Nephropathy

KIDNEY & BLOOD PRESSURE RESEARCH

Losartan plus pioglitazone provides superior renoprotection than losartan alone

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

1 This Chinese study was undertaken in order to ascertain whether adding pioglitazone to losartan was more effective in slowing the progression of chronic renal failure in people with diabetic nephropathy.

2 Sixty individuals were enrolled in this randomised, controlled trial. Inclusion criteria were: type 2 diabetes; diabetic nephropathy (chronic kidney disease stage 3 or 4); aged 42–80 years.

3 The 60 participants were split into 2 groups depending on the severity of their CKD: 30 with stage 3 and 30 with stage 4. Each group were randomly assigned to monotherapy (losartan 100mg daily) or dual therapy (losartan 100mg daily plus pioglitazone 30mg daily).

4 All participants received the same basic care: low-protein diet, conventional insulin therapy and antihypertensives. Measurements (blood pressure, fasting blood glucose, HbA_{1c} and renal markers) were recorded at baseline, and at 3-month intervals over 12 months.

5 The groups receiving dual therapy had significantly lower serum creatinine ($P<0.01$), fasting blood glucose ($P<0.01$), and proteinuria ($P<0.001$) at 12 months. Declines in creatinine clearance (except in stage 4) and mean GFR in all dual therapy groups were significantly slower than the monotherapy group ($P<0.01$ and $P<0.02$, respectively).

6 The authors conclude that losartan provides greater renoprotection when combined with pioglitazone.

Jin HM, Pan Y (2007) Renoprotection provided by losartan in combination with pioglitazone is superior to renoprotection provided by losartan alone in patients with type 2 diabetic nephropathy. *Kidney & Blood Pressure Research* **30**: 203–11

Beyond blood pressure and glucose control

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Over the past 25 years, the central role of blood pressure control in reducing the rate of decline of renal function in diabetic nephropathy has become embedded in clinical practice – with blockade of the renin–angiotensin system (RAS) the cornerstone of current antihypertensive treatment regimens. However, despite our best attempts to control both blood pressure and blood glucose rigorously, many people with diabetes and nephropathy progress to end-stage renal disease.

Work in experimental nephropathy led to the later demonstration of the efficacy of RAS blockade in human diabetic nephropathy. A relationship between reduction in proteinuria and amelioration of decline in renal function has been known for some time and this may, in part, explain some of the differential effects of the antihypertensive drug classes on the progression of diabetic nephropathy. If blood pressure is controlled rigorously (< 120/75 mmHg), and that is a big 'if' for many people, does the possibility of reducing proteinuria by other means offer advantages to the person with diabetic nephropathy, and is reduction in proteinuria a surrogate marker of other important changes occurring in the kidney at a cellular level?

Thiazolidinediones (TZDs) have been shown to reduce proteinuria in experimental nephropathy and short-term human studies. Jin and Pan's study (summarised on the right) shows that in people with type 2 diabetes and nephropathy the addition of pioglitazone both controlled blood pressure (with blockade of the RAS) and significantly reduced proteinuria at 1 year. Convincing evidence of renoprotection requires the demonstration of more than lowering of proteinuria, and longer-term studies are needed to see if this intervention will lead to meaningful benefits in preventing loss of renal function. It is to be hoped that the current uncertainties over the long-term cardiovascular safety of TZDs does not translate into loss of a potential new therapeutic approach to nephropathy in type 2 diabetes.

TRANSPLANTATION

Islet transplantation does not appear to affect renal function

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

1 This paper presents the interim results of a single-centre, prospective, crossover, cohort study comparing intensive medical therapy with islet cell transplant on the progression of renal complications in people with type 1 diabetes.

2 There have been 44 people with type 1 diabetes enrolled in the study between January 2002 and January 2005. All receive intensive medical therapy and as islet cell donors become available, the best-matched person receives the transplant. There were 21 transplants to December 2006.

3 The primary endpoint is rate of change in measured GFR, with secondary endpoints of rate of eGFR and albuminuria.

4 The transplantees have been followed up for a median of 29 months and their results have been compared with those receiving medical therapy (median 29.5 months).

5 The results show that there is no significant difference in rate of decline in measured GFR between the two groups. There was also no difference between the groups in terms of secondary endpoints.

Fung MA, Warnock GL, Ao Z et al (2007) The effect of medical therapy and islet cell transplantation on diabetic nephropathy: an interim report. *Transplantation* **84**: 17–22

"Adding irbesartan early was more cost-saving and cost-effective than delaying treatment until nephropathy was advanced"

CLINICAL THERAPEUTICS

Early use of irbesartan is cost-effective in Canada

✓	
✓✓	
✓✓	

1 The aim of this Canadian study was to determine whether or not early treatment with irbesartan is cost-effective relative to conventional care in hypertensive people with type 2 diabetes and a history of renal disease. The study also assessed whether it is cost-effective to treat earlier or later in the development of renal disease.

2 Compared in this study were three strategies for the management of hypertension in people with early renal disease and type 2 diabetes: conventional treatment for hypertension excluding angiotensin II receptor antagonists; early addition of irbesartan 300mg daily to conventional treatment; late addition of irbesartan to conventional treatment.

3 A Markov model was used to simulate progression of renal disease in people with type 2 diabetes and hypertension over 25 years and a cost-effectiveness analysis was conducted with the outcome measured in life years gained (LYG).

4 Adding irbesartan early was more cost-saving and cost-effective than delaying treatment until nephropathy was advanced (Canadian $54 000 saved, 0.45 LYG) and conventional antihypertensive treatment (Canadian $68 400 saved, 0.62 LYG).

5 These savings were accrued by offsetting the increased drug cost of irbesartan against the savings to the health service from delaying overt nephropathy.

6 The authors suggest that the earlier irbesartan is added to hypertension treatment in people with type 2 diabetes without overt nephropathy, the greater the savings to the Canadian health system.

Coyle D, Rodby R, Soroka S et al (2007) Cost-effectiveness of irbesartan 300 mg given early versus late in patients with hypertension and a history of type 2 diabetes and renal disease: a Canadian perspective. *Clinical Therapeutics* **29**: 1508–23

"Angiotensin II receptor blockers (such as valsartan) are renoprotective, irrespective of BP"

HYPERTENSION RESEARCH

Valsartan is renoprotective despite change in BP

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

1 This Japanese study was undertaken to investigate the effects of replacing or adding valsartan to a calcium channel blocker in hypertensive people with type 2 diabetes and diabetic nephropathy (urinary albumin excretion [UAE] 30–300mg/g creatinine).

2 Twenty-eight people who had been on a calcium channel blocker for 6 months were assigned to two groups depending on their blood pressure (BP).

3 Those with a BP>130/85 mmHg (n=17) had valsartan added to their calcium channel blocker, while those who had a BP<130/85 mmHg (n=11)had the calcium channel blocker replaced with valsartan. Both groups were followed up at 3, 6 and 12 months.

4 In both groups UAE decreased significantly following addition of valsartan. The amount that UAE decreased was not significantly different between the groups.

5 This decrease in UAE suggests that angiotensin II receptor blockers (such as valsartan) are renoprotective, irrespective of BP.

Katayama S, Yagi S, Yamamoto H et al (2007) Is renoprotection by angiotensin receptor blocker dependent on blood pressure?: the Saitama Medical School, Albuminuria Reduction in Diabetics with Valsartan (STAR) study. *Hypertension Research* **30**: 529–33

KIDNEY INTERNATIONAL

Histone deacetylase inhibitors: Novel therapeutic agents?

Readability	✓
Applicability to practice	N/A
WOW! factor	✓✓

1 Histone deacetylase inhibitors regulate gene transcription.

2 They are currently undergoing clinical trials as anti-cancer agents and have shown significant activity against a variety of tumours at well-tolerated doses.

3 A few trials have demonstrated the antifibrotic and renoprotective effects of histone deacetylase inhibitors in diabetic kidneys and are investigating the possible mechanisms of this. One study has shown that a dose of a histone deacetylase inhibitor that did not affect blood glucose, but significantly decreased proteinuria in rats with diabetes.

4 The authors of this review conclude that while our knowledge of the biology of these agents is limited, they may prove to be a novel class of therapeutic agents for diabetic nephropathy.

Lee HB, Noh H, Seo JY et al (2007) Histone deacetylase inhibitors: A novel class of therapeutic agents in diabetic nephropathy. *Kidney International* **72**: S61–6

KIDNEY INTERNATIONAL

Blocking ROS-activated pathways may prevent CKD

Readability	✓
Applicability to practice	N/A
WOW! factor	✓✓

1 Evidence suggests that reactive oxygen species (ROS) play a major part in the development of diabetes-related complications, including CKD.

2 The production of free radicals is increased in people with diabetes and antioxidants may be helpful in treating people with diabetes and CKD.

3 ROS mediate high glucose and angiotensin II signals in renal cells, and so are important in hyperglycaemia and renal fibrosis.

4 The authors suggest that combining strategies to prevent overproduction of ROS and to block ROS-activated pathways may be effective in the prevention of the development and progression of CKD in diabetes.

Lee HB, Seo JY, Yu MR et al (2007) Radical approach to diabetic nephropathy. *Kidney International* **72**: S67–70