



# Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease

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# Contents

# 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.[1] More than a quarter of patients who are on dialysis in the UK have diabetes.[2] 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.[3]

This guidance is for the variety of clinicians who manage patients with diabetic kidney disease, including GPs and specialists in diabetes, cardiology and nephrology. It intends 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

## Search strategy

The recommendations are based on a systematic review that was carried out between October 2013 and December 2016. We searched the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase, using the following key terms: type 1 diabetes, type 2 diabetes, hypertension, albuminuria, microalbuminuria, microvascular complications, nephropathy, chronic kidney disease, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid antagonists.

**Table 1** Differentiating renal disease in diabetes

| | |
|---|---|
| **Diabetic nephropathy (DN)** | Damage to the glomerular capillaries in patients with diabetes mellitus resulting in albuminuria in the absence of other causes of albuminuria. |
| **Diabetes mellitus with chronic kidney disease (DM CKD)** | The presence for more than 3 months of structural renal abnormalities with reduced glomerular filtration in patients with diabetes mellitus. |

**Fig 1** Kidney Disease Improving Global Outcomes (KDIGO): Prognosis of CKD by GFR and albuminuria category
(www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf)

| **eGFR** (ml/min/1.73m$^2$) | **Urinary albumin:creatinine ratio** | | | **CKD grade** (Previously CKD stages 1–5) |
|---|---|---|---|---|
| | **<3 mg/mmol** | **3–29 mg/mmol** | **≥30 mg/mmol** | |
| | **<30 mg/g** | **30–299 mg/g** | **≥300 mg/g** | |
| >90 | **No CKD in the absence of markers of kidney damage** | | | G1 Normal or high GFR |
| 60–89 | | | | G2 Slight ↓ in GFR |
| 45–59 | | | | G3a Mild-moderate ↓ in GFR |
| 30–44 | | | | G3b Moderate-severe ↓ in GFR |
| 15–29 | | | | G4 Severe ↓ in GFR |
| <15 | | | | G5 Renal failure |
| | **A1** **Normal or slight** | **A2** **Microalbuminuria** | **A3** **Macroalbuminuria** | |

Increasing risk

Increasing risk

# 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 $m^2$) 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?

## Introduction

Despite improvements in prognosis, diabetic nephropathy in patients with type 1 diabetes remains a major cause of end-stage renal disease.[4] The onset of micro- and macroalbuminuria in patients with type 1 diabetes heralds not only an increased risk of renal disease, but also an increased risk of cardiovascular disease.[5] Early prospective studies suggested that around 30–50% of patients with type 1 diabetes will develop microalbuminuria, in whom a 6% increase in risk of coronary heart disease is seen per 5 mg increase in 24-hour albumin excretion rate (AER).[5] The natural history of diabetic nephropathy in patients with type 1 diabetes has, however, changed over the last 4 decades. Studies in the 1970s and 1980s suggested that progression to end-stage renal disease in patients with macroalbuminuria would occur within 7 years.[6] More recent follow-up data of significant numbers of patients with type 1 diabetes suggest that end-stage renal disease occurs in around 3% of patients who have had diabetes for 10 years[7] and in around 8% of patients who have had diabetes for 30 years.[8]

There is a significant body of evidence to suggest that over-activation of the RAAS plays a major role in the pathogenesis of diabetic nephropathy in patients with type 1 diabetes.[9] Over-activation of the RAAS is observed in patients with type 1 diabetes, even in the absence of diabetic nephropathy.[10] Angiotensin II-mediated increase in intraglomerular pressure appears to be an important mechanism by which renal disease progresses in patients with type 1 diabetes who have diabetic nephropathy,[11,12] and reductions in intraglomerular pressure may ameliorate glomerular injury. Angiotensin II also has mitogenic effects that may lead to mesangial expansion

that is characteristic of diabetic nephropathy.[13] Over-activation of the RAAS may be mediated by hyperglycaemia,[10] and blockade of the RAAS may in turn be impaired by hyperglycaemia.[14] RAAS over-activation is also described in patients with type 1 diabetes who have glomerular hyperfiltration.[15]

## Hypertension in patients with type 1 diabetes

Risk factors for the development of nephropathy in patients with type 1 diabetes include increasing age, duration of diabetes, male gender and hyperglycaemia.[16] The possible role of genetic factors has long been hypothesised, due to the observation that a family history of hypertension appears to predict the development of nephropathy.[17] It has been suggested that a family history of hypertension could be the basis for more intensive antihypertensive therapy in patients with type 1 diabetes.

The risk factor that has the strongest association with progression of diabetic nephropathy is hypertension. Prospective evaluation of 148 patients with type 1 diabetes who were normoalbuminuric showed that patients who developed microalbuminuria had a significantly higher baseline blood pressure compared with patients who remained normoalbuminuric (138/82 mmHg versus 123/73 mmHg).[18] Similarly, follow-up of a Scandinavian cohort of over 300 children and adolescents with type 1 diabetes showed that systolic blood pressure was a major risk factor for the development of microalbuminuria over 5 years.[19] More recently, analysis of 1,441 patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) cohorts suggests that systolic blood pressure levels below 120 mmHg are associated with a 41% reduction in macroalbuminuria (95% confidence interval [CI] 5% to 63%) and a 68% reduction in CKD stage 3 (95% CI 25% to 84%).[20]

The threshold for diagnosis of hypertension in patients with type 1 diabetes varies according to national and international guidelines. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest a blood pressure goal of less than or equal to 140/90 mmHg if urinary AER is under 30 mg per 24 hours, or less than or equal to 130/80 mmHg if AER exceeds 30 mg per 24 hours, although they do not distinguish between type 1 and type 2 diabetes.[21] National Institute for Health and Care Excellence (NICE) guidelines on the management of patients with type 1 diabetes suggest a blood pressure target of 130/80 mmHg in a patient with albuminuria (135/85 mmHg in patients who were normoalbuminuric).[22] The American Diabetes Association and American Society of Nephrology consensus guidelines suggest that a blood pressure of less than 140/90 mmHg should be attained in all patients with diabetes and renal disease, but they do not suggest a lower target and they do not distinguish between type 1 and type 2 diabetes.[23] In children with type 1 diabetes, the International Society for Pediatric and Adolescent Diabetes (ISPAD) defines hypertension 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, and suggests a target blood pressure of 130/80 mmHg.[24] Given the younger age of many adult patients with type 1 diabetes and the consequent longer lifetime blood pressure burden, we support the targets of 130–135/80–85 mmHg according to the presence or absence of albuminuria.

The role of home and ambulatory blood pressure measurement in the diagnosis and management of hypertension in patients with type 1 diabetes and nephropathy is unclear. Small cohort studies of children and adults with type 1 diabetes suggest that an increase in nocturnal systolic blood pressure or blunting of nocturnal dipping is an important factor in progression to microalbuminuria in patients with type 1 diabetes.[25,26] Due to a lack of robust evidence, no guidelines currently recommend ambulatory or home blood pressure monitoring to diagnose or manage hypertension in patients with type 1 diabetes, although the ISPAD guidelines suggest that there may be a role for 24-hour blood pressure monitoring in the diagnosis of hypertension in children.[24]

The importance of lifestyle measures (weight loss and salt intake reduction) are highlighted by a number of guidelines, and indeed a recent study suggests that lower sodium intake may improve the efficacy of RAAS blockade.[27]

There is evidence to suggest that management of blood pressure in patients with type 1 diabetes may be suboptimal. In a large cross-sectional study of patients with type 1 diabetes in Scandinavia, patients on antihypertensives who were achieving a blood pressure below 130/80 mmHg varied according to degree of albuminuria.[28] Blood pressure above 130/80 mmHg was seen in 74.6% of patients who were normoalbuminuric; 71.2% of patients who were microalbuminuric; 80.0% of patients who were macroalbuminuric; 88.1% of patients who were treated with dialysis; and 90.4% of patients who had received a renal transplant.

An important point to consider is the presence of postural hypotension in patients with type 1 diabetes. Autonomic neuropathy is often associated with postural hypotension, and patients with type 1 diabetes should have their supine and standing blood pressure checked. A significant drop in blood pressure on standing (greater than 20 mmHg) might alert the clinician to ensure that care is taken not to treat the patient's blood pressure over-aggressively. We advocate the use of upright (sitting or standing) blood pressure as the target blood pressure, as per British Hypertension Society guidelines.[29]

## Modulation of the RAAS in patients with type 1 diabetes

### a Normoalbuminuria

There has been some interest in the use of agents that block the RAAS in the primary prevention of diabetic renal disease. The use of ACEIs has been tested in patients who are normotensive and normoalbuminuric, and there is little evidence of a protective effect on the development of diabetic nephropathy. Importantly, however, many of these studies have used definitions of blood pressure that would now be considered to be too high. A multicentre European study examined 530 patients with type 1 diabetes and blood pressure under 155/90 mmHg.[30] The study found that, during 2 years of treatment with lisinopril versus placebo, the ACEI showed no protective effect against the development of microalbuminuria. Similar findings have been shown with candesartan.[31] Furthermore, a renal biopsy study of 285 patients with type 1 diabetes who were normotensive and normoalbuminuric showed no effect of enalapril or losartan in the development of renal lesions.[32] One short study did suggest a significant reduction in albumin:creatinine ratio (ACR) in 89 patients with type 1 diabetes who were normotensive and normoalbuminuric and who were treated with placebo or perindopril for 4 months.[33] Currently, however, the use of ACE inhibition in patients with type 1 diabetes who are normotensive and normoalbuminuric cannot be recommended on the basis of trial evidence.

### b Microalbuminuria

The onset of microalbuminuria in a patient with type 1 diabetes was once thought to lead to inevitable progression to macroalbuminuria and thence to progressive kidney disease.[34] More recently, however, it has become clearer that microalbuminuria may remit in up to 40% of patients with type 1 diabetes.[35–37] In addition, microalbuminuria may not progress to macroalbuminuria in a significant number of patients.[38] In the Renin-Angiotensin System Study, onset of microalbuminuria correlated poorly with renal biopsy findings of diabetic glomerulopathy.[32] Previous studies have also described progressive renal impairment without microalbuminuria in patients with type 1 diabetes.[39,40]

In adolescents with type 1 diabetes, modest but persistent elevations of ACR in the normal range may be associated with progression to persistent microalbuminuria.[41] Furthermore, a persistently raised ACR at the upper limit of the reference range in adolescents is associated with increasing aortic intima-media thickening, which is a sensitive marker of early atherosclerosis.[42]

It is, however, recognised that the presence of microalbuminuria may not be the ideal risk marker for progressive renal dysfunction in patients with type 1 diabetes.[43] Microalbuminuria may progress, stabilise or regress, and factors that govern this change are unclear, especially in adolescents and young adults who have improved glycaemia control.[36] Therefore, more reliable biomarkers or genetic markers are needed to predict which patients are at the greatest risk of progressive renal disease. Many studies have looked at putative genetic loci within the RAAS for a genetic predisposition to diabetic nephropathy, but no clear correlation with nephropathy risk has been found in most studies.[44] Some authorities suggest that determination of serum cystatin C in patients with diabetes and albuminuria may provide better risk stratification of subsequent end-stage renal disease than determination of serum creatinine.[45] Serum concentration of tumour necrosis factor (TNF) receptors 1 or 2 (TNFR1, TNFR2) may also be predictors of future development of CKD stage 3 in patients with type 1 diabetes.[46] If patients who are at high risk of progression to diabetic nephropathy could be identified early, more intensive systematic therapy could be considered, for example pancreas transplantation.[47]

There are few long-term studies that suggest that treating patients with type 1 diabetes, microalbuminuria and normal blood pressure reduces end-stage renal disease. There are, however, more short-term studies that focus on a change in AER rather than a change in renal function. A multicentre European study examined 79 patients with microalbuminuria and blood pressure below 155/90 mmHg, and found a significant reduction in AER in the group of patients who were treated with lisinopril compared with the patients who were treated with a placebo (-34.2 mg/min).[28] In an 8-year follow-up of a small number of patients with type 1 diabetes and microalbuminuria, 10% of patients who were treated with captopril progressed to macroalbuminuria, compared with 40% of patients who were treated with a placebo;[48] therefore, treatment with captopril was associated with a reduction in progression of renal disease. Similarly, the Microalbuminuria Collaborative Study Group treated 235 patients with microalbuminuria and blood pressure less than 160/90 mmHg with placebo or captopril.[49] Progression to macroalbuminuria was seen in 21.9% of the placebo-treated group compared with 7.2% of the captopril-treated group (the risk reduction was 69%). The Ace-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects (ATLANTIS) study used ramipril versus placebo in 140 patients with type 1 diabetes and microalbuminuria and normotension, and it showed regression to normoalbuminuria in 20% of the ramipril-treated group, compared with 4% of the placebo-treated group.[50] A further study of 20 patients with type 1 diabetes, microalbuminuria and normal blood pressure who were treated with placebo or enalapril showed a reduction in progression to macroalbuminuria and a significant number of patients regressed to normoalbuminuria.[51]

RAAS blockade may have positive longer-term impacts on renal haemodynamics in people with type 1 diabetes even when therapy is stopped. In the 5-year Renin-Angiotensin System Study, patients who were on RAAS blockade during the trial, but who stopped therapy after the trial, showed significantly greater renal haemodynamic responses to clamped hyperglycaemia and flow-mediated vasodilatation, which suggests that RAAS blockade has sustained, long-term protective effects.[32]

In patients who are hypertensive and have microalbuminuria, however, there is relatively strong evidence to suggest that ACE inhibition slows progression of diabetic nephropathy in patients with type 1 diabetes and microalbuminuria.[52] Meta-analysis suggests that ACEIs reduce progression of microalbuminuria to macroalbuminuria (odds ratio 0.38; 95% CI 0.25 to 0.57).[53] Outcomes in terms of the prevention of end-stage renal disease, however, have not been reported.

### c Macroalbuminuria

For decades, the presence of macroalbuminuria in patients with type 1 diabetes has been considered to be a stage of irreversible kidney disease. However, recent long-term follow-up of 159 patients with type 1 diabetes in the Diabetes Control and Complications Trial / Epidemiology

of Diabetes Interventions and Complications (DCCT/EDIC) study shows that 10 years after onset of macroalbuminuria, the cumulative incidence of reduction to microalbuminuria was 52%.[38] The cumulative incidence of CKD stage 3 (estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m$^2$) was 32%, and the cumulative incidence of end-stage renal disease was 16% after 10 years, with better glucose and blood pressure control being the main factors associated with a lower risk of CKD progression. Therefore, while macroalbuminuria appears to be an important renal disease risk marker, it is far from inevitable that relentless progression to end-stage renal disease will occur.

Seminal studies in the 1980s suggested that early aggressive antihypertensive therapy could reduce the rate of decline of renal function in patients with diabetic nephropathy,[54] and further studies of patients with type 1 diabetes, hypertension and macroalbuminuria demonstrated the specific protective effects of ACEI drugs on progression of albuminuria and renal disease.[55–57] Meta-analysis of these studies suggest a long-term beneficial effect on preventing doubling of serum creatinine and development of end-stage renal disease.[58]

### d Use of other agents that modulate the RAAS

Candesartan has been studied in patients with type 1 diabetes and diabetic retinopathy.[14,59] A beneficial effect of candesartan was seen in the progression of retinopathy; although in one study, this was limited to patients with poor glucose control (glycated haemoglobin (haemoglobin A1c) greater than 7.5%).[14] Studies using angiotensin II receptor blockers (ARBs) have not been widely reported in type 1 diabetes and nephropathy. In a small Danish study, losartan was seen to attenuate AER in patients with type 1 diabetes.[60] In the Renin-Angiotensin System Study, however,[32] use of losartan did not appear to protect patients from developing microalbuminuria: indeed 17% of patients on losartan developed microalbuminuria compared with 6% on a placebo and 4% on enalapril over 5 years.

It has been suggested that aldosterone escape during long-term RAAS blockade may be a mechanism by which ACE inhibition fails to prevent progressive renal disease in patients with type 1 diabetes.[61] Thus the use of aldosterone antagonists in such patients may be useful. Spironolactone has been investigated in a small study of patients with type 1 diabetes and microalbuminuria.[62] Spironolactone added to standard antihypertensive therapy reduced AER by 60%, with no drop in blood pressure and a minor drop in eGFR, although severe hyperkalaemia was seen in a small number of patients.

Aliskiren, the direct renin inhibitor, has been trialled in patients with type 2 diabetes and diabetic nephropathy, and no significant effect on renal outcomes has been noted, although a reduction in AER has been noted.[63] A small study of patients with type 1 diabetes who were treated with aliskiren shows positive effects on renal haemodynamic indices and systemic vascular responses.[64] Furthermore, dual blockade with ACEI also shows beneficial effects on arterial compliance, flow-mediated dilatation and renal vasodilatation.[65] Further study of this group of drugs in type 1 diabetes is warranted.

Early studies of beta-blockade in patients with diabetic nephropathy and type 1 diabetes suggest an equivalent effect to ACEI.[66] This is some suggestion that non-dihydropyridine calcium channel blockade may have some of the benefits of dihydropyridine calcium channel blockers in the management of diabetic nephropathy.[67]

Through their ability to reduce intraglomerular pressure, blood pressure and uric acid levels, sodium glucose cotransporter-2 (SGLT-2) inhibitors may offer the possibility of renal protection. One study suggests that SGLT-2 inhibitors can offer a reduction in glomerular hyperfiltration.[68] Recent analysis of the Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG) study suggests significant renoprotection.[69] However, the risk that these agents can cause ketoacidosis when they are given to patients with type 1 diabetes may limit their potential use in this group of patients.[70]

## e Use of dual blockade in patients with type 1 diabetes and diabetic nephropathy

Meta-analysis of a number of these studies of patients with type 2 diabetes and nephropathy suggest a reduction in albuminuria, but at the expense of an increased risk of severe hyperkalaemia and episodes of acute kidney injury (AKI).[71,72,73] More recently, however, a large randomised controlled trial involving patients with type 2 diabetes suggests that RAAS dual blockade has no benefit in terms of mortality, but that it may increase the risk of hyperkalaemia and AKI.[74]

It is currently unclear whether there is a role for dual blockade in patients who have type 1 diabetes and a normal eGFR (greater than 60 ml/min/1.73m$^2$) in whom albuminuria is uncontrolled or increasing. While this may reduce albuminuria, there is no evidence of a reduction in other renal or cardiovascular end points.

In type 1 diabetes the pathogenic processes that occur in the development and progression of diabetic nephropathy may be very different. Use of ACEIs is associated with a compensatory increase in plasma renin activity, and this effect may be ameliorated by the use of ARB drugs. There are, however, few studies on the use of dual RAAS blockade and outcomes in type 1 diabetes. One small study from India of 30 patients who were treated for a short period with telmisartan and ramipril resulted in a reduction in ACR and blood pressure, with a slightly increased risk of hyperkalaemia.[75] A further small study of 21 patients with type 1 diabetes showed that the addition of irbesartan to ACEI therapy in patients with type 1 diabetes resulted in a 37% reduction in AER, along with significant reductions in blood pressure.[76] Further studies of dual RAAS blockade in type 1 diabetes are needed.

## f When should RAAS blockade be stopped?

The use of RAAS-blocking drugs in early pregnancy has been associated with harm to the fetus, including cardiovascular, neurological and renal malformations,[77] although more recent surveys do not suggest that there is a high risk of these problems occurring.[78] Pregnancy is associated with a high risk of progression of diabetic nephropathy in patients with type 1 diabetes, and the benefits of RAAS blockade in such patients may outweigh the risks, but current advice is that RAAS-blocking drugs should be stopped when pregnancy is confirmed, and indeed when pregnancy is planned.

Drugs that block the RAAS reduce intraglomerular pressure and may lead to a rise in serum creatinine of up to 30%, which should then stabilise.[79] Some studies suggest that clinically significant renal artery stenosis may be quite common among people with diabetes, especially those with type 2 diabetes.[80] While the use of drugs that modulate the RAAS may increase the risk of deterioration in renal function in patients with renovascular disease, in practice such deterioration is rare.[81,82]

RAAS blockade can lead to hyperkalaemia, which may be managed by dietary methods, diuretics or use of sodium bicarbonate. However, if the hyperkalaemia is severe and refractory to these measures, RAAS blockade may need to be stopped or reduced.[83] A further possible clinical scenario is a patient with type 1 diabetes having deteriorating renal function despite having well-controlled blood pressure on ACEI drugs. Once renal dysfunction continues to escape, despite optimal therapy, a decision may need to be made about cessation of ACEI therapy, especially if there may be a degree of ischaemic nephropathy, renovascular disease or postural hypotension. RAAS blockade may also increase the risk of AKI in patients with diabetes, and advice to patients to stop these drugs during periods of acute illness should be considered.[84]

# 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 $m^2$) 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?

## Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease and it is characterised by a triad of persistent albuminuria, hypertension and a decline in glomerular filtration rate (GFR). The presence of diabetic nephropathy increases cardiovascular morbidity and mortality and also increases progression to end-stage renal disease.[85–87] After approximately 20–25 years, 40% of patients with type 2 diabetes develop evidence of diabetic nephropathy.[88] Both hypertension and hyperglycaemia are strong risk factors in determining progression of end-stage renal disease and cardiovascular complications in diabetic nephropathy. Microalbuminuria is one of the earliest manifestations of kidney disease in patients with diabetes and it predicts increased cardiovascular morbidity and mortality in patients with both type 1 and type 2 diabetes.[89,90] The prevalence of microalbuminuria in patients who have had type 2 diabetes for 10 years is 25%, with an annual rate of progression to overt nephropathy of approximately 3%.[88]

The risk of new as well as progressive microalbuminuria is significantly associated with high blood pressure.[91] In patients with diabetes, cardiovascular and renal outcomes are adversely affected by the presence of hypertension and albuminuria.[92] Thus controlling blood pressure and reducing albuminuria are important treatment goals in diabetic nephropathy. Baseline blood pressure levels have been shown to be a powerful determinant of subsequent kidney failure in large population-based studies.[93,94] Unlike patients with type 1 diabetes, a high proportion of patients with type 2 diabetes often have microalbuminuria and overt nephropathy at diagnosis. Without intervention, 20–40% of patients with type 2 diabetes and microalbuminuria will progress to overt

nephropathy. After 20 years of overt nephropathy, approximately 20% of those patients will progress to end-stage renal disease.

## The renin-angiotensin-aldosterone system

Dysregulation of the renin-angiotensin-aldosterone system (RAAS) plays a vital role in the pathogenesis of diabetic nephropathy, including pathogenesis of both micro- and macrovascular complications. Hyperglycaemia is associated with increased production of angiotensin II following RAAS over-activation in glomerular mesangial cells.[95] Thus, mechanisms to block the RAAS are an important therapeutic target in patients with type 2 diabetes and nephropathy.

## Hypertension in patients with type 2 diabetes

In nearly one-third of patients with type 2 diabetes, hypertension is present at the time of their diagnosis. Hypertension and type 2 diabetes may be related to underlying diabetic nephropathy, to co-existing essential hypertension or to renovascular disease, or it may be part of the complex insulin resistance syndrome. Hypertension in patients with type 2 diabetes is generally associated with expanded plasma volume, increased peripheral vascular resistance and low renin activity.[96]

The threshold for diagnosis and aims for hypertension control in patients with type 2 diabetes vary according to national and international guidelines. In the UK, for the management of hypertension in patients with diabetes and for those with a urinary albumin:creatinine ratio (ACR) of 70 mg/mmol or more and CKD, National Institute for Health and Care Excellence (NICE) guidance recommends a target blood pressure of less than 130/80 mmHg.[29] The American Diabetes Association and the American Society of Nephrology recommend a blood pressure of less than 140/90 mmHg in all patients with type 2 diabetes and renal disease.[97] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a blood pressure of less than or equal to 140/90 mmHg in those who have an albumin excretion rate (AER) of less than 30 mg per 24 hours (ACR greater than 3 mg/mmol), or less than or equal to 130/80 mmHg if the AER is greater than 30 mg per 24 hours (ACR greater than 3 mg/mmol) in patients with type 2 diabetes.[21]

There is little evidence base for recommending blood pressure targets in older patients who have CKD. Most randomised controlled trials excluded patients who were over 70 years of age (mean age 65 years: about 2.5% were older than 85 years of age) but some indirect inferences can be drawn from studies of older populations who do not specifically have CKD. While there is some evidence regarding the treatment of high blood pressure in much older people (that is, older than 80 years of age) from the Hypertension in the Very Elderly Trial (HYVET),[98] it applies to a blood pressure target of 150/80 mmHg in patients with CKD who have an eGFR greater than 40 ml/min/1.73m$^2$. The KDIGO guidelines[21] suggests tailoring blood pressure treatment in older patients with CKD to consider age, comorbidities and other therapies, with a gradual escalation of treatment and close attention to electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and side effects of medications.

Thus it would seem reasonable to suggest a target upright systolic blood pressure of no less than 150 mmHg in much older patients with CKD, taking into account side effects of medications and comorbidities.

## The role of home and ambulatory blood pressure measurement

Although home and ambulatory blood pressure monitoring is thought to be more representative of real-life blood pressure, their exact role in the diagnosis and management of hypertension is unclear because a limited number of studies have been conducted in patients with type 2 diabetes who have CKD. However, it is recognised that high ambulatory blood pressure

measurement systolic pressures and nocturnal non-dipping are associated with increased mortality and a decline in eGFR.[99–101] A small study of ambulatory blood pressure measurement in patients with CKD, where 436 patients who were hypertensive were prospectively followed up, showed that it was much more accurate in predicting both renal and cardiovascular outcomes than office blood pressure.[102] Self blood pressure monitoring and ambulatory blood pressure measurement utilises oscillometric assessment of blood pressure at the elbow, which may be influenced by irregularities of pulse and high pulse pressures. In the UK, NICE guidelines recommend confirming hypertension with ambulatory home monitoring before starting or increasing antihypertensive agents.[29] Given the technical and economic barriers, and the lack of randomised controlled trials using these methods for blood pressure assessment in patients with type 2 diabetes with CKD, these methods are not currently recommended.

## Lifestyle modification and impact on blood pressure

There is good evidence from a number of observational studies and randomised controlled trials that factors like salt intake, weight and body mass index (BMI), exercise frequency and alcohol intake all have a significant impact on blood pressure levels.[103–106]

### a Salt intake

The KDIGO guidelines suggest lowering salt intake to less than 90 mmol of sodium per day (less than 2 g of sodium, which corresponds to 5 g of sodium chloride). High salt intake has a greater impact on blood pressure for patients with diabetes, especially in patients with CKD, due to their reduced ability to excrete salt load in their urine. Restricting salt intake lowers blood pressure by a moderate amount, as shown in a systemic review of seven trials where salt intake was restricted to 4–6 g (70–100 mmol), systolic blood pressure was reduced by 4.7 mmHg and diastolic blood pressure was reduced by 2.5 mmHg.[107]

Given that salt restriction is inexpensive and it helps to lower blood pressure in the general population, despite a lack of availability of large-scale, long-term randomised controlled trials of salt restriction in patients with CKD, there is no reason to believe that blood pressure reduction through salt reduction will not be beneficial, although it would add to the dietary restrictions for managing diabetes. A low-salt diet has been shown to reduce blood pressure and albuminuria in the short term in patients who are on angiotensin receptor blockers (ARBs) and it may be a consideration for those with high blood pressure who have had a poor response to ACEIs or ARBs.[108,109]

### b Weight and BMI

The KDIGO guidelines recommend achieving or maintaining a healthy weight (BMI 20–25). Some observational studies, but not randomised trials, suggest that weight loss is likely to improve blood pressure in patients with CKD, but there is a lack of high-quality randomised controlled trials in this area.

Although obesity has been proposed to be a potential mediator of CKD progression, trials are conflicting and reliable data remain sparse. There is no role of weight loss diets in CKD either. Overall, achieving a healthy body weight will improve blood pressure levels and prognosis in CKD, particularly in the early stages (stages 1–2). Malnutrition needs to be avoided in more advanced stages of CKD.[110]

### c Exercise programme

The KDIGO guidelines recommend undertaking an exercise programme that is compatible with cardiovascular health and tolerance, aiming for at least 30 minutes of exercise five times per week. Increased physical exercise has a broad range of positive health outcomes in the general population. However, there are no randomised controlled trials in the CKD population: there are

mostly observation studies. The benefits of exercise on blood pressure and on general health are likely to be similar in the CKD population to the benefits in the general population.[111]

### d Alcohol intake

The KDIGO guidelines suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. Most of the effects of alcohol reduction are related to its effect on blood pressure; that is, suggesting that restricting alcohol intake would lower blood pressure. All the trial evidence is mostly related to the general population and there are no specific data on patients with CKD, but the effects of alcohol intake on blood pressure are expected to be similar.[112]

## Blood pressure lowering agents

In patients with type 2 diabetes and CKD, three or more blood pressure agents are frequently required. There is increasing emphasis on individualisation of therapy. Eventually, the choice of agent is less important than the actual reduction in blood pressure that is achieved. There is little evidence to support the use of any particular agent in controlling blood pressure in CKD, nor are there any data to suggest the choice of second- or third-line medications. The exception to this rule is the use of ACEIs or ARBs in patients with CKD who have albuminuria. ACEIs and ARBs have each been shown to be effective in delaying disease progression in patients with type 2 diabetes who have microalbuminuria or established diabetic nephropathy. There is a need to escalate to the maximal doses of ACEI or ARB in patients who have diabetes and albuminuria before moving on to additional agents in order to achieve the required blood pressure targets. However, there is no evidence that these agents are effective in the primary prevention of diabetic nephropathy. The use of ACEIs or ARBs in patients with type 2 diabetes reduces microalbuminuria and retards the progressive loss of renal function.[56,113–115] ARBs are said to provide renoprotection over and above their blood pressure lowering effect and short-term albuminuria reduction, and they are said to have a long-term favourable effect on renal prognosis.[116]

## RAAS blockade in patients with type 2 diabetes without albuminuria

The use of RAAS blockade has significant benefits on cardiovascular and renal end points in people with diabetes, independent of their blood pressure lowering effect, as shown in the Heart Outcomes Prevention Evaluation (HOPE) trial and the European trial on reduction of cardiac events with perindopril in stable coronary artery disease.[117,118] Whereas most guidelines favour the use of RAAS blockade as first-line treatment for people with diabetes, hypertension and CKD (the American Diabetes Association, the American Society of Hypertension, the International Society of Hypertension),[119,120] the European Society of Cardiology / European Society of Hypertension guidelines from 2013 and the eighth Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure from 2014 recommend the use of *any* class of antihypertensive agent in people with diabetes in the *absence* of albuminuria, but suggest the use of RAAS blockade as first-line treatment *only* in the presence of albuminuria.[121,122]

This is based on the findings of 19 randomised controlled trials that enrolled 25,414 participants with diabetes, with a total of 95,910 patient years of follow-up. The results of this study from head-to-head randomised trials of RAAS blockade versus other antihypertensive agents failed to show superiority of RAAS blockade in people with diabetes and *no albuminuria*, and it suggested that any class of antihypertensive agents can be used in such patients.[123]

## RAAS blockade in patients with type 2 diabetes and albuminuria or microalbuminuria

In the UK, NICE guidance suggests offering a low-cost RAAS antagonist to people with CKD and diabetes who have: an ACR of 3 mg/mmol or more; hypertension and an ACR of 30 mg/mmol or more; or an ACR of 70 mg/mmol or more irrespective of hypertension or cardiovascular disease.[124] The favourable effects of RAAS blockade have been seen mainly in placebo controlled trials[115,117] and it has been postulated that the benefits of RAAS blockade on renal outcomes was probably as a result of their blood pressure lowering effect.[125] Several major trials have also demonstrated clear benefits of ARB use in patients who have diabetic nephropathy.[126,127]

## Use of ACEIs and ARBs (dual blockade) in diabetic nephropathy

ACEIs and ARBs block the RAAS at different sites and, in theory, dual blockade should provide more effective and complete blockade of the RAAS. The rationale for dual blockade is based on a phenomenon called 'angiotensin II escape', whereby evidence suggests that standard doses of ACEIs only offer a partial blockade of the angiotensin-converting enzyme (ACE).[128] It is said that enzymes such as chymase and cathepsin G can generate angiotensin II from angiotensinogen and other peptide substrates.[129]

Several early studies had suggested that using a combination of ACEI/ARB provided additional benefit in diabetic nephropathy in terms of surrogate albuminuria lowering. However, there remains substantial controversy about whether ACEIs and ARBs should be combined, given that most of these studies were small in size and short in duration.

In one meta-analysis of 10 trials, 156 patients received a combination of ACEI/ARB and 159 received an ACEI only (the duration of the study was 8–12 weeks). The combination was shown to reduce albuminuria at the expense of statistically and clinically significant reductions in eGFR. There was a suggestion that this decrease could be secondary to a reduction in blood pressure alone.[71] Most of the evidence base for combination dual blockade therapy initially came from studies about heart failure without any long-term data to support it (the candesartan and lisinopril microalbuminuria (CALM) study).[130] This study evaluated the effects of dual blockade of candesartan and lisinopril on blood pressure and microalbuminuria in 199 patients with type 2 diabetes (the duration of the study was 24 weeks). At the end of the study, combination therapy was found to be significantly more effective in reducing urinary ACR (50% with combination, 24% with candesartan and 39% with Lisinopril) and diastolic blood pressure (16.3 mmHg, 10.4 mmHg and 10.7 mmHg reduction, respectively) than either agent alone. Criticisms of some of these studies were that there were no long-term follow-up data and that maximal doses of ACEIs were not used. It is also questionable whether the effects were specifically related to combination therapy or whether it was blood pressure reduction *per se* that was instrumental.

The ONTARGET study involved telmisartan and ramipril, and showed that the primary renal outcome (ie dialysis, doubling of serum creatinine and death) was similar for telmisartan (13.4%) and ramipril (13.5%), but was increased with combination therapy (14.5%, p=0.037). The combination therapy, although associated with reduced albuminuria, caused the greatest decline in eGFR.[131]

The KDIGO guidelines provide specific advice on dual blockade.[21,132] In the UK, a NICE guideline explicitly states that combination therapy should not be used. The European Renal Best Practice working group has the same viewpoint as NICE.[133] The Canadian Health Education Programme's (CHEP's) 2009 recommendation advised against the use of dual blockade for patients with non-proteinuric CKD or in patients with diabetes and normal urinary albumin levels.[134]

Overall, therefore, there is no current evidence to suggest a beneficial effect of ACEI/ARB combination on the progression of diabetic nephropathy. Instead, combination therapy resulted in clinically significant decreases in eGFR and hyperkalaemia.[135] In one meta-analysis involving 17,337 patients, the adverse effects of dual blockade revealed significantly high rates of

discontinuation because of a worsening of renal function, hyperkalaemia and symptomatic hypotension.[136]

It is to be noted, however, that most studies published so far with regard to dual blockade have involved patients with *normal renal function* who did not have a clinically significant rise in serum potassium or creatinine with dual blockade. However, in real life, widespread use of these agents would most likely involve patients with resistant hypertension with chronic renal impairment, and such patients therefore will tend to have more of these side effects.

## Aldosterone blockade in patients with diabetic nephropathy

Aldosterone, the principal physiological mineralocorticoid, has deleterious effects on both the cardiovascular system and the kidneys. There is evidence to suggest that initial RAAS blockade suppresses aldosterone levels. However, due to the phenomenon of aldosterone escape, aldosterone levels rise subsequently and can often exceed the baseline. ACEIs or ARBs do not directly block the effects of aldosterone at the receptor level.[137]

Most evidence of the use of aldosterone antagonists like spironolactone, eplerenone and (more recently) finerenone come from heart failure trials. In one study of type 2 diabetes patient with early nephropathy and normal renal function, adding spironolactone to ACEI treatment was shown to be clinically useful and safe for patients who showed aldosterone escape during ACEI treatment and who no longer showed maximal antiproteinuric effects of ACE inhibition.[138,139] In another study of patients with type 2 diabetes, macroalbuminuria and serum creatinine of less than 160 µmol/l, treatment with spironolactone was found to be superior to cilazapril in reducing albuminuria.[140] In that study, 50 mg of spironolactone was used and blood pressure of less than 135/85 mmHg was pre-treated with atenolol and hydrochlorothiazide before randomisation. The authors concluded that the superior effect of spironolactone was independent of its hypotensive effect, although 15% of patients had to discontinue spironolactone because of hyperkalaemia.

There is also evidence for additive effects of eplerenone (an aldosterone antagonist that does not have the oestrogenic side effects of spironolactone) like in the other aldosterone antagonist trials. Eplerenone was found to have beneficial effects on microalbuminuria in patients with type 2 diabetes when it was added to enalapril, although there was a much higher incidence of hyperkalaemia.[141] In the largest randomised controlled trial available using eplerenone, patients with CKD, elevated urinary albumin levels and type 2 diabetes (177 patients) received 50–100 mg of eplerenone and 91 patients received a placebo. The addition of eplerenone to enalapril 20 mg per day resulted in a 40–50% reduction in AER by 12 weeks in the eplerenone group, but by less than 10% in the placebo group. Small reductions in eGFR and systolic blood pressure were noted, as was hyperkalaemia.[142]

More recently, finerenone, a novel non-steroidal mineralocorticoid antagonist with greater receptor selectivity than spironolactone and eplerenone, has been shown to provide a greater reduction in albuminuria and end organ damage, compared with spironolactone or eplerenone. This was shown in the Mineralocorticoid Receptor Antagonist Tolerability – diabetic nephropathy (ARTS-DN) study involving 1,501 patients who were already receiving an ACEI or ARB (the mean age of the patients was 64.2 years, 37% of the patients had a urinary ACR greater than 30 mg/mmol and 40% had an eGFR of 60 ml/min/1.73m$^2$ or lower). Finerenone reduced the urinary ACR at day 90 (relative to the baseline) more significantly than the placebo, and the pre-specified secondary outcome of hyperkalaemia leading to discontinuation was not observed either in the placebo or the finerenone group at various dosages. Also, there was no difference in terms of the incidence of a greater than 30% decrease of eGFR in either group. Thus 2.5–10 mg finerenone per day reduced albuminuria from the baseline in patients with CKD and heart failure with a lower incidence of hyperkalaemia than spironolactone. It has thus been postulated that this new mineralocorticoid receptor antagonist may be able to address the unmet medical need of safely managing albuminuria without effecting serum potassium in patients with type 2 diabetes who

have nephropathy. The strength of the study is that there was only a modest reduction in blood pressure at the highest dose of finerenone: quite unlike any other mineralocorticoid antagonist study in the past. The limitations of the study, however, include its short duration, the lack of a control group and that 60% of patients had an eGFR above 60 ml/min/1.73m$^2$, which put them at relatively low risk of hyperkalaemia.[143]

From the above evidence, it may be reasonable to consider adding in an aldosterone antagonist, particularly for patients with an eGFR of greater than 60 ml/min/1.73m$^2$ and a serum potassium of less than 5 mmol with worsening albuminuria despite being on a maximal dose of ACEI or ARB.

## Use of direct renin inhibitors in diabetic nephropathy

The use of aliskiren in patients with type 2 diabetes and nephropathy has been shown to reduce AER, although no significant effects on renal outcomes have been noted. In the ALTITUDE trial, where aliskiren or a matching placebo was used on top of an ACEI or ARB in patients with diabetic nephropathy, there were significant reductions in albuminuria but the trial was stopped early due to the low likelihood of ever demonstrating a benefit and the suggestion of an increased risk of non-fatal stroke, renal complications, hyperkalaemia and hypotension.[144] The drug has subsequently been withdrawn from the market.

In another trial involving 599 patients, aliskiren was used either alone or in combination with losartan for 6 months. This resulted in a reduction of urinary ACR by 20% compared with the use of losartan alone. There were small differences in blood pressure between the two groups but no difference was found between the rates of adverse events.[145] Direct renin inhibitors are not currently recommended for use in diabetic nephropathy.

## When should RAAS blockade be stopped?

Although ACEIs and ARBs are valuable blood pressure lowering agents in patients with type 2 diabetes and CKD, they are not without their side effects.

### a Hyperkalaemia

In the UK, NICE guidance suggests measuring serum potassium and eGFR before starting RAAS blockade, and repeating the measurements 1–2 weeks after starting RAAS blockage and after each dose increase. NICE further says not to offer these agents if the patient's pre-treatment serum potassium is greater than 5 mmol/l.[29] NICE also suggests that these agents should be stopped if the serum potassium concentration increases to 6 mmol/l or more, and other drugs known to promote hyperkalaemia have been discontinued. No specific guidance is available from any other organisation.

### b A drop in eGFR or an increase in serum creatinine

Given the basic pathophysiological mechanism of RAAS blockade, these agents cause a reduction in eGFR and urinary albumin excretion through efferent and afferent glomerular arteriolar dilatation, with a resultant fall in intra-glomerular blood pressure. A reversible reduction of eGFR of up to 30% can be expected. Greater reductions may indicate underlying renal artery stenosis.

NICE guideline states that if there is a decrease in eGFR of greater than 25% or an increase in serum creatinine of greater than 30% with RAAS blockade, renal function tests need to be repeated within 1–2 weeks. If the eGFR drops by 25% or more, or there is a change in serum creatinine by 30% or more, NICE guidance suggests conducting further investigations to identify a cause of renal deterioration, such as volume depletion or non-steroidal inhibitor / potassium-sparing diuretic use.[146,147]

### c Pregnancy

Given the potentially teratogenic nature of RAAS blockade drugs, the KDIGO guidelines suggest that the use of these drugs in women of childbearing age should be balanced with the risk of pregnancy.[148]

### d Inter-current illness

There are risks of large reductions in eGFR with RAAS blockade, particularly during intercurrent illness or with intravascular fluid depletion (diarrhoea, vomiting and high fever). It is therefore recommended to reduce the dose or to hold off ACEI or ARB use until recovery is made, because ensuing hypotension may cause an acute decline in eGFR in patients with type 2 diabetes with CKD who are taking ACEIs or ARBs. These precautions should especially be taken if a patient is on a combination involving non-steroidal anti-inflammatory drugs or diuretics.[149–151]

## Other agents for blood pressure lowering in patients with type 2 diabetes and nephropathy

Most of the evidence for the use of other antihypertensive agents (apart from ACEIs or ARBs) is extrapolated from the general population and there is little evidence of their specific use or rationale in patients with type 2 diabetes and CKD.

### a Calcium channel blockers

There is good evidence to suggest that non-dihydropyridine calcium channel blockers (verapamil and diltiazem) reduce albuminuria.[67,152] A multicentre trial in patients with type 2 diabetes and nephropathy suggested that adding a non-dihydropyridine calcium channel blocker to an ACEI-based regime can be effective at lowering residual albuminuria with or without a significant reduction in systolic blood pressure.[153] Thus non-dihydropyridine calcium channel blockers can be used as a valid additive or alternative to ACEIs or ARBs in patients with type 2 diabetes, suggesting that their renal protective effects are over and above blood pressure lowering alone.

### b Beta-blockers

Much of the bad publicity about beta-blockers is related to the use of atenolol, which has been the most frequent comparator in most randomised controlled trials. However, beta-blockers are not a homogenous class of drug, and agents like celiprolol, carvedilol and nebivolol have vasodilating properties and do not share the negative properties of atenolol (that is, a lack of 24-hour antihypertensive effect and withdrawal effects). In the UK, NICE guidance does not favour beta-blockers as the first-line choice in the treatment of hypertension in the general population. There is evidence that in patients with type 2 diabetes with advanced CKD and a high risk of sudden death, beta-blockers may prove to be beneficial by lowering heart rate apart from lowering sympathetic hyperactivity and preventing ventricular arrhythmias.[154,155] A meta-analysis of beta-blockers used to treat CKD supports the use of beta-blockers in patients with CKD who have heart failure, but it does not provide evidence of their efficacy in preventing mortality, cardiovascular events or renal disease progression in patients with CKD who do not have heart failure.[156]

### c Diuretics

In the UK, NICE guidance prefers agents with a thiazide-like action such as chlorthalidone and indapamide, and this is relevant for patients with CKD who have type 2 diabetes.[29] Chlorthalidone was used in the largest randomised controlled trial in hypertension (the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study).[157] The evidence base for indapamide is through the Hypertension in the Very Elderly Trial (HYVET).[98] The PROGRESS trial

involved a combination of indapamide and perindopril, and was shown to reduce the risk of stroke.[158] The additional advantage of indapamide is its potassium-depleting effect, and this may be convenient when it is combined with ACEIs or ARBs, particularly in patients with type 2 diabetes who have CKD. Loop diuretics like furosemide would be particularly useful for treatment of hypertension in patients with type 2 diabetes with advanced CKD (stages 4–5), as fluid overload is invariably a major contributing factor in such patients.

### d Alpha-blockers

Drugs like doxazosin could be an adjunctive treatment for hypertension in patients with type 2 diabetes and CKD in whom other therapies have failed or not been tolerated, particularly if symptoms of prostatic hypertrophy are present. Alpha-blockers are generally not recommended first line because of the common side effects of postural hypotension, tachycardia and headache.

### e Centrally acting alpha adrenergic agonists

Centrally acting alpha adrenergic agonists cause vasodilation by reducing sympathetic outflow from the brain. Common agents in this category are methyldopa, clonidine and moxonidine. Doses of methyldopa and clonidine are not generally required to be reduced in patients with CKD. Although moxonidine is extensively excreted by the kidney, one randomised controlled trial that compare it with a calcium channel blocker added to an ACEI or ARB plus a loop diuretic indicated that it is safe to be used in advanced CKD.[159] Common side effects of moxonidine include headache, tiredness, dizziness and gastrointestinal symptoms, which occur in 10–15% of patients. These agents should not be used first line, but they are generally used in conjunction with other antihypertensive agents in patients with type 2 diabetes who have hypertension.

# 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?

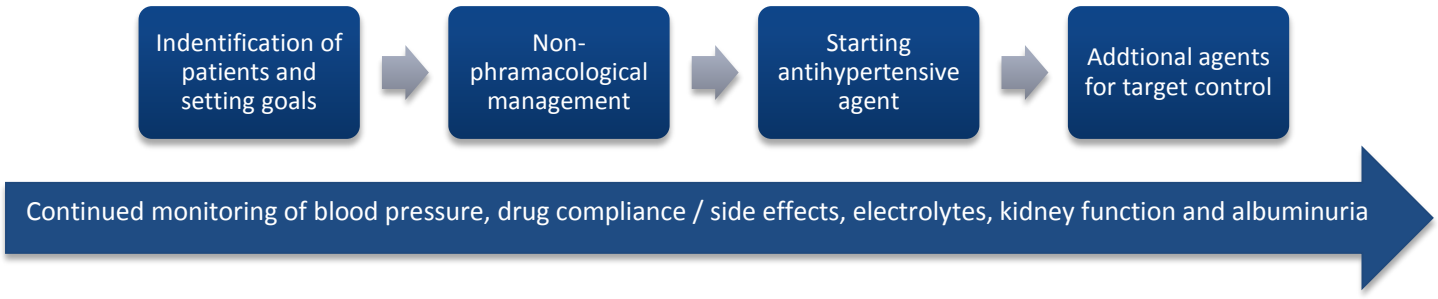
4 What is the effect of long-term use of novel potassium binders together with RAAS blockade on renal and cardiac outcomes in patients with diabetes and CKD stages 4 and 5?

## Introduction

Advanced stages of CKD (stages 4 and 5) are more frequently associated with hyperkalaemia, fluid retention and anaemia, which require erythropoiesis-stimulating agents that may further increase blood pressure. Hyperkalaemia (greater than 5.5 mmol/l) is present in 31% of patients in the advanced kidney disease clinics.[160] In a large population, hyperkalaemia (greater than 5.5 mmol/l) occurred more frequently in patients with CKD (eGFR of less than 60 ml/min/1.73m$^2$) who were on RAAS blockers than those who were not (eight versus two events per 100 patient-months; $p<0.001$).[161] Hyperkalaemia is more common in patients with diabetes and CKD than in patients with CKD who do not have diabetes.[162] In a blood pressure control trial with patients who have CKD, the risk of hyperkalaemia was seven times higher in patients with an eGFR of less than 30 ml/min/1.73m$^2$ compared with patients with an eGFR of greater than 50 ml/min/1.73m$^2$, and seven times higher among patients taking ramipril compared with those taking amlodipine.[163] Hence blood pressure control in patients with diabetes and CKD stages 4–5, and particularly with an ACEI, requires careful monitoring and management of serum potassium.

This section of the guidance addresses identification, treatment goals, non-pharmacological management, pharmacological management and electrolyte / renal function monitoring for hypertension in patients with diabetes and CKD stages 4 and 5 (see Fig 2).

**Fig 2** Steps in the management of hypertension in patients with diabetes and CKD stages 4 and 5



## Identification and monitoring of patients with diabetes and CKD stages 4 and 5

The rise in blood pressure in diabetic nephropathy patients is associated with higher mortality and increased risk of macro- and microvascular complications:[3,164] treatment lowers the risk of cardiovascular events, strokes and all-cause mortality.[165–167] Hence patients with diabetes and CKD stages 4 to 5 should be regularly screened to identify and manage high blood pressure. It is necessary to identify patients who are hypertensive early, to avoid delays in management while avoiding unnecessary anxiety and the inconvenience related to too frequent visits with doctors and nurses. With the use of RAAS blockers, monitoring of serum potassium is important to avoid dangerous hyperkalaemia.[168] Frequent blood testing also identifies patients who are more likely to progress to renal replacement therapy.[169] Most clinical trials have monitored patients' clinical characteristics and laboratory values every 3 to 12 months and have demonstrated the identification of new-onset hypertension, albuminuria and hyperkalaemia in this time frame.[163,170,171] The recommendations for monitoring from NICE are: three times a year for patients with CKD stages 3 and 4 and greater than or equal to four times a year for patients with CKD stage 5; however, monitoring can be tailored according to a patient's needs.[124]

## Target blood pressure in patients with diabetes and CKD stages 4 and 5, with or without significant albuminuria

Several observational and prospective studies have demonstrated the significant impact of blood pressure on mortality, cardiovascular events and renal failure in patients with diabetes and CKD.[3] Among patients from advanced CKD clinics, high blood pressure (particularly systolic) is associated with progression to dialysis and mortality.[172]

Very few studies have examined the impact of tight blood pressure control for patients with diabetes and CKD stages 4 and 5. Some studies have examined the role of intense blood pressure lowering in patients with diabetes who have mild CKD: a small proportion of patients demonstrated the advantage of lowering blood pressure below 140/90 mmHg but not below 130/80 mmHg.[173] In a study of African-American patients with non-diabetes CKD and an eGFR of 20–65 ml/min/1.73m$^2$, the tight blood pressure control arm (achieved 128/78 mmHg) suffered similar renal end points compared with the less tight blood pressure control arm (achieved 141/85 mmHg).[174] In the recently completed SPRINT trial, which included 2,646 patients who did not have diabetes but who had an eGFR of 20–60 ml/min/1.73m$^2$, intensive blood pressure control (a target of less than 120 mmHg) was not associated with improved composite renal outcomes, compared with standard control in patients with CKD (a target of less than 140 mmHg).[171] However no patients with diabetes were included in the SPRINT trial. In another large randomised controlled trial of high-risk patients with diabetes, the intensive blood pressure control arm (target systolic blood pressure less than 120 mmHg; achieved pressure 119 mmHg) was associated with a higher chance of having an eGFR of less than 30 ml/min/1.73m$^2$ (99 versus 52 events; $p<0.001$) than the normal blood pressure control arm (target systolic blood pressure less than 140 mmHg; achieved pressure 133 mmHg), without any benefit in reducing cardiovascular complications.[170] In the same study there was no difference in new-onset microvascular complications with intensive blood pressure control and half of the patients who had progressive renal disease did not have albuminuria.[175] The issue of determining beneficial target and achieved diastolic blood pressures is even more contentious (in terms of whether the target should be 90 mmHg or 80 mmHg), with certain cardiovascular disease outcomes in patients with diabetes being reduced in some studies that had tighter diastolic blood pressure control[166,176] but not in patients with a creatinine greater than 1.5 mg/dl or with an eGFR of less than 60 ml/min/1.73m$^2$.[177,178] Reanalysis of a large randomised study in patients with diabetes and coronary artery disease (less than 5% with raised creatinine) did not demonstrate any benefit of tight blood pressure control, and reanalysis of a small randomised trial of intensive diastolic blood

pressure control (target less than 75 mmHg versus 80–90 mmHg) was not associated with improved cardiovascular or renal outcomes.[173,178] In addition, progression of renal disease was not reduced with intensive blood pressure control,[176,178] although reduced renal function at the baseline did not affect the achieved blood pressure control.[176] Pragmatically, diastolic blood pressure values of less than 90 mmHg should be seen as being more achievable, with levels of 80–90 mmHg being seen as beneficial.

Several studies have shown that the presence of significant albuminuria is associated with poor cardiovascular outcomes, and the reduction of albuminuria is associated with improvement. Analysis of data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, a trial of ARB use in diabetic nephropathy, demonstrated an approximate doubling of the risk of cardiovascular outcome with high albuminuria at the baseline (ACR greater than 3 g/g compared with less than 1.5 g/g of creatinine), and an 18% lowering of the cardiovascular events with a 50% lowering of albuminuria.[179] The evidence that there is a better outcome with tighter blood pressure control with high albuminuria is mainly observational and derived from post hoc analysis of large randomised controlled trials. The RENAAL study, which included a significant number of patients with CKD stages 3 and 4, demonstrated a baseline higher risk with systolic blood pressure greater than 140 mmHg (there was no difference when comparing systolic blood pressure of less than 130 mmHg to systolic blood pressure of 130–140 mmHg), and a 23% risk reduction for end-stage renal disease with achieved blood pressure of less than 140/90 mmHg compared with blood pressure of greater than 140/90 mmHg.[180] Analysis of data from two large ARB trials (the Irbesartan Diabetic Nephropathy Trial (IDNT) and the RENAAL study) indicates that the benefits of cardiovascular risk reduction exist with systolic blood pressure of less than 130 mmHg (particularly when albuminuria was reduced to lower levels); however, the risk increased with systolic blood pressure of less than 120 mmHg.[181] Post hoc analysis of the IDNT trial demonstrated that heart failure events were reduced with systolic blood pressure of less than 130 mmHg but that there was a possible increased risk with systolic blood pressure of less than 120 mmHg. Also, a diastolic blood pressure of less than 85 mmHg was associated with an increased risk of myocardial infarction (MI) and congestive heart failure (CHF).[182] Hence there is a suggestion of better cardiovascular outcomes with a reduction of systolic blood pressure to below 130 mmHg but not to below 120 mmHg. With a target blood pressure of less than 130/80 mmHg in the STENO-2 randomised trial, there was a reduction in cardiovascular mortality; however most patients had CKD stages 1 and 2, and in the presence of other interventions, it is difficult to tease out the effect of tight blood pressure control.[183] Thus a lower target for blood pressure of less than 130/80 mmHg may be suggested in patients with significant albuminuria, as suggested by other guidelines (KDIGO and NICE) but better evidence is needed.[124,184] This guideline proposes a target upright blood pressure of less than or equal to 140/90 mmHg for all patients with diabetes, no significant albuminuria and CKD stages 4 and 5, as improved cardiovascular outcomes have been demonstrated in randomised controlled trials with blood pressures of less than or equal to 140/90 mmHg, but inconsistent results have been recorded with lower blood pressure targets. However, for patients with significant albuminuria, the proposed upright blood pressure target is less than or equal to 130/80 mmHg because this level is associated with a reduction in albuminuria of diabetic kidney disease, which may improve renal and cardiovascular outcomes.

## RAAS blockade for blood pressure control in patients with diabetes and CKD stages 4 and 5

In a study of African-American patients with an eGFR of 20–65 ml/min/1.73m$^2$, use of the ACEI ramipril was associated with a significant reduction in clinical composite outcome compared with use of metoprolol (22% (95% CI 1–38%; p=.04)) or amlodipine (38% (95% CI 14–56%; p=.004)).[174] In a randomised controlled trial of patients with diabetes (30% with mild CKD), use of Enalapril was associated with fewer cardiovascular events compared with nisoldipine (five versus 25;

p<0.001).[185] In a recent meta-analysis of 119 trials, use of ACEIs or ARBs in 64,768 patients with CKD was associated with a reduced risk of kidney failure, compared with other antihypertensives (odds ratios of 0.65 (95% CI 0.51–0.80) for ACEIs and odds ratio of 0.75 (95% CI 0.54–0.97) for ARBs).[186] Hence ACEIs should be used in patients with diabetes and CKD stages 4 and 5, with careful monitoring of kidney function and serum potassium. In a meta-analysis, ACEI use in patients with diabetes was shown to reduce all-cause mortality, cardiovascular mortality and cardiovascular events but the same reductions did not result from ARB use.[187,188] A recent network meta-analysis showed a reduction in end-stage renal disease with ACEI and/or ARB use, but did not demonstrate an overall survival benefit.[189] Thus there is strong evidence for using ACEIs as the first-choice antihypertensive in patients with diabetes and CKD.

In a study of combination therapy of ACEIs with ARBs in patients with diabetes and an ACR of greater than 30 mg/mmol and an eGFR of 30–90 ml/min/1.73m$^2$, there was no difference in mortality but there was a significant increase in hyperkalaemia (6.3 events versus 2.6 events per 100 person-years with monotherapy; p<0.001) and acute kidney injury (AKI) (6.7 versus 0.2 events per 100 person-years, p<0.001).[74] A combination of ACEIs with ARBs was not associated with a benefit in primary endpoints but it was associated with more side effects, and hence it should be avoided. However a network meta-analysis suggested that there is a potential benefit of dual blockade if it can be administered safely; therefore there is a need for further trials of dual blockade in patients with diabetes, CKD and albuminuria.[132,189]

During an acute illness, particularly when a patient has volume depletion, there is a risk that patients with diabetes and CKD stages 4 and 5 who are taking an ACEI and an ARB will develop acute kidney injury (AKI). Such risk can be avoided by stopping the ACEI or the ARB for the duration of the illness and for 24–48 hours post recovery.

With the initiation of ACEI therapy, a rise in serum creatinine up to 30% is not uncommon and a rise of potassium by 0.5 mmol/l is also not uncommon.[79] However this does not require any change in the planned therapy with ACEI. Hence no modification of ACEI or ARB therapy is necessary if the rise in creatinine from the baseline is less than 30% or if the drop in the eGFR is less than 25%.

The addition of spironolactone and further inhibition of the RAAS may provide an additional antiproteinuric effect, as seen in small studies, which indicates the need to conduct further large trials with more clinically relevant outcomes.[190]

## Management of hyperkalaemia with RAAS blockade in patients with diabetes and CKD stages 4 and 5

Hyperkalaemia is common in patients with diabetes and CKD. It is very common (greater than 30%) in patients who have advanced CKD who are managed in the low-kidney-clearance clinics.[160] The cause of such hyperkalaemia can be multifactorial, including renal failure, type IV renal tubular acidosis, diet and drugs. The presence of hyperkalaemia limits the use of RAAS blockers. Chronically high potassium levels have traditionally been controlled with restricted diet, diuretics and avoiding drugs that cause hyperkalaemia.

Traditionally hyperkalaemia has been managed with dietary potassium restriction and correction of acidosis with sodium bicarbonate. Where bicarbonate is less than 22 mmol/l, sodium bicarbonate can be added at a dose of 500 mg bd: larger doses can be used but often require a concomitant increase or addition of a loop diuretic dose. New potassium binding agents have been tested for safety and efficacy in randomised controlled trials for management of chronic hyperkalaemia in patients with CKD. They cause an early and sustained lowering of potassium in patients with CKD who are on RAAS blocker therapy.[191] In 306 patients with diabetes and CKD stages 3 and 4 who were treated with RAAS blockade (an ACEI or ARB with or without spironolactone), the use of a novel potassium-binding polymer (patiromer) was associated with a

significant and sustained decrease in serum potassium over 52 weeks.[192] In a study of 237 patients with CKD, the same potassium binder was able to reduce serum potassium by 1 mmol/l over 4 weeks.[193] In another study of 243 patients (more than 50% of whom had diabetes) the potassium binder achieved an approximately 1 mmol/l reduction in serum potassium over 4 weeks in patients with and without heart failure.[194] The treatment with patiromer was associated with decreased aldosterone levels and decreased blood pressure, which may provide additional benefits.[195] However the above mentioned trials were of short duration and the possible ACEI or ARB use facilitated with potassium binders has not been shown to improve cardiovascular events or mortality.

In future, the novel potassium binder may be very useful in treating patients with diabetes and CKD, particularly when it is associated with left ventricular dysfunction.

## Non-pharmacological management of hypertension in patients with diabetes and CKD stages 4 and 5

In randomised controlled trials, dietary sodium restriction in patients with CKD is associated with a significant lowering of blood pressure, but longer-term benefits of dietary intervention are unknown.[196,197] Dietary advice is best provided by a trained dietitian, due to the complex and frequently changing needs of this group of patients. Patients with CKD stages 4 and 5 would benefit most from dietary input, and they are best managed in a multidisciplinary clinic with expert nurses and dietitians. Dietary potassium restriction is useful in continuing RAAS blockers for patients with diabetes and CKD, but clinical trial evidence is yet to be generated.

# 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?

## Introduction

Hypertension is a common finding in patients with diabetes as well as those with CKD stage 5D. Elevated blood pressure,[198,199] diabetes[3,200] and CKD[201–203] are all major risk factors for adverse cardiovascular events.

According to the UK Renal Registry and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Renal Registry, 23–36% of incident dialysis patients had diabetes as their primary renal disease.[204,205] Patients with diabetes who are on haemodialysis have a poorer survival rate compared with dialysis patients who do not have diabetes.[206,207] This is mainly due to cardiovascular disease.[208–210] Control of hypertension in hypertensive dialysis patients was shown to be associated with improved survival.[211]

It is therefore logical that, in order to reduce cardiovascular risk and improve survival, optimal blood pressure control should be achieved in patients with diabetes and CKD stage 5D. However, there is insufficient evidence from data in the published literature to decide how best to manage blood pressure in patients with diabetes who are on dialysis. This is in part because patients with CKD, including those with stage 5D, are 'often' excluded from clinical trials of hypertension.

There are emerging, although not consistent, data delineating how best to measure blood pressure, to target blood pressure and to use pharmacological and non-pharmacological therapies to optimise blood pressure control in patients with CKD stage 5D. However, these data are not specific to the population with diabetes.

Furthermore, blood pressure control in patients who are on dialysis is complex. Many factors affect blood pressure in patients who are on dialysis, including fluid status, salt intake,

sympathetic nervous system activity and the renin-angiotensin-aldosterone system (RAAS). Patients with diabetes who are undergoing haemodialysis often have autonomic dysfunction,[212] which increases the risk of cardiovascular instabilities during dialysis. Haemodialysis causes severe orthostatic reduction in cerebral blood flow velocity in patients with diabetes and may subsequently increase the risk of cerebrovascular injury post haemodialysis.[213] This makes management of hypertension in patients with diabetes who are on dialysis even more challenging.

## Blood pressure measurement in patients with diabetes who are on haemodialysis

In UK dialysis units, measuring pre- and post-dialysis blood pressure is the standard technique for monitoring blood pressure in patients who are on dialysis. However, blood pressure measurement in patients who are on haemodialysis is complex. There are conflicting data as to whether blood pressure measurements pre- and post-dialysis are predictive of interdialytic blood pressure in comparison with ambulatory blood pressure measurement and/or home blood pressure measurement. Ambulatory blood pressure measurement is considered to be the most accurate method for studying blood pressure in patients who are on haemodialysis[214] and in the general population it provides a more accurate prediction of cardiovascular outcomes in comparison with clinic blood pressure measurement.[215] A meta-analysis of 18 studies that involved 692 patients who were on dialysis showed that pre-dialysis blood pressure and post-dialysis blood pressure are imprecise estimates of interdialytic ambulatory blood pressure.[216] Patients with diabetes were included in most of these studies[208,214] at a rate that varied from 8% to 54%. The presence of diabetes made no difference to the outcome.

In an extensive review of the literature by Agarwal *et al*,[217] evidence from several studies was presented to show that, in patients on haemodialysis, blood pressure measurement at home[218] or ambulatory blood pressure measurement[219,220] are stronger predictors of LVH[221] and mortality[222,223] compared with blood pressure obtained in the dialysis unit. In predicting LVH, weekly average home systolic blood pressure measurement was similar to interdialytic ambulatory blood pressure measurement and was superior to pre-dialysis and post-dialysis blood pressure measurement.[221] In contrast to home blood pressure measurement, ambulatory blood pressure measurement can diagnose nocturnal non-dipping and offers great insights into circadian rhythm.[224] Loss of diurnal rhythm, which is a feature of diabetic nephropathy, is reported to lead to worse outcomes in patients who are on dialysis.[219] In a study of 89 patients who are on haemodialysis by Liu *et al*, the incidence of cardiovascular events and deaths were 3.5–9 times higher in non-dippers (that is, those who lose their diurnal blood pressure variation) compared with dippers.[225] Ambulatory blood pressure measurement can therefore be advantageous in selecting high-risk patients and can guide treatment. However, to date, there have been no specific studies to address ambulatory blood pressure measurement in patients with diabetes who are on dialysis.

## Target blood pressure in patients with diabetes who are on dialysis

The relationship between blood pressure level and cardiovascular outcome is unclear in patients who are on dialysis. Observational studies have shown an increased risk of mortality in patients who are on haemodialysis who have a low pre- or post-dialysis systolic blood pressure of less than 110 mmHg,[226] and in patients who are on peritoneal dialysis with a pre-dialysis systolic blood pressure of less than 110 mmHg.[227] Further observational studies in haemodialysis cohorts[228,229] continued to show a reverse epidemiology phenomenon, with the highest mortality rate being in patient groups with lower pre-dialysis blood pressures. However, the phenomenon may be 'U' shaped, as other observational studies have shown that increased mortality among patients who

are on haemodialysis is associated with pre-dialysis systolic blood pressure of greater than 160 mmHg[230] and post-dialysis blood pressure of greater than 180 mmHg.[231]

Interestingly, in the Tassin group in France where the 5-year survival rate of 87% is the best reported in patients who are on haemodialysis, the pre-dialysis blood pressure that was achieved was less than 130/85 mmHg (mean arterial pressure (MAP) less than 101 mmHg).[232]

Prospective randomised controlled studies on the effect of ARBs,[233] ACEIs,[234] beta-blockers[235] and calcium channels blockers[236] on cardiovascular events have been conducted to evaluate the roles of these agents in patients who are on dialysis.

Two meta-analyses have shown that blood pressure treatment in patients who are on dialysis is associated with improved outcome. The first analysis was by Heerspink *et al*, published in 2009.[237] This meta-analysis included eight randomised trials that provided data from 1,679 patients who are on dialysis, of whom 588 patients had diabetes. The trials included patients who were on haemodialysis and peritoneal dialysis. The analysis showed that blood pressure lowering treatment was associated with lower risks of cardiovascular events, all causes of mortality and cardiovascular mortality, and that the effect seemed to be consistent across a range of patient groups that were included in the studies. Reduction in systolic blood pressure was similar, regardless of whether the patient had diabetes or antihypertensive drug use. Similarly, the second meta-analysis by Agarwal and Sinha (also published in 2009)[238] showed that in patients with hypertension who were on haemodialysis, antihypertensive therapy reduced the combined hazard ratio for cardiovascular events by 31–38% compared with the placebo group. The meta-analysis showed that blood pressure lowering was well tolerated, with no suggestion of increased adverse events in patients with diabetes. The analysis showed no difference in cardiovascular outcomes caused by different drug classes and the data from the two meta-analyses suggest that RAAS blockers, beta-blockers and calcium channel blockers are all suitable for use in patients who are on dialysis.

However, a randomised controlled trial by Agarwal *et al* in 2014,[239] including 200 patients who were on haemodialysis of whom nearly half had diabetes, showed that a beta-blocker-based hypertensive treatment was superior to an ACEI-based treatment in preventing cardiovascular morbidity in patients who are on dialysis.

Irrespective of the type of the antihypertensive agents that are used, the timing of the administration of such agents in relation to dialysis treatment needs to be taken into account when prescribing antihypertensive drugs for patients who are on dialysis. ARBs, calcium channel blockers and alpha-blockers are not cleared with dialysis. However, ACEIs (apart from fosinopril) and a number of beta-blockers are largely cleared on dialysis.[240]

To date, optimum blood pressure goals for patients who are on dialysis (including patients with diabetes) have not been defined in randomised prospective controlled trials.[240] The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends a pre-dialysis blood pressure goal of less than 140/90 mmHg and a post-dialysis blood pressure goal of less than 130/80 mmHg.[241] However, this is largely based on studies that were performed in the non-dialysis population who have normal renal function. Patients who are on haemodialysis have different characteristics to the general population. For example, studies have shown that patients who are on dialysis lose their diurnal blood pressure variation (that is, they are non-dippers), which is an independent risk factor for LVH and subsequent adverse cardiovascular outcome.[219] Patients who are on haemodialysis also have increased pulse pressure, which is associated with adverse cardiovascular outcome.[242] Therefore, the KDOQI-recommended blood pressure target may not be applicable to the haemodialysis population.

Furthermore, patients with diabetes who are on dialysis are at increased risk of haemodynamic instabilities and orthostatic intolerance post-dialysis, and therefore a blood pressure that is higher than 140 mmHg systolic may be indicated in the presence of significant orthostatic change in

blood pressure. A randomised controlled trial is needed to identify the optimal blood pressure target for patients with diabetes who are on dialysis.

## Volume control in patients with diabetes who are on dialysis

Increased extracellular volume or volume overload is an important contributor in the pathogenesis of high blood pressure in patients who are on dialysis.[243] Removal of extracellular volume without causing intolerable hypotension defines the 'dry weight'[244] that was first reported by Thomson in 1967.[245] This is difficult to define clinically. Achieving dry weight and normalising blood pressure is not immediate and can take months, which is something that is best described as a 'lag phenomenon'.[246]

In the Tassin group, hypertension control without medication, achieved by aggressive control of extracellular volume and dietary sodium intake, was shown to be the best single marker of survival in 449 patients who were on haemodialysis who were followed for 20 years.[232]

Observational studies showed that volume control is associated with improvement in blood pressure in the majority of patients on haemodialysis[247] and peritoneal dialysis.[248] A randomised controlled trial (DRIP) showed that volume control in haemodialysis improves blood pressure control.[249] In that study, 150 patients were randomised to an additional ultrafiltration group (40/100 patients had diabetes) or control group (19/50 patients had diabetes). Without increasing time or frequency of haemodialysis, reduction in dry weight (defined by clinical signs and symptoms) resulted in a reduction in interdialytic ambulatory blood pressure, leading to the conclusion that dry weight reduction is an effective strategy in blood pressure control in patients who are on haemodialysis.

The concept that 'volume control' improves blood pressure control is further supported by the increasing reports that daily dialysis[250,251] or nocturnal dialysis[252,253] improves blood pressure and reduces LVH with less risk of inducing intradialytic hypotension. Reducing the risk of intradialytic hypotension is important. An observational study by Shoji T *et al* showed that haemodialysis-associated hypotension is an independent risk factor for 2-year mortality in patients who are on haemodialysis.[254]

The risk of intradialytic hypotension increases with an ultrafiltration rate of greater than 10 ml/kg/hr and was reported in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (which included 16,420 patients on haemodialysis) as an independent risk factor for mortality.[255] This is similar to another study with 5 years' follow-up data by Movilli,[256] in which an ultrafiltration rate of over 12.7 ml/kg/hr was identified as an independent risk factor for mortality given the risk of hypotension-related serious adverse events especially in patients who are on dialysis and who have diabetes; however, this strategy requires close supervision and markers to assess volume status.

Bioimpedance spectroscopy devices,[257] brain natriuretic peptide (BNP) level[258] and assessment of vena cava diameter[259] have been used to determine dry weight. This has been primarily to reduce the risk of inducing intradialytic hypotension. Further studies are needed to explore and evaluate the role of bioimpedance spectroscopy devices as markers of volume status, especially in patients with diabetes who are on dialysis.

## Salt restriction in patients with diabetes who are on dialysis

Reducing dietary salt to control blood pressure in patients who are on dialysis was first reported by Hegstrom RM *et al* in 1961.[260] Salt restriction to 1 g per day or less helps to decrease thirst and to control interdialytic weight gain in patients who are on haemodialysis.[261]

Evidence for the association between salt restriction and blood pressure control in patients who are on dialysis comes from observational studies where dietary salt restriction was in combination

with strict volume control. Craswell *et al*[262] (in a study of 89 patients who were on dialysis), Covic *et al*[263] (in a study of 286 patients) and Ozkahya *et al*[264] (in a study of 218 patients) all showed that salt restriction to less than 5 g per day along with strict volume control led to a significant reduction of blood pressure and interdialytic weight gain. Similarly, in the Tassin group, dietary salt reduction to less than 5 g per day along with extracellular volume control was shown to normalise blood pressure in patients who were on haemodialysis.[232]

In a cross-sectional study by Kayikcioglu *et al* in 204 patients on dialysis, dietary salt restriction to 5 g per day along with dialysate sodium reduction, led to a reduction in interdialytic weight gain, the number of antihypertensive medications and LVH.[265] Maduell and Navarro (in a cross-sectional study of 15 patients) reported that salt restriction alone resulted in a significant reduction in interdialytic weight gain and blood pressure.[266] In the Haemodialysis (HEMO) Study, dietary sodium intake was associated with a greater adjusted risk of all-cause mortality.[267] In practical terms, adherence may be more sustainable if a threshold restriction of less than 6 g dietary salt is applied in the diabetes cohort who have additional restrictions placed on them, but this has yet to be formally evaluated.

Diuretic therapy may provide an additional means by which to promote natriuresis in patients who are on dialysis who have residual urine output. In the DOPPS study, Bragg-Gresham *et al* reported that diuretic use was associated with reduced interdialytic weight gain, fewer intradialytic hypotensive episodes and reduced cardiac-specific mortality, but not all-cause mortality.[255] Patients with residual renal function who were on diuretics were twice as likely to retain residual renal function compared with patients who were not on diuretics after 1 year in the study. The authors concluded that patients with residual renal function may benefit from continuing diuretic use rather than automatically discontinuing it at the start of dialysis. Furthermore, in a prospective randomised study by Medcalf *et al* on patients who are on peritoneal dialysis, frusemide given at a dose of 250 mg once daily produced clinically significant preservation in urine volume over 1 year, but it had no influence on residual renal function.[268]

Interestingly, and independent of its diuretic property, spironolactone has been shown, in a randomised controlled trial that included patients with diabetes, to be more effective than placebo in treating refractory hypertension in patients on dialysis.[269] There is emerging evidence from a number of randomised controlled trials that spironolactone has a cardiac protective effect in patients on dialysis,[270] but it will be interesting to see what emanates from the current ongoing larger randomised controlled trial (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST)), which is exploring the potential cardiac protective role of spironolactone in patients who are on dialysis.[271] It might help to show whether this effect is dependent or independent of spironolactone's property as a diuretic and/or antihypertensive agent.

To date there have been, therefore, no randomised controlled trials to address the question of whether salt restriction or diuretic use in patients with diabetes who are on dialysis may influence blood pressure control or cardiovascular outcome. In the absence of such evidence, individualisation of dietary sodium intake is required, depending on the patient's interdialytic weight gain, extracellular volume status, haemodynamic stability and nutritional status.

**Table 2** BP targets in patients with diabetes through stages of kidney function impairment

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

CKD = chronic kidney disease; BP = blood pressure.

# 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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- Damian Fogarty has received honoraria for delivering educational meetings and/or attending advisory boards from AstraZeneca, Sanofi, Vifor Pharmaceuticals and Baxter. He provides consultancy for adjudication of endpoint in RCTs to ACI.
- 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.
- Peter Winocour has received honoraria for delivering educational meetings and/or attending advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, MSD, Janssen and Vifor Pharmaceuticals.

# References


1 Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999;341:1127–33.

2 Gilg J, Caskey F, Fogarty D. UK Renal Registry 18th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2014: National and Centre-specific Analyses. *Nephron* 2016;132(Suppl 1):9–40.

3 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–44.

4 Rosolowsky ET, Skupien J, Smiles AM *et al*. Risk for ESRD in type 1 diabetes remains high despite renoprotection. *J Am Soc Nephrol* 2011;22:545–53.

5 Deckert T, Yokoyama H, Mathiesen E *et al*. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;312:871–4.

6 Watkins PJ, Parsons V, Bewick M. The prognosis and management of diabetic nephropathy. *Clin Nephrol* 1977;7:243–9.

7 Finne P, Reunanen A, Stenman S *et al*. Incidence of end-stage renal disease in patients with type 1 diabetes. *JAMA* 2005;294:1782–7.

8 de Boer IH, Rue TC, Cleary PA *et al*. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med* 2011;171:412–420.

9 Hollenberg NK, Price DA, Fisher ND *et al*. Glomerular hemodynamics and the renin-angiotensin system in patients with type 1 diabetes mellitus. *Kidney Int* 2003;63:172–8.

10 Miller JA. Impact of hyperglycaemia on the renin-angiotensin system in early human type 1 diabetes. *J Am Soc Nephrol* 1999;10:1775–8.

11 Lafayette RA, Mayer G, Park SK, Meyer TW. Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1992;90:766–71.

12 Rosenberg ME, Smith LJ, Correa-Rotter R, Hostetter TH. The paradox of the renin-angiotensin system in chronic renal disease. *Kidney Int* 1994;45:403–10.

13 Ray PE, Aguilera G, Kopp JB *et al*. Angiotensin II receptor-mediated proliferation of cultured human fetal mesangial cells. *Kidney Int* 1991;40:764–71.

14 Harindhanavudhi T, Mauer M, Klein R *et al*. Benefits of Renin-Angiotensin blockade on retinopathy in type 1 diabetes vary with glycemic control. *Diabetes Care* 2011;34:1838–42.

15 Sochett EB, Cherney DZ, Curtis JR *et al*. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol* 2006;17:1703–9.

16 Raile K, Galler A, Hofer S *et al*. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. *Diabetes Care* 2007;30:2523–8.

17 Chowdhury TA, Kumar S, Barnett AH, Bain SC. Nephropathy in type 1 diabetes: the role of genetic factors. *Diabet Med* 1995;12:1059–68.

18 Microalbuminuria Collaborative Study Group, United Kingdom. Risk factors for development of microalbuminuria in insulin dependent diabetic patients: a cohort study. *BMJ* 1993;306:1235–9.

19 Rudberg S, Dahlquist G. Determinants of progression of microalbuminuria in adolescents with IDDM. *Diabetes Care* 1996;19:369–71.

20 Ku E, McCulloch CE, Mauer M *et al*. Association between blood pressure and adverse renal events in type 1 diabetes. *Diabetes Care* 2016;30:2218–24.

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

22 National Institute for Health and Care Excellence. *Type 1 diabetes in adults: diagnosis and management*, NICE guideline NG17, 2016. Available from: www.nice.org.uk/guidance/ng17 [Accessed May 2017].

23 Tuttle KR, Bakris GL, Bilous RW *et al*. Diabetic kidney disease: a report from an ADA Consensus Conference. *Am J Kidney Dis* 2014;64:510–33.

24 Donaghue KC, Wadwa RP, Dimeglio LA *et al*. ISPAD Clinical Practice Consensus Guidelines 2014. Microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes* 2014;15(Suppl 20):257–69.

25 Lurbe E, Redon J, Kesani A *et al*. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med* 2002;347:797–805.

26 Shalaby NM, Shalaby NM. Study of ambulatory bloods pressure in diabetic children: prediction of early renal insult. *Ther Clin Risk Manag* 2015;11:1531–7.

27 Lambers Heerspink HJ, Holtkamp FA, Parvin HH *et al*. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int* 2012;82:330–7.

28 Lithovius R, Harjutsalo V, Forsblom C *et al*. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. *Diabetes Care* 2014;37:709–17.

29 National Institute for Health and Care Excellence. *Hypertension in adults: diagnosis and management*, NICE guideline CG127, 2011. Available from: www.nice.org.uk/guidance/CG127 [Accessed May 2017].

30 The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;349:1787–92.

31 Bilous R, Chaturvedi N, Sjølie AK *et al*. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med* 2009;151:11–20.

32 Mauer M, Zinman B, Gardiner R *et al*. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40–51.

33 Kventy J, Gregersen G, Smith Pedersen R. Randomized placebo-controlled trial of perindopril in normotensive, normoalbuminuric patients with type 1 diabetes mellitus. *QJM* 2001;94:89–94.

34 Almdal T, Norgaard K, Feldt-Rasmussen B, Deckert T. The predictive value of microalbuminuria in IDDM. A five-year follow-up study. *Diabetes Care* 1994;17:120–5.

35 Hovind P, Tarnow L, Rossing P *et al*. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. *BMJ* 2004;328:1105–9.

36 Perkins BA, Ficociello LH, Silva KH *et al*. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;348:2285–93.

37 Forsblom CM, Groop PH, Ekstrand A, Groop LC. Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration. *BMJ* 1992;305:1051–3.

38 de Boer IH, Afkarian M, Rue TC *et al*. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. *J Am Soc Nephrol* 2014;25:2342–50.

39 Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. *Curr Opin Nephrol Hypertens* 2011;20:246–57.

 

40 Perkins BA, Ficociello LH, Roshan B *et al*. In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. *Kidney Int* 2010;77:57–64.

41 Dunger DB, Schwarze CP, Cooper JD *et al*. Can we identify adolescents at high risk for nephropathy before the development of microalbuminuria? *Diabet Med* 2007;24:131–6.

42 Maftei O, Pena AS, Sullivan T *et al*. Early atherosclerosis relates to urinary albumin excretion and cardiovascular risk factors in adolescents with type 1 diabetes: Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). *Diabetes Care* 2014;37:3069–75.

43 Krolewski AS. Progressive Renal Decline: The New Paradigm of Diabetic Nephropathy in Type 1 Diabetes. *Diabetes Care* 2015;38:954–62.

44 Rahimi Z, Moradi M, Nasri H. A systematic review of the role of renin angiotensin aldosterone system genes in diabetes mellitus, diabetic retinopathy and diabetic neuropathy. *J Res Med Sci* 2014;19:1090–8.

45 Krolewski AS, Warram JH, Forsblom C *et al*. Serum concentration of cystatin C and risk of end-stage renal disease in diabetes. *Diabetes Care* 2012;35:2311–6.

46 Gohda T, Niewczas MA, Ficociello LH *et al*. Circulating TNF receptors 1 and 2 predict stage 3 of CKD in type 1 diabetes. *J Am Soc Nephrol* 2012;23:516–524.

47 Cantarovich D, Perrone V. Pancreas transplant as treatment to arrest renal function decline in patients with type 1 diabetes and proteinuria. *Semin Nephrol* 2012;32:432–6.

48 Mathiesen ER, Hommel E, Hansen HP *et al*. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. *BMJ* 1999;319:24–5.

49 The Microalbuminuria Collaborative Study Group. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 1996;35:587–93.

50 O'Hare P, Bilbous R, Mitchell T *et al*. Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension: results of a randomized controlled trial. *Diabetes Care* 2000;23:1823–9.

51 Marre M, Chatellier G, Leblanc H *et al*. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *BMJ* 1998;297:1092–5.

52 Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA* 1994;271:275–279.

53 The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;134:370–9.

54 Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983;8335:1175–9.

55 Parving HH, Hommel, Smidt U. Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *BMJ* 1988;297:1086–91.

56 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Eng J Med* 1993;1456–62.

57 Björck S, Mulec H, Johnsen SA *et al*. Renal protective effect of enalapril in diabetic nephropathy. *BMJ* 1992;304:339–43.

58 Sarafidis PA, Stafylas PC, Kanaki AI, Lasaridis AN. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. *Am J Hypertens* 2008;21:922–9.

59 Chaturvedi N, Porta M, Klein R *et al*. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 2008;372:1394–402.

60 Andersen S, Tarnow L, Rossing P *et al*. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int* 2000;57:601–6.

61 Schjoedt KJ, Andersen S, Rossing P *et al*. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. *Diabetologia* 2004;47:1936–9.

62 Nielsen SE, Persson F, Frandsen E *et al*. Spironolactone diminishes urinary albumin excretion in patients with type 1 diabetes and microalbuminuria: a randomized placebo-controlled crossover study. *Diabetic Med* 2012;29:e184–90.

63 Heerspink HJ, Persson F, Brenner BM *et al*. Renal outcomes with aliskiren in patients with type 2 diabetes: a prespecified secondary analysis of the ALTITUDE randomised controlled trial. *Lancet Diabetes Endocrinol* 2016;4:309–17.

64 Cherney DZ, Scholey JW, Jiang S *et al*. The effect of direct renin inhibition alone and in combination with ACE inhibition on endothelial function, arterial stiffness, and renal function in type 1 diabetes. *Diabetes Care* 2012;35:2324–30.

65 Cherney DZ, Lai V, Scholey JW *et al*. Effect of direct renin inhibition on renal hemodynamic function, arterial stiffness, and endothelial function in humans with uncomplicated type 1 diabetes: a pilot study. *Diabetes Care* 2010;33:361–5.

66 Elving LD, Wetzels JFM, van Lier HJJ *et al*. Captopril and atenolol are equally effective in retarding progression of diabetic nephropathy. Results of a 2 year randomised study. *Diabetologia* 1994;37:604–9.

67 Bakris GL, Weir MR, Secic M *et al*. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004;65:1991–2002.

68 Cherney DZ, Perkins BA, Soleymanlou N *et al*. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129:587–97.

69 Wanner C, Inzucchi SE, Lachin JM *et al*. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016;375:323–34.

70 Peters AL, Buschur EO, Buse JB *et al*. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care* 2015;38:1687–93.

71 Jennings DL, Kalus JS, Coleman CI *et al*. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Diabet Med* 2007;24:486–93.

72 Pham JT, Schmitt BP, Leehey DJ. Effects of dual blockade of the renin-angiotensin system in diabetic kidney disease: a systematic review and meta-analysis. *J Nephrol Therapeut* 2012;(Suppl 2):003.

73 Maione A, Navaneethan SD, Graziano G *et al*. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. *Nephrol Dial Transplant* 2011;26:2827-47.

74 Fried LF, Emanuele N, Zhang JH *et al*. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892–903.

75 Anantharaman R, Bhansali A, Bhadada SK *et al*. Anti-albuminuric efficacy of a combination of angiotensin converting enzyme inhibitor & angiotensin receptor blocker in type 1 DM with nephropathy. *Indian J Med Res* 2010;132:42–7.

 

76 Jacobsen P, Andersen S, Rossing K *et al*. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. *Nephrol Dial Transplant* 2002;17:1019–24.

77 Cooper WO, Hernandez-Diaz S, Arbogast PG *et al*. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;354:2443–51.

78 Li D, Yang C, Andrade S *et al*. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. *BMJ* 2011;343:d5931.

79 Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685–93.

80 Postma CT, Klappe EM, Dekker HM, Thien T. The prevalence of renal artery stenosis among patients with diabetes mellitus. *Eur J Intern Med* 2012;23:639–42.

81 Chowdhury TA. Taking precautions with angiotensin converting enzyme inhibitors. Clinically significant deterioration in renal function occurs rarely (letter). *BMJ* 1999;318:258.

82 Reams GP, Bauer JH, Gaddy P. Use of the converting enzyme inhibitor enalapril in renovascular hypertension. Effect on blood pressure, renal function, and the renin-angiotensin-aldosterone system. *Hypertension* 1986;8:290–7.

83 Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;351:585–92.

84 Anonymous. Sick day rules in kidney disease. *Drug and Therapeutics Bulletin* 2015;53:37.

85 Rossing P. Diabetic Nephropathy: worldwide epidemic and effects of current treatment on natural history. *Curr Diab Rep* 2006;6:479–483.

86 Schena FP, Gesualdo L. Pathogenic mechanisms of diabetic nephropathy. *J Am Soc Nephrol* 2005;16(Suppl 1):S30–3.

87 Adler S. Diabetic nephropathy: Linking histology, cell biology, and genetics. *Kidney Int* 2004;66:2095–106.

88 Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 1999;34:795–808.

89 Adler AI, Stevens RJ, Manley SE *et al.* Development and progression of nephropathy in type 2 diabetes: the United Kingdom Perspective Diabetes Study (UKPDS 64). *Kidney Int* 2003;63:225–32.

90 Angélique ME, Spoelstra-de Man, Catherine B *et al*. Rapid Progression of Albumin Excretion is an Independent Predictor of Cardiovascular Mortality in Patients with Type 2 Diabetes and Microalbuminuria. *Diabetes Care* 2001;24:2097–101.

91 Ritz E, Dikow R. Hypertension and antihypertensive treatment of diabetic nephrology. *Nat Clin Pract Nephrol* 2006;2:562–567.

92 Parving HH, Osterby R, Ritz E. Diabetic Nephropathy. In: Brenner BM, Levine S, editors. *The Kidney*. 6th ed. Philadelphia: WB Saunders, 2000: 1731–73.

93 Klag MJ, Whelton PK, Randall BL *et al*. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;334:13–18.

94 O'Seaghdha CM, Perkovic V, Lam TH *et al*. Blood pressure is a major risk factor for renal death: an analysis of 560 352 participants from the Asia-Pacific region. *Hypertension* 2009;54:509–15.

95 Singh R, Singh AK, Alavi N, Leehey DJ. Mechanism of increased angiotensin II levels in glomelular mesangial cells cultured in high glucose. *J Am Soc Nephrol* 2003;14:873–80.

96 American Diabetes Association: Hypertension Management in Adults with Diabetes (position statement). *Diabetes Care* 2004;27(Suppl 1):S65–7.

97 Tuttle KR, Bakris GL, Bilous RW *et al*. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864–83.

98 Beckett NS, Peters R, Fletcher AE *et al*. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–98.

99 Agarwal R, Andersen MJ. Prognostic Importance of clinic and home blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006;69:406–11.

100 Agarwal R, Andersen MJ. Blood pressure recordings within and outside the clinic and cardiovascular events in chronic kidney disease. *Am J of Nephrol* 2006;26:503–10.

101 Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with subsequent decline in glomerular filtration rate. *Arch Intern Med* 2006;166:846–52.

102 Minutolo R, Agarwal R, Borrelli S *et al*. Prognostic role of ambulatory blood pressure measurement in patients with non-dialysis kidney disease. *Arch Intern Med* 2011;171:1090–8.

103 Alderman MH. Salt, Blood Pressure and Human Health. *Hypertension* 2000;36:890–3.

104 Jones DW, Kim JS, Andrew ME *et al*. Body mass index and blood pressure in Korean men wnd Women: the Korean National Blood Pressure Survey. *J Hypertens* 1994;12:1433–7.

105 Whelton SP, Chin A, Xin X, HE J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Inter Med* 2002;136:493–503.

106 Chen L, Smith GD, Harbord RM, Lewis SJ. Alcohol intake and blood pressure: a systematic review implementing a Mendelian randomization approach. *PLoS Med* 2008;5:e52.

107 Dickinson HO, Mason JM, Nicolson DJ *et al*. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens* 2006;24:215–33.

108 Slagman MC, Waanders F, Hemmelder MH *et al*. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011;343:d4366.

109 Vogt L, Waanders F, Boomsma F *et al*. Effects of Dietary Sodium and Hydrochlorothiazide on the Antiproteinuric Efficacy of Losartan. *J Am Soc Nephrol* 2008;19:999–1007.

110 Navaneethan SD, Yehnert H, Moustarah F *et al*. Weight Loss Interventions in Chronic Kidney Disease. A Systematic Review and Meta-analysis. *Clin J Am Soc Nephrol* 2009;4:1565–74.

111 Chen JL, Lerner D, Ruthazer R *et al*. Association of physical activity with mortality in chronic kidney disease. *J Nephrol* 2008;21:243–52.

112 World Health Organization. *International guide for monitoring alcohol consumption and related harm*. Geneva: WHO, 2000.

113 Ravid, M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin dependent diabetes mellitus: A 7-year follow-up study. *Arch Intern Med* 1996;156:286–9.

114 Parving HH, Lehnert H, Bröchner-Mortensen J *et al*. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Eng J Med* 2001;345:870–8.

115 Brenner BM, Cooper ME, de Zeeuw D *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–9.

116 Rossing P, Hommel E, Schmidt UM, Parving HH. Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetalogia* 1994;37:511–6.

117 Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and the MICRO-HOPE substudy. *Lancet* 2000;355:253–9.

118 Standards of Medical Care in Diabetes – 2015: Summary of Revisions. *Diabetes Care* 2015;38(Suppl 1):S4.

 

119 Weber MA, Schiffrin EL, White WB *et al*. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. *J Hyperten* 2014;32:3–15.

120 KDOQI. Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kid Dis* 2007;49(Suppl 2):S12–154.

121 Mancia G, Fagard R, Narkiewicz K *et al*. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281–357.

122 James PA, Oparil S, Carter BL *et al*. 2014 evidence-based guidance for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–20.

123 Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016;352:i438.

124 National Institute for Health and Care Excellence. *Chronic kidney disease in adults: assessment and management*, NICE guideline CG182, issued July 2014 and modified March 2015.

125 Casas JP, Chua W, Loukogeorgakis S *et al*. Effects of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: system review and meta-analysis. *Lancet* 2005;366:2026–33.

126 Lewis EJ, Hunsicker LG, Clarke WR *et al*. Renoprotective effect of angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Eng J Med* 2001;345:851–60.

127 Barnett AH, Bain SC, Bouter P *et al*. Angiotensin-receptor blocker versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Eng J Med* 2004;351:1952–61.

128 Ennezat PV, Berlowitz M, Sonnenblick EH, Le Jemtel DH. Therapeutic implications of escape from angiotensin-converting enzyme inhibition in patients with chronic heart failure. *Curr Cardiol Rep* 2000;2:258–62.

129 Balcells E, Meng QC, Johnson WH Jnr *et al*. Angiotensin II formation from ACE and chymase in human and animal hearts: methods and species considerations. *Am J Physiol* 1997;273:H1769–74.

130 Mogensen CE, Neldam S, Tikkanen I *et al*. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440–4.

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

132 Perkovic V, Agarwal R, Fioretto P *et al*. Management of patients with diabetes and CKD: conclusions from a 'Kidney Disease: Improving Global Outcomes' (KDIGO) Controversies Conference. *Kidney Int* 2016;90:1175–83

133 Biesen WV, Fouque D, Wiecek A, Cochat P *et al*. A European renal best practice position statement on kidney disease and endorsement of KDIGO guidelines with some caveats for real life application. *Nephrol Dial Transplant* 2013;0:1–8.

134 Campbell NR, Khan NA, Hill MD *et al*. 2009 Canadian Hypertension Education Program Recommendations: the scientific summary – an annual update. *Can J Cardiol* 2009;25:271–7.

135 Dalla Vestra M, Simioni N, Masiero A. Renal effects of dual renin-angiotensin-aldosterone system blockade in patients with diabetic nephropathy. *Int Urol Nephrol* 2009;41:119–126.

136 Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. *Arch Intern Med* 2007;167:1930–6.

137 Rocha R, Stier CT Jnr, Kifor I *et al*. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology* 2000;141:3871–8.

138 Struthers AD. Aldosterone: cardiovascular assault. *Am Heart J* 2002;144:S2–7.

139 Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 2003;41:64–8.

140 Rachmani R, Slavachevsky I, Amit M *et al*. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study. *Diabet Med* 2004;21:471–5.

141 Epstein M, Buckalew V, Altamirano J *et al*. Eplerenone reduces proteinuria in type II diabetes: Implications for aldosterone involvement in the pathogenesis of renal dysfunction (Abstract). *J Am Coll Cardiol* 2002;39(Suppl A):249A.

142 Epstein M, Williams GH, Weinberger M *et al*. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;1:940–51.

143 Bakris GL, Agarwal R, Chan JC, Cooper ME *et al*. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;314:884–94.

144 Parving HH, Brenner BM, McMurridge AJ *et al*. Aliskiren trial in type 2 diabetes using cardiorenal end-points (ALTITUDE): Rationale and study design. *Nephrol Dial Transplant* 2009;24:1663–71.

145 Parving HH, Persson F, Lewis JB *et al*. Aliskiren combined with lorsartan in type 2 diabetes and nephropathy. *N Eng J Med* 2008;358:2433–46.

146 Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI Clinical Practice Guidelines on hypertension and antihypertensive agents in Chronic Kidney Disease. *Am J Kid Dis* 2004;43(5 Suppl 1):S1–290.

147 Weir MR. Acute fall in glomerular filtration rate with renin-angiotensin system inhibition: a biomeasure of therapeutic success? *Kidney Int* 2011;80:235–7.

148 US Food and Drug Administration. Public Health Advisory: Angiotensin-converting enzyme inhibitor (ACE inhibitor) drugs and pregnancy, 2006. Available from www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053113.htm [Accessed May 2017].

149 Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Eng J Med* 2002;347:1256–61.

150 Bridoux F, Hazzan M, Pallot JL *et al*. Acute renal failure after the use of angiotensin-converting enzyme inhibitors in patients without renal artery stenosis. *Nephrol Dial Transplant* 1992;7:100–104.

151 Kohli HS, Bhaskaran MC, Muthukmar T *et al*. Treatment-related acute renal failure in the elderly: a hospital-based prospective study. *Nephrol Dial Transplant* 2000;15:212–7.

152 Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectively of proteinuria in diabetic glomerulopathy. *Kidney Int* 1998;54:889–96.

153 Toto RD, Tian M, Fakouhi K *et al*. Effects of calcium channel blockers on proteinuria in patients with diabetic nephropathy. *J Clin Hypertens* 2008;10:761–9.

154 Neumann J, Ligtenberg G, Klein II *et al*. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004;65:1568–76.

155 Bleyer AJ, Hartman J, Brannon PC *et al*. Characteristics of sudden death in haemodialysis patients. *Kidney Int* 2006;69:2268–73.

 

156 Badve SV, Roberts MA, Hawley CM *et al*. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:1152–61.

157 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting inhibitor or calcium channel blocker vs diuretic: The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–97.

158 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke on transient ischaemic attack. *Lancet* 2001;358:1033–41.

159 Vonend O, Marsalek P, Russ H *et al*. Moxonidine treatment of hypertensive patients with advanced renal failure. *J Hypertens* 2003;21:1709–17.

160 Sarafidis PA, Blacklock R, Wood E *et al*. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;7:1234–41.

161 Einhorn LM, Zhan M, Hsu VD *et al*. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;169:1156–62.

162 Loutradis C, Tolika P, Skodra A *et al*. Prevalence of Hyperkalemia in Diabetic and Non-Diabetic Patients with Chronic Kidney Disease: A Nested Case-Control Study. *Am J Nephrol* 2015;42:351–60.

163 Weinberg JM, Appel LJ, Bakris G *et al*. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. *Arch Intern Med* 2009;169:1587–94.

164 Adler AI, Stratton IM, Neil HA *et al*. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–19.

165 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–13.

166 Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755–62.

167 Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;352:i717.

168 Takahashi S, Katada J, Daida H *et al*. Effects of mineralocorticoid receptor antagonists in patients with hypertension and diabetes mellitus: a systematic review and meta-analysis. *J Hum Hypertens* 2016;30:534–42.

169 Lambers Heerspink HJ, Tighiouart H, Sang Y *et al*. GFR decline and subsequent risk of established kidney outcomes: a meta-analysis of 37 randomized controlled trials. *Am J Kidney Dis* 2014;64:860–6.

170 ACCORD Study Group, Cushman WC, Evans GW *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–85.

171 SPRINT Research Group, Wright JT Jnr, Williamson JD *et al*. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;373:2103–16.

172 Banerjee D, Brincat S, Gregson H *et al*. Pulse pressure and inhibition of renin-angiotensin system in chronic kidney disease. *Nephrol Dial Transplant* 2005;21:975–8.

173 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23(Suppl 2):B54–64.

174 Wright JT Jnr, Bakris G, Greene T *et al*. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;288:2421–31.

175 Ismail-Beigi F, Craven TE, O'Connor PJ *et al*. Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. *Kidney Int* 2012;81:586–94.

176 Ruilope LM, Salvetti A, Jamerson K *et al*. Real function and intensive lowering of blood pressure in hypertensive participants of the Hypertension Optimal Treatment (HOT) Study. *J Am Soc Nephrol* 2001;12:218–25.

177 Cooper-DeHoff RM, Gong Y, Handberg EM *et al*. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304:61–8.

178 Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086–97.

179 de Zeeuw D, Remuzzi G, Parving HH *et al*. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004;110:921–7.

180 Bakris GL, Weir MR, Shanifar S *et al*. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003;163:1555–65.

181 Holtkamp FA, de Zeeuw D, de Graeff PA *et al*. Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. *Eur Heart J* 2011;32:1493–9.

182 Berl T, Hunsicker LG, Lewis JB *et al*. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol* 2005;16:2170–9.

183 Gaede P, Vedel P, Larsen N *et al*. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93.

184 Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int* 2013;83:377–83.

185 Estacio RO, Jeffers BW, Hiatt WR *et al*. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645–52.

186 Xie X, Liu Y, Perkovic V *et al*. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. *Am J Kidney Dis* 2016;67:728–41.

187 Cheng J, Zhang W, Zhang X *et al*. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. *JAMA Intern Med* 2014;174:773–85.

188 Imai E, Chan JC, Ito S *et al*. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia* 2011;54:2978–86.

189 Palmer SC, Mavridis D, Navarese E *et al*. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;385:2047–56.

190 van den Meiracker AH, Baggen RG, Pauli S *et al*. Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. *J Hypertens* 2006;24:2285–92.

 

191 Bushinsky DA, Williams GH, Pitt B *et al*. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney Int* 2015;88:1427–33.

192 Bakris GL, Pitt B, Weir MR *et al*. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *JAMA* 2015;314:151–61.

193 Weir MR, Bakris GL, Bushinsky DA *et al*. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;372:211–21.

194 Pitt B, Bakris GL, Bushinsky DA *et al*. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail* 2015;17:1057–65.

195 Weir MR, Bakris GL, Gross C *et al*. Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors. *Kidney Int* 2016;90:696–704.

196 McMahon EJ, Bauer JD, Hawley CM *et al*. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 2013;24:2096–2103.

197 de Brito-Ashurst I, Perry L, Sanders TA *et al*. The role of salt intake and salt sensitivity in the management of hypertension in South Asian people with chronic kidney disease: a randomised controlled trial. *Heart* 2013;99:1256–60.

198 MacMahon S, Peto R, Cutler J *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74.

199 Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996;275:1571–6.

200 Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979;59:8–13.

201 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32(Suppl 3):S112–9.

202 Foley RN, Murray AM, Li S *et al*. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;16:489–95.

203 M Kessler, F Zannad, P Lehert *et al.* Predictors of cardiovascular events in patients with end-stage renal disease: an analysis from the Fosinopril in Dialysis study. *Nephrol Dial Transplant* 2007;22:3573–79.

204 Stel VS, van de Luijtgaarden MW, Wanner C *et al*. The 2008 ERA-EDTA Registry Annual Report – a précis. *NDT Plus* 2011;4:1–13.

205 Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report, Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014. *Nephron* 2016;132(Suppl 1)145–54.

206 Vonesh EF, Snyder JJ, Foley RN *et al*. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int* 2004;66:2389–401

207 Liem YS, Wong JB, Hunink MG *et al*. Comparison of hemodialysis and peritoneal dialysis survival in the Netherland. *Kidney Int* 2007;71:153–8.

208 Collins AJ. Cardiovascular mortality in end-stage renal disease. *Am J Med Sci* 2003;325:163–7.

209 Sarnak MJ. Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis* 2003;41(Suppl):11–7.

210 Collins AJ, Foley R, Herzog C *et al*. Excerpts from the United States Renal Data System 2007 annual data report. *Am J Kidney Dis* 2008;51(Suppl 1):S1–320.

211 Agarwal R. Hypertension and survival in chronic hemodialysis patients – past lessons and future opportunities. *Kidney Int* 2005;67:1–13.

212 Hirakata H, Onoyama K, Hori K *et al*. The hemodynamic and humoral responses to tilting in diabetic patients on chronic hemodialysis treatment. *Clin Nephrol* 1987;27:298–303.

213 Itsuko I, Hirakata H, Sugimori H *et al*. Hemodialysis causes severe orthostatic reduction in cerebral blood flow velocity in diabetic patients. *Am J Kidney Dis* 1999;34:1096–104.

214 Peixoto AJ, Santos SF, Mendes RB *et al*. Reproducibility of ambulatory blood pressure monitoring in hemodialysis patients. *Am J Kidney Dis* 2000;36:983–90.

215 Dolan E, Stanton A, Thijs L *et al*. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005;46:156–61.

216 Agarwal R, Peixoto AJ, Santos SF, Zoccali C. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. *Clin J Am Soc Nephrol* 2006;1:389–98.

217 Agarwal R, Peixotob AJ, Santosc SF, Zoccalid C. Out-of-office blood pressure monitoring in chronic kidney disease. *Blood Press Monit* 2009;14:2–11.

218 Moriya H, Ohtake T, Kobayashi S. Aortic stiffness, left ventricular hypertrophy and weekly averaged blood pressure (WAB) in patients on haemodialysis. *Nephrol Dial Transplant* 2007;22:1198–204.

219 Rahman M, Griffin V, Heyka R, Hoit B. Diurnal variation of blood pressure; reproducibility and association with left ventricular hypertrophy in hemodialysis patients. *Blood Press Monit* 2005;10:25–32.

220 Zoccali C, Mallamaci F, Tripepi G *et al*. Prediction of left ventricular geometry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodialysis patients: CREED investigators. *J Hypertens* 1999;17:1751–8.

221 Agarwal R, Brim NJ, Mathenthiran J *et al*. Out-of-haemodialysis-unit blood pressure is a superior detriment of left ventricular hypertrophy. *Hypertension* 2006;47:62–8.

222 Amar J, Vernier I, Rossignol E *et al*. Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. *Kidney Int* 2000;57:2485–91.

223 Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2007;2:1228–34.

224 Verdecchia P, Angeli F. How can we use the results of ambulatory blood pressure monitoring in clinical practice? *Hypertension* 2005;46:25–6.

225 Liu M, Takahashi H, Morita Y *et al*. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrol Dial Transplant* 2003;18:563–9.

226 Port FK, Hulbert-Shearon TE, Wolfe RA *et al*. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis* 1999;33:507–17.

227 Goldfarb-Rumyantzev AS, Baird BC, Leypoldt JK, Cheung AK. The association between BP and mortality in patients on chronic peritoneal dialysis. *Nephrol Dial Transplant* 2005;20:1693–1701.

228 Kalantar-Zadeh K, Kilpatrick RD, Kopple JD. Reverse epidemiology of blood pressure in dialysis patients. *Kidney Int* 2005;67:2067; author reply 2067–8.

229 Li Z, Lacson E Jnr, Lowrie EG *et al*. The epidemiology of systolic blood pressure and death risk in hemodialysis patients. *Am J Kidney Dis* 2006;48:606–15.

230 Mazzuchi N, Carbonell E, Fernández-Cean J. Importance of blood pressure control in hemodialysis patient survival. *Kidney Int* 2000;58:2147–54.

231 Zager PG, Nikolic J, Brown RH *et al*. 'U' curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int* 1998;54:561–9.

 

232 Charra B, Calemard E, Ruffet M *et al*. Survival as an index of adequacy of dialysis. *Kidney Int* 1992;41:1286–91.

233 Suzuki H, Kanno Y, Sugahara S *et al*. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. *Am J Kidney Dis* 2008;52:501–6.

234 Zannad F, Kessler M, Lehert P *et al*. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006;70:1318–24.

235 Cice G, Ferrara L, D'Andrea A *et al*. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003;41:1438–44.

236 Tepel M, Hopfenmueller W, Scholze A *et al*. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant* 2008;23:3605–12.

237 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 randomised controlled trials. *Lancet* 2009;373:1009–15.

238 Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. *Hypertension* 2009;53:860–6.

239 Agarwal R, Sinha AD, Pappas MK *et al*. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant* 2014;29:672–81.

240 Levin NW, Kotanko P, Eckardt KU *et al*. Blood pressure in chronic kidney disease stage 5D – report from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2007;77:273–84.

241 K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45(Suppl 3):S1–153.

242 Klassen PS, Lowrie EG, Reddan DN *et al*. Association between pulse pressure and mortality in patients undergoing maintenance haemodialysis. *JAMA* 2002:287:1548–55.

243 Wilson J, Shah T, Nissenson AR. Role of sodium and volume in the pathogenesis of hypertension in hemodialysis. *Seminars in dialysis* 2004;17260–4.

244 Agarwal R, Weir MR. Dry-Weight: A Concept Revisited in an Effort to Avoid Medication-Directed Approaches for Blood Pressure Control in Hemodialysis Patients. *CJASN* 2010;5:1255–60.

245 Thomson GE, Waterhouse K, McDonald HP Jnr, Friedman EA. Hemodialysis for chronic renal failure. Clinical observations*. Arch Intern Med* 1967;120:153–67.

246 Charra B, Bergström J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. *Am J Kidney Dis* 1998;32:720–4.

247 Ozkahya M, Toz H, Qzerkan F *et al*. Impact of volume control on left ventricular hypertrophy in dialysis patients. *J Nephrology* 2002;15:655–60.

248 Aşci G, Özkahya M, Duman S *et al*. Volume control associated with better cardiac function in long-term peritoneal dialysis patients. *Peritoneal dialysis International* 2006;26: 85–8.

249 Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive haemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009;53:500–7.

250 Luik AJ, Charra B, Katzarski K *et al.* Blood pressure control and hemodynamic changes in patients on long time dialysis treatment. *Blood Purif* 1998;16:197–209.

251 Zilch O, Vos PF, Oey PL *et al.* Sympathetic hyperactivity in haemodialysis patients is reduced by short daily haemodialysis. *J Hypertens* 2007;25:1285–9.

252 Culleton BF, Walsh M, Klarenbach SW *et al*. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* 2007;298:1291–9.

253 Pierratos A, Ouwendyk M, Francoeur R *et al*. Nocturnal hemodialysis: three-year experience. *J Am Soc Nephrol* 1998;9:859–68.

254 Shoji T, Tsubakihara Y, Masamitsu F *et al*. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 2004;66:1212–20.

255 Bragg-Gresham JL, Fissell RB, Mason NA *et al*. Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). *Am J Kidney Dis* 2007;49:426–31.

256 Movilli E, Gaggia P, Zubani R *et al*. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. *Nephrol Dial Transplant* 2007;22:3547–52.

257 Onofriescu M, Hogas S, Voroneanu L *et al*. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2014;64:111–8.

258 Roueff S, Martin E, Chauffert ML *et al*. Brain natriuretic peptide variations are linked to volume status in hemodialysis patients. *Clin Nephrol* 2008;70:508–13.

259 Brennan JM, Ronan A, Goonewardena S *et al*. Handcarried ultrasound measurement of the inferior vena cava for assessment of intravascular volume status in the outpatient hemodialysis clinic. *Clin J Am Soc Nephrol* 2006;1:749–53.

260 Hegstrom RM, Murray JS, Pendras JP *et al*. Hemodialysis in the treatment of chronic uremia. *Trans Am Soc Artif Intern Organs* 1961;7:136–52.

261 Rigby-Matthews A, Scriber BH, Ahmad S. Control of interdialytic weight gain does not require fluid restriction in hemodialysis (HD) patients (Abstract). *J Am Soc Nephrol* 1999;10:267A.

262 Craswell PW, Hird VM, Judd PA *et al*. Plasma renin activity and blood pressure in 89 patients receiving maintenance haemodialysis therapy. *Br Med J* 1972;4:749–53.

263 Covic A, Goldsmith DJ, Venning MC, Ackrill P. Long-hours home haemodialysis – the best renal replacement therapy method? *QJM* 1999;92:251–260.

264 Ozkahya M, Ok E, Toz H *et al*. Long-term survival rates in haemodialysis patients treated with strict volume control. *Nephrol Dial Transplant* 2006;21:3506–13.

265 Kayikcioglu M, Tumuklu M, Ozkahya M *et al*. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant* 2009;24:956–62.

266 Maduell F, Navarro V. Dietary salt intake and blood pressure control in haemodialysis patients. *Nephrol Dial Transplant* 2000;15:2063.

267 Mc Causland FR, Waikar SS, Brunelli SM. Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. *Kidney Int* 2012;82:204–11.

268 Medcalf JF, Harris KP, Walls J. Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. *Kidney Int* 2001;59:1128–33.

269 Ni X, Zhang J, Zhang P *et al*. Effects of spironolactone on dialysis patients with refractory hypertension: a randomized controlled study. *J Clin Hypertension (Greenwich)* 2014;16:658–63.

270 Georgianos PI, Agarwal R. Pharmacotherapy of hypertension in chronic dialysis patients. *Clin J Am Soc Nephrol* 2016;11:2062–27.

271 University Hospital Brest, Clinical Trial: NCT01848639: ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST), 2013. Available from https://clinicaltrials.gov/ct2/show/NCT01848639 [Accessed May 2017].

 

The Association of British Clinical Diabetologists (ABCD) is the national organisation of consultant physicians in Britain who specialise in diabetes mellitus. Most are also acute general physicians, and many are also specialists in endocrinology and lipid metabolism.

The Renal Association is the professional body for UK nephrologists and renal scientists in the UK. From its foundation in 1950, the Renal Association has been active in promoting and disseminating research that may ultimately improve outcomes for patients with kidney disease.

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