Managing the cardiovascular complications of chronic kidney disease

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Summary

Patients with chronic kidney disease have risk factors for cardiovascular disease which are additional to those found in the general population. Many patients will die of cardiovascular disease before they require dialysis for their kidney disease. While lifestyle modification is essential, it is important to manage the patient's anaemia, dyslipidaemia and hypertension. Managing heart failure can be difficult because of the need to adjust the patient's fluid balance according to renal and cardiac function. If the progression of chronic kidney disease can be slowed, cardiac risk may be reduced.

Key words: anaemia, heart failure, hyperlipidaemia, hypertension.

(Aust Prescr 2008;31:154–8)

Introduction

Chronic kidney disease, defined by a glomerular filtration rate (GFR) under 60 mL/min/1.73 m^2 or evidence of kidney damage (for example, proteinuria) for at least three months, is a major public health problem. At least one in seven Australian adults has at least one marker of kidney damage or dysfunction.[1]

Chronic kidney disease is one of the most potent risk factors for cardiovascular disease. Patients with advanced chronic kidney disease have up to a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls.[2] These patients are up to 20 times more likely to die from cardiovascular disease than to survive to require dialysis.[3] However, patients with chronic kidney disease who also have cardiovascular disease are more likely to progress to renal failure than those without cardiovascular disease.[4]

The 'traditional' risk factors, listed in Table 1, are independent predictors of cardiovascular disease in chronic kidney disease, but do not account for the total increased risk. There are also many 'non-traditional' cardiovascular risk factors which play a potentially important role in chronic kidney disease. There is randomised controlled trial evidence that timely intervention can substantially reduce the progression of renal failure, and can reduce cardiovascular risk by up to 50%.[5]

Table 1

'Traditional' and 'non-traditional' cardiovascular risk factors in chronic kidney disease [2]

Traditional risk factors	Non-traditional risk factors
Older age	Albuminuria
Male	Elevated homocysteine
Hypertension	Elevated lipoprotein (a)
Dyslipidaemia (high LDL and low HDL cholesterol)	Anaemia
Diabetes	Abnormal calcium and phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Oxidative stress
Family history of (premature onset) cardiovascular disease	Inflammation (C-reactive protein)
Left ventricular hypertrophy	Malnutrition
	Thrombogenic factors

LDL low density lipoprotein
HDL high density lipoprotein

Modifying cardiovascular risk in patients with chronic kidney disease

As chronic kidney disease accelerates cardiovascular disease, management of the risk factors should begin as soon as possible.

Lifestyle modification

Lifestyle modification underpins all other therapeutic approaches and must continue to be practised throughout the treatment of chronic kidney disease.[6] Particular attention should be paid to smoking, nutrition, alcohol and physical activity (Table 2).[7] Successful modification of the patient's lifestyle can reduce blood pressure.

All guidelines recommend a reduction of dietary sodium for patients with hypertension and chronic kidney disease. A meta-analysis of 20 randomised trials involving patients with hypertension found that halving salt intake (from approximately 10 g per day to 5 g per day) for four or more weeks had a modest but important effect on lowering blood pressure (–5.06 mmHg (95% CI* –5.81 to –4.31) for systolic and –2.70 mmHg (95% CI –3.16 to –2.24) for diastolic blood pressure).[8] In addition to direct

* CI confidence interval

Table 2

Treatment targets for patients with chronic kidney disease [15]

Parameter	Target
Smoking	Cease smoking
Weight	BMI 18–25 kg/m^2 Waist circumference ≤94 cm (male), ≤80 cm (female)
Nutrition	Dietary salt intake 40–100 mmol/day
Alcohol	<2 standard glasses alcohol/day (men) <1 standard glass alcohol/day (women)
Physical activity	>30 mins physical activity/day
Blood pressure	<130/80 mmHg <125/75 mmHg if proteinuria >1 g/day
Proteinuria	>50% reduction of baseline value
Cholesterol	Total <4.0 mmol/L LDL <2.5 mmol/L
Blood glucose (for people with diabetes)	Pre-prandial blood glucose 4.4–6.7 mmol/L HbA1c <7.0%

BMI body mass index
LDL low density lipoprotein

effects on blood pressure, lowering the extracellular volume by limiting sodium intake significantly enhances the response to most antihypertensive drugs, especially angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists.

The consensus on dietary protein intake in Australia for people with chronic kidney disease is to advise a normal intake (0.75–1.0 g/kg body weight/day).[5] Reduced protein intake is of inconsistent benefit and may accentuate the chance of malnutrition.

Hypertension

In patients with chronic kidney disease, hypertension is the most powerful risk factor for the progression of kidney dysfunction and the development of cardiovascular disease. The most important goal for reducing cardiovascular risk in patients with chronic kidney disease is to lower blood pressure to a target (<130/80 mmHg if proteinuria less than 1 g/day or <125/75 mmHg if proteinuria more than 1 g/day).[5,6] In order to reach these targets, multiple (often 3–4) antihypertensive drugs are often needed, particularly in more advanced chronic kidney disease.[5]

The activity of the renin-angiotensin-aldosterone system is increased so ACE inhibitors are the first-line therapy for patients with chronic kidney disease, although angiotensin receptor antagonists may provide comparable renoprotection (preservation of renal function) and therefore cardioprotection. The degree of renoprotection appears to be greater in patients with more severe kidney failure and in those who experience a greater initial increase in serum creatinine concentration when treatment begins.[5] It is therefore important not to withdraw ACE inhibitors or angiotensin receptor antagonists in patients with chronic kidney disease who experience an acute rise in plasma creatinine concentration of less than 30% which stabilises within the first two months of treatment. These individuals are the ones who are most likely to derive the greatest renoprotective benefit.[5,6] However, if the rise in creatinine is more than 30% above the baseline value, stop the drugs and consider investigating the possibility of bilateral renal artery stenosis.[6]

ACE inhibitors and angiotensin receptor antagonists should also be withdrawn if the serum potassium concentration exceeds 6 mmol/L, despite dose reduction, dietary potassium restriction and concomitant diuretic therapy. However, the frequency of this complication in patients with chronic kidney disease is less than 2%, with the average rise in serum potassium being of the order of 0.5 mmol/L.

Other antihypertensive drugs have a role, as optimal blood pressure control often requires combination therapy. Diuretics, beta blockers and calcium channel blockers are commonly used. When a diuretic is given to treat hypertension or oedema in a patient with chronic kidney disease, a loop diuretic is generally preferred, because thiazide diuretics become less effective as monotherapy when the GFR falls below 50 mL/min/1.73 m^2.[6] However, thiazides still produce additive effects when co-administered with a loop diuretic.

Dyslipidaemia

Chronic kidney disease is associated with hyperlipidaemia. A meta-analysis of 50 randomised trials involving over 30 000 patients found that statin use significantly reduced fatal cardiovascular events by 19% and non-fatal cardiovascular events by 22%, irrespective of the stage of chronic kidney disease.[9] Although there have been concerns about an increased incidence of rhabdomyolysis with statins in chronic kidney disease, their adverse effect profile in this large group of patients was similar to that of placebo. Current guidelines therefore recommend that statins be used to reduce cardiovascular risk in patients with chronic kidney disease. Aim for a serum total cholesterol below 4 mmol/L and a low density lipoprotein cholesterol below 2.5 mmol/L.

Glycaemic control in patients with diabetes mellitus

Diabetes is a common cause of renal failure. Intensive blood glucose control significantly reduces the risk of developing chronic kidney disease and reduces cardiovascular risk. Current guidelines recommend aiming for a glycated haemoglobin (HbA1c) of less than 7%.

Metformin is the first-line drug and can be used in patients with chronic kidney disease with a GFR above 60 mL/min/1.73 m^2. In patients with a GFR of 30–60 mL/min/1.73 m^2, the maximum recommended dose should be halved. Avoid metformin if the GFR is under 30 mL/min/1.73 m^2. All patients should be warned

to cease metformin for up to a few days during intercurrent illness or around the time of receiving radiographic contrast media. Dose reduction is often required for oral hypoglycaemic drugs (and insulin) as kidney function declines.

Caution should be exercised with thiazolidinediones in chronic kidney disease, particularly as there is the possibility of significant fluid retention.

Anaemia

Anaemia is a common complication of chronic kidney disease and is associated with the development of left ventricular hypertrophy and increased cardiovascular risk. This complication starts when the GFR is below 60 mL/min/1.73 m^2 and its prevalence increases with decreasing GFR. Treatment of anaemia in chronic kidney disease can be accomplished with iron supplementation and erythropoiesis stimulating drugs (such as epoietin alfa, epoietin beta, darbepoietin alfa). Erythropoiesis stimulating drugs have substantial health benefits for patients with chronic kidney disease, including improved quality of life, reduced blood transfusion requirements, decreased left ventricular mass, diminished sleep disturbance and enhanced exercise capacity. The vast majority of patients treated with erythropoiesis stimulating drugs require concomitant iron supplementation, either as oral iron or as a periodic intravenous dose.

There is currently no evidence that normalising haemoglobin concentrations in patients with chronic kidney disease improves clinical outcomes. Two large randomised controlled trials and a meta-analysis[10] have shown increased morbidity and mortality with higher haemoglobin targets. Current practice guidelines therefore recommend a haemoglobin target of 11–12 g/dL for all patients with chronic kidney disease.

Calcium and phosphate metabolism

Hyperphosphataemia and hyperparathyroidism in chronic kidney disease have been associated with increased vascular calcification, cardiovascular risk and death. This often manifests when the GFR falls below 60 mL/min/1.73 m^2. It becomes more prevalent as kidney function declines and is present in most patients having dialysis. Although there is no definitive evidence yet that correcting calcium-phosphate balance or secondary hyperparathyroidism improves cardiovascular outcomes, current clinical practice guidelines recommend treatment. This includes varying combinations of dietary phosphate restriction (preferably with the assistance of a renal dietitian), phosphate binder administration with meals (e.g. calcium carbonate, aluminium hydroxide, sevelamer, lanthanum carbonate, magnesium trisilicate), vitamin D supplementation (calcitriol or a vitamin D analogue such as paricalcitol) or calcimimetic therapy (cinacalcet). Recommended targets for treatment include a serum phosphate below 1.65 mmol/L, a serum calcium within the normal range and serum parathyroid hormone approximately 2–3 times the upper reference limit.

Aspirin and other treatments

Low-dose aspirin should be considered in patients with chronic kidney disease, especially in those with established cardiovascular disease. The only published controlled trial in patients with chronic kidney disease found that aspirin reduced the risk of myocardial infarction, but did not reduce the overall risk of cardiovascular death.[11] The potential benefit must be weighed against the risk of gastrointestinal bleeding, which is increased in patients with chronic kidney disease.

There is currently no convincing evidence to recommend routine prescription of folic acid, antioxidants (such as vitamin E or N-acetylcysteine) or fibrates to reduce cardiovascular risk in chronic kidney disease.

Managing cardiovascular disease in chronic kidney disease

Those with chronic kidney disease are more likely to be hospitalised for cardiovascular disease than those without.[12] Controlling the progression of renal disease may help to limit these complications.

Cardiac failure

Cardiac and renal failure often coexist because dysfunction of one organ frequently causes dysfunction of the other or because common systemic diseases, such as diabetes mellitus and extensive atherosclerosis, often cause both cardiac and renal dysfunction. Cardiac failure is present in up to 40% of patients with chronic kidney disease.[12] Hospitalisations for cardiac failure are five times more common in patients with chronic kidney disease than in other patients. The incidence is further increased by 30% in patients having dialysis.[12] Cardiac failure in renal disease should be managed as usual.

Diuretics are frequently required for symptomatic management and to control fluid retention in chronic kidney disease. The combined effects of renal failure (impaired delivery to site of action) and cardiac failure (impaired response) mean that patients with cardiorenal failure require frequent administration of large doses of loop diuretics (e.g. frusemide 120 mg twice a day) to achieve an adequate diuretic response.[7] This attempt to remove fluid must be balanced against the need to avoid dehydration and further deterioration of kidney function. Clinical signs of excessive fluid removal include postural hypotension (postural drop in systolic blood pressure of more than 10 mmHg) and postural tachycardia (postural rise in pulse rate of more than 10 beats/min). Daily weighing and fluid balance records may assist with optimisation of fluid balance.

Blockade of the renin-angiotensin-aldosterone system (ACE inhibitors and angiotensin receptor antagonists) and beta

blockade (bisoprolol, carvedilol or long-acting metoprolol) improves prognosis. ACE inhibitors and angiotensin receptor antagonists are underused in patients who have heart failure with chronic kidney disease, possibly due to fears about the effects on renal function.[13] However, prescription of these drugs is associated with a significant reduction in deaths (adjusted one-year mortality) in these patients.[13] Adding the angiotensin receptor antagonist telmisartan to an ACE inhibitor in a randomised controlled trial in 303 haemodialysis patients with symptomatic heart failure significantly reduced both all-cause mortality (20% risk reduction) and hospitalisations due to congestive heart failure. If patients cannot tolerate ACE inhibitor or angiotensin receptor antagonist therapy, consider giving them a combination of hydralazine and nitrate therapy to improve their prognosis.

Carvedilol significantly improved all-cause mortality (49% risk reduction), cardiovascular death (68% risk reduction) and hospitalisations (56% risk reduction) in a randomised, placebo-controlled trial of 114 patients with heart failure having dialysis.[14] Spironolactone and eplerenone should not be given to patients with a creatinine clearance of less than 30 mL/min/1.73 m^2. Caution should still be exercised when giving these drugs to patients with milder degrees of renal impairment, especially if they are taking an ACE inhibitor or angiotensin receptor antagonist. There is a significant potential for hyperkalaemia, as well as deterioration in renal function.

Ischaemic heart disease

Ischaemic heart disease is very common in patients with chronic kidney disease. It progresses at a more rapid rate than in people without chronic kidney disease and is often undertreated.[12] A study of patients with ischaemic heart disease and chronic kidney disease managed in primary health care showed that their risk factors for coronary heart disease were not as well controlled as those of patients with normal GFR.[15] Even though patients with chronic kidney disease had a higher prevalence of diabetes mellitus and hypertension, the rate of prescription of evidence-based cardiovascular therapies (aspirin, beta blockers, ACE inhibitors, statins) was lower than for those with normal renal function. This situation is undesirable, but may be caused in part by the perception of a higher number of complications, fear of adverse effects, and less evidence from controlled trials in this population.

Current recommendations are that patients with chronic kidney disease with ischaemic heart disease should be prescribed aspirin, beta blockers, ACE inhibitors and statins to achieve similar targets to those currently suggested for patients without chronic kidney disease. International best practice clinical guidelines also recommend that percutaneous coronary intervention and coronary artery bypass grafting are appropriate revascularisation techniques for patients with chronic kidney disease who have obstructive lesions in their coronary arteries.

When angiography is to be performed, some strategies to decrease the risk of contrast nephropathy might include:

- minimising contrast load
- temporary cessation of drugs such as ACE inhibitors, angiotensin receptor antagonists, diuretics (if practical) and metformin around the time of contrast exposure (typically for 24–48 hours before and 24–48 hours after the procedure)
- gentle pre-hydration, for example 1 L of saline infused over 12 hours before the procedure.

Conclusion

Chronic kidney disease is a common, under-recognised and eminently treatable condition that affects one in seven Australians. It is also a major risk factor for cardiovascular disease. Patients with chronic kidney disease are far more likely to die of ischaemic heart disease or congestive cardiac failure than to end up on dialysis. Cardiovascular risk factor modification is an important part of the management of chronic kidney disease. There is considerable overlap between the management of chronic kidney disease, diabetes and cardiovascular risk reduction. Additional risk factor reduction strategies in patients with chronic kidney disease include treatment of anaemia and calcium and phosphate disorders. Management of cardiac failure and ischaemic heart disease in patients with chronic kidney disease is not dissimilar to that in patients without chronic kidney disease, except that more intensive diuresis is often necessary in cardiorenal failure.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 167)

5. Treating hypertension can reduce the decline of the glomerular filtration rate in patients with chronic kidney disease.
6. Diuretics are contraindicated for the treatment of heart failure in patients with chronic kidney disease.

Book review

Therapeutic Guidelines: Cardiovascular. Version 5.

Melbourne: Therapeutic Guidelines Limited; 2008. 241 pages. Price $39, students $30, plus postage

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This book provides recommendations for assessment and management of common clinical problems as well as expert advice on 'evidence-poor' areas. A notable difference from the previous Cardiovascular edition is the inclusion of an opening chapter explaining how the guidelines were produced, including the role of the expert group and the process of formulating and revising the recommendations. This explanation is important for the reader's understanding of the basis of the guidelines and represents a useful addition to the text.

Other differences between the revised version and its predecessor are the absence of the cardiovascular drug interactions chapter and the management of cerebral arterial disease (it still discusses peripheral arterial disease), and the logical transfer of the section on treatment of endocarditis to Therapeutic Guidelines: Antibiotics. This edition also has a focus on cardiovascular disease risk reduction as well as including the updated indications for statin therapy that are consistent with current Pharmaceutical Benefits Schedule guidelines.

The layout of this edition is familiar and navigable. However, overall I have found using the electronic form of Therapeutic Guidelines (eTG) easier to use in general practice as the search function is very user-friendly and information from the entire series can be accessed without needing to refer to individual books.