Management of hypertension in renal disease

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Abstract

The management of hypertension in renal disease is best understood by classifying patients according to the stage of their chronic kidney disease (CKD). Many of the pathophysiological mechanisms are common to all patients, but in post-transplant recipients there are additional factors to be considered. The benefits of good blood pressure control in CKD are a slowing in the rate of progression of renal disease and a reduction in cardiovascular morbidity and all-cause mortality. In CKD stage 5, the aim is solely to reduce cardiovascular morbidity and mortality; the evidence of benefit here is more controversial, with several studies showing worse outcomes in patients with low blood pressure. In renal transplant recipients, good blood pressure control is advantageous for the long-term outcome of graft survival, in addition to reducing cardiovascular morbidity and mortality. Renal transplant recipients are generally treated according to the guidelines for CKD. However, consideration of the dosing of corticosteroids and choice of calcineurin inhibitors can play an important role in reducing the incidence of hypertension.

Keywords Blood pressure; chronic kidney disease; hypertension; MRCP; renal disease; renal transplant

Key points

- Treatment of hypertension in chronic kidney disease (CKD) can reduce cardiovascular morbidity and mortality and delay the progression of renal disease
- Blood pressure targets in CKD stages 3 and 4 are determined by the presence of proteinuria
- In dialysis patients, the treatment of interdialysis hypertension reduces cardiovascular mortality and morbidity
- For transplant patients, maintaining a blood pressure <130/80 mmHg contributes to prolonged graft survival

Introduction

The approach to hypertension in renal disease varies according to the stage of chronic kidney disease (CKD). Here, renal disease is considered under the following headings:

- CKD stages 3 and 4 (estimated glomerular filtration rate (eGFR) 15–60 ml/minute/1.73 m ^{2})
- CKD stage 5 and dialysis (eGFR <15 ml/minute/1.73 m ^{2})
- kidney transplant recipients.

Hypertension in CKD stages 3 and 4

In CKD stages 3 and 4, the aims of blood pressure reduction are, first, to lower cardiovascular morbidity and mortality,[1] and second, to reduce the rate of progression of renal disease.

Lifestyle modification should be encouraged, aiming for a body mass index of 20–25 kg/m^2, a lowering of alcohol intake and regular exercise in addition to a reduction in dietary sodium.[2] In CKD, extracellular volume expansion as a result of impaired natriuresis is thought to play an important role in the pathogenesis of hypertension. It is therefore recommended that dietary sodium intake should be <100 mmol/day (2.3 g sodium/day or 6 g salt/day).[2] This has also been shown to enhance the effect of antihypertensive medications.

There has been some variability in the blood pressure targets for CKD patients as a result of contradictory results from meta-analyses; however, several international guidelines (KDIGO/NICE/RA/ESC/ESH)[2] agree that targets should be based on the degree of proteinuria. In individuals with urinary albumin excretion <30 mg/24 hours (or equivalent), treatment is recommended if normal clinic blood pressures are >140 mmHg systolic or >90 mmHg diastolic. In those with diabetes mellitus or urinary albumin excretion of 30 mg/24 hours or higher, or equivalent, the threshold for treatment is lower, at 130 mmHg systolic or 80 mmHg diastolic pressure.[2]

A recent large meta-analysis showed an all-cause reduction in mortality in CKD stages 3–5 for a reduction in mean systolic blood pressure to 132 mmHg.[1] The decrease in all-cause mortality with more intensive blood pressure lowering was also demonstrated in the SPRINT trial; however, in the CKD subgroup, those given more intensive therapy did not have a significant reduction in risk for the primary composite endpoint of cardiovascular morbidity and mortality.[3] Post hoc analysis of some studies has warned of the increased mortality associated with systolic hypotension (<120 mmHg). More recently, others have suggested that blood pressure should be lowered until proteinuria has been eradicated or minimized, which at least allows individualized treatment targets for patients.

Angiotensin-converting enzyme (ACE) inhibitors have become first-line agents in treating hypertension in CKD stages 1–4 patients with proteinuria (>1 g/day) irrespective of their diabetic status. ACE inhibitors have been shown clearly to reduce the rate of progression of renal failure. Studies in diabetes mellitus have demonstrated similar benefits for angiotensin receptor blockers (ARBs).

Hypertension in CKD stage 5 and dialysis

In this group of patients, the main reason for treating hypertension is to reduce cardiovascular morbidity and mortality.

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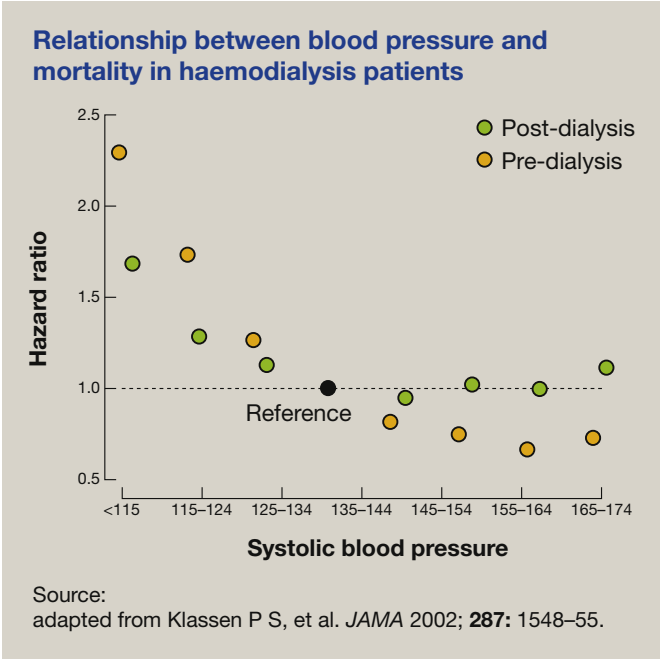

Figure 1

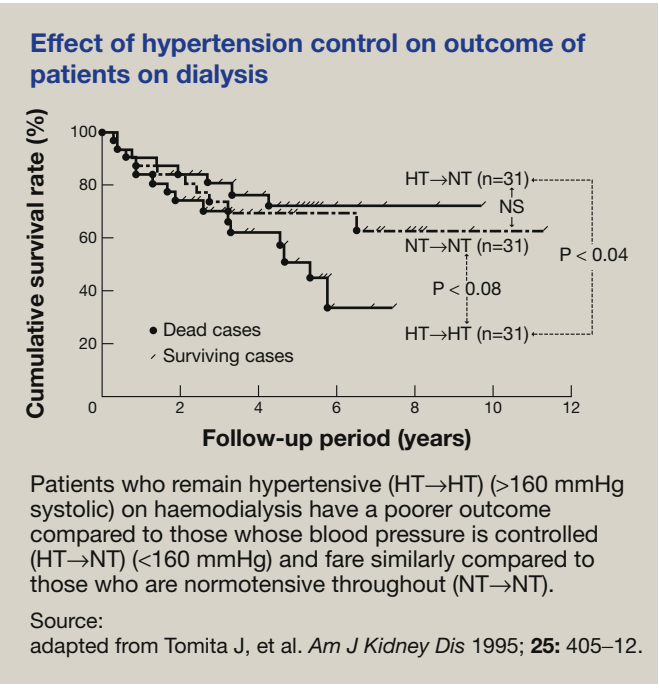

Figure 2

Hypertension is commonplace among dialysis patients (up to 85% in some studies). This is commonly secondary to salt and water overload, but renin-driven hypertension, an imbalance between naturally occurring vasodilators/vasoconstrictors, sympathetic overactivity, and the recently recognized high prevalence of obstructive sleep apnoea can all contribute.

Specific blood pressure targets for dialysis patients have been withdrawn, partly because aiming for these targets could result in increased episodes of dialysis hypotension. However, a 2009 meta-analysis showed that blood pressure lowering medications reduced the risk of cardiovascular events in dialysis patients.[4] Most recent data have been based on initiating treatment according to interdialysis home blood pressure measurements.

The data point to a 'reverse J'-shaped relationship between blood pressure and mortality (Figure 1), where lower blood pressure both before and after dialysis is associated with higher mortality. This is counterintuitive and has to be interpreted with caution as such data are cross-sectional and non-interventional. There is also the reverse causality argument: individuals with lower blood pressure have already developed significant left ventricular dysfunction, which results in higher death rates. There is additional concern that lower blood pressures increase haemodialysis access thromboses. There have been some interventional studies to indicate that treating hypertension improves prognosis. A study from Japan has shown that patients with systolic blood pressure >160 mmHg at the start of dialysis fared better if their blood pressure was lowered to <160 mmHg, compared with those who remained hypertensive (Figure 2).[5]

The treatment of hypertension should include reduction of dietary salt and strict fluid restriction. Optimization of dialysis and dry weight assessment can correct blood pressure in up to 60% of patients. Many patients require antihypertensive therapy, and although there is little evidence to favour the use of a particular agent, β-adrenoceptor blockers are often used because of their cardioprotective properties.

Hypertension in kidney transplant recipients

The benefits of treating hypertension in kidney transplant recipients are similar to those in CKD stages 3 and 4. Most transplant recipients fall into this category (i.e. eGFR <60 ml/minute/1.73m^2). The mechanism of post-transplant hypertension is similar to that in CKD stages 3 and 4, with additional factors such as the presence of diseased native kidneys, drugs (calcineurin inhibitors, corticosteroids) and transplant renal artery stenosis. Delayed graft function and allografts from deceased donors with a family history of hypertension are also risk factors.

The current KDIGO guidelines suggest that clinic blood pressures should be <130/80 mmHg, regardless of proteinuria, as higher blood pressures are associated with increased risk of graft loss and mortality. There are few data to support the choice of a particular antihypertensive. For early treatment (first 3 months), calcium channel blockers are thought to provide better outcomes, but for later treatment (>3 months), ACE inhibitors and ARBs are preferred. They have the added benefit of treating or preventing post-transplant erythrocytosis, which was commonly seen before the use of these drugs, but can, however, have a cumulative effect in conjunction with calcineurin inhibitors in increasing serum potassium levels. Newer immunosuppressive regimens that avoid corticosteroids have been shown to reduce the incidence of hypertension. Perhaps more importantly, switching to non-calcineurin inhibitors after the initial post-transplant period might improve blood pressure control. ◆

KEY REFERENCES

1 Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. *J Am Med Assoc Intern Med* 2017; **177:** 1498–505.

2 Williams B, Mancia G, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **33:** 3021–104.

3 SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373:** 2103–16.

4 Heerspink HJ, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomized controlled trials. *Lancet* 2009; **373:** 1009–15.

5 Tomita J, Kimura G, Inoue T, et al. Role of systolic blood pressure in determining prognosis of hemodialyzed patients. *Am J Kidney Dis* 1995; **25:** 405–12.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 52-year-old man presented for review. He had type 2 diabetes mellitus and chronic kidney disease (CKD).

On clinical examination, his blood pressure was 164/93 mmHg.

Investigations

- HbA_{1C} 73 mmol/mol (20–42); 8.8%
- Estimated glomerular filtration rate 48 ml/minute/1.73 m^2 (>60)
- Urinary albumin 154 mg/24 hours (<30)

What is the best management to delay the progression of CKD?

A. Renin–angiotensin system blockade
B. Better control of the diabetes
C. β-Adrenoceptor blocking agents
D. Loop diuretics
E. Low-protein diet

Question 2

A 67-year-old woman presented for review on the morning before her usual dialysis session for chronic kidney failure. She had been undergoing dialysis via a left brachio-cephalic arteriovenous fistula for 3 years.

On clinical examination, her blood pressure (right arm) was 184/94 mmHg.

What is the most appropriate investigation to guide further management of the blood pressure?

A. Intradialysis blood pressures
B. Echocardiogram
C. Interdialysis home blood pressure readings
D. Repeat clinic blood pressure reading
E. Twenty-four-hour blood pressure monitoring on dialysis days

Question 3

A 41-year-old woman presented for review 3 months after being given a deceased donor kidney transplant. The primary cause of her end-stage renal disease had been immunoglobulin A nephropathy, and she had been undergoing peritoneal dialysis for 2 years before the transplant. Her blood pressure had previously been noted as well controlled.

On clinical examination, her blood pressure was 150/98 mmHg. Currently her medications are as follows: prednisolone (5 mg), mycophenolate mofetil, tacrolimus, co-trimoxazole (prophylaxis), Adcal-D3 and atorvastatin.

Which factor is most likely to contribute to the post-transplant hypertension?

A. The cause of the primary renal disease
B. A family history of hypertension
C. The duration of previous dialysis
D. The modality of the previous dialysis
E. The initiation of a calcineurin inhibitor