What are the best treatments for early chronic kidney disease?

A Background Paper prepared for the UK Consensus Conference on Early Chronic Kidney Disease

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Introduction

The two principle outcomes of chronic kidney disease (CKD) are progressive loss of renal function, and the development and progression of cardiovascular disease (CVD) [1]. The aim of this Background Paper is to discuss the evidence for treatments to slow the progression of both CKD and the attendant CVD, and to discuss treatments for the metabolic consequences of CKD. The evidence was gathered using a Medline search of primarily meta-analyses where available, as well as randomized controlled trials (RCTs) from 1996–2006.

Slowing the progression of CKD

Although the rate of progression of CKD is related to some non-modifiable characteristics such as race, baseline renal function, male gender and increased age, there are a number of modifiable characteristics. It is important to note, however, that the three most widely studied interventions, blood pressure (BP), proteinuria and drugs to reduce both, are inextricably linked in their effects on glomerular filtration rate (GFR).

Blood pressure

Hypertension is both a cause and consequence of CKD. The prevalence of hypertension is inversely related to GFR [2,3]. Observational and interventional studies show that BP reduction slows the rate of progression of CKD [4–7]. In a meta-analysis of 84 randomized and non-randomized trials in CKD patients, for each 10 mmHg drop in mean arterial pressure (MAP) there was an improvement in rate of loss of GFR of 0.18 ml/min/1.73 m²/month [4]. Similarly, in a meta-analysis of 20 RCTs, including 52,400 patients, for each tertile decrease in achieved BP there was a relative risk reduction of 26% for progression to end-stage renal disease (ESRD) [5].

In respect of specific BP targets, the United Kingdom Prospective Diabetes Survey (UKPDS) trial randomized 1148 type 2 diabetics to BP goals of <150/85 mmHg and <180/105 mmHg. The mean achieved BPs were 144/82 mmHg and 154/87 mmHg, respectively. There were 37% fewer microvascular complications (including ESRD) in the group with the lower target [8]. The Modification of Diet in Renal Disease (MDRD) trial randomized 840 patients with CKD 3 and 4 to a ‘usual BP’ goal (140/90 mmHg if <60 year, 150/95 mmHg if ≥60 year) or a ‘low BP’ goal (125/75 mmHg and 135/80 mmHg, respectively).

In all patients, there was a linear relation between increasing MAP and rate of loss of GFR, the effect being greater in patients with higher degrees of proteinuria. The rate of CKD progression increased significantly in patients with proteinuria <3.0 g/day when their MAP was >98 mmHg (>135/80 mmHg). For patients with proteinuria ≥3 g/day this occurred at a MAP of >92 mmHg (~125/75 mmHg) [9]. In a meta-analysis of 11 RCTs including 1860 patients with non-diabetic kidney disease, the lowest risk of CKD progression was seen with systolic BPs of 110–119 mmHg in patients with >1 g/day proteinuria (an effect not seen with lower grade proteinuria). There was a significant increase in the risk of CKD progression at a systolic BP of >130 mmHg [6].

Recommendation

In light of the above analyses, multiple societies [9–13] all suggest a BP target of <130/80 mmHg for patients with CKD and <125/75 mmHg for those with >1 g/day of proteinuria [14].
**Proteinuria**

Proteinuria is common in CKD patients and is a strong independent risk factor for progression [6,9]. Reducing proteinuria reduces the risk of CKD progression [15–20]. In non-diabetic CKD, Jafar et al. [20] demonstrated an 80% reduction in the relative risk of CKD progression per gram/day reduction in proteinuria. In a post hoc analysis of the African American Study of Kidney Disease (AASK) study (1094 patients with hypertensive renal disease), every doubling of baseline urinary protein : creatinine ratio was associated with a 0.54 ± 0.05 ml/min/1.73 m²/year greater rate of loss of GFR even in participants with baseline urinary protein levels <300 mg/day [17]. Similarly, in a post hoc analysis of two smaller RCTs in patients with IgA nephropathy (154 patients) the urinary protein excretion at 1 year was a strong predictor of subsequent ESRD [19].

BP reduction will reduce proteinuria [16,20]. A meta-analysis of 84 studies demonstrated that proteinuria reduction was proportional to BP reduction in both diabetic and non-diabetic renal disease [4]. However, some studies are able to show an effect of proteinuria reduction on CKD progression independent of BP control [15,21]. In a post hoc analysis of 273 patients with proteinuric nephropathies, patients with the greatest short-term reductions in proteinuria had the slowest declines in GFR, regardless of BP control [16]. In a post hoc analysis of the Reduction in Endpoints in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study of type 2 diabetics, every 50% reduction in albuminuria produced a 36% risk reduction for doubling of serum creatinine and 45% for ESRD during later follow-up [15]. The Irbesartan Diabetic Nephropathy Trial (IDNT) study, again in type 2 diabetics, demonstrated the risk of ESRD doubled for each doubling of baseline proteinuria, and conversely for each halving of proteinuria over the treatment year the risk of ESRD was reduced by more than half [21].

**Recommendation**

Proteinuria reduction should be targeted to slow CKD progression.

**Anti-hypertensive drugs**

Specific anti-hypertensive drugs may reduce proteinuria and slow CKD progression independent of BP effects, with the most rigorous data supporting the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [22].

**Proteinuria reduction.** In non-diabetic CKD, meta-analyses demonstrate that ACEIs [5,20,23] and ARBs [5] can reduce proteinuria. In diabetic CKD, meta-analyses demonstrate that ACEIs in type 1 diabetics, [24] and both ACEIs and ARBs in type 2 diabetics, [25] increase the probability of regression from microalbuminuria to no albuminuria. One study found that this effect was not completely abolished by adjusting for BP [24]. ACEIs also reduce the rate of progression of microalbuminuria to macroalbuminuria in type 1 and 2 diabetics [24–26] as do ARBs in type 2 diabetics [25]. Finally, two further meta-analyses demonstrate that ACEIs can reduce albuminuria in diabetics [27,28].

Combination therapy with ACEIs and ARBs has also been assessed in two meta-analyses that included diabetic and non-diabetic patients with CKD 3. Combination therapy significantly reduced proteinuria independent of BP [29,30], without causing clinically relevant changes in serum potassium levels or GFR [30].

In terms of other agents, one meta-analysis has reviewed the effects of calcium channel blocker (CCB) subclasses on CKD progression. Non-dihydropyridine CCBS significantly reduced proteinuria independent of BP changes when compared with dihydropyridine CCBS [31]. There are also RCTs supporting the use of the thiazide diuretic indapamide in type 2 diabetes with hypertension with a reduction in microalbuminuria comparable with that achieved with the ACEIs, enalapril [32] and captopril [33]. Future studies may increase the body of evidence supporting the use of these drugs in CKD.

**CKD progression.** Three meta-analyses have also demonstrated a reduction in the rate of progression of CKD with both ACEIs and ARBs [20,26,34]. Two demonstrated that ACEIs reduced the risk of CKD progression by 30–40% but could not confirm the independence of this effect from BP control alone [26,34]. In the other, including 1860 patients with non-diabetic CKD, ACEIs reduced the risk of progression of CKD by about 30% adjusting for BP and proteinuria. However, the benefit of ACEIs was unclear below a baseline urinary protein excretion of 0.5 g/day [20].

Three meta-analyses question the renoprotective effects of renin-angiotensin-aldosterone system (RAAS) blockade [5,23,25]. One demonstrated a significant reduction in proteinuria in 142 patients with polycystic kidney disease (PKD) treated with ACEI, but only a trend towards slowing CKD progression. Its small size may be responsible for the non-significant outcome, alternatively PKD may behave differently from other CKDs [23]. Another meta-analysis of diabetic nephropathy progression showed a trend only to risk reduction with ACEIs. However, this included a large study assessing those with a high cardiovascular risk rather than renal risk per se which may have skewed the analysis [25]. Finally, although a recent meta-analysis of 13 RCTs including 37,089 patients with various causes of CKD demonstrated a reduced risk of progression of CKD in those on ACEIs or ARBs, no benefit was seen in the diabetic sub-population. However, the largest trial in this meta-analysis Anthihypertensive and Lipid-Lowering Treatment to Prevent Heart attack Trial
(ALLHAT) accounted for 33,357 of the patients studied. Not only was there a lower BP in the control group of this study which could have negated the benefits of RAAS blockade, but again, this was a cardiovascular study in patients at low risk for CKD progression [5].

**Recommendation**

ACEIs and/or ARBs should be used in all diabetics who tolerate them and in non-diabetic CKD patients with >0.5 g/day proteinuria to reduce proteinuria and slow the rate of progression of CKD. Where RAAS-active drugs cannot be tolerated, non-dihydropyridine calcium channel blockers or indapamide can be considered. Further research is needed to clarify the benefit of these drugs beyond BP control alone in patients without proteinuria.

**Strict glycaemic control**

The Diabetes Control and Complications Trial (DCCT) demonstrated the benefit of glycaemic control on proteinuria. 1441 patients were randomized to ‘intensive’ or ‘conventional’ insulin therapy for an average follow-up of 6.5 years. Achieved mean glycosylated haemoglobin (HbA1c) was 7.2 and 9.1%, respectively. Microalbuminuria was reduced by 39% and macroalbuminuria by 54% in the ‘intensive’ group compared with the ‘conventional’ group [35]. However, the effect on CKD progression was less clear due to the limited number of patients with microalbuminuria at baseline [35]. UKPDS showed a 25% reduction in microvascular end-points including renal failure in the ‘intensive’ arm (achieved HbA1c 7.0%) vs ‘conventional therapy’ (7.9%) [36]. The Kumamoto study (110 patients with type 2 diabetes) showed that, at 6 years, the occurrence and progression of diabetic nephropathy was 6.6% in patients with ‘multiple injection insulin therapy’ compared with 28% in patients on ‘conventional insulin therapy’. This trial also suggested that the glycaemic threshold to prevent the onset and progression of diabetic microangiopathy was an HbA1c of <6.5% [37].

**Recommendation**

The Joint British Society guidelines recommend an HbA1c level of ≤6.5% to significantly reduce the risk of developing diabetic complications. However, any reduction in HbA1c levels is still considered beneficial to reduce the onset and progression of diabetic complications [38].

**Lipid-lowering therapy**

Three analyses address the issue of lipid-lowering and CKD progression [39–41]. One suggested that the current evidence for benefit was lacking [40], whilst another suggested that lipid-lowering may reduce proteinuria and retard the progression of CKD [39]. A post hoc analysis of three combined RCTs showed that pravastatin slightly reduced the progression of stage 3 CKD [41], but the effect was small equating to a reduction in the rate of decline of GFR by 0.22 ml/min/1.73 m²/year.

**Recommendation**

Current evidence is insufficient to recommend lipid-lowering therapy to slow the progression of CKD. However, large trials, Prevention of Renal and Vascular End-stage disease Intervention Trial (PREVEND-IT) [42] and Study of Heart and Renal Protection (SHARP) [43], are underway in CKD patients in an attempt to address this.

**Smoking and alcohol**

Observational studies have highlighted the nephrotoxic nature of smoking. Analysis of National Health and Nutrition Examination Survey (NHANES) II data on 9082 patients demonstrated a relative risk of 2.3 for developing CKD in people smoking >20 cigarettes per day compared with non-smokers [44]. Chronic smoking increases the risk of proteinuria [45,46] and accelerates the rate of decline of GFR [47,48]. Observational studies show stopping smoking slows CKD progression [49,50].

The role of alcohol in the development and progression of CKD is less clear. In a longitudinal study of 3392 patients without CKD at baseline, heavy drinking, particularly with concurrent smoking, was associated with an increased risk of CKD [51]. However, NHANES II data do not support a relationship between alcohol consumption and CKD [44]. There are no data on the effects of reducing alcohol consumption on CKD progression.

**Recommendation**

There is evidence to show that smoking cessation slows CKD progression. However, although there is insufficient evidence that alcohol moderation slows CKD progression, it should be encouraged as best practice [38].

**Dietary modification**

The evidence for dietary modification reducing CKD progression is limited for stages 1–3 CKD. The MDRD study demonstrated a ‘low protein’ diet (0.58 g/kg/day) produced an initial rapid decline in GFR in 1585 patients with stage 3 CKD which slowed after 4 months such that the projected decline in GFR at 3 years was not different from a ‘usual protein’
diet (1.3 g/kg/day) [52]. Three smaller RCTs in diabetic patients with stages 2–3 CKD did not show any benefit of protein restriction on CKD progression (0.6–0.8 g/kg/day) [53–55]. One small trial in non-diabetic patients with CKD stage 3 demonstrated a positive effect of protein restriction (0.6 g/kg/day) on CKD progression, but this was at the expense of an overall deterioration in nutritional status [56]. One RCT [57] and one meta-analysis, though not specifically in CKD patients, [58] showed that a reduction in dietary sodium reduces blood pressure.

### Recommendation

There is insufficient evidence to recommend low protein diets to slow the progression of early CKD [14]. There is some evidence to support sodium restriction in order to reduce blood pressure [38].

### Exercise and weight loss

Two studies suggest weight loss is beneficial for renal function. One small observational study showed an improvement in glomerular hyperfiltration [59], whilst a small randomized study showed a significant improvement in proteinuria with moderate weight loss [60]. Although exercise is an important part of weight reduction, there is preliminary evidence from a small cohort study that swimming reduces proteinuria in patients with CKD [61].

### Recommendation

There is insufficient evidence to show that weight reduction or exercise affect the progression of CKD. Best practice should be to encourage regular exercise and the attainment of a body mass index of \( \leq 25 \) [38].

### Treating the consequences of CKD

#### Anaemia

‘Renal’ anaemia is due to a combination of factors, primarily erythropoietin deficiency, but also functional or absolute iron deficiency, uraemic inhibitors [e.g. elevated parathyroid hormone (PTH)] and vitamin deficiency [62]. In the NHANES III study, the prevalence of anaemia (haemoglobin level \(< 12 \text{ g/dl in men, } < 11 \text{ g/dl in women} \) was 1% at an eGFR of 60 ml/min/1.73 m², 9% at an eGFR of 30 ml/min/1.73 m² and 33% (men) to 67% (women) at an eGFR of 15 ml/min/1.73 m² [63]. Untreated, chronic anaemia affects morbidity and mortality, particularly cardiovascular mortality [64,65]. Whether the early treatment of anaemia affects CKD progression and cardiovascular morbidity and mortality is currently under study in large trials [66,67]. However, correction of anaemia pre-dialysis can improve quality of life and exercise capacity [68].

### Recommendation

European Best Practice Guidelines recommend that patients with CKD should maintain a target haemoglobin concentration >11 g/dl using erythropoiesis-stimulating agents where all other causes of anaemia have been excluded [69].

#### Acidosis

The incidence of metabolic acidosis increases with declining renal function, but tends not to occur until CKD stage 4 [70]. The detrimental effects of acidosis include muscle wasting, loss of bone mass, impaired insulin sensitivity and exacerbation of \( \beta_2 \)-microglobulin accumulation [70–72]. However, evidence that correcting acidosis improves any of these is limited. Small and short-term studies have indicated that correcting acidosis can result in beneficial effects in terms of bone and muscle metabolism [72], however, there have been no RCTs investigating acidosis correction on a clinical outcome.

### Recommendation

There is insufficient evidence to make recommendations on the treatment of metabolic acidosis. It would not be unreasonable to adopt the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines for dialysis patients, i.e. maintenance of serum bicarbonate levels at \( \geq 22 \text{ mmol/l} \) [71] pending further studies of this area.

#### Calcium and phosphate homeostasis

Disturbances in calcium and phosphate metabolism and secondary hyperparathyroidism occur with increasing frequency and severity as GFR declines. Serum phosphate levels begin to rise below an eGFR 60 ml/min/1.73 m² due to phosphate retention, with serum calcium levels falling due to reduced activity of vitamin D (reduced renal 1{\lowercase{a}}-hydroxylation) in promoting calcium absorption from the gut. Parathyroid hormone (PTH) levels begin to rise as a consequence of both low calcium and high phosphate below an eGFR 60 ml/min/1.73 m². These changes not only affect bone integrity, but may also promote soft tissue and vascular calcification over time increasing cardiovascular morbidity and mortality in later CKD stages [73]. Prevention and management of these metabolic disturbances early in the course of CKD may have a significant impact on morbidity and mortality later on. However, there is currently no robust clinical evidence for this. Observational data and experimental evidence suggests that early intervention is appropriate [11].
Recommendation

The treatment targets in CKD 3 are currently more a matter of opinion than evidence. UK guidelines suggest that an assessment of serum calcium, phosphate and intact PTH level be made in all patients with an eGFR <60 ml/min/1.73 m² [11]. Only the current US National Kidney Foundation suggests targets for CKD 3: 'intact' PTH 35–70 pg/ml, serum phosphate 0.87–1.49 mmol/l, and serum calcium within the normal range [74]. Initial therapy for hyperphosphataemia includes dietary phosphate restriction and the use of oral phosphate binders. Secondary hyperparathyroidism is initially treated with the replacement of deficient 1α-calcidol. The current UK guidelines are that such therapies are initiated and supervised by a nephrologist at CKD 4 and 5 [11].

Reducing the risk of cardiovascular disease

Patients with CKD frequently have cardiovascular disease (CVD) and this association becomes progressively more significant as GFR declines. This detrimental association has led to the recognition that patients with CKD, particularly stage 3 CKD or above, be considered in the 'highest risk group' for subsequent cardiovascular events [12,75,76]. Evidence for the benefit of cardiovascular risk factor modification specifically in patients with CKD is limited and largely derives from post hoc sub-group analysis of cardiovascular trials. However, trials in progress aim to address some of these issues specifically in CKD [43].

Hypertension. There is a large body of evidence that BP reduction reduces CVD risk in the general population, with the greatest absolute risk reduction being those at highest risk [38]. In a CKD population specifically, RAAS blockade may reduce cardiovascular risk. A post hoc analysis of the Heart Outcomes and Prevention Evaluation (HOPE) study demonstrated the increased cardiovascular risk of 'mild renal impairment', and the beneficial effect of ramipril [77]. One meta-analysis in diabetic nephropathy has shown that ACEIs, but not ARBs, have a beneficial effect on cardiovascular mortality [25]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study in non-diabetic CKD suggested that amlodipine + perindopril was associated with less cardiovascular risk than atenolol + bendrofluazide [78]. Captopril post myocardial infarction reduced the risk of further cardiovascular events more in CKD patients than in non-CKD patients [79].

Aspirin. A re-analysis of the Hypertension Optimal Treatment (HOT) study could only suggest that aspirin together with optimal BP control offered additional benefit in hypertensive patients with CKD [80].

Lipids. In one study, atorvastatin reduced cardiovascular events by 40% in patients with CKD (serum creatinine up to 200 μmol/l) over 5 years [81]. In a meta-analysis of three RCTs including 4491 patients with CKD 3, Pravastatin reduced cardiovascular outcomes by 23%. This was comparable with patients who had normal kidney function, but the absolute benefit in patients with CKD was greater due to their higher baseline risk [41]. SHARP will give more information on this outcome in CKD [43].

Recommendation

In the absence of prospective RCTs specifically in CKD, evidence must be extrapolated from clinical trials in the general population. This is not unreasonable as 'traditional' CVD risk factors persist in CKD. The importance of lifestyle modification (diet, exercise, smoking cessation and alcohol moderation) also must not be overlooked [38]. In considering patients with CKD a 'high risk group', the use of aspirin and lipid-lowering therapy can be equated to a secondary prevention strategy, with the target total cholesterol being 4 mmol/l [38]. ACEIs may be of benefit.

Conclusions

The current evidence would favour the following treatment goals in order to both slow the progression of CKD and reduce CVD risk:

- **BP** <130/80 mmHg (<125/75 mmHg if >1 g/day proteinuria) to reduce proteinuria, slow CKD progression and reduce cardiovascular risk.
- **ACEIs and ARBs** to reduce proteinuria and slow CKD progression.
- **Non-dihydropyridine calcium channel blockers** to reduce proteinuria.
- **HbA1c <6.5% in diabetics** to reduce microvascular complications.
- **Total cholesterol <4 mmol/l.**
- **Smoking cessation.**
- **Dietary modification** (weight reduction, alcohol and salt limitation, and avoidance of excess protein intake).
- **Encourage exercise.**

Additionally, acidosis, anaemia and disturbances of calcium and phosphate metabolism should be looked for and treated in patients with CKD stage 3 or above. To extend the evidence base further, more interventional studies specifically in CKD patients are required particularly in the area of CVD risk reduction. Additionally, clarification of the benefits of the interventions discussed for non-proteinuric compared with proteinuric CKD is required. Finally, most of the trials reviewed have age restrictions in the recruitment criteria (generally <70 years). There is currently no evidence to say if the benefit of the interventions discussed persists at higher ages.
and given the increasing incidence of CKD with age, trials in older age groups would be of value.

Conflict of interest statement. None declared.

References


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