studies, 5261 patients; RR 1.18, 95% CI 0.41-3.44). There was no significant trial heterogeneity identified in any of these analyses. ACEI compared with placebo/no treatment resulted in significant reductions in the risks of ESKD (RR 0.60, 95% CI 0.39-0.93) and progression from micro- to macroalbuminuria (RR 0.45, 95% CI 0.29-0.69), together with a significant increase in regression from micro- to normoalbuminuria (RR 3.06, 95% CI 1.76-5.35). Similar results were demonstrated for ARB compared with placebo/no treatment: risk of doubling of serum creatinine concentration (RR 0.79, 95% CI 0.67-0.93), progression from micro- to macroalbuminuria (RR 0.49, 95% CI 0.32-0.75), and regression from micro- to normoalbuminuria (R 1.42, 95% CI 1.05-1.93). The major limitations of this study were the lack of direct comparative data for ACEI versus ARB, small sample size, suboptimal quality of included studies, and potential for publication bias.

Combination therapy with Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor blockers (ARB)

The majority of patients require multiple anti-hypertensive agents. There remains conflicting evidence, including 2 meta-analyses [44, 45], regarding the use of combination therapy with ACEI and ARBs. Doulton et al. [45] performed a meta-analysis of 14 RCTs which compared intervention with combined ACEI and ARB therapy with either class of drug. Combination therapy had an additive effect on blood pressure lowering and was associated with a greater reduction in proteinuria, compared to monotherapy with an ACEI (30%; 95% CI, 23 – 37%) or ARB (39%; 95% CI, 31 – 48%). However, excluding the COOPERATE study [46], the meta-analysis was limited by RCTs with small numbers (number of patients receiving combination therapy in trials ranged from 10 to 67) and short durations of intervention (4 – 12 weeks). Most importantly, the pivotal COOPERATE study [46], which supported the use of dual ACEI and ARB therapy has now been formally retracted by the [47] due to concerns of scientific misconduct. Kunz et al. [44] also performed a meta-analysis of 49 RCTs (6181 participants) of ARBs vs placebo, ACEIs, CCBs or combination therapy. ARBs and ACEIs were similar in efficacy in reducing proteinuria in patients with both diabetic and non-diabetic CKD, but combination therapy was more effective than either drug alone. However, this meta-analysis was similarly limited by studies which were small, of variable quality and of relatively short duration.

The VALERIA study [48] compared the efficacy and safety of valsartan and lisinopril with either class of drug in patients with hypertension and microalbuminuria (133 patients, over 30 weeks). Normalisation of microalbuminuria was significantly more frequent in the combination therapy group, compared to lisinopril monotherapy (38% vs 17%, P < 0.05) but not with valsartan monotherapy (31%).

Militating against the use of combination therapy, the ONTARGET study [49] was a double-blind RCT of 25 620 patients, aged 55 years or older at high risk of cardiovascular disease, treated with telmisartan 80 mg daily, ramipril 5 mg daily or both (median follow-up of 56 months). The primary composite outcome (death from CV causes, myocardial infarction, stroke or hospitalisation from heart failure) was similar between telmisartan and ramipril (16.7% and 16.5%, respectively). Combination therapy was associated with an increase in adverse events (compared to ramipril, the risk of hypotensive symptoms was 4.8% vs 1.7% (P < 0.001) and the relative risk of death was 1.07 (95% CI, 0.98 – 1.16, NS) with no increase in benefit (primary outcome rate of 16.3%)). The pre-specified renal sub-study [50] confirmed non-inferiority of telmisartan compared to ramipril with the composite primary renal outcome of dialysis, doubling of serum creatinine and death. Interestingly, urine albumin to creatinine ratio (UACR) increased to a lesser extent with combination therapy than monotherapy but was associated with an increased primary outcome rate (HR 1.09, 1.09 – 1.18; P < 0.05). More patients also discontinued therapy due to hypotensive symptoms (406 patients on combination therapy vs 149 patients on ramipril vs 229 patients on telmisartan). A post hoc analysis of the ONTARGET and TRANSCEND studies did not support combination therapy over monotherapy in high-vascular risk patients with low GFR or albuminuria[51].

Use of ACEI or ARBs in combination with other anti-hypertensive agents

Substantial evidence correlates microalbuminuria and blood pressure with cardiovascular risk and renal progression. The GUARD trial[52] was a double blind RCT of benazepril + hydrochlorothiazide (B + HCTZ) vs benazepril + amlodipine (B + A) in 332, type 2 diabetic patients with hypertension and albuminuria, over a 52-week period. Patients treated with B + HCTZ had a greater reduction in UACR (72.1 vs 40.5 %; P < 0.0001 vs baseline, and P < 0.0001 vs B + A). However, B + A therapy was associated with a slower rate of decline in eGFR (-2.03 ± 14.2 vs -13.64 ± 15.1 ml/min; P < 0.0001) and a greater reduction in diastolic, but not systolic, blood pressure (DBP: -13.1 vs -9.97; P < 0.05). These mixed results suggest that both B + HCTZ and B + A combination therapy are favourable in reducing renal outcomes, without convincingly favouring one therapy over the other, and indicate dissociation between reductions in blood pressure and albuminuria.

A meta-analysis of 6 RCTs (5,972 participants) of β-blocker therapy (≥3 months) compared with placebo in patients with stages 3-5 CKD and chronic systolic heart failure demonstrated that β-blocker treatment reduced the risks of all-cause mortality (RR 0.72, 95% CI 0.64-0.80) and cardiovascular mortality (RR 0.66, 95% CI 0.49-0.89), but increased the risks of bradycardia (RR 4.92, 95% CI 3.20-7.55) and hypotension (RR 5.08, 95% CI 3.48-7.41)[53]. Analysis of 2 ACEI-comparator trials involving 977 participants not known to have heart failure were insufficient to conclude whether β-blockers conferred a benefit due to trial heterogeneity and lack of informative data. Renal outcomes were not studied.

In a RCT of 60 hypertensive patients with stage 3 CKD, combination therapy with the maximum recommended daily dose of losartan of 100 mg and a low dose of hydrochlorothiazide of 12.5 mg ameliorated proteinuria and reduced blood pressure more effectively over 24 weeks than treatment with losartan 100 mg alone[54]. The study was limited by small sample size, short follow-up duration and reliance on surrogate outcome measures.

Similarly, the addition of benidipine (2-8 mg/day, n=118) or cilnidipine (5-20 mg/day, n=115) for 12 months reduced urinary protein excretion in hypertensive patients with CKD who were already being treated with ARBs (effect first observed at 3 months)[55]. The difference between the 2 groups was not statistically significant.

Aliskiren

Despite therapy with ACEI or ARB, many patients still progress to end-stage kidney disease. More optimal blockade of the renin-angiotensin-aldosterone system (RAAS) may afford a greater degree of

renoprotection. Parving et al. [56] conducted a double-blind RCT of 599 patients with type 2 diabetes and nephropathy (defined as UACR > 300 mg/g or > 200 mg/g in patients already receiving RAS blockade therapy), treated with aliskiren (a direct inhibitor of renin) or placebo, in addition to maximal therapy with losartan. Aliskiren led to a greater reduction in UACR at 6 months (24.7% or patients achieved a fall in UACR by 50% or more, compared to 12.5% in those who received placebo; P < 0.001), an effect that appeared independent of its blood pressure-lowering effect. A current international, randomized, double-blind, placebo-controlled, parallel-group study (ALTITUDE) aims to determine whether aliskiren 300 mg once daily reduces the risk of the composite endpoint of cardiovascular death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease or doubling of baseline serum creatinine concentration in high-risk patients with type 2 diabetes compared with placebo superimposed on conventional ACEI or ARB treatment[57].

Aldosterone antagonists

Six RCTs have examined the effect of aldosterone antagonism [58-63]. This heterogeneous group of studies, in diabetic and non-diabetic populations, were generally limited by small sample sizes (21 to 165 patients), variable quality and short durations (2 to 12 months). The most recent study by Mehdi et al. [58] randomised 81, predominantly type 2, diabetic patients, with hypertension and UACR $\geq$ 300 mg/g, to treatment with placebo, losartan 100 mg/d or spironolactone 25 mg/d, in addition to lisinopril 80 mg/d. After 48 weeks, there was a significant UACR percentage change for spironolactone vs placebo (-34.0%; 95% CI, -51.0%, -11.2%; P = 0.007) and losartan vs placebo (-16.8%; 95% CI, -37.3%, +10.5%), an effect that appeared independent of blood pressure or glycaemic control. Navaneethan et al. [64] conducted a systematic review of aldosterone antagonism in patients with CKD currently treated with ACEI and/or ARB. Ten RCTs and quasi-RCTs (845 patients) were examined. Aldosterone antagonists contributed to a reduction in 24-hour proteinuria (7 studies, 372 patients; MD -0.80 g, 95% CI -1.23 to -0.38) without a significant improvement in glomerular filtration rate (5 studies, 306 patients; MD -0.70 mL/min/1.73m^2, 95% CI -4.73 to 3.34). Additionally, treatment was associated with an increase in risk of hyperkalaemia (8 studies, 436 patients; RR 3.06, 95% CI 1.26 to 7.41).

Blood pressure targets

Existing guidelines are reasonably concordant in their recommendations for blood pressure targets, albeit with a limited evidence base. De Galan et al. [65] examined more closely the renal outcomes of type 2 diabetic patients in the ADVANCE study (n = 12 877) who were treated with a fixed combination of perindopril-indapamide or placebo. During a mean follow-up of 4.3 years, treatment reduced the risk for renal events (a composite outcome consisting of new-onset microalbuminuria / nephropathy, doubling of serum creatinine above 200 μmol/L, or end-stage kidney disease) by 21% (P < 0.0001). Participants were also analysed in 2 sets of 4 blood pressure groups: SBP <120, 120 – 139, 140 – 159 and $\geq$ 160 mmHg, and DBP < 70, 70 – 79, 80 – 89 and $\geq$ 90 mmHg. Of note, the renoprotective effects were seen in all subgroups, suggesting that, in patients with diabetic kidney disease, a blood pressure limit below currently recommended guidelines may be beneficial. An important limitation of this study was that the results represented a post hoc analysis of an outcome that was not the primary outcome measure of the original study. The results are therefore hypothesis-generating only. In a study[66] of 1094 black patients with hypertensive CKD randomly allocated to receive either intensive BP control (mean BP 130/78 mm Hg) or standard BP control (mean BP 141/86 mm Hg), no significant between-group difference was observed in the risk of the primary composite outcome of doubling of serum creatinine level, ESKD or death (HR 0.91, p=0.27), although a benefit of intensive BP control was identified for patients with urine protein:creatinine ratios >0.22 mg/g (HR 0.73, p=0.01). Recently, Upadhyay et al [67] published the results of a systematic review of randomised controlled trials comparing lower versus higher blood pressure targets in adult patients with non-diabetic CKD. Three trials with a total of 2272 participants were included. Overall, the trials did not demonstrate that a lower blood pressure target of less than 125/75 to 130/80 mm Hg was more beneficial than a target of less than 140/90 mm Hg. Lower-quality evidence suggested that a low target may have been 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. The authors suggested 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.

With regards to CV outcomes in patients with CKD, there remains scant evidence to support blood pressure targets below 140/90. The recent systematic review by Upadhyay et al [67] did not suggest benefit for a blood pressure target of 125/75, compared to 140/90, in terms of CV outcomes. Some evidence, not specific to patients with CKD, exists for lower targets in patients with diabetes and impaired fasting glucose. Bangalore et al [68] published a recent meta-analysis and meta-regression analysis of 13 randomised clinical trials (n = 37 736) comparing intensive blood pressure (achieved systolic blood pressure $\leq$ 135 mmHg) vs standard blood pressure (achieved systolic blood pressure $\leq$ 140 mmHg) therapy in patients with type 2 diabetes mellitus or impaired fasting glucose/tolerance. Overall, the trials suggested that intensive blood pressure control was beneficial in terms of all-cause mortality (odds ratio, 0.90; 95% confidence interval, 0.83 to 0.98) and stroke (odds ratio, 0.83; 95% confidence interval, 0.73 to 0.95), with a continued risk reduction for stroke to a systolic BP of $\leq$120 mmHg. There was, however, no benefit with regards to CV mortality, heart failure or myocardial infarction and there was a significant (40%) increase in serious adverse effects at levels $\leq$ 130 mmHg. Included within these trials was the ACCORD study [69], a randomised controlled trial of 4733 patients with type 2 diabetes who were assigned to intensive therapy (target systolic pressure $\leq$ 120 mmHg; mean achieved systolic pressure 119.3 mmHg) vs standard therapy (target systolic pressure $\leq$ 140 mmHg; mean achieved systolic pressure 133.5 mmHg). This trial indicated that intensive therapy did not reduce the rate of the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. Specific to CKD, a retrospective cohort study of patients (n = 3099) aged 75^{+} years with CKD found that patients with a baseline systolic blood pressure < 130 mmHg had poorer outcomes in terms of mortality and CV hospitalisations.[70]

SUMMARY OF EVIDENCE

Substantial evidence favours the use of treatment regimens which include ACEI / ARBs in reducing albuminuria and retarding the progression of CKD. Such evidence is most compelling for patients with established diabetic kidney disease. Recent large-scale RCTs suggest that ARBs are not inferior to ACEIs but conflicting evidence remains for the use of combination ACEI and ARB blockade. The most recent studies suggest not only the absence of a clinical benefit over monotherapy but also an increase in adverse events. Several RCTs demonstrate efficacy of combining ACEI or ARB monotherapy with other second-line agents, including thiazide diuretics, non-dihydropyridine CCBs, spironolactone and aliskiren. However, limitations include sample size and study duration, and concerns remain with regard to tolerability and side effects. There is reasonable evidence to indicate that lowering SBP is associated with slowing progression to end-stage kidney disease and patients with proteinuric and/or diabetic kidney disease should be treated to lower BP targets. However, the threshold below which this benefit is lost remains unclear.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:[27]

7.2 Target blood pressure for CVD risk reduction in CKD should be <130/80 mmHg

7.3 Antihypertensive agents should be prescribed as follows, when possible:

7.3.a Preferred agents for CKD should be used first.

8.2 Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB.

9.2 Patients with non-diabetic kidney disease and spot urine total protein to creatinine ratio ≥200 mg/g, with or without hypertension, should be treated with an ACE inhibitor or ARB.

7.3.b Diuretics should be included in the antihypertensive regimen in most patients.

7.3.c Choose additional agents based on cardiovascular disease-specific indications to achieve therapeutic and preventive targets and to avoid side-effects and interactions.

7.4 The antihypertensive regimen should be simplified as much as possible.

7.4.a Long-acting (once-daily agents) should be used when possible.

7.4.b Two agents, either as separate prescriptions or as a fixed-do

se combination containing preferred agents, may be considered as initial therapy for SBP >20 mm Hg above goal according to the stage of CKD and CVD risk.

7.4.c Fixed-dose combinations may be used for maintenance therapy after the antihypertensive regimen has been established.

Canadian Society of Nephrology (CSN):[28]

Patients without diabetes

1.1.1 For patients with proteinuric chronic kidney disease (urine ratio of albumin to creatinine ≥ 30 mg/mmol), antihypertensive therapy should include an ACE inhibitor or an angiotensin-receptor blocker in cases of intolerance to ACE inhibitors.

1.1.2 Blood pressure should be targeted to less than 130/80 mmHg.

1.1.3 For patients with non-proteinuric chronic kidney disease (urine ratio of albumin to creatinine < 30 mg/mmol), antihypertensive therapy should include either an ACE inhibitor, an angiotensin receptor blocker, a thiazide diuretic, a blocker (patients aged 60 years or less) or a long-acting calcium channel blocker.

Patients with diabetes

1.2.1 Antihypertensive therapy should include either an ACE inhibitor or an angiotensin-receptor blocker.

1.2.2 Blood pressure should be targeted to less than 130 mmHg systolic and less than 80 mmHg diastolic.

European Best Practice Guidelines (EBPG): No recommendations

International Guidelines:

Kidney Check Australia Taskforce:[71]

Treatment of blood pressure

- Lifestyle modification
- ACEI and/or ARB first-line

Target blood pressure < 130/80 mmHg (< 125/75 mmHg if proteinuria > 1g/24hrs)

National Institute for Clinical Excellence (NICE):[26]

R39 In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120 – 139 mmHg) and the diastolic blood pressure below 90 mmHg.

R40 In people with diabetes and CKD or when the ACR is ≥ 70 mg/mmol, or PCR ≥ 100 mg/mmol (approximately equivalent to urinary protein excretion ≥ 1.0g/24h) aim to keep the systolic blood pressure below 130 mmHg (target range 120 – 129 mmHg) and the diastolic blood pressure below 80 mmHg.

R42 Offer ACE inhibitors/ARBs to people with diabetes and ACR more than 2.5mg/mmol (men) or more than 3.5mg/mmol (women) irrespective of the presence of hypertension or CKD stage.

R43 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and hypertension and ACR 30mg/mmol or more (approximately equivalent to PCR 50mg/mmol or more, or urinary protein excretion of 0.5g/24 h or more)

R44 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and ACR 70mg/mmol or more (approximately equivalent to PCR 100mg/mmol or more, or urinary protein excretion 1 g/24 h or more) irrespective of the presence of hypertension or cardiovascular disease.

R45 Offer non-diabetic people with CKD and hypertension and ACR less than 30 mg/mmol (approximately equivalent to PCR less than 50 mg/mmol, or urinary protein excretion less than 0.5 g/24 h) a choice of antihypertensive treatment according to the NICE guidance on hypertension (NICE clinical guideline 34) to prevent or ameliorate progression of CKD.

R46 When using ACE inhibitors/ARBs, titrate them to the maximum tolerated therapeutic dose before adding a second line agent.

R48 In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACEI/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase.

R49 ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically > 5.0 mmol/l).

R52 Stop ACEI/ARB therapy if the serum potassium concentration rises to above 6.0 mmol/l and other drugs known to promote hyperkalaemia have been discontinued.

R54 If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1 – 2 weeks. Do not modify the ACEI/ARB dose if the change in eGFR < 25% or change in plasma creatinine is < 30%.

Scottish Intercollegiate Guidelines Network (SIGN):[72]

3.1.1 Blood pressure should be controlled to slow the deterioration of glomerular filtration rate and reduce proteinuria. Patients with > 1 g/day of proteinuria (approximately equivalent to a

protein/creatinine ratio of 100mg/mmol) should have a target maximum systolic blood pressure of 130 mmHg.

3.3.1 Patients with chronic kidney disease and type 1 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor irrespective of blood pressure.

- Patients with chronic kidney disease and type 2 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker irrespective of blood pressure.
- Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are the agents of choice to reduce proteinuria in patients without diabetes but who have chronic kidney disease and proteinuria.
- Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers should be used as agents of choice in patients (with or without diabetes) with chronic kidney disease and proteinuria ($\geq$ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol) in order to reduce the rate of progression of chronic kidney disease.

3.4.1 Non-dihydropyridine calcium channel blockers should be considered in patients with chronic kidney disease and proteinuria who are intolerant of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

Canadian Hypertension Education Program Recommendations 2010:[73]

For lifestyle modifications to prevent and treat hypertension:

- restrict dietary sodium to 1500 mg (65 mmol) per day in adults 50 years of age or younger, to 1300 mg (57 mmol) per day in adults 51 to 70 years of age, and to 1200 mg (52 mmol) per day in adults older than 70 years of age
- perform 30 min to 60 min of moderate aerobic exercise four to seven days per week; maintain a healthy body weight (body mass index 18.5 kg/m(2) to 24.9 kg/m(2)) and waist circumference (less than 102 cm for men and less than 88 cm for women)
- limit alcohol consumption to no more than 14 standard drinks per week for men or nine standard drinks per week for women
- follow a diet that emphasizes fruits, vegetables and low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources, and that is low in saturated fat and cholesterol; and consider stress management in selected individuals with hypertension

For the pharmacological management of hypertension, treatment thresholds and targets should be predicated on the patient's global atherosclerotic risk, target organ damage and comorbid conditions. Blood pressure should be decreased to less than 140/90 mmHg in all patients, and to less than 130/80 mmHg in patients with diabetes mellitus or chronic kidney disease. Most patients will require more than one agent to achieve these target blood pressures. Antihypertensive therapy should be considered in all adult patients regardless of age (caution should be exercised in elderly patients who are frail). For adults without compelling indications for other agents, considerations for initial therapy should include thiazide diuretics, angiotensin- converting enzyme (ACE) inhibitors (in patients who are not black), long-acting calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) or beta-blockers (in those younger than 60 years of age). A combination of two first-line agents may also be considered as initial treatment of hypertension if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target. The combination of ACE inhibitors and ARBs should not be used, unless compelling indications are present to suggest consideration of dual therapy. Agents appropriate for first-line therapy for isolated systolic hypertension include thiazide diuretics, long-acting dihydropyridine CCBs or ARBs. In patients with coronary artery disease, ACE inhibitors, ARBs or beta-blockers are recommended as first-line therapy; in patients with cerebrovascular disease, an ACE inhibitor/diuretic combination is preferred; in patients with proteinuric non-diabetic chronic kidney disease, ACE inhibitors or ARBs (if intolerant to ACE inhibitors) are recommended; and in patients with diabetes mellitus, ACE inhibitors or ARBs (or, in patients without albuminuria, thiazides or dihydropyridine CCBs) are appropriate first-line therapies. In selected high-risk patients in whom combination therapy is being considered, an ACE inhibitor plus a long-acting dihydropyridine CCB is preferable to an ACE inhibitor plus a thiazide diuretic. All hypertensive patients with dyslipidaemia should be treated using the thresholds, targets and agents outlined in the Canadian lipid treatment guidelines. Selected patients with hypertension who do not achieve thresholds for statin therapy, but who are otherwise at high risk for cardiovascular events, should nonetheless receive statin therapy. Once blood pressure is controlled, low-dose acetylsalicylic acid therapy should be considered.

National Vascular Disease Prevention Alliance:[29]

CBR7: Pharmacotherapy for blood pressure-lowering should aim towards the following targets while balancing the risks / benefits:

- ≤140/90 mmHg for adults without CVD (including those with CKD)
- ≤130/80 mmHg for adults with micro or macro albuminuria (UACR >2.5 mg/mmol in males and >3.5 mg/mmol in females)
- ≤130/80 mmHg for all adults with diabetes

SUGGESTIONS FOR FUTURE RESEARCH

Future studies are still needed to define appropriate BP targets in patients with CKD.

Sub-group analyses of existing RCTs of ACEI or ARB interventions in patients with early (stages 1-3) CKD are needed. Investigators should also make these data available for meta-analysis.

CONFLICT OF INTEREST

Richard Phoon has a level II b. conflict of interest for receiving speaker fees and honoraria from several companies related to anaemia, CKD-MBD and cardiovascular disease between 2008 and 2012.

David Johnson has a level II b. conflict of interest for receiving speaker honoraria and advisor's fees from several companies related to anaemia, CKD-MBD, hypertension and cardiovascular disease between 2008 and 2012.

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APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptor blockers (ARB)					
Burgess et al (2009) [35]	269	RCT (multicentre)	Participants aged 18 to 80 years with persistent proteinuria (≥ 1 g/day) were randomised into three groups	30 weeks	• The mean difference of the percentage change in proteinuria for patients receiving 128 mg/day candesartan compared with those receiving 16 mg/day candesartan was -33.05% (95%CI: -45.70 to -17.44; P<0.0001) • Reductions in BP were not different across the three groups • Elevated serum potassium levels (K^+ > 5.5 mEq/L) led to early withdrawal of 11 patients • Persistent proteinuria can be reduced by increasing the dosage of candesartan, but serum potassium levels need to be monitored
Casas et al (2005) [36]	127 studies	Systematic review and meta-analysis	The effects of ACE inhibitors or ARBs in placebo-controlled trials were compared with the effects seen in trials that used an active comparator drug.	Mean 4.2 years	• Comparing the effects of ACEi or ARBs with other antihypertensive drugs on glomerular filtration rate, results showed no significant benefit • A small reduction in favour of ACEi / ARBs was found (13 studies, 37 089 patients, RR 0.87, 95%CI: 0.75 to 0.99) on the occurrence of end-stage renal disease • In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on the doubling of creatinine (6 studies, 3 044 patients, RR 1.09, 95%CI: 0.55 to 2.15), end-stage renal disease (4 studies, 14 437 patients, RR 0.89, 95%CI: 0.74 to 1.07), glomerular filtration rate (37 studies, 15 742 patients, MD -1.19 mL/min, 95%CI: -2.69 to 0.31), or creatinine amounts (18 studies, 4 315 patients, MD -1.77 µmol/L, 95%CI: -7.07 to 3.54).
Balamuthusamy et al (2008) [37]	25 studies (N = 45 758)	Meta-analysis	Analysis of cardiovascular outcomes in patients with CKD/proteinuria treated with renin angiotensin system (RAS) blockade (ACEi /ARBs) compared with placebo and control (β-blocker, calcium-channel blockers and other anti-hypertensives)	N/A	• RAS blockade decreased the risk for heart failure in patients with diabetic nephropathy 0.78 (95%CI: 0.66 to 0.92, P = 0.003) when compared with placebo, and 0.63 (95%CI: 0.47 to 0.86, P = 0.003) when compared with control therapy. • In non-diabetic nephropathy patients with CKD, the risk for CV outcomes was decreased with RAS blockade (0.56, 95%CI: 0.47 to 0.67, P <0.001) when compared with control therapy • For all patients with CKD there was a significant reduction of CV outcomes (0.84, 95%CI: 0.78 to 0.91, P <0.0001), myocardial infarction (0.78, 95%CI: 0.65 to 0.97, P = 0.03), and heart failure (0.74, 95%CI: 0.58 to 0.95, P = 0.02) when compared RAS blockade to placebo.

Study ID	N	Study design	Participants	Follow up	Comments and results
Sharma et al (2011)[38]	4 RCTs (n=2,177)	Systematic review, meta-analysis	Studies including non-diabetic patients with CKD (stage 1 to 3) where included. Three studies compared angiotensin converting enzyme inhibitor (ACEi) with placebo and one study compared ACEi with Angiotensin Receptor Blocker (ARB)	NA	• In people with stage 3 CKD, ACEi had no effect on all-cause mortality (relative risk (RR) 1.80: 95%CI: 0.17-19.27; P = 0.63) or cardiovascular events RR 0.87 (95%CI: 0.66-1.14; P = 0.31) compared to placebo (2 studies, low to moderate quality evidence) • Treatment with ACEi in people with an eGFR >45 mL/min/1.74 m2, showed no difference in the risk of end-stage kidney disease RR 1.00 (95%CI: 0.09-1.11; P = 0.99) compared to placebo (1 study with low risk of bias) • The study comparing ACEi and ARB had high risk of bias. Both treatments significantly reduced urinary protein excretion at 48 weeks, in patients with moderate proteinuria. ACEi reduced it from 2.7 g/day to 1.2 g/day (P < 0.05) and ARB reduced it from 2.7 g/day to 1.6 g/day (P < 0.05) • For patients with mild proteinuria, there was a significant reduction in blood pressure from baseline to 48 weeks for both ACEi and ARB. For ACEi: from 148/86 mmHg to 131/74 mmHg; P< 0.05 (difference of mean 17/12 mmHg). For ARB: from 154/86 mmHg to 137/71 mmHg; P < 0.05 (difference of mean 17/15 mmHg) • For patients with moderate proteinuria a significant reduction in BP was noted in the ACEi group (P < 0.01) with a less significant reduction noted in the ARB group (P < 0.05)
Strippoli et al (2006)[43]	49 RCTs (n=12,067)	Systematic review, meta-analysis	Studies including patients with diabetic kidney disease were included. Treatments included angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (AIIRA) compared with each other or against placebo.	NA	• 38 studies compared ACEi with placebo, 4 compared AIIRA with placebo and 7 compared ACEi and AIIRA. • There was no significant difference for all-cause mortality for ACEi or AIIRA compared to placebo (RR 0.91, 95%CI: 0.71-1.17) and (RR 0.99, 95%CI: 0.85-1.17) respectively. • A significant reduction in the risk of all-cause mortality was noted with the use of full-dose ACEi (RR 0.78, 95%CI: 0.61-0.98) compared with half or less than half dose. • There was a significant reduction in risk of end-stage kidney disease and in progression from micro to macro-albuminuria, for ACEi versus placebo/no treatment. RR 0.60 (95%CI: 0.39-0.93; P = 0.023) and 0.45 (95%CI: 0.29-0.69; P = 0.0003) respectively. • There was a significant increase in regression from micro- to normoalbuminuria RR3.06 (95%CI: 1.76-5.35; P = 0.00008) for ACEi versus placebo/no treatment.
Combination therapy with Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor blockers (ARB)					

Study ID	N	Study design	Participants	Follow up	Comments and results
Doulton et al (2005) *[45]	14 RCTs (434 participants)	Meta-analysis	Randomised trials of combined renin-angiotensin system (RAS) inhibition with an ACEi and ARB compared with monotherapy with either class of drug	N/A	• ACEi and ARB combination therapy reduced ambulatory blood pressure by: 4.7/3.0 mmHg (95%CI: 2.9 to 6.5/1.6 to 4.3) when compared with ACEi monotherapy and by 3.8/2.9 mmHg (95%CI: 2.4 to 5.3/0.4 to 5.4) when compared with ARB monotherapy. • ACEi and ARB combination therapy reduced clinic blood pressure by: 3.8/2.7 mmHg (95%CI: 0.9 to 6.7/0.8 to 4.6) when compared with ACEi and 3.7/2.3 mmHg (95%CI: 0.4 to 6.9/0.2 to 4.4) compared with ARB. • Proteinuria was reduced by 30% (95%CI: 23% to 37%) with combination therapy compared with ACEi and by 39% (95%CI: 31% to 48%) when compared with ARB monotherapy
Kunz et al (2008)[44]	49 RCTs (6,181 participants)	Meta-analysis	Randomised trials of ARBs vs placebo, ACE inhibitors, calcium-channel blockers, or the combination of ARBs and ACE inhibitors in patients with or without diabetes and with microalbuminuria or proteinuria.	N/A	• The ARBs reduced proteinuria compared with placebo or calcium-channel blockers over 1 to 4 months (ratio of means, 0.57 (95%CI: 0.47 to 0.68) and 0.69 (95%CI: 0.62 to 0.77), respectively. • ACE inhibitors reduced proteinuria to a similar degree • Combination of ACEi and ARBs, reduced proteinuria more than either agent alone • The ratio of means for combination therapy vs ARBs was 0.76 (95%CI: 0.68 to 0.85) over 1 – 4 months and 0.75 (95%CI: 0.61 to 0.92) over 5 to 12 months • The ratio of means for combination therapy vs ACEi was 0.78 (95%CI: 0.72 to 0.84) over 1 to 4 months, and 0.82 (95%CI: 0.67 to 1.01) over 5 to 12 months.
Menne et al (2008) [48]	133	RCT	Participants between 18 and 75 years old with essential hypertension and microalbuminuria. (VALERIA Trial)	30 weeks	• The geometric mean urine albumin creatinine ratio decreased in all three groups by: 41% (from 9.6 mg/mmol to 5.7 mg/mmol) for the lisinopril group; 51% (from 9.1 mg/mmol to 4.5 mg/mmol) for the valsartan group; and 62% (from 9.5 mg/mmol to 3.6 mg/mmol) for the valsartan/lisinopril group • Normalization of microalbuminuria was greatest with valsartan/lisinopril (38% of patients), followed by valsartan (31%) and lisinopril (17%) • Difference between the valsartan/lisinopril and lisinopril groups was statistically significant (P=0.03) • 6.4% of patients on lisinopril, 7.1% on valsartan, and 2.5% on valsartan/lisinopril still had macroalbuminuria at the end of the study period (differences were not statistically significant)

Study ID	N	Study design	Participants	Follow up	Comments and results
Yusuf et al. The ONTARGET Investigators (2008) [49]	25,620	RCT	Participants ≥ 55 years of age, with atherosclerotic vascular disease or with diabetes with end-organ damage. Participants were randomised into three groups. (ONTARGET Study)	56 months (median)	• 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) • 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 < 0.001), syncope (0.3% vs. 0.2%, P=0.03) and renal dysfunction (13.5% vs. 10.2%, P<0.001) as compared with the ramipril group. • The telmisartan monotherapy group had lower rates of cough (1.1% vs. 4.2%, P<0.001) and angioedema (0.1% vs. 0.3%, P=0.01) and higher rate of hypotensive symptoms (2.6% vs. 1.7%, P<0.001) as compared with the ramipril group.
Mann et al (2008) [50]	25,620	RCT	Participants ≥ 55 years of age, with atherosclerotic vascular disease or with diabetes with end-organ damage. Participants were randomised into three groups. Trial ran from 2001 to 2007. (ONTARGET Study)	56 months (median)	• 406 patients on combination therapy, 149 on ramipril and 229 on telmisartan discontinued therapy because of hypotensive symptoms • The primary outcome (dialysis, doubling of serum creatinine and death) was similar for telmisartan and ramipril 13.4% (n=1147) and 13.5% (1150) respectively, with a hazard ratio (HR) 1.00 (95%CI: 0.92 to 1.09, P=NS), but was increased with combination therapy 14.5% (1233) HR 1.09 (95%CI: 1.01 to 1.18, P=0.037) • Increase in urinary albumin excretion was less with telmisartan (P=0.004) or with combination therapy (P=0.001) than with ramipril • eGFR declined least with ramipril compared with telmisartan (-2.12 [SD 17.2] vs. -4.12 [17.4] mL/min/1.73m^2,P<0.0001) or with combination therapy (-6.11 [17.9] mL/min/1.73m^2, P<0.0001)
Use of ACEI or ARBs in combination with other anti-hypertensive agents					
Bakris et al (2008) [52]	332	RCT	Participants 21 to 85 years old with type 2 diabetes mellitus, albuminuria and hypertension. Participants were randomised into two combination therapy groups. (GUARD Study)	1 year	• Patients treated with benazepril and hydrochlorothiazide (B+HCTZ) had a greater reduction in UACR (-72.1%, range: -98.4 to 590%) compared with (-40.5%, range: -98.3 to 880%) for the benazepril and amlodipine (B+A) group (P<0.0001) • Mean reduction in both SBP and DBP was greater in the B+A group than in the B+HCTZ group (SBP: -20.5 vs -18.8, P=0.19; DBP: -13.1 vs -9.97, P=0.02) • Mean reduction in eGFR was less in the B+A group than in the B+HCTZ group (-2.03±14.2 vs -13.64±16.1 mL/min; P<0.0001)

Study ID	N	Study design	Participants	Follow up	Comments and results
Badve et al (2011)[53]	8 RCTs (n=6,949)	Systematic review, meta-analysis	Participants with chronic systolic heart failure and CKD (6 studies; n= 5,972) and 2 studies (n=977) including participants with CKD but no known heart failure. Beta-adrenergic antagonists (β-blockers) compared with placebo or with ACEi.	NA	• Compared with placebo, B-blocker treatment reduced the risk of all-cause mortality (RR 0.72, 95%CI: 0.64-0.80; P < 0.001) (6 trials) and cardiovascular mortality (RR 0.66, 95%CI: 0.49-0.89; P = 0.006) (4 trials) in patients with CKD and heart failure. However it increased the risk of bradycardia and hypotension (RR 4.92, 95%CI: 3.20-7.55; P < 0.001) (4 trials) and (RR 5.08, 95%CI: 3.48-7.41; P < 0.001) (4 trials) respectively. • Analysis was not conducted in the non-heart failure studies due to study heterogeneity and lack of data.
Abe et al (2009)[54]	60	RCT	Patients with stage 3 CKD and hypertension. Combination group – losartan 100 mg/day + hydrochlorothiazide 12.5 mg/day Control – losartan (100 mg/day) Single centre, Japan	24 weeks	• Blood pressure significantly decreased from baseline (158/90 mmHg to 133/79 mmHg, at 24 weeks) in the combination group compared with the control group. • Serum creatinine increased and the estimated glomerular filtration rate decreased significantly in both groups. However, combination therapy significantly lowered the urinary protein:creatinine ratio
Aliskiren					
Parving et al (2008) [56]	599	RCT	Patients 18 to 85 years old with hypertension, type 2 diabetes and nephropathy. Patients were randomised into two groups of combination therapy. Study was conducted in 15 countries (150 centres).	6 months	• Treatment with losartan and aliskiren, reduced the mean urinary to albumin-creatinine ratio by 20% (95%CI: 9 to 30; P<0.001), 24.7% of patients on the aliskiren group reduced their UACR by ≥50% compared with 12.5% of those in the placebo group (P=0.07) • There was a small drop in blood pressure in the aliskiren group (SBP: -2 mmHg, P=0.07; DBP: -1 mmHg, P+0.08) • Number of adverse and serious adverse events were similar between the groups
Aldosterone antagonists					
Mehdi et al (2009) [58]	81	RCT	Participants 20 to 65 years old with diabetes, hypertension and albuminuria. Patients were given lisinopril in addition to placebo, losartan or spironolactone. (August 2003 to March 2007)	48 weeks	• The albumin-to-creatinine ratio (ACR) decreased by 34.0% (95%CI: -51.0 to -11.2%; P = 0.007) for the spironolactone vs placebo group and decreased by 16.8% (95%CI: -37.3 to 10.5%; P = 0.20) for the losartan vs placebo group • BP, creatinine clearance, sodium and protein intake and glycaemic control did not differ between the groups. • The addition of spironolactone to a regimen of ACE inhibition, gives greater reno-protection in diabetic nephropathy

Study ID	N	Study design	Participants	Follow up	Comments and results
Navaneethan et al (2009) [64]	10 studies (845 patients)	Systematic review	Evaluated the benefits and harms of adding aldosterone antagonists in patients with CKD currently treated with ACEi and/or ARB.	N/A	• Non-selective aldosterone antagonists along with ACEi and/or ARB significantly reduced 24-hour proteinuria (7 studies, 372 patients; MD -0.80g, 95%CI: -1.23 to -0.38) compared to ACEi and/or ARB plus placebo. • There was also a significant reduction in both systolic and diastolic blood pressure with the addition of non-selective aldosterone antagonists, however there was no improvement in glomerular filtration rate (5 studies, 306 patients, MD -0.70mL/min/1.73m^2, 95%CI: -4.73 to 3.34) • The addition of non-selective aldosterone antagonists increased the risk of hyperkalaemia (8 studies, 436 patients; RR 3.06, 95%CI: 1.26 to 7.41) • Aldosterone antagonists contribute to the reduction of proteinuria but increase the risk of hyperkalaemia
Blood pressure targets					
De Galan et al (2009) ADVANCE Study [65]	11, 140	RCT	Participants ≥ 55 years old with type 2 diabetes, were randomly assigned to fixed combination perindopril-indapamide or placebo. ADVANCE Study: 215 centres in 20 countries	4.3 years	• Active treatment reduced the risk for renal events by 21% (P<0.0001) and also reduced the risk for developing microalbuminuria (P < 0.0001) and macroalbuminuria (P < 0.003) • Active treatment achieved lower systolic BP, which was associated with progressively lower rates of renal events. • Treatment with perindopril-indapamide given to individuals with type 2 diabetes provides reno-protection even among those with BP < 120/70 mmHg
Appel et al (2010)[66]	1,094	RCT	Black adult patients with hypertensive chronic kidney disease. Patients were randomised to intervention group (intensive blood pressure (BP) control: MAP 92 mmHg) or control (standard BP control: MAP 102 to 107 mmHg). Multicentre, two phase study (trial and cohort) USA	8.8 to 12.2 years	• The mean blood pressure was 130/78 mmHg and 141/86 mmHg during the trial phase for the intensive and control groups, respectively. During the cohort phase the mean BP remained stable 131/78 mmHg for the intensive group and decreased to 134/78 mmHg for the control group. This was because the blood pressure target was decreased to 130/80 mmHg for both groups. • There was no significant difference between the groups in the risk of doubling of serum creatinine level, end-stage renal disease, or death HR 0.91 (95%CI: 0.77-1.08; P = 0.27), However, there was a significant difference between the groups was identified for patients with a protein:creatinine ratio >0.22 mg/g (HR 0.73, 95%CI: 0.58-0.93; P = 0.01)
Upadhyay et al (2011) [67]	3 trials (2,277 patients)	Systematic review	To summarize trials comparing lower versus higher blood pressure targets in adult patients with CKD and focus on proteinuria as an effect modifier	NA	• A blood pressure target of <125/70 to 130/80 mmHg did not show to be more beneficial than a target of <140/90 mmHg. • Lower quality evidence suggests that a low target may be beneficial in subgroups with proteinuria >300 to 1000mg/day. • Slightly higher rate of adverse effects were detected in participants in the low target group due to increased use of antihypertensive medication • No study included diabetic patients

Table 1a. Characteristics of randomised trials

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Burgess et al (2009) [35]	269	Randomised controlled clinical trial	Multicentre, Canada	Participants with persistent proteinuria	Candesartan 64 or 128 mg/day	Candesartan 16mg/day	7.5 months	Trial with three arms lowest dosage used as reference (active control)
Menne et al (2008) [48]	133	Randomised controlled clinical trial	Multicentre, Hungary & Germany	Participants with essential hypertension and microalbuminuria	Valsartan monotherapy or Lisinopril monotherapy	Valsartan/Lisinopril combination therapy	7.5 months	Trial with three arms combination therapy versus high dose monotherapies
Yusuf et al. The ONTARGET Investigators (2008) [49]	25,620	Randomised controlled clinical trial	Multicentre, International study	Patients with atherosclerotic vascular disease or with diabetes with end-organ damage	Telmisartan (80mg) or combination therapy (telmisartan +ramipril)	Ramipril (10mg)	56	
Mann et al (2008) [50]	25,620	Randomised controlled clinical trial	Multicentre, 40 countries	Patients with atherosclerotic vascular disease or with diabetes with end-organ damage	Telmisartan (80mg) or combination therapy (telmisartan +ramipril)	Ramipril (10mg)	56	
Bakris et al (2008) [52]	322	Randomised controlled clinical trial	Multicentre, US	Participants with type 2 diabetes, albuminuria and hypertension	Benazepril + amlodipine	Benazepril + hydrochlorothiazide	12	Non-inferiority design
Parving et al (2008) [56]	599	Randomised controlled clinical trial	Multicentre, multinational	Participants with hypertension, type 2 diabetes and nephropathy	Aliskiren + Lisinopril	Placebo + Lisinopril	6	
Mehdi et al (2009) [58]	81	Randomised controlled clinical trial	Single centre, US	Participants with diabetes, hypertension and albuminuria	Losartan + Lisinopril or Spironolactone + Lisinopril	Placebo + Lisinopril	11	
De Galan et al (2009) ADVANCE Study [65]	11,140	Randomised controlled clinical trial	Multicentre, 20 countries	Participants with type 2 diabetes and with elevated risk for vascular disease	Perindopril-indapamide (fixed-combination)	Placebo	51.6	

Table 2a. Methodological quality of randomised trials

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Comments ‡
		(participants)	(investigators)	(outcome assessors)			
Burgess et al (2009) [35]	Central	Yes	Yes	Yes	Yes	1.5	+
Menne et al (2008) [48]	Central	Yes	Yes	Yes	Yes	3	+
Yusuf et el. The ONTARGET Investigators (2008) [49]	Central	Yes	Yes	Yes	Yes	0.2	+
Mann et al (2008) [50]	Central	Yes	Yes	Yes	Yes	Unclear	Ø
Bakris et al (2008) [52]	Not specified	Yes	Yes	Yes	Yes	3.6	Ø
Parving et al (2008) [56]	Central	Yes	Yes	Yes	Yes	0.2	+
Mehdi et al (2009) [58]	Central	Yes	Yes	Yes	Yes	8.6	+
De Galan et al (2009) ADVANCE Study [65]	Not specified	Yes	Yes	Yes	Yes	No	Ø

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

‡ Quality score – "How successfully do you think the study minimised bias?" Choose between: very well (+); okay (Ø); poorly (–).

Table 3a. Results and quality rating for dichotomous outcomes

Outcomes	Study ID (author, year)	Intervention group (no. of patients with events/no. of patients exposed)	Control group (no. of patients with events/no. of patients exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]	Importance**
Death from cardiovascular causes	Yusuf et el. The ONTARGET Investigators (2008) [49]	Telmisartan 598 / 8542	603 / 8576	1.00 (0.89. 1.11)	-0.00 (-0.01, 0.01)	Critical
		Combination 620 / 8502	603 / 8576	1.04 (0.93, 1.16)	0.00 (-0.01, 0.01)	
Myocardial infarction	Yusuf et el. The ONTARGET Investigators (2008) [49]	Telmisartan 440 / 8542	413 / 8576	1.07 (0.94, 1.22)	0.00 (-0.00, 0.01)	Critical
		Combination 438 / 8502	413 / 8576	1.07 (0.94, 1.22)	0.00 (-0.00, 0.01)	
Stroke	Yusuf et el. The ONTARGET Investigators (2008) [49]	Telmisartan 369 / 8542	405 / 8576	0.91 (0.80, 1.05)	-0.00 (-0.01, 0.00)	Critical
		Combination 373 / 8502	405 / 8576	0.93 (0.81, 1.07)	-0.00 (-0.01, 0.00)	
Hospitalisation for heart failure	Yusuf et el. The ONTARGET Investigators (2008) [49]	Telmisartan 394 / 8542	354 / 8576	1.12 (0.97, 1.29)	0.00 (-0.00, 0.01)	Critical
		Combination 332 / 8502	354 / 8576	0.95 (0.82, 1.10)	-0.00 (-0.01, 0.00)	
Chronic dialysis	Mann et al (2008) [50]	Telmisartan 31 / 8542	33 /8576	0.94 (0.58, 1.54)	-0.00 (-0.00, 0.00)	Critical
		Combination 34 / 8502	33 /8576	1.04 (0.64, 1.68)	0.00 (-0.00, 0.00)	
Doubling serum creatinine (from baseline value)	Mann et al (2008) [50]	Telmisartan 155 / 8542	140 / 8576	1.11 (0.89, 1.39)	0.00 (-0.00, 0.01)	Important
		Combination 166 / 8502	140 /8576	1.20 (0.96, 1.49)	0.00 (-0.00, 0.01)	
Doubling serum creatinine (>200 µmol/L)	De Galan et al (2009) ADVANCE Study [65]	55 / 5569	45 / 5571	1.22 (0.83, 1.81)	0.00 (-0.00, 0.01)	Important
End-stage kidney disease (renal replacement therapy or renal death)	De Galan et al (2009) ADVANCE Study [65]	25 / 5569	21 / 5571	1.19 (0.67, 2.12)	0.00 (-0.00, 0.00)	Critical
New-onset microalbuminuria	De Galan et al (2009) ADVANCE Study [65]	1094 / 3995	1317 / 3991	0.83 (0.78, 0.89)	-0.06 (-0.08, -0.04)	Important
New-onset macroalbuminuria	De Galan et al (2009) ADVANCE Study [65]	114 / 5436	163 / 5412	0.70 (0.55, 0.88)	-0.01 (-0.02, -0.00)	Important
All renal events	De Galan et al (2009) ADVANCE Study [65]	1243 / 5569	1500 / 5571	0.83 (0.78, 0.88)	-0.05 (-0.06, -0.03)	Important

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

Table 3b. Results and quality rating for continuous outcomes

Outcomes	Study ID (author, year)	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means (95% CI)	Importance**
Urinary protein excretion	Burgess et al (2009) [35]	*NA	NA	NA	Important
Urine albumin creatinine ratio	Menne et al (2008) [48]	*NA	NA	NA	Important
	Bakris et al (2008) [52]	*NA	NA	NA	
	Parving et al (2008) [56]	*NA	NA	NA	
	Mehdi et al (2009) [58]	*NA	NA	NA	

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

* NA – not applicable