Managing hypertension in patients with chronic kidney disease

Hypertension is a common clinical problem in patients with chronic kidney disease. This article should equip the non-specialty doctor with the general principles pertaining to the investigation and treatment of hypertension in these patients. It also offers a guide to situations that warrant specialty referral.

Hypertension can be either a cause or a complication of chronic kidney disease and is therefore ubiquitous in this patient group. Higher blood pressure and urine albumin excretion are both strong, independent predictors of progressive kidney disease and cardiovascular risk. Lowering blood pressure can reduce these risks, making this an integral component of chronic kidney disease management. The greatest benefit from blood pressure reduction is seen in those at highest risk, e.g. those with very high initial blood pressure, those with albuminuria, and those with diabetes mellitus.

Targets for treatment

The current national and international guidelines differ slightly in their recommendations regarding treatment targets for hypertension in chronic kidney disease (Kidney Disease Improving Global Outcomes (KDIGO), 2012; National Institute for Health and Care Excellence, 2014). *Figure 1* details the KDIGO (2012) guidance. The differing recommendations are minor, and reflect the lack of high-quality evidence for all relevant treatment decisions.

All guidelines agree on the importance of blood pressure control in patients with chronic kidney disease and on the need for individualized treatment, particularly among those with comorbidities, in whom the risk:benefit ratio of blood pressure reduction may differ. For instance, those with postural hypotension caused by autonomic neuropathy may be at increased risk of falls if systolic blood pressure is reduced too far, and those with coronary artery disease may be at increased risk of subendocardial myocardial ischaemia if diastolic blood pressure is reduced too far.

In the last few years, many guidelines have tended to recommend less 'aggressive' blood pressure reduction than was previously the case, in particular among patients with diabetes mellitus without albuminuria. These changes were prompted largely by the ACCORD study, which compared a systolic blood pressure target of <140 mmHg with a target of <120 mmHg in people with type 2 diabetes, approximately one-third of whom had chronic kidney disease stages 1–3 (patients with advanced chronic kidney disease were excluded). Intensive blood pressure control showed a reduction in stroke, but a higher risk of adverse events including acute kidney injury in those allocated to the lower systolic blood pressure target group (Cushman et al, 2010).

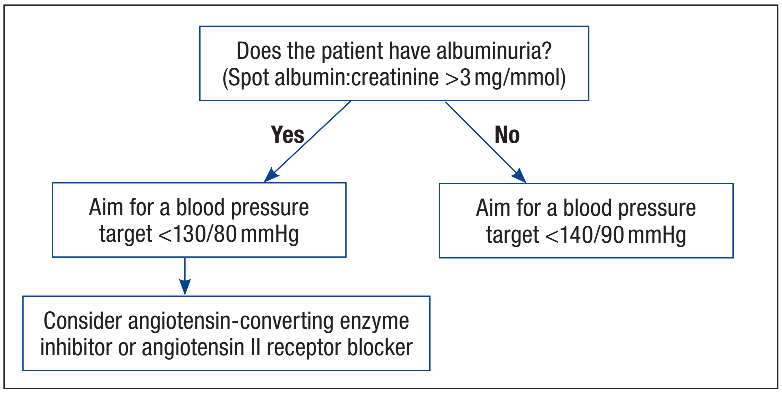

Figure 1. Kidney Disease Improving Global Outcomes (2012) recommendations for blood pressure targets.

Guidelines with a specific focus on kidney disease have universally recommended a lower systolic blood pressure target for patients with albuminuria, for several reasons:

1. Albuminuria is a powerful predictor of progressive kidney damage and also of cardiovascular disease (Hillege et al, 2002; Hallan et al, 2009; Matsushita et al, 2010)
2. Post-hoc analyses of trials of blood pressure-lowering drug treatment in patients with diabetes have shown that the greater the early reduction in albuminuria, the lower the risk of later progressive kidney damage
3. Albuminuria has been shown, at least in experimental models, to cause tubular toxicity resulting in interstitial renal fibrosis, contributing to progressive loss of kidney function
4. There is randomized controlled trial evidence that a lower mean arterial blood pressure target results in lower rates of loss of glomerular filtration rate over time among patients with albuminuria (Klahr et al, 1994).

Dr IR Logan is Clinical Lecturer and Specialty Registrar in Nephrology, Institute for Cellular Medicine, Newcastle University, Newcastle upon Tyne NE2 4HH

Dr CRV Tomson is Consultant Nephrologist in the Urology and Renal Services, Freeman Hospital, Newcastle upon Tyne

Correspondence to: Dr IR Logan (i.r.logan@ncl.ac.uk)

Table 1. Investigations in hypertension

Investigation	Diagnostic or prognostic value
Ambulatory blood pressure monitoring	Accurate, non-clinic blood pressure
Urine dipstick, spot albumin:creatinine ratio (protein:creatinine is cheaper, but less specific and insensitive at low levels of albuminuria, so should only be used for quantitation of heavy proteinuria)	Proteinuria predicts outcome and influences management. Haematuria might indicate accelerated hypertension
Urea and electrolytes	Creatinine for estimated glomerular filtration rate, low potassium as clue to Conn's or Cushing's syndrome or pseudoaldosteronism (off certain treatments)
Electrocardiogram, echocardiogram	Left ventricular hypertrophy, cardiac failure, coarctation of aorta
Fundoscopy	End organ damage or accelerated hypertension
*Renin:aldosterone ratio (ideally taken while the patient is taking no drugs that can influence renin or aldosterone secretion, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blocker, calcium channel blockers, beta-blockers, diuretics; uninterpretable if the patient is taking spironolactone (Stowasser et al, 2012)), thyroid function, serum metadrenaline or normetadrenaline, timed urinary cortisol or dexamethasone suppression test	Screening for Conn's syndrome, hypothyroidism, hyperthyroidism, phaeochromocytoma or paraganglioma, Cushing syndrome
*Magnetic resonance imaging of renal arteries and/or angiogram	Renal artery stenosis

** indicates specialist investigation, not applicable to all. Local variations in practice will exist for certain investigations*

One small trial specifically tested the hypothesis that up-titration of blood pressure-lowering drug treatment (using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers against albuminuria, rather than blood pressure, would result in better outcomes (Hou et al, 2007). The results were positive – up-titration halved the risk of renal progression or death – but no other study has yet tested this approach, which used higher than conventional doses of antihypertensive drugs.

Investigations

Although chronic kidney disease itself is often the cause of hypertension, it is still important to consider investigation for other, treatable, underlying causes in patients with chronic kidney disease including sleep apnoea, phaeochromocytoma, aldosterone-producing adrenal adenomas, and Cushing's disease. As per guidance in non-chronic kidney disease (National Institute for Health and Care Excellence, 2011), judicious use of particular investigations for individuals with signs or symptoms suggestive of a secondary cause of hypertension is appropriate. Other, standard investigations apply to all (*Table 1*).

Lifestyle management in hypertension

Many data are extrapolated from general populations rather than those with chronic kidney disease. Conservative measures include dietary restriction of sodium aiming for maximum 5–6 g/day (shown to enhance angiotensin-converting enzyme inhibitors; Esnault et al, 2005), high dietary potassium intake from fruit and vegetables (Appel et al, 1997), a regular exercise programme, and correction of obesity. Moderation of alcohol intake should be recommended. Smoking cessation should be advised to lower cardiovascular risk but does not itself have a clear impact on blood pressure.

Therapeutic management

This should commence as part of a wider strategy to lower cardiovascular risk with lifestyle measures and drugs such as statins or other cholesterol-lowering agents (National Institute for Health and Care Excellence, 2014). The response of individual patients to different antihypertensive drugs varies widely, both in terms of blood pressure-lowering effect and side effects. The choice of antihypertensive agent would ideally be based on being able to predict which drug will be most effective in any given individual. The National Institute for Health and Care Excellence algorithm for initial choice of antihypertensive drug and subsequent combinations (*Figure 2*) relies on the assumption that younger people are more likely to have high-renin hypertension, and older people and those of African-Caribbean ancestry are more likely to have low-renin hypertension. Although these assumptions have not specifically been tested in populations with chronic kidney disease, the algorithm remains a reasonable starting point. Importantly, however, the presence of albuminuria supports the preferential use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (*Figure 1*).

There is broad agreement, partly supported by clinical studies, that:

1. Patient factors and clinical circumstances dictate the use of particular agents (*Table 2*)

2. Combination antihypertensive therapy is usually required, possibly as a result of higher blood pressure in patients with chronic kidney disease (Chobanian et al, 2003), and is generally more effective than single agent therapy
3. Reduction in long-term cardiovascular risk is associated with reduced blood pressure, rather than specific agents, and even sub-optimal reductions in blood pressure are likely to be risk-lowering
4. Intensive blood pressure control can cause adverse events, so individualized blood pressure targets are appropriate, particularly considering the J-shaped relationship between blood pressure and outcome in elderly patients (Oates et al, 2007).

Angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker

These drugs reduce blood pressure by blocking conversion of angiotensin I to angiotensin II and reducing bradykinin degradation. However, they also reduce proteinuria by

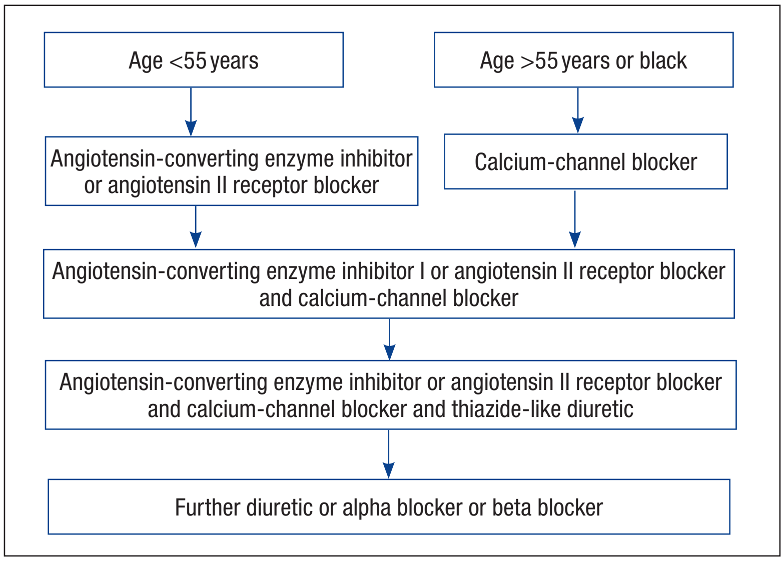

Figure 2. National Institute for Health and Care Excellence (2011) algorithm for antihypertensive drug treatments.

Table 2. Commonly used antihypertensives, indications and contraindications for prescribing

Drug class or specific agents		Compelling indications	Potentially beneficial situations	Cautions or contraindications
Angiotensin-converting enzyme inhibitor, e.g. ramipril		Proteinuria, cardiac failure, myocardial infarction, stroke, young age	Numerous	Pregnancy, renovascular disease, angioedema, hyperkalaemia, volume depletion or hypotension, e.g. diarrhoea, sepsis
Angiotensin receptor blocker, e.g. losartan		See angiotensin-converting enzyme inhibitor	Intolerance or allergy, e.g. angiotensin-converting enzyme inhibitor-induced cough, otherwise see angiotensin-converting enzyme inhibitor. Uricosuric effect in gout (specific to losartan; not a class effect)	See angiotensin-converting enzyme inhibitor
Loop diuretics, e.g. furosemide		Fluid overload	Advanced chronic kidney disease	Volume depletion or hypotension
Thiazide and related diuretics, e.g. bendroflumethiazide, indapamide		Cardiac failure, hypercalciuria	Numerous	Gout (can give with allopurinol). Higher doses required to achieve the same effect in patients with lower glomerular filtration rate
Calcium-channel blockers	Dihydropyridine, e.g. amlodipine	Elderly, people of black ethnic origin (see text), Raynaud's	Numerous	Cardiac failure, ankle swelling, proteinuria
	Non-dihydropyridine, e.g. verapamil or diltiazem	Atrial fibrillation, supraventricular tachycardia, angina, migraine	Proteinuria	Concomitant beta blocker, bradycardia or heart block, cardiac failure
Alpha blockers, e.g. doxazosin		Bladder outflow obstruction	Resistant hypertension	Falls, postural hypotension, urinary incontinence
Aldosterone antagonists, e.g. spironolactone		Cardiac failure, proteinuria	Resistant hypertension, particularly with hypokalaemia	Hyperkalaemia, volume depletion
Beta blockers, e.g. bisoprolol		Myocardial infarction, cardiac failure, angina, dysrhythmias		Peripheral arterial disease, asthma, bradycardia or heart block, diabetes mellitus, chronic obstructive pulmonary disease*
Centrally acting agents, e.g. moxonidine, methyldopa, minoxidil			Resistant hypertension, drug intolerances	Other sedative drugs

*Resistant hypertension or use of multiple drug intolerances is an indication for specialist referral. *Patients with chronic obstructive pulmonary disease may derive survival benefit from beta blockers, so cautious use of cardioselective variants such as bisoprolol could be used with specialist input where a concomitant indication exists.*

Table 3. Potential harmful effects of certain combinations of commonly used antihypertensives	
Combination	**Potentially unwanted effect**
Non-dihydropyridine calcium-channel blocker and beta blocker	Bradycardia, complete heart block
Angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker	Hyperkalaemia
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and aldosterone antagonist or other potassium-sparing diuretic	Hyperkalaemia
Calcium-channel blocker and other vasodilator, e.g. doxazosin	Peripheral oedema

decreasing glomerular afferent arteriole vascular tone, thereby decreasing intraglomerular filtration pressure. The presence of proteinuria is therefore a compelling indication for use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. In diabetic chronic kidney disease with proteinuria, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers are first line, and in non-diabetic chronic kidney disease they are indicated in the presence of >30 mg albuminuria (KDIGO, 2012) or cardiac failure (*Table 2*, Jafar et al, 2003; Balamuthusamy et al, 2008). In non-diabetic, non-proteinuric chronic kidney disease or diabetic, non-proteinuric chronic kidney disease the role of these agents is less clear and standard antihypertensive strategies apply (*Figure 2*).

Angiotensin-converting enzyme inhibitors also slow the development of fibrosis, the histopathological end point common to all forms of chronic kidney disease, and reduce aldosterone levels. However, no data suggest any particular angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker as possessing superior blood pressure control and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are generally safe in combination with other drugs (see *Table 3* for exceptions).

Although the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker appears to reduce the risk of progressive kidney disease in diabetic nephropathy, and probably in other proteinuric diseases, the protection is far from complete. This could be the result of incomplete inhibition of the renin–angiotensin–aldosterone axis. Several trials have examined the potential of dual blockade, using a combination of angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. Dual therapy is more effective in reducing blood pressure and proteinuria than monotherapy (Kunz et al, 2008). However, no single study has yet demonstrated improved 'hard' outcomes (e.g. risk of kidney failure) with dual therapy.

Two large randomized controlled trials (ON-TARGET and VA-NEPHRON-D) have suggested that the risks of dual blockade – acute kidney injury, particularly during acute illness, and hyperkalaemia – might balance any potential benefit (Mann et al, 2008; Fried et al, 2013), although a meta-analysis argues that dual blockade is associated with a lower risk of kidney failure than angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker monotherapy in patients with diabetes (Palmer et al, 2015). Current national guidance is that dual therapy should not be used in patients with chronic kidney disease (National Institute for Health and Care Excellence, 2014); however, some nephrologists will continue to recommend dual therapy for patients with heavy proteinuria and/or poorly controlled hypertension in whom the risk of acute kidney injury is judged to be acceptable compared to the risks of less aggressive treatment.

Debate exists in using angiotensin-converting enzyme inhibitor in patients with advanced chronic kidney disease, owing to the concern over hyperkalaemia or precipitous reductions in glomerular filtration rate (Baweja et al, 2011). Guidance suggests avoiding their use if the pre-treatment potassium level is greater than 5.0 mmol/litre, and discontinuation if potassium levels reach 6 mmol/litre or above (National Institute for Health and Care Excellence, 2014). Current practice is to check plasma creatinine and potassium levels before, and 7–14 days after commencing an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and again after subsequent dose adjustments. A maximal reduction in glomerular filtration rate of 25% or increase in plasma creatinine of 30% is often cited as acceptable; a reduction in glomerular filtration rate after initiation of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is an expected effect as a result of the reduction in intraglomerular pressure as described above.

In a post-hoc analysis of one randomized controlled trial in diabetic nephropathy, the extent of the early fall in glomerular filtration rate predicted long-term stability of kidney function (Holtkamp et al, 2011). However, a fall in glomerular filtration rate after initiation of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker can also indicate hazardous reductions in glomerular perfusion pressure, for instance caused by severe renal artery stenosis: in this setting, continuing the drug will cause a further fall in glomerular filtration rate and possibly progression to kidney failure. Increases in potassium with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment may favour addition of potassium-wasting thiazide diuretics (*Table 4*), or discontinuation of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in favour of an alternative class of agent, particularly if no compelling indication, such as proteinuria or cardiac failure, exists.

Diuretics

Salt and water retention are contributing factors to hypertension in chronic kidney disease, meaning that diuretics have a role in this setting (*Table 2*). Thiazides in particular have few side effects (*Table 4*), are more likely to cause a fall in serum potassium level (which can be useful in patients with chronic kidney disease), and their antihypertensive effects are longer acting than loop diuretics. They can be also used safely in combination with most other agents. The National Institute for Health and Care Excellence (2011) guidelines specifically recommend a thiazide-like diuretic (e.g. hydrochlorothiazide, indapamide) over a pure thiazide (e.g. bendroflumethiazide), although the studies on which this recommendation were based did not include many patients with chronic kidney disease. Thiazide and thiazide-like diuretics retain some effect in chronic kidney disease, particularly when used in combination with other diuretics (Fliser et al, 1994).

Loop diuretics may be used in preference to thiazides in patients with advanced chronic kidney disease. However, their use is more common in the treatment of oedema than hypertension per se (*Table 2*).

Amiloride and triamterene, examples of non-aldosterone-related potassium-sparing diuretics, are less effective diuretics than thiazides or loop diuretics, and the associated risk of hyperkalaemia means that they are often avoided in patients with chronic kidney disease.

Calcium-channel blockers

Non-dihydropyridine calcium-channel blockers (commonly diltiazem and verapamil) have particular indications (*Table 2*), and exhibit anti-proteinuric effects. They can cause myocardial depression in the context of cardiac failure so must be used with caution. Commonly prescribed dihydropyridine agents such as amlodipine act more selectively on vascular smooth muscle and, although well tolerated, can increase proteinuria so should be used with care. They can also exacerbate fluid retention and ankle oedema in patients with chronic kidney disease (*Table 4*). No data demonstrate particular antihypertensive efficacy of one calcium-channel blocker over another.

> “Loop diuretics may be used in preference to thiazides in patients with advanced chronic kidney disease.”

Aldosterone antagonists

These compounds are potassium-sparing diuretics. Spironolactone has been used with increasing popularity as an antihypertensive in modest doses (*Table 2*). The related agent eplerenone, which has fewer oestrogenic side effects (*Table 4*), might be similarly useful, but both agents should be used in caution in patients with chronic kidney disease owing to their risk of hyperkalaemia and reduction in glomerular filtration rate, especially during intercurrent illness. While aldosterone antagonists reduce proteinuria, especially in combination with angiotensin-converting enzyme inhibitors (Epstein et al, 2006), it is not yet known whether they retard chronic kidney disease progression, and the combination can produce hyperkalaemia so is not routinely recommended (*Table 3*).

Other agents

Beta blockers, α blockers and other agents such as methyldopa, clonidine and moxonidine are not used routinely in the management of hypertension in patients with chronic kidney disease but might be useful in the context of resistant hypertension (defined as hypertension despite use of three antihypertensive agents, ideally including a diuretic). Beta blockers can accumulate in patients with advanced chronic kidney disease leading to side effects; α blockers can cause unwanted side effects, particularly in the elderly (*Table 4*).

Table 4. Side effects of commonly prescribed antihypertensives (list not exhaustive)

Drug or class		Side effect
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker		First dose hypotension especially with concurrent diuretic therapy, dry cough (angiotensin-converting enzyme inhibitor), hyperkalaemia, rash, angioedema, leukopenia
Diuretics (loop, thiazides)		Volume depletion, hyponatraemia, hypokalaemia, hypomagnesaemia, blood dyscrasia, pancreatitis, disproportionate risk in blood urea in advanced kidney disease. Thiazides in particular: increased risk of diabetes (long-term use), hyperuricaemia and hypercholesterolaemia, lithium toxicity
Beta blocker		Bradycardia, hyperkalaemia, bronchospasm, impotence
Alpha blocker		Postural hypotension, diarrhoea, ankle swelling
Spironolactone		Hyperkalaemia, gynaecomastia, menstrual upset, metabolic acidosis
Calcium-channel blocker	Dihydropyridines	Ankle oedema, headache, flushing, accumulation of some immunosuppressants
	Non-dihydropyridines	Worsening cardiac failure, cardiac conduction defects, accumulation of some immunosuppressants

KEY POINTS

- Treatment of hypertension slows progression of chronic kidney disease and reduces cardiovascular risk.
- The presence of proteinuria influences management.
- Multiple agents will usually be required to control blood pressure, especially in patients with chronic kidney disease.
- Aggressive lowering of blood pressure can produce adverse effects.

The direct renin inhibitor aliskiren has been approved in the treatment of hypertension but its utility as an antihypertensive in patients with chronic kidney disease is currently unclear (Parving et al, 2008). The role of endothelin antagonists is under investigation.

Direct vasodilators including hydralazine and minoxidil have limited utility in chronic kidney disease, principally as a result of fluid retention and other side effects. They could, rarely, be considered in resistant hypertension.

Indications for specialist referral

Aside from the possibility of secondary hypertension, the following situations should mandate specialist referral: accelerated hypertension (particularly with retinopathy or neurological sequelae), pregnancy or pre-eclampsia, young age, aortic dissection, resistant or severe hypertension, and multiple drug intolerances or contraindications.

Tips for compliance

Although not evidence based, simple measures to improve medication compliance might include minimizing tablet number, dose rescheduling (including taking some tablets last thing at night), continuity of care, and providing information for patients and carers. **BJHM**

Conflict of interest: none.

Appel LJ, Moore TJ, Obarzanek E et al (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* **336**(16): 1117–24 (doi: 10.1056/NEJM199704173361601)

Balamuthusamy S, Srinivasan L, Verma M et al (2008) Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J* **155**(5): 791–805 (doi: 10.1016/j.ahj.2008.01.031)

Baweja S, Holt SG, McMahon LP et al (2011) The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* **26**(5): 1752–3 (doi: 10.1093/ndt/gfr027)

Chobanian AV, Bakris GL, Black HR et al (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **42**(6): 1206–52 (doi: 10.1161/01.HYP.0000107251.49515.c2)

Cushman WC, Evans GW, Byington RP et al (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* **362**(17): 1575–85 (doi: 10.1056/NEJMoa1001286)

Epstein M, Williams GH, Weinberger M et al (2006) Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* **1**(5): 940–51 (doi: 10.2215/CJN.00240106)

Esnault VL, Ekhlas A, Delcroix C, Moutel MG, Nguyen JM (2005) Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. *J Am Soc Nephrol* **16**(2): 474–81 (doi: 10.1681/ASN.2004060505)

Fliser D, Schroter M, Neubeck M, Ritz E (1994) Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. *Kidney Int* **46**(2): 482–8 (doi: 10.1038/ki.1994.298)

Fried LF, Emanuele N, Zhang JH et al (2013) Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* **369**(20): 1892–903 (doi: 10.1056/NEJMoa1303154)

Hallan SL, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR (2009) Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* **20**(5): 1069–77 (doi: 10.1681/ASN.2008070730)

Hillege HL, Fidler V, Diercks GF et al (2002) Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* **106**(14): 1777–82 (doi: 10.1161/01.CIR.0000031732.78052.81)

Holtkamp FA, de Zeeuw D, Thomas MC et al (2011) An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* **80**(3): 282–7 (doi: 10.1038/ki.2011.79)

Hou FF, Xie D, Zhang X et al (2007) Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol* **18**: 1889–98 (doi: 10.1681/ASN.2006121372)

Jafar TH, Stark PC, Schmid CH et al; AIPRD Study Group (2003) Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* **139**(4): 244–52 (doi: 10.7326/0003-4819-139-4-200308190-00006)

KDIGO Blood Pressure Work Group (2012) KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* **2**(Suppl): 337–414

Klahr S, Levey AS, Beck GJ et al (1994) The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* **330**: 877–84 (doi:10.1056/NEJM199403313301301)

Kunz R, Friedrich C, Wolbers M, Mann JF (2008) Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* **148**(1): 30–48 (doi: 10.7326/0003-4819-148-1-200801010-00190)

Mann JF, Schmieder RE, McQueen M et al (2008) Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* **372**(9638): 547–53 (doi: 10.1016/S0140-6736(08)61236-2)

Matsushita K, van der Velde M, Astor BC et al (2010) Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* **375**(9731): 2073–81 (doi:10.1016/S0140-6736(10)60674-5)

National Institute for Health and Care Excellence (2011) *Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34.* www.nice.org.uk/guidance/cg127 (accessed 19 September 2016)

National Institute for Health and Care Excellence (2014) *Chronic kidney disease in adults: assessment and management.* CG 182. www.nice.org.uk/guidance/cg182 (accessed 19 September 2016)

Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM (2007) Blood pressure and survival in the oldest old. *J Am Geriatr Soc* **55**(3): 383–8 (doi: 10.1111/j.1532-5415.2007.01069.x)

Palmer SC, Mavridis D, Navarese E et al (2015) Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* **385**(9982): 2047–56 (doi: 10.1016/S0140-6736(14)62459-4)

Parving HH, Persson F, Lewis JB et al (2008) Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* **358**(23): 2433–46 (doi: 10.1056/NEJMoa0708379)

Stowasser M, Ahmed AH, Pimenta E, Taylor PJ, Gordon RD (2012) Factors affecting the aldosterone/renin ratio. *Horm Metab Res* **44**(3): 170–6 (doi: 10.1055/s-0031-1295460)