Slowing the progression of chronic kidney disease

Progression of chronic kidney disease can be slowed by careful management of risk factors. The most effective treatments are aggressive blood pressure control, renin–angiotensin system inhibition in proteinuric patients and tight glycaemic control in diabetics. Patients should be educated to avoid nephrotoxins and maintain a healthy lifestyle.

Progression of chronic kidney disease to require renal replacement therapy is associated with significant morbidity and mortality. An estimated glomerular filtration rate less than 30 ml/min/1.73m^2 is associated with a relative risk of a cardiovascular event or death of 2.8 and 3.2 respectively (Go et al, 2004). The number of patients requiring renal replacement therapy is predicted to rise by 6% per annum and is unlikely to stabilize until 2020. Aggressive treatment of chronic kidney disease may reduce this burden.

This article highlights the most important interventions that slow progression of chronic kidney disease, many of which will also reduce cardiovascular risk. Where the evidence is inconclusive, pragmatic advice is given based on available data.

Definition and classification

Chronic kidney disease is renal dysfunction for at least 3 months. It can be defined on the basis of either an estimated glomerular filtration rate <60 ml/min/1.73m^2 or markers of kidney damage irrespective of estimated glomerular filtration rate (*Table 1*). An isolated estimated glomerular filtration rate, as routinely reported by laboratories, is unhelpful in assessing if a patient has progressive chronic kidney disease as serial measurements are needed.

Table 1. Stages of chronic kidney disease

Stage	Description
1	eGFR >90 ml/min/1.73m^2 with abnormal urine and/or kidney structure or histology
2	eGFR 60–90 ml/min/1.73m^2 with abnormal urine and/or kidney structure or histology
3	eGFR 30–60 ml/min/1.73m^2
4	eGFR 15–30 ml/min/1.73m^2
5	eGFR <15 ml/min/1.73m^2 or on dialysis

eGFR = estimated glomerular filtration rate. From Renal Association (2009)

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Prevalence

The prevalence of chronic kidney disease depends on its definition. A study of primary care databases in Manchester, Surrey and Kent using UK definitions reported the prevalence of chronic kidney disease stage 3 to 5 to be 10.6% in females and 5.8% in males (Stevens et al, 2007). This suggests that chronic kidney disease is more prevalent than diabetes mellitus. It is important to appreciate that the current chronic kidney disease classification does not recognize the natural fall of estimated glomerular filtration rate with age and that the majority of chronic kidney disease stage 3 and 4 in the elderly does not progress to require renal replacement therapy (Hemmelgarn et al, 2006). These patients are much more likely to die from cardiovascular disease. The prevalence of end-stage renal disease in the UK is 0.1%.

Diabetes mellitus is the commonest cause of progressive chronic kidney disease and end-stage renal disease in the UK, accounting for 22% of new dialysis patients (Ansell et al, 2007). Its increasing prevalence and the ageing population explain the increase in patients on renal replacement therapy (*Figure 1*).

Pathogenesis of progressive chronic kidney disease

Unilateral nephrectomy reduces nephron number but progressive decline in estimated glomerular filtration rate is uncommon. Chronic kidney disease thus may require both an initiating factor to cause kidney damage (sometimes progressive in itself) and another factor or factors responsible for continuing decline in function. Prospective studies have identified risk factors for progression. They include:

- Hypertension
- Proteinuria
- Poor glycaemic control in diabetics
- Dyslipidaemia
- Obesity
- Smoking
- Age
- Male sex
- Family history.

Some initiating causes of renal disease have specific treatments (e.g. lupus nephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis). However, all modifiable

risk factors should be managed in chronic kidney disease patients, irrespective of the underlying diagnosis.

Modifiable risk factors for progression

Hypertension

Hypertension is both a cause and a common consequence of chronic kidney disease and even mild hypertension is associated with an increased risk of end-stage renal disease and death.

The Modification of Diet in Renal Disease (MDRD) study, from which the widely used estimated glomerular filtration rate formula was derived, demonstrated that non-diabetic patients with chronic kidney disease stage 3 to 5, in whom a blood pressure of 125/75 mmHg was achieved, had a significantly lower risk of dialysis when compared to patients who achieved a blood pressure of 140/90 mmHg (hazard ratio 0.68 at 9 years, $P<0.001$) (Sarnak et al, 2005). Furthermore, patients with baseline proteinuria of more than 1 g/day have a higher rate of glomerular filtration rate decline (*Figure 2*). In these patients it is important to achieve a blood pressure of 125/75 mmHg or less in order to slow the progressive decline in glomerular filtration rate. A trend is also seen in patients with proteinuria 0.25–1 g/day. In patients with proteinuria of less than 0.25 g/day, the effect is not seen or may just be too small to achieve significance (Peterson et al, 1995).

The African-American Study of Kidney Disease and Hypertension (AASK) studied hypertensive kidney disease in the American black population. There was a renoprotective effect of achieving a blood pressure of 128/78 mmHg *vs* 141/85 mmHg (Wright et al, 2002). In a study of diabetics, a mean blood pressure reduction from 137/81 mmHg to 128/75 mmHg reduces development of microalbuminuria and progression to overt diabetic nephropathy (Schrier et al, 2002).

Targeting the renin–angiotensin system is the first choice of treatment in chronic kidney disease as it reduces both systemic and glomerular hypertension. The African-American Study of Kidney Disease and Hypertension trial randomized hypertensive patients to receive metoprolol, ramipril or amlodipine as initial treatment. Only patients who received ramipril had a significant reduction in a clinical composite outcome of 50% fall in glomerular filtration rate, dialysis or death (Wright et al, 2002). Benazepril in non-diabetic patients with creatinine levels of between 132 and 442 µmol/litre reduces doubling creatinine, dialysis or death by 43% after 3.4 years compared to those treated with conventional antihypertensives ($P<0.005$) (Hou et al, 2006).

Angiotensin-converting enzyme inhibitors can be used in renovascular disease providing there is not a greater than 20% increase in creatinine level on starting therapy. Commonly used second-line agents include loop diuretics, α-blockers, β-blockers and calcium-channel blockers. The choice is dictated by coexisting medical problems, physician preference and patient tolerances.

Proteinuria

The MDRD study, like many preceding studies, demonstrated that proteinuria is independently associated with progression of chronic kidney disease (*Figure 2*). The aggressive blood pressure targets in proteinuric chronic kidney disease have already been discussed. There are good data suggesting that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have a renoprotective effect in patients with proteinuria.

Captopril reduces doubling of creatinine, dialysis or death in type 1 diabetics with overt nephropathy compared to conventional antihypertensives (Lewis et al, 1993). The Irbesartan Diabetic Nephropathy trial and the RENAAL study demonstrated a similar benefit from angiotensin II receptor blockers in type 2 diabetics (Brenner et al, 2001; Lewis et al, 2001).

The RENAAL study also reinforced proteinuria as a strong predictor of progression in diabetic nephropathy. Patients with proteinuria over 3 g/day were eight-fold more likely to progress to dialysis compared to patients with less than 1.5 g/day. For every 50% reduction in proteinuria at 6 months, there was a 45% relative risk reduction for dialysis (de Zeeuw et al, 2004). Although angiotensin-converting enzyme inhibitors have been more extensively studied in type 1 diabetes mellitus and

Figure 1. Causes of incident end-stage renal disease. From Ansell et al (2007).

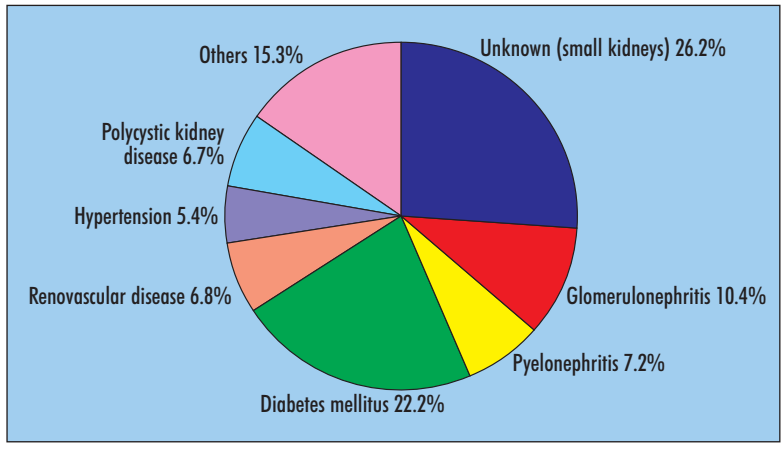
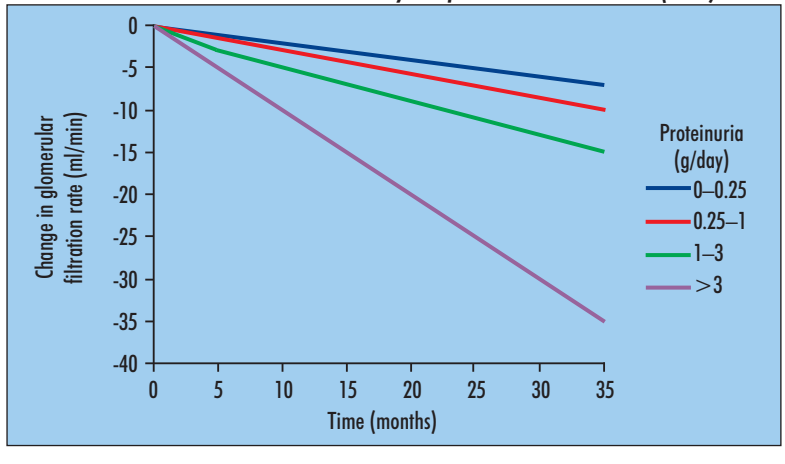


Figure 2. Rate of glomerular filtration rate decline stratified by degree of proteinuria in the Modification of Diet in Renal Disease study. Adapted from Peterson et al (1995).



angiotensin II receptor blockers in type 2 diabetes, there are no good studies comparing them head-to-head. They are generally regarded as equivalent.

The Ramipril Efficacy in Nephropathy (REIN) study demonstrated the superiority of angiotensin-converting enzyme inhibitors over conventional antihypertensive agents in non-diabetic kidney disease with proteinuria greater than 1 g/day. The study arm with patients with heavy proteinuria (>3 g/day) was stopped early because of a very significant decline in glomerular filtration rate in the conventional treatment group. The 1–3 g/day arm also had a significant reduction of progression to dialysis or nephrotic range proteinuria with ramipril by the end of the study (Ruggenenti et al, 1999).

Dual blockade with a combination of an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker does result in a further reduction of proteinuria but is controversial. The COOPERATE study of 263 patients concluded this was beneficial (Nakao et al, 2003). However, the results have been excluded from meta-analyses because there were serious inconsistencies (Kunz et al, 2008). More recent data have also cast doubt on the safety of dual blockade in patients without significant proteinuria. In the ONTARGET study of 25 620 adults, dual blockade was associated with a higher incidence of doubling of creatinine, dialysis or death compared with monotherapy. Combination therapy had no clear benefit in the highest renal risk group (overt diabetic nephropathy) (Mann et al, 2008).

The safety of dihydropyridine calcium-channel blocker use (e.g. nifedipine or amlodipine) in patients with proteinuric chronic kidney disease has been questioned. However, amlodipine is equivalent to placebo in the irbesartan diabetic nephropathy trial and over 80% of patients in both arms of the RENAAL study received a calcium-channel blocker without jeopardizing the effectiveness of losartan (Lewis et al, 2001; Segura et al, 2005).

Diabetes mellitus and glycaemic control

Diabetic nephropathy has a complicated pathogenesis. It is clear that advanced glycation end-products adversely affect endothelial function, but there is also abnormal activation of the renin–angiotensin system which results in glomerular hypertension with hyperfiltration (Soldatos and Cooper, 2008). Untreated microalbuminuria which progresses to albuminuria heralds overt diabetic nephropathy. The Diabetes Control Complications Trial (DCCT) demonstrated that intensive insulin therapy in type 1 diabetes reduces the incidence of new microalbuminuria by 39% and albuminuria by 54% (The DCCT Research Group, 1993). The UK Prospective Diabetes Study (UKPDS) confirmed that these findings are also applicable to type 2 diabetics (The UKPDS Group, 1998). However, direct evidence that good glycaemic control slows the rate of progression in patients with established diabetic nephropathy is limited to small studies in patients receiving a successful pancreas transplant.

In type 2 diabetes, metformin is the preferred first-line treatment since it offers cardiovascular benefits, particularly in obese patients but should be used with caution below a glomerular filtration rate of 60 ml/min and stopped below 30 ml/min (Herrington and Levy, 2008). However, genuine metformin-induced lactic acidosis is probably a rare occurrence (Salpeter et al, 2006). Short-acting sulphonylureas (e.g. gliclazide) and pioglitazone are safe in advancing chronic kidney disease although the latter may encourage oedema.

Dyslipidaemia

High levels of low-density lipoprotein and low levels of high-density lipoprotein cholesterol are associated with an increased cardiovascular risk. A low high density lipoprotein cholesterol level is also an independent predictor of more rapid renal progression of chronic kidney disease (Hunsicker et al, 1997). The benefits of lipid-lowering therapy have not been conclusively demonstrated in chronic kidney disease, but subgroup analyses of primary and secondary prevention trials do demonstrate a greater absolute reduction in the risk of cardiovascular events with pravastatin *vs* placebo in patients with both chronic kidney disease and diabetes (Tonelli et al, 2005).

A meta-analysis of statin studies that included measurements of kidney function or proteinuria concluded that statin therapy significantly slowed glomerular filtration rate decline by a modest 1.22 ml/min/year (Sandhu et al, 2006). Gemfibrozil did not exert any clinical effect on glomerular filtration rate decline.

The Study on Heart and Renal Protection, a 9000 patient placebo-controlled trial of ezetimibe and simvastatin in chronic kidney disease, which is due to report in 2010, will hopefully answer the question of whether there are renoprotective or cardiovascular benefits of lowering cholesterol in chronic kidney disease.

Lifestyle and dietary factors

High dietary protein induces hyperfiltration and hypertension in experimental models of chronic kidney disease and increases the prevalence of microalbuminuria in diabetics. However, the MDRD study conclusively demonstrated no benefit from protein restriction (Levey et al, 1996).

Salt restriction lowers blood pressure in a proportion of patients and also enhances the antiproteinuric effect of targeting the renin–angiotensin system independent of blood pressure (Sacks et al, 2001; Vogt et al, 2008). Patients with metabolic syndrome may be more sensitive to this effect, but there is no direct evidence that salt restriction reduces progression of chronic kidney disease.

Obesity is associated with hypertension and diabetes mellitus and may be an independent risk factor for chronic kidney disease. Extreme obesity has also been associated with focal segmental glomerulosclerosis. Dramatic weight loss after bariatric surgery is associated with improvements in blood pressure, lipid profile and

microalbuminuria. A diet that emphasizes fruit, vegetables, low-fat dairy and whole grain foods compared with a diet high in sugar and saturated fat reduces blood pressure (Sacks et al, 2001).

Interestingly, there are no significant associations between alcohol consumption and chronic kidney disease. However, there is increasing evidence that smoking harms the kidney. The Prevention of Renal and Vascular Endstage Disease trial found a correlation between albuminuria and the number of cigarettes smoked (Hogan et al, 2007). Smoking is associated with more rapid progression in a variety of causes of chronic kidney disease. Prospective data suggest that stopping smoking preoperatively reduces renal transplant survival (Orth and Hallan, 2008).

Avoiding nephrotoxic agents

The risk of dialysis-dependent acute renal failure increases progressively with the degree of renal impairment (Hsu et al, 2008). Physicians and patients alike should be reminded about potentially renal toxic medication and appropriate dose reductions. The authors advise patients to avoid over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) and to stop angiotensin-converting enzyme inhibitors during acute illness.

There is a risk of contrast-induced nephropathy in patients with an estimated glomerular filtration rate less than 45 ml/min/1.73m^2 (Weisbord et al, 2008). In these patients, alternative imaging modalities that avoid contrast should be considered. However, if there is a genuine clinical need for a contrast-enhanced investigation, the risk of contrast-induced nephropathy should not stop referral. Irreversible impairment of function or dialysis secondary to contrast-induced nephropathy is comparatively rare (Goldenberg et al, 2008). The risk of contrast-induced nephropathy is reduced by adequate peri-procedure hydration (1 ml/kg/hour of isotonic saline for 6 hours before and 12 hours after). The authors do not routinely use N-acetylcysteine because the evidence is contradictory and ensuring adequate hydration is the priority. There may be a role for N-acetylcysteine in coronary angiography when large volumes of contrast are used.

Anaemia, acidosis and calcium–phosphate balance

A recent randomized control trial demonstrated that correction of renal acidosis with sodium bicarbonate significantly slows decline in estimated glomerular filtration rate and improves nutritional markers (de Brito-Ashurst et al, 2009). However, there is currently no clinical evidence that correcting anaemia with erythropoietin and optimizing calcium phosphate balance with phosphate binders slows chronic kidney disease progression. These are obviously important interventions to maintain other aspects of the health of chronic kidney disease patients and are subject to UK guideline targets (*Table 2*).

Other factors and future developments

Hyperuricaemia is common in chronic kidney disease and observational studies have linked it to progression. A small Chinese randomized trial of allopurinol in chronic kidney disease found a significant reduction in rate of progression (Siu et al, 2006), but larger trials are required.

Aldosterone does more than regulate extracellular fluid volume and electrolyte balance. It is produced locally in the renal cortex where it may be harmful. Spironolactone and epelerone reduce albuminuria when added to enalapril. However, hyperkalaemia frequently limits the use of these drugs and more efficacy and safety data are required.

The underlying molecular pathways that mediate tubulo-interstitial fibrosis in chronic kidney disease are becoming better understood. Potential future treatments currently under investigation include antagonists of tissue growth factor-β and other components of its signalling pathway, direct inhibitors of fibroblast proliferation and collagen synthesis, and antioxidants (Khwaja et al, 2007).

Conclusions

Chronic kidney disease is an increasingly recognized problem. Risk factors for progression can be managed generically and independent of the underlying cause. Nephrologists, hospital and primary care physicians should all play an important role in modifying these. Management requires aggressive blood pressure control, inhibition of the renin–angiotensin system in proteinuric patients and tight glycaemic control in diabetics. Education to avoid nephrotoxins and to maintain a healthy lifestyle is also important. Management of risk factors for progression also effectively reduce cardiovascular risk.

Despite optimal management of chronic kidney disease, progression may still occur. Nephrology services should be accessed at the appropriate time for establishing the primary diagnosis, access to erythropoietin and planning of renal replacement therapy. UK guidelines are available on the Renal Association website (www.renal.org/ckd). BJHM

Conflict of interest: none.

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Table 2. Chronic kidney disease treatment targets

	Target
Haemoglobin on erythropoietin	10.5–12.5 g/dl
Phosphate	0.9–1.5 mmol/litre
Calcium x phosphate product	<4.8 mmol^2/litre^2
Bicarbonate	22–26 mmol/litre

From Renal Association (2009)

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KEY POINTS

- The target blood pressure for chronic kidney disease patients is 130/80 mmHg, and should be reduced to 125/75 mmHg in the presence of proteinuria greater than 1 g/day. The angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker dose should be maximized in all patients with proteinuria.
- Dual blockade is not generally recommended but can be considered in patients with heavy proteinuria on maximal monotherapy, in whom control of oedema is difficult.
- Haemoglobin A_{1c} should be maintained below 7.5%.
- All patients with a greater than 20% risk of 10-year cardiovascular disease should be treated with statin therapy to target a total cholesterol less than 4.0 mmol/litre or a 25% reduction from baseline.
- Patients should be advised to restrict salt intake to 100 mmol/day, have a healthy diet, aim for a body mass index between 20 and 25 kg/m^2 and stop smoking.
- Oral sodium bicarbonate should be used to maintain a serum bicarbonate level between 22 and 26 mmol/litre.
- Avoid nephrotoxic drugs and remember that chronic kidney disease may necessitate drug dose modification. Ensure adequate hydration before giving intravenous radio-opaque contrast.