Renal complications

Lowering blood pressure targets

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The emergence of systolic blood pressure (BP) as a major determinant of renal and cardiovascular morbidity and mortality has led to a progressive lowering of recommended treatment and target thresholds.

While previous BP treatment thresholds were determined by evidence from randomised trials, the current treatment thresholds have arisen from a combination of observational data (e.g. Adler et al, 2000) and data from non-diabetic proteinuric renal disease (e.g. Peterson et al, 1995). The direct confirmation of both the safety and efficacy of more aggressive BP lowering in people with diabetes from clinical trials has been lacking.

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The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial (de Galan et al, 2009; summarised alongside) adds flesh to the bones of the argument for more aggressive BP lowering in people with diabetes. As part of the ADVANCE trial design, angiotensin-converting enzyme inhibitor and diuretic therapy, or placebo, was given to people with type 2 diabetes. Participants with an initial systolic BP <120 mmHg and those with BP 120–139 mmHg demonstrated similar reductions in the onset of microalbuminuria and progression of albuminuria to participants with BP >140 mmHg. Benefits to glomerular filtration rate and progression to end-stage renal disease (ESRD) were not observed, which was at least in part the result of a low incidence of chronic kidney disease (CKD) in the study population.

The ADVANCE trial suggests that, unlike aggressive glucose control in type 2 diabetes (where safety has been questioned), more aggressive BP control appears to be safe, at least in the age group studied (mean age 66 years).

In a single centre cohort study of people with CKD – half of whom had diabetes – Agarwal (2009, summarised overpage) again confirms the benefits of controlled BP (<130/80 mmHg) on the development of ESRD and death. However, in older participants (aged >65 years), and particularly those with advanced CKD, a BP <110/70 mmHg was associated with increased all-cause mortality. Agarwal's (2009) findings suggesting that more aggressive BP lowering should be avoided in older people with CKD.

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

Peterson JC, Adler S, Burkart JM et al (1995) Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* **123**: 754–62

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Improved renoprotection following BP-lowering treatment

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 An important determinant of kidney disease among people with diabetes is blood pressure (BP), with recommended thresholds for treatment to lower BP being 130/80 mmHg for those with diabetes and 125/75 mmHg for those with nephropathy.

2 The authors of this study aimed to determine whether lowering BP further than the current recommendations would result in improved renal outcomes among participants in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) study.

3 Participants (n=11 140; average BP 145/81 mmHg) had type 2 diabetes and, regardless of their BP at the start of the study, were randomised to receive either placebo (n=5571; mean age 66 years) or a fixed-dose combination of perindopril-indapamide (n=5569; mean age 66 years).

4 During the mean 4.3 years of follow-up, those randomised to receive perindopril-indapamide experienced a 21% reduction in the risk of a renal event (P<0.0001), which followed from the reduced risk of micro- and macroalbuminuria (both P<0.003).

5 The authors found that lowering BP using perindopril-indapamide provided renoprotection that was seen even among those whose BP on randomisation was below the current recommendations for initiation of such treatment.

de Galan BE, Perkovic V, Ninomiya T et al (2009) Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* **20**: 883–92

CLINICAL JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Systolic and diastolic BP predict ESRD and all-cause mortality

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 While mean arterial blood pressure (BP) is a measure frequently used in clinical trials, the pulsatile component of BP is known to influence outcomes in older people.

2 The author of this study examined systolic and diastolic BP as indicators of the of risk of end-stage renal disease (ESRD) and mortality among those with chronic kidney disease (CKD).

3 In this prospective cohort study, undertaken at a veterans affairs hospital in the US, 218 participants (mean age 68.4 years) with CKD (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), 48% of whom had diabetes, were enrolled.

4 Follow-up was up to 7 years and, by study end, 63 participants had progressed to ESRD. Participants with moderate systolic BP control (130–149 mmHg) had a hazard ratio of 3.87, and those with poor control (>150 mmHg) had a hazard ratio of 9.09, when compared with well controlled individuals (<130 mmHg), for ESRD (P<0.001).

5 All-cause mortality was found to be more accurately predicted by a higher systolic BP and lower diastolic BP than by the comparison of either BP component individually.

6 The author concluded that BP may have disparate effects on ESRD and mortality outcomes, and, therefore, lowering BP beyond 110/70 mmHg in older people with CKD should be avoided.

Agarwal R (2009) Blood pressure components and the risk for end-stage renal disease and death in chronic kidney disease. *Clin J Am Soc Nephrol* **4**: 830–7

ARCHIVES OF DISEASE IN CHILDHOOD

No improvement in UK prevalence of childhood microalbuminuria

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓

1 Microalbuminuria (a predictor of diabetic nephropathy) was prospectively investigated in children aged <16 years with type 1 diabetes to assess whether improved glycaemic control has reduced its prevalence.

2 Participants were being treated in the UK and were assigned to three groups based on their year of diagnosis (A: 1986–9, n=165; B: 1990–3, n=179; C: 1994–6, n=183), and were followed-up for 10 years.

3 While glycaemic control improved during the study period (P<0.001), the risk of developing microalbuminuria was not improved by year of diagnosis (hazard ratio 1.05, 95% confidence interval 0.99–1.12, P=0.11).

4 The authors called for more renoprotective drug intervention for children with type 1 diabetes.

Amin R, Widmer B, Dalton RN, Dunger DB (2009) Unchanged incidence of microalbuminuria in children with type 1 diabetes since 1986: a UK based inception cohort. *Arch Dis Child* **94**: 258–62

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Avosentan reduces albumin excretion

Readability	✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓

1 In this randomised controlled study, the effect of avosentan on urinary albumin excretion rate (UAER) in people with diabetic nephropathy was investigated.

2 Participants (n=286; UAER 0.2–5.6 mg/min; blood pressure <180/110 mmHg) were randomised to receive either avosentan (5, 10, 25 or 50 mg) or placebo over a 12-week period, in addition to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

3 Mean relative UAER decreased significantly for all avosentan doses (20.9, 16.3, 25.0 and 29.9%, respectively), but increased (35.5%) among those receiving placebo (P<0.01 for all dosages). Higher doses of avosentan (≥25 mg) were significantly associated with oedema (P=0.01).

4 The authors concluded that there may be a clinically valuable role for avosentan in conjunction with ACE inhibitors and ARBs.

Wenzel RR, Littke T, Kuranoff S (2009) Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* **20**: 655–64

DIABETES RESEARCH AND CLINICAL PRACTICE

Higher HbA_{1c} linked to increased mortality during haemodialysis

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The impact of glycaemic control on survival among people (n=122; mean age 59.9±11.9 years) with diabetes on haemodialysis was studied over a mean of 46±19 months.

2 Poor glycaemic control (mean HbA_{1c} ≥6.3% [≥45 mmol/mol]) was significantly associated with lower cumulative survival than good glycaemic control (mean HbA_{1c} <6.3% [<45 mmol/mol; P=0.0084]).

3 The authors concluded that poor glycaemic control is an independent predictor of poor prognosis among those on haemodialysis, and glycaemic control should be carefully managed in this at-risk population.

Ishimura E, Okuno S, Kono K et al (2009) Glycemic control and survival of diabetic hemodialysis patients – importance of lower hemoglobin A1C levels. *Diabetes Res Clin Pract* **83**: 320–6

> *"Poor glycaemic control is an independent predictor of poor prognosis among those on haemodialysis, and glycaemic control should be carefully managed in this at-risk population."*