

# **Association of British Clinical Diabetologists (ABCD) and Renal Association clinical guidelines: Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease**

## **Summary of recommendations**

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## Introduction

A significant percentage of patients with diabetes develop chronic kidney disease (CKD), and diabetes is also a leading cause of end-stage renal disease.<sup>1</sup> More than a quarter of patients who are on dialysis in the UK have diabetes.<sup>2</sup> Diabetic kidney disease is associated with high morbidity and mortality, which are predominantly related to cardiovascular complications and the progression of kidney disease that requires renal replacement therapy. Hypertension is a modifiable risk factor for cardiovascular complications and progression of CKD.<sup>3</sup>

The recommendations outlined here are for the variety of clinicians who manage patients with diabetic kidney disease, including GPs and specialists in diabetes, cardiology and nephrology. They are intended to harmonise practices of blood pressure monitoring, and pharmacological and non-pharmacological management of hypertension, which may vary considerably.

## Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations; the suggested audit standards; and the questions for areas that require future research.

- 1A – Strong recommendation: high-quality evidence
- 1B – Strong recommendation: moderate-quality evidence
- 1C – Strong recommendation: low-quality evidence
- 1D – Strong recommendation: very low-quality evidence
- 2A – Weak recommendation: high-quality evidence
- 2B – Weak recommendation: moderate-quality evidence
- 2C – Weak recommendation: low-quality evidence
- 2D – Weak recommendation: very low-quality evidence

# 1 Hypertension management and renin-angiotensin-aldosterone system blockade in patients with type 1 diabetes

## Recommendations

The following are recommendations for renin-angiotensin-aldosterone system (RAAS) blockade and hypertension management in patients with type 1 diabetes.

- 1 In patients with type 1 diabetes and normoalbuminuria, we suggest a threshold for blood pressure therapy of a persistent upright (sitting or standing) blood pressure that is greater than or equal to 140/80 mmHg (Grade 2D).  
  
In children and adolescents with type 1 diabetes, hypertension is defined as average systolic blood pressure and/or diastolic blood pressure that is greater than the 95th percentile for the patient's gender, age and height on more than three occasions (Grade 1B).
- 2 We recommend that angiotensin-converting-enzyme inhibitor (ACEI) therapy should be used as a first-line agent for blood pressure lowering and, if ACEI therapy is contraindicated or not tolerated, angiotensin receptor blockers (ARBs) should be considered (Grade 1B).
- 3 In most adults with type 1 diabetes and persistent microalbuminuria or macroalbuminuria, we recommend that ACEI therapy should be considered irrespective of blood pressure, and that the target upright blood pressure should be less than or equal to 130/80 mmHg. We recommend that the dose of ACEI should be titrated to the maximum tolerated (Grade 1B).
- 4 There is no current evidence to support a role for ACEI therapy for blood pressure control or renal protection in patients with type 1 diabetes who are normotensive and normoalbuminuric (Grade 1C).
- 5 There is some evidence to support the use of candesartan to prevent the development or progression of retinopathy in patients with type 1 diabetes who are normotensive and normoalbuminuric (Grade 1C).
- 6 There is no firm evidence to support a role of dual blockade of the RAAS in patients with type 1 diabetes (Grade 1C).
- 7 We recommend that women of childbearing age should be encouraged to stop RAAS-blocking drugs prior to actively considering pregnancy (Grade 1B).
- 8 We suggest that patients with type 1 diabetes with significant renal function impairment (eGFR <45 ml/min/1.73 m<sup>2</sup>) should be advised to withhold RAAS-blocking drugs during periods of acute illness (not graded).

## Audit standards

The following are suggested as audit standards for RAAS blockade and hypertension management in patients with type 1 diabetes.

- 1 The proportion of patients with type 1 diabetes, with micro- or macroalbuminuria who are treated with an ACEI or ARB at the maximum tolerated doses.
- 2 The proportion of patients with type 1 diabetes, with micro- or macroalbuminuria who are achieving blood pressure of less than 130/80 mmHg.

- 3 The proportion of patients with type 1 diabetes and albuminuria who are on submaximal doses of ACEIs or ARBs due to hyperkalaemia or adverse reactions.

### **Areas that require further research**

The following areas lack good-quality evidence for RAAS blockade and hypertension management in patients with type 1 diabetes, and hence further research is necessary.

- 1 In light of the fact that the presence of microalbuminuria in patients with type 1 diabetes may not be the best predictor of whether they will develop progressive renal disease, what is the role for other markers (such as kidney injury molecule-1 (KIM-1)) in predicting the risk of renal disease in patients with type 1 diabetes?
- 2 What is the role of dual RAAS blockade in patients with type 1 diabetes and nephropathy?
- 3 What is the role of aldosterone receptor blockers or direct renin inhibitors in patients with type 1 diabetes and nephropathy?
- 4 Is there a role for home or ambulatory blood pressure monitoring in the diagnosis and management of hypertension in patients with type 1 diabetes, particularly in those who have diabetic autonomic neuropathy?
- 5 Does measurement of plasma renin activity have a role in screening and managing hypertension in patients with type 1 diabetes?
- 6 Does tight glycaemic control and blood pressure lowering reduce the incidence of patients developing microvascular complications?
- 7 What is the role of RAAS-blocking agents in patients who have type 1 diabetes, progressive renal decline and normoalbuminuria?

## 2 Hypertension management and renin-angiotensin-aldosterone system blockade in patients with type 2 diabetes, nephropathy and/or early chronic kidney disease (stages 1–3)

### Recommendations

The following are recommendations for RAAS blockade and hypertension management in patients with type 2 diabetes, nephropathy and/or early CKD.

- 1 In patients with type 2 diabetes and hypertension, we recommend salt intake of less than 90 mmol per day (less than 2 g per day of sodium – equivalent to 5 g of sodium chloride) (Grade 1C).
- 2 In patients with type 2 diabetes, CKD and urine albumin excretion rate (AER) of less than 30 mg per 24 hours (albumin:creatinine ratio (ACR) less than 3 mg/mmol), we recommend that their target upright blood pressure should be less than 140/90 mmHg, using antihypertensive therapy in the maximum tolerated doses (Grade 1D).
- 3 In patients with type 2 diabetes, CKD and urine AER of greater than 30 mg per 24 hours (ACR greater than 3 mg/mmol), we suggest aiming for a target upright blood pressure that is consistently less than 130/80 mmHg, using antihypertensive therapy in the maximum tolerated doses (Grade 2D).
- 4 There is no evidence to support either ACEI or ARB therapy as first-line blood pressure lowering agents in comparison with other antihypertensive agents in patients with type 2 diabetes, normal renal function and normal urine AER (less than 30 mg per 24 hours or ACR less than 3 mg/mmol) (Grade 1A).
- 5 We suggest that ACEIs (or ARBs if ACEIs are not tolerated) should be preferentially used in patients with type 2 diabetes and CKD who have urine AER above 30 mg per 24 hours (ACR greater than 3 mg/mmol). We suggest that the dose of ACEI (or ARB) should be titrated to the maximum tolerated (Grade 2D).
- 6 There is currently no evidence to support the role of home or ambulatory blood pressure monitoring in patients with type 2 diabetes and CKD stages 2 and 3 (Grade 1D).
- 7 There is currently no evidence to support the role of dual blockade of the RAAS in patients with type 2 diabetes and CKD stages 1 to 3 (Grade 1B).
- 8 Upright blood pressure targets should be set at no lower than 150/90 mmHg in those with type 2 diabetes who are aged 80 years or over (Grade 2B).
- 9 We suggest that patients with type 2 diabetes with significant renal function impairment (eGFR <45 ml/min/1.73 m<sup>2</sup>) should be advised to withhold RAAS-blocking drugs during periods of acute illness (not graded).

## **Audit standards**

The following are suggested as audit standards for RAAS blockade and hypertension management in patients with type 2 diabetes, early CKD and/or albuminuria.

- 1 The percentage of patients with type 2 diabetes who have CKD and urine AER of greater than 30 mg per 24 hours (ACR of greater than 3 mg/mmol) who are achieving the target upright blood pressure of less than 130/80 mmHg.
- 2 The proportion of patients with type 2 diabetes who have CKD and urine AER of greater than 30 mg per 24 hours (ACR of greater than 3 mg/mmol) who are on ACEIs or ARBs.
- 3 The percentage of patients with type 2 diabetes who have CKD and urine AER of greater than 30 mg per 24 hours (ACR of greater than 3 mg/mmol) who are not on ACEIs or ARBs (or who are on a suboptimal dosage) due to hyperkalaemia or a decrease in estimated glomerular filtration rate (eGFR) of greater than 25% or an increase in serum creatinine of greater than 30%.
- 4 The number of patients with type 2 diabetes and CKD who are on dual blockade of the RAAS.

## **Areas that require further research**

The following areas lack good-quality evidence for RAAS blockade and hypertension management in patients with type 2 diabetes, nephropathy and/or early CKD, and hence further research is necessary.

- 1 What is the best method for blood pressure measurement in patients with type 2 diabetes who have CKD?
- 2 What is the evidence-based lower limit for blood pressure reduction in patients with type 2 diabetes who have CKD?
- 3 Does reduction in albuminuria with agents that do not modify blood pressure improve hard cardiovascular and renal outcomes?
- 4 Should RAAS inhibition be maximised in patients with CKD?
- 5 Can potassium binders enable a higher dosage of RAAS inhibitors with better attainment of blood pressure control and reduction in hyperkalaemia?
- 6 Is the use of mineralocorticoid antagonists beneficial in patients with type 2 diabetes and nephropathy?
- 7 What are the best second- and third-line blood pressure lowering agents in patients with type 2 diabetes who have CKD and albuminuria?
- 8 Is there a need for long-term outcome studies of non-dihydropyridine calcium channel blockers in diabetic nephropathy?

### 3 Hypertension management and renin-angiotensin-aldosterone system blockade in patients with type 2 diabetes, nephropathy and/or later stage chronic kidney disease – stages 4 and 5 (non-dialysis)

#### Recommendations

The following are recommendations for the management of hypertension in patients with diabetes and chronic kidney disease (CKD) stages 4 and 5 (non-dialysis).

- 1 We recommend regular monitoring of blood pressure, urine albumin, blood electrolytes and kidney function in patients with diabetes and CKD stages 4 and 5 (Grade 1B).
- 2 We recommend that if blood pressure is uncontrolled, electrolytes are abnormal or kidney disease is progressive, they should be monitored two to four times per year, depending on the stage of CKD and the patient's need (Grade 1C).
- 3 We recommend that all patients with diabetes, advanced CKD and high blood pressure follow a low salt (sodium chloride) diet, ideally restricted to less than 5 g per day (Grade 1B).
- 4 We recommend the initiation of antihypertensive agents in patients who have diabetes and CKD stages 4 and 5 and an ACR of less than 30 mg/mmol when their blood pressure is greater than 140/90 mmHg. We also recommend aiming for a target upright blood pressure of less than or equal to 140/90 mmHg during therapy (Grade 1B).
- 5 We suggest initiation of antihypertensive agents in patients with diabetes and CKD stages 4 and 5 and an ACR of greater than 30 mg/mmol when their blood pressure is greater than 130/80 mmHg, and we suggest aiming for a target upright blood pressure of less than or equal to 130/80 mmHg (Grade 2C).
- 6 We recommend the use of an ACEI (or ARB if ACEI is not tolerated) as the first choice blood pressure lowering agent in patients with diabetes and CKD stages 4 and 5 and micro- or macroalbuminuria. We recommend that the dose of ACEI (or ARB) should be titrated to the maximum tolerated (Grade 1B).
- 7 We do not recommend the use of combinations of ACEIs and ARBs in patients with diabetes and CKD stages 4 and 5 (Grade 1C).
- 8 We suggest dietary advice, correction of acidosis and loop diuretic therapy to lower serum potassium as necessary in patients with diabetes and CKD stages 4 and 5 for safe use of an ACEI (or ARB). In the presence of hyperkalaemia, where bicarbonate is less than 22 mmol/l, sodium bicarbonate can be added at a dose of 500 mg twice daily: larger doses can be used but often require a concomitant increase or addition of a loop diuretic dose (not graded).
- 9 We suggest that patients with type 2 diabetes and advanced CKD should be advised to withhold RAAS-blocking drugs during periods of acute illness (not graded).

## **Audit standards**

The following are suggested as audit standards for the management of hypertension and RAAS blockade in patients with diabetes and CKD stages 4 and 5.

- 1 The proportion of patients with blood pressure less than or equal to 140/90 mmHg who have diabetes and CKD stages 4 and 5 with an ACR of less than 30 mg/mmol.
- 2 The proportion of patients with blood pressure less than or equal to 130/80 mmHg who have diabetes and CKD stages 4 and 5 with an ACR of greater than 30 mg/mmol.
- 3 The proportion of patients who are taking an ACEI or ARB and have a serum potassium greater than 5.5 mmol/l.
- 4 The proportion of patients who have a potassium level of greater than 5.5 mmol/l and are being seen by a dietitian.
- 5 The proportion of patients who are not on ACEIs or ARBs (or who are on a submaximal dosage) due to hyperkalaemia (greater than 5.5 mmol/l) or a decrease in estimated glomerular filtration rate (eGFR) of greater than 25%.
- 6 The number of patients with type 2 diabetes and CKD who are on dual blockade of the RAAS.

## **Areas that require further research**

The following areas lack good-quality evidence for the management of hypertension in patients with diabetes and CKD stages 4 and 5, and hence further research is necessary.

- 1 What is the effect of intensive blood pressure lowering (less than or equal to 130/80 mmHg) on renal and cardiac outcomes in patients with diabetes and CKD stages 4 and 5?
- 2 What is the impact of dual blockade with an ACEI and ARB on renal and cardiac outcomes in patients with diabetes, CKD stages 4 and 5 and albuminuria?
- 3 What is the impact of aldosterone blockade on renal and cardiac outcomes in patients who have diabetes and CKD stages 4 and 5?
- 4 What is the effect of long-term use of novel potassium binders together with RAAS blockade on renal and cardiac outcomes in patients with diabetes and CKD stages 4 and 5?



## 4 Hypertension management in patients with diabetes and chronic kidney disease who are on dialysis (stage 5D)

### Recommendations

The following are recommendations for blood pressure control in patients with diabetes and CKD stage 5D.

- 1 We recommend that ambulatory blood pressure measurement or home blood pressure measurement should be used to monitor blood pressure in patients with diabetes who are on dialysis (Grade 1C).
- 2 Where ambulatory blood pressure measurement or home measurement are not feasible to monitor blood pressure in patients with diabetes who are on dialysis, we suggest using pre-, intra- and post-dialysis blood pressure measurements for patients who are on haemodialysis, and using clinic blood pressure measurements for patients who are on peritoneal dialysis (Grade 2D).
- 3 We recommend volume control as a first-line management to optimise blood pressure control in patients with diabetes who are on dialysis (Grade 1B).
- 4 We suggest salt restriction to less than 5 g per day to optimise blood pressure control in patients with diabetes who are on dialysis (Grade 2C).
- 5 We suggest a target upright interdialytic blood pressure of less than 140/90 mmHg for patients with diabetes who are on dialysis. Individualisation of the blood pressure target may be indicated in other patients who are burdened with multiple comorbidities, in order to reduce adverse events of blood pressure lowering (Grade 2D).
- 6 We recommend that intradialytic hypotension should be avoided in patients with diabetes who are on haemodialysis (Grade 1B).
- 7 We suggest using ACEIs or ARBs (but not in combination), beta-blockers and calcium channel blockers to reduce cardiovascular complications in patients with diabetes and hypertension who are on dialysis (Grade 2B).
- 8 We suggest the use of diuretics in patients with diabetes who are on dialysis and have residual renal function (Grade 2C).

### Audit standards

The following are suggested as audit standards for blood pressure control in patients who have diabetes and CKD stage 5D.

- 1 The proportion of patients with diabetes who are on dialysis who achieve an upright interdialytic blood pressure target of less than 140/90 mmHg.
- 2 The proportion of patients with diabetes who are on dialysis who achieve an upright interdialytic blood pressure target of less than 140/90 mmHg without the use of blood pressure lowering medication.
- 3 The proportion of patients with diabetes who are on dialysis with an interdialytic blood pressure of greater than 140/90 mmHg who are not being treated with ACEIs, ARBs, beta-blockers or calcium channel blockers in whom such drugs are not contraindicated.

- 4 The proportion of patients with diabetes who are on dialysis and on diuretics following commencement of dialysis.

### **Areas that require further research**

The following areas lack good-quality evidence for blood pressure control in patients with diabetes and CKD stage 5D, and hence further research is necessary.

- 1 Which blood pressure measurement should be used to predict left ventricular hypertrophy (LVH) and mortality in patients with diabetes who are on dialysis: pre-dialysis, post-dialysis, home or ambulatory blood pressure measurement?
- 2 What is the optimal upright blood pressure target for patients with diabetes who are on dialysis?
- 3 Can bioimpedance spectroscopy devices be used to determine a target weight and predict the risk of cardiovascular morbidity and mortality in patients with diabetes who are on dialysis?
- 4 Does treatment with ACEIs, ARBs, beta-blockers or calcium channel blockers to lower blood pressure in patients with diabetes who are on dialysis reduce cardiovascular morbidity and mortality?
- 5 Is there a role for diuretic therapy in patients with diabetes who are on dialysis and have residual renal function?
- 6 Does strict salt restriction (to less than 5 g per day versus less than 6 g per day) in patients with diabetes who are on dialysis influence blood pressure control or cardiovascular outcome?

**Table 1** BP targets in patients with diabetes through stages of kidney function impairment

	Stage of kidney function impairment				
	Normal kidney function	Normal kidney function	CKD 1–3	CKD 4–5 (non-dialysis)	CKD 5 (dialysis)
	Normoalbuminuria	Microalbuminuria			
Type 1 diabetes in mmHg (evidence grade)	≤140/80 (2D)	≤130/80 (1B)	≤130/80 (1B)	≤140/90 (1B) ≤130/80 for proteinuric (2C)	≤140/90 (2D) (interdialytic BP)
Type 2 diabetes in mmHg (evidence grade)	≤140/90 (1D) ≤150/90 (2B) (for ≥80 years)	≤130/80 (2D)	≤130/80 (2D)	≤140/90 (1B) ≤130/80 for proteinuric (2C)	≤140/90 (2D) (interdialytic BP)

CKD = chronic kidney disease; BP = blood pressure.

## References

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## Declarations of interest

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- Stephen Bain has received honoraria, teaching and research sponsorship/grants from: Abbott, AstraZeneca, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GSK, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, Schering-Plough and Servier & Takeda. He has also received funding for the development of educational programmes from: Cardiff University, Doctors.net, Elsevier, OnMedica, OmniaMed and Medscape. He is a partner in Glycosmedia, which carries sponsorship declared on its website.
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- Andrew Frankel has received research grants, and he prepares educational materials and attends drug advisory boards for Boehringer Ingelheim/Lilly Alliance, AstraZeneca, Novo Nordisk, Merck and Johnson & Johnson.
- Parijat De has received honoraria for educational meetings from Astra Zeneca, Janssen, Boehringer Ingelheim, Novo, Sanofi, Novartis, Abbott, MSD, Takeda, Roche, Lilly, Ascensia, BD, Internis, GSK, Menarini, Bayer and Besins.
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