Nephropathy

Blocking the RAAS: Some answers but more questions

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Attempts to delay progression of diabetic nephropathy continue to centre on more intensive blockade of the renin-angiotensin-aldosterone system (RAAS), the hypothesis being that greater lowering of proteinuria will afford greater "renoprotection" – leading ultimately to slower progression and, ideally, arrest of the decline to end-stage renal disease.

A number of antihypertensive drug classes lower both blood pressure and proteinuria, with some degree of the latter being a direct result of a fall in the former. Clarification of the specific contribution to proteinuria lowering of these agents has proved challenging as a result of poor study design and sub-maximal dosing. Furthermore, reduction in proteinuria is still a surrogate measure for the hard clinical endpoints of end-stage renal disease and death.

A direct comparison of the renal effects of angiotensin receptor (AR) blockade and mineralocorticoid receptor antagonism in diabetic nephropathy has not previously been made. Medhi et al (2009; summarised alongside) studied individuals from a multi-ethnic USA-based population with type 2 diabetes to determine the effects of AR blockade (losartan 100 mg), mineralocorticoid receptor antagonism (spironolactone 25 mg) or placebo in people already treated with supramaximal doses of the angiotensin-converting enzyme (ACE) inhibitor lisinopril (80 mg). In addition to the ACE inhibitor, participants received, on average, a further three antihypertensive drugs, although no calcium channel blockers were used for intensive blood-pressure lowering.

Average blood pressure across the study period was <130/80 mmHg in all treatment arms. Proteinuria reduction was significantly greater in the spironolactone treatment arm than in the placebo and losartan arms. Although proteinuria also reduced in the losartan arm, the sample size (n=27 in that arm) lacked power to demonstrate statistical significance.

Hyperkalaemia sufficient to require discontinuation was observed only in the spironolactone arm in two of the 27 people randomsied to that treatment. A significant rise in serum creatinine was observed in one case each in the placebo and spironolactone arms. Spironolactone treatment would appear to be relatively safe when used in people with serum creatinine levels <160 µmol/L and afford greater proteinuria reduction than supramaximal doses of an ACE inhibitor or an add-on AR blockade. However, given the findings of the ONTARGET study (Mann et al, 2008), we still need hard endpoint studies before mineralocorticoid antagonism is adopted as part of routine clinical practice.

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

HYPERTENSION RESEARCH

Diabetes linked to sustained uncontrolled HPT

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

1 Factors associated with uncontrolled hypertension (HPT) were assessed using Japan Home vs Office Blood Pressure Measurement Evaluation Study data.

2 People (n=3303; mean age 66.2±10.5 years; men 44.7%) with HPT were enrolled and blood pressure (BP) was measured morning and evening. A BP >135/85 mmHg was considered to be indicative of HPT.

3 Sustained uncontrolled HPT (morning and evening) occurred in 42.0% of participants and was associated with male sex, renal disease and diabetes.

4 Uncontrolled morning HPT was associated with poorer prognosis and should be considered useful in evaluating cardiovascular disease risk.

Obara T, Ito K, Ohkubo T et al (2009) Uncontrolled hypertention base on morning and evening home blood pressure measurements from the J-HOME study. *Hypertens Res* **32**: 1072–8

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Greater reno-protection with MRA added to ACE

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

1 The authors sought to determine whether the addition of either an angiotensin receptor blocker (ARB) or mineralocorticoid receptor antagonist (MRA) to a maximal angiotensin-converting enzyme (ACE) inhibitor would provide greater renoprotection for people with diabetes, hypertension and albuminuria.

2 Participants (n=81) all received lisinopril (80 mg daily) at baseline and were randomised to one of three arms: placebo (n=27); losartan (100 mg daily); or spironolactone (25 mg daily) for 48 weeks.

3 Blood, urine and blood pressure measures were taken at baseline and weeks 24 and 48.

4 A significant decrease in the urine albumin:creatinie ratio (34.0%; CI 95%, –51.0 to –11.2%) was observed in the spironolactone arm compared with placebo (P=0.007). While a reduction in the urine albumin:creatinie ratio occurred in the losartan arm (16.8%; 95% CI, –37.3 to 10.5%), the decrease was not significantly different to that of the placebo group (P=0.20).

5 There was no difference between groups in blood pressure, creatinine clearance, glycaemic control or sodium and protein intake.

6 While the effect on blood pressure was similar, the authors concluded that people with diabetes are afforded greater renoprotection with the addition of spironolactone, rather than losartan, to a maximal dose of ACE inhibitors.

Mehdi UF, Adams-Huet B, Raskin P (2009) Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* **20**: 2641–50

NEPHROLOGY DIALYSIS TRANSPLANTATION

Diabetes associated with poorer survival while on dialysis

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

1 End-stage renal disease (ESRD) survival, and factors influencing survival, impact clinical and psychological patient management and resource planning.

2 In this multicentre, prospective, observational cohort study the authors sought to assess the impact of a range of variables on survival for >90 days on dialysis. Likelihood of receiving a transplant was also assessed.

3 A consecutive series of 884 people treated with renal replacement therapy were recruited from four teaching hospitals in the UK.

4 Comorbidities were analysed using the Stoke Score and included ischaemic heart disease, diabetes and peripheral vascular disease.

5 Mean follow-up was 4.6 years, at which time survival was 29%.

6 Age (relative risk [RR], 1.52; 95% CI, 1.41–1.65; $P<0.0001$), greater than two and greater than three comorbidities (both, $P<0.001$) were all significantly associated with worse survival.

7 Paticipants were most significantly unlikely to receive a transplant if they were black (RR, 0.10; 95% CI, 0.02–0.34; $P<0.001$) or had diabetes (RR, 0.06; 95% CI, 0.01–0.23; $P<0.001$), and every decade of age reduced the likelihood of receiving a transplant (RR, 0.55; 95% CI, 0.49–0.61; $P<0.001$).

8 The authors suggested that risk stratification of people with ESRF prior to commencement of dialysis may predict survival in patient groups.

Jain P, Cockwell P, Little J et al (2009) Survival and transplantation in end-stage renal disease: a prospective study of a multiethnic population. *Nephrol Dial Transplant* **24**: 3840–6

CIRCULATION

Sudden cardiac death on dialysis increases with HbA_{1c} among people with diabetes

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

1 The association between glycaemic control and cardiovascular (CV) events in people with diabetes receiving dialysis was assessed using data from 4D Study based in Germany.

2 Participants ($n=1255$) were followed-up for a median of 4 years and Cox regression analyses were performed to determin hazard ratios (HRs) for pre-specified endpoints (sudden cardiac death [SCD], myocardial infarction, stroke, CV events, death by heart failure, all-cause mortality) according to baseline HbA_{1c}.

3 Mean age of participants was 66±8 years and mean HbA_{1c} was 6.7±1.3% (50±14 mmol/mol), with 54% of the cohort being men.

4 A 1% (11 mmol/mol) increase in HbA_{1c} was found to be associated with an 18% increased risk of SCD and an 8% increase in CV events and all-cause mortality.

5 For people with diabetes on dialysis poor glycaemic control was strongly associated with SCD. Whether tighter glycaemic control decreases SCD requires investigation.

Drechsler C, Krane V, Ritz E et al (2009) Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation* **120**: 2421–8

JOURNAL OF HYPERTENSION

High-dose valsartan more effective in black people

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

1 The effectiveness of various doses of valsartan on blood pressure (BP) in African-Americans (AAs) and non-AAs with diabetes and albuminuria was investigated.

2 AAs ($n=110$) enrolled had a mean BP of 150/87 mmHg, while in non-AAs ($n=281$) it was 151/89 mmHg.

3 Valsartan (160 mg/day) was given for 4 weeks, following which participants were randomised to receive 160, 320 or 640 mg/day for 26 weeks.

4 Four-week reduction in BP was significantly higher in non-AAs than AAs ($P<0.05$), while 26-week reductions were greater in the AAs randomised to 320, 640 mg/day than non-AAs at these higher doses.

Weir MR, Hollenberg NK, Zappe DH et al (2010) Antihypertensive effects of double the maximum dose of valsartan in African-American patients with type 2 diabetes mellitus and albuminuria. *J Hypertens* **28**: 186–93

NEPHROLOGY DIALYSIS TRANSPLANTATION

Ethnic people with diabetes survive longer on dialysis

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

1 Data from a UK renal replacement therapy (RRT) registry from 1997–2006 were analysed to determine survival rates based on ethnicity.

2 South Asian (SA; $n=2495$) and black ($n=1218$) people were younger, and had a higher adjusted rate of CV comorbidities, compared with white people.

3 Significantly better survival was observed both before and after day 90 of RRT in black and SA people than in white people, with a 50% lower risk of mortality after day 90 in black and 30% in SA people.

4 Research is required on the impact of ethnicity on RRT survival.

Roderick P, Byrne C, Casula A et al (2009) Survival of patients from South Asian and Black populations starting renal replacement therapy in England and Wales. *Nephrol Dial Transplant* **24**: 3774–82

"Significantly better survival was observed both before and after day 90 of renal replacement therapy in black and south Asian people than in white people."