Nephropathy

RAS blockade for primary prevention of nephropathy in type 1 diabetes

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The increased mortality associated with type 1 diabetes remains most strongly associated with the presence of macroalbuminuria and chronic kidney disease (Groop et al, 2009; summarised overpage). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) used in aggressive blood pressure (BP) management are effective in slowing the progression of diabetic nephropathy, but premature death or progression to end-stage renal disease remain inevitable in this setting, making primary prevention strategies increasingly important if the mortality burden is to be reduced.

Firm data supporting a role for renin–angiotensin system (RAS) blockade in preventing the development of nephropathy in normotensive people with type 1 diabetes and normal levels of albuminuria (normoalbuminuria) is lacking. The low incidence of microalbuminuria and long timescale of the development of nephropathy in type 1 diabetes make answering the RAS blockade question a considerable challenge.

The EUCLID Study Group (1997) reported a small reduction in albuminuria at 2 years with the ACE inhibitor lisinopril (10–20 mg) in people with type 1 diabetes and normoalbuminuria, as well as a lower, but not statistically significant, rate of progression to microalbuminuria.

The DIRECT Prevent and DIRECT Protect trials (Bilous et al, 2009; summarised overpage) studied the effect of maximum dose candesartan (32 mg) on retinopathy and albumin excretion in people with type 1 diabetes and normal BP, and albumin excretion over a longer period (median 4.7 years). Although the studies were not powered for renal endpoints, Bilous et al (2009) do provide us with some useful data on ARB therapy in preventing microalbuminuria in type 1 diabetes. While the incidence of microalbuminuria was 3-fold greater over the study period in the participants with underlying retinopathy (DIRECT Protect), candesartan had no statistically significant effect on the overall incidence of microalbuminuria in the trials, and only a modest and non-significant effect on the rate of rise of albumin excretion.

> ***"The door remains open for longer and adequately powered investigations into the effect of full dose RAS blockade on preventing or slowing onsert of microalbuminuria in normotensive, normoalbuminuric people with type 1 diabetes."***

This data set – the largest to date – fails to make the case for the routine clinical use of ARBs in people with type 1 diabetes and normoalbuminuria. Low doses of losartan (50 mg) and enalapril (10 mg) also failed to demonstrate significant effects on albuminuria progression and renal morphology in people with type 1 diabetes and normoalbuminuria (Mauer et al, 2009; summarised alongside).

Despite the findings to date, the door remains open for longer (>5 years) and adequately powered investigations into the effect of full dose RAS blockade on preventing or slowing onset of microalbuminuria in normotensive, normoalbuminuric people with type 1 diabetes.

EUCLID study group (1997) Randomised controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* **349**: 1787–92

NEJM

Renin–angiotensin blockade ineffective in slowing progression to nephropathy

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

1 The authors investigated whether the progression to nephropathy and retinopathy could be slowed by blockade of the renin–angiotensin system through early drug administration.

2 This multicentre, controlled trial involved the randomisation of 285 normotensive participants with type 1 diabetes who had normoalbuminuria to receive losartan (100 mg daily), enalapril (20 mg daily) or placebo. Follow-up was for 5 years.

3 The primary end-point was change in the fraction of glomerular volume that was occupied by mesangium assessed by kidney biopsy.

4 Analysis was performed on an intention-to-treat basis. A total of 90% of participants completed a renal biopsy at 5 years.

5 No significant difference in the mesangial fractional volume per glomerulus was found between the control, enalapril (P=0.38) and losartan (P=0.26) groups during the study period.

6 The 5-year cumulative incidence of microalbuminuria was significantly higher for the losartan group (17%; P=0.01 log rank test) than for control (6%). Enalapril was not significantly different (4%; P=0.96 log rank test).

7 Conversely, enalapril and losartan reduced the odds of progression to retinopathy by 65% (95% confidence interval [CI] 0.14–0.85) and 70% (95% CI 0.12–0.73), respectively.

8 These data suggest that progression to nephropathy is not slowed by early administration of agents that block the renin–angiotensin system.

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

DIABETES CARE

Structured care improves renal outcomes in T2D

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

1 Structured care has previously been shown to reduce the complications of type 2 diabetes (T2D). The authors sought to apply this success to the management of renal complications.

2 Chinese people (n=205) with T2D and plasma creatinine levels 150–350 µmol/L were randomly assigned to receive structured (n=104) or usual (n=101) care.

3 Those receiving structured care were managed according to a protocol consisting of five treatment goals: blood pressure <130/80 mmHg, HbA_{1c} <7% (<53 mmol/mol), low-density lipid cholesterol <2.6 mmol/L, triglyceride <2 mmol/L, and ongoing therapy with renin–angiotensin blockers.

4 Primary end-points were death, creatinine >500 µmol/L or dialysis at 2 years follow-up.

5 Following adjustment for study site, age and sex, the structured and usual care groups achieved similar results for end points (23.1% and 23.8%, respectively).

6 After adjustment, a significantly greater number of people in the structured care group achieved ≥three of the protocol's treatment goals (P<0.001) and those who achieved three goals had reduced risk of the primary end points (relative risk 0.43; 95% confidence interval 0.21–0.86).

7 The authors concluded that protocol-driven, structured care for people with T2D and renal insufficiency increased the likelihood that multiple treatment targets would be achieved, which reduced the risk of end-stage renal disease or death.

Chan JC, So WY, Yeung CY et al (2009) Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care* **32**: 977–82

ANNALS OF INTERNAL MEDICINE

Angiotensin-receptor blocker fails to prevent microalbuminuria

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

1 The angiotensin-receptor blocker candesartan was compared with placebo to determine its relationship to new onset microalbuminuria and rate of change in albuminuria.

2 Participants (n=5231) were mostly normotensive, all were normoalbuminuric and were assigned to candesartan 16–32 mg/day or placebo.

3 Candesartan did not reduce the risk of microalbuminuria compared with placebo at a median of 4.7 years (P=0.60). A 5.53% reduction in the rate of change in albuminuria was found in the candesartan group compared with placebo (P=0.024).

4 In a patient population that was largely normotensive, candesartan failed to prevent microalbuminuria.

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

DIABETOLOGIA

BP changes predict microalbuminuria in young people with T1D

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

1 The authors investigated whether ambulatory blood pressure (ABP) was associated with albumin excretion, and if BP changes could act as predictors of microalbuminuria in young people with type 1 diabetes (T1D).

2 The ABP of 509 young people with T1D (10.7–22.6 years) were recorded along with annual assessment of three morning urinary albumin: creatinine ratios (ACRs), and HbA_{1c}, daytime and nocturnal BP.

3 Participants were followed for a median of 2.2 years. A total of 19 participants developed microalbuminuria by study end.

4 Following adjustment for potential confounders, ABP at baseline was found to be independently associated with ACR (P<0.001).

5 Changes in BP may identify people at risk of microalbuminuria and allow early therapy for prevention.

Marcovecchio ML, Dalton RN, Schwarze CP et al (2009) Ambulatory blood pressure measurements are related to albumin excretion and are predictive for risk of microalbuminuria in young people with type 1 diabetes. *Diabetologia* **52**: 1173–81

DIABETES

T1D mortality can be graded by presence and severity of CKD

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

1 As part of the FinnDiane study, the authors assessed premature all-cause mortality among people with type 1 diabetes (T1D) (n=4201).

2 By study end, 291 people had died, giving a 3.6-fold (95% confidence interval 3.2–4.0) increase in deaths than in the age- and sex-matched general population.

3 Microalbuminuria, macroalbuminuria and end-stage chronic kidney disease (CKD) were associated with 2.8, 9.2, 18.3 times higher standardised mortality ratio, respectively. Participants with normoalbuminuria were not found to have a mortality excess beyond the general population.

4 The authors showed a graded association between CKD and mortality, highlighting the clinical importance of preventing kidney disease in people with T1D.

Groop PH, Thomas MC, Moran JL et al (2009) The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes* **58**: 1651–8

> *"The authors showed a graded association between chronic kidney disease and mortality, highlighting the clinical importance of preventing kidney disease in people with type 1 diabetes."*