The real picture….

Abassi, Biochem Pharm, 2009
Resistant Hypertension; Case based discussion

Moving Targets?
RAAS blockade in hypertensive CKD

Sarah Roxburgh
Dialysis Nephrology Transplantation Meeting
March 30th 2011
Mr RH, age 72

- Referral August 2010
  - “Thanks for seeing regarding his hypertensive management – along with associated diabetic/hypertensive nephropathy”
Background

• T2DM;
  – > 30 yr duration
  – Insulin requiring since early 2010
  – No diabetic retinopathy, mild Sx peripheral neuropathy
  – No macrovascular disease

• Multiagent Hypertension

• Hyperlipidaemia

• Ex smoker

• C2H5OH, prior excess

• Family history; father RIP ESKD/ T2DM, age 72
Presenting issues

• Small bowel obstruction June 2010, conservative management
  • Normal upper and lower endoscopies

• 7 kg weight gain over past year, associated increasing peripheral oedema

• BPs increasingly labile over past 2-3 months; up to 210/95 in GP office
Medications at presentation

- Metoprolol 50 mg bd
- Prazosin 2.5 mg bd
- Ramipril 10 mg po mane
- Lercanidipine 20 mg po nocte
- Aspirin 100 mg po daily
- Atorvastatin 20 mg po nocte
- Lantus bd
Physical examination

- BP 170/90 L and R. HR 56. Weight 87.2 kg, BMI 33, waist circumference 103 cm.
- JVP 3 cm, small bibasal effusions, pitting peripheral oedema to upper 1/3 calves
- ABND. HS dual +nil
- No renal/epigastric bruit. PPP. Nil carotid or femoral bruit.
- UA; 3+ protein, trace blood, no leukocytes
- Reduced reflexes in lower limbs
Serum creatinine
Albuminuria
HbA1c
Other results

• Hb 118  NNA. Iron stores; ferritin 96, iron sats 16 %
• 24 hr urine; 1.9 g total protein, urinary creatinine clearance 28 mls/minute
• Albumin 41, LFTs normal, PTH 19 pg/L, Corr Ca 2.34, PO4 1.2
• Sediment; nil microhaematuria / casts/ other
• lgs, C3/ C4, ANA, EPG/IEPG all normal/ negative

• Renal ultrasound; right kidney 11.1 cm, left 12.1 cm “suggestion of increased echogenicity and some parenchymal thinning”
Summary

• 1. Multiagent hypertension- poor control
• 2. Proteinuric CKD Stage 4 (1.9 g)
  – No biopsy (for now?)
  – Presumed hypertensive small vessel ischaemic nephropathy +/- diabetic glomerulosclerosis +/- secondary FSGS
? Other workup
? Other workup

- TTE; normal LV function, mild concentric LVH
- Renal artery dopplers; elevated RIs, no RAS
Initial management; BP reduction

- What is the BP target?

- What anti hypertensive cocktail will you use to achieve it?
BP target?

- A. 140/90
- B. 130/80
- C. 125/75
- D. other?
<table>
<thead>
<tr>
<th>Follow-up Year</th>
<th>P:C Ratio &gt;0.22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard control</td>
</tr>
<tr>
<td>0</td>
<td>176</td>
</tr>
<tr>
<td>1</td>
<td>165</td>
</tr>
<tr>
<td>2</td>
<td>134</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Year</th>
<th>P:C Ratio ≤0.22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard control</td>
</tr>
<tr>
<td>0</td>
<td>376</td>
</tr>
<tr>
<td>1</td>
<td>373</td>
</tr>
<tr>
<td>2</td>
<td>362</td>
</tr>
<tr>
<td>3</td>
<td>353</td>
</tr>
<tr>
<td>4</td>
<td>332</td>
</tr>
<tr>
<td>5</td>
<td>302</td>
</tr>
<tr>
<td>6</td>
<td>267</td>
</tr>
<tr>
<td>7</td>
<td>234</td>
</tr>
<tr>
<td>8</td>
<td>214</td>
</tr>
<tr>
<td>9</td>
<td>196</td>
</tr>
<tr>
<td>10</td>
<td>128</td>
</tr>
</tbody>
</table>
All Patients

Patients Reaching Primary End Point (%)

Years of Observation

Conventional

Intensified

P=0.02

No. at Risk
Intensified
Conventional
182 167 152 142 135 126 119 110 102 97 90
190 168 154 142 131 122 112 107 97 86 75

October 2009
Results of Efficacy Outcomes in Randomized, Controlled Trials of Blood Pressure Targets (Low Versus Usual) in Adults With CKD.

**Table 3. Results of Efficacy Outcomes in Randomized, Controlled Trials of Blood Pressure Targets (Low Versus Usual) in Adults With CKD**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MDRD Study</th>
<th>AASK Trial</th>
<th>REIN-2 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial</td>
<td>Observational Follow-up</td>
<td>Trial</td>
</tr>
<tr>
<td>≥50% decrease (or ≥25 mL/min per 1.73 m²) in GFR, kidney failure, or death</td>
<td>–</td>
<td>–</td>
<td>Risk reduction, 2% (95% CI, −22% to 21%); *P = 0.85</td>
</tr>
<tr>
<td>Kidney failure or death</td>
<td>Study A: RR, 1.12 (CI, 0.77 to 1.61); *P = 0.62</td>
<td>Study B: RR, 0.85 (CI, 0.60 to 1.22); *P = 0.33</td>
<td>Risk reduction, 2% (CI, −13% to 32%); *P = 0.31</td>
</tr>
<tr>
<td>50% decrease in GFR or kidney failure‡</td>
<td>–</td>
<td>–</td>
<td>Risk reduction, −2% (CI, −31% to 20%); *P = 0.87</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>HR, 0.76 (CI, 0.52 to 1.10); *P = 0.15</td>
<td>HR, 0.68† (CI, 0.57 to 0.82); *P &lt; 0.001</td>
<td>Risk reduction, 6% (CI, −29% to 31%); *P = 0.72</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>2 vs. 1; *P = ND</td>
<td>10 vs. 6; *P = ND</td>
<td>2 vs. 2; *P = ND</td>
</tr>
<tr>
<td>CV mortality</td>
<td>–</td>
<td>–</td>
<td>HR, 0.98 (CI, 0.48 to 2.01); *P = 0.96</td>
</tr>
<tr>
<td>CVD events</td>
<td>RR, 1.03$ (CI, 0.59 to 1.79)</td>
<td>–</td>
<td>2% vs. 3%; *P = ND</td>
</tr>
<tr>
<td>Rate of annual GFR decline, mL/min per 1.73 m²</td>
<td>Study A: 1.6</td>
<td></td>
<td>(CI, −0.8 to 3.9); *P = 0.18</td>
</tr>
</tbody>
</table>

AASK = African American Study of Kidney Disease and Hypertension; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GFR = glomerular filtration rate; HR = hazard ratio; MDRD = Modification of Diet in Renal Disease; ND = no data; REIN-2 = Ramipril Efficacy in Nephropathy 2; RR = risk ratio; Scr = serum creatinine.

* Doubling of Scr concentration, kidney failure, or death for follow-up.
‡ Doubling of Scr concentration or kidney failure for follow-up.
§ CV hospitalization.
|| Less in the low target group in MDRD Study A.
† Low vs. usual target group.

## Results of Interaction Tests and Subgroup Analyses by Baseline Proteinuria in Trials of Blood Pressure Targets (Low Versus Usual) in Patients With Chronic Kidney Disease

**Appendix Table 2. Results of Interaction Tests and Subgroup Analyses by Baseline Proteinuria in Trials of Blood Pressure Targets (Low Versus Usual) in Patients With Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MDRI Study</th>
<th>Observational Follow-up</th>
<th>Proteinuria Category</th>
<th>AASK Study</th>
<th>Observational Follow-up</th>
<th>Proteinuria Category</th>
<th>REIN-2 Trial</th>
<th>Observational Follow-up</th>
<th>Proteinuria Category</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>⩾50% decrease in GFR (or 25 mL/min per 1.73 m²), kidney failure, or death*</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target with increased proteinuria (P = 0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &lt;100 mg/d</td>
<td>NS</td>
<td>Favors low target</td>
<td></td>
<td>NS</td>
<td>Favors low target (HR, 0.73 [CI, 0.58–0.92]; P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE 100–500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.61 [CI, 0.43–0.85]; P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.62 [CI, 0.40–0.96]; P = 0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interaction test</td>
<td></td>
<td>Interaction test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% decrease in GFR or kidney failure†</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target with increased proteinuria (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &lt;100 mg/d</td>
<td>NS</td>
<td>Favors low target</td>
<td></td>
<td>NS</td>
<td>Favors low target with increased proteinuria (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE 100–500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.55 [CI, 0.34–0.89]; P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.55 [CI, 0.33–0.90]; P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interaction test</td>
<td></td>
<td>Interaction test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target with increased proteinuria (P = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &lt;100 mg/d</td>
<td>NS</td>
<td>Favors low target</td>
<td></td>
<td>NS</td>
<td>Favors low target with increased proteinuria (P = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE 100–500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.94 [CI, 0.63–1.41]; P = 0.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR, 0.93 [CI, 0.54–1.61]; P = 0.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interaction test</td>
<td></td>
<td>Interaction test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of GFR decline</td>
<td>Overall</td>
<td>NS</td>
<td>Favors low target</td>
<td>Overall</td>
<td>NS</td>
<td>Favors lower target with increased proteinuria (P = 0.004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &lt;100 mg/d</td>
<td>NS</td>
<td>Favors low target</td>
<td></td>
<td>NS</td>
<td>Favors lower target with increased proteinuria (P = 0.004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE 100–500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR = 0.92 in Study A and 0.91 in Study B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPE &gt;500 mg/d</td>
<td>NS</td>
<td>Favors low target (HR = 0.92 in Study A and 0.91 in Study B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* AASK = African-American Study of Kidney Disease and Hypertension; CVD = cardiovascular disease; GFR = glomerular filtration rate; HR = hazard ratio; MDRI = Modification of Diet in Renal Disease; NS = not significant; REIN-2 = Ranolax’s Efficacy in Nephropathy 2; SCR = serum creatinine; UPCR = urinary protein-creatinine ratio; UPE = urinary protein excretion.

* Doubling of SCR, kidney failure, or death for follow-up.

† Doubling of SCR or kidney failure for follow-up.

§ Annual GFR decrease of 4.0 vs. 5.0 mL/min per 1.73 m². Estimate from a figure.

|| Annual GFR decrease of 3.5 vs. 3.3 mL/min per 1.73 m² in Study A and 4 vs. 5.5 mL/min per 1.73 m² in Study B. Estimates from a figure.

Author’s conclusions

In summary, evidence does not conclusively show that a currently recommended blood pressure target less than 130/80 mm Hg improves clinical outcomes more than a conventional target less than 140/90 mm Hg in adults with CKD. A lower target may be beneficial in persons with proteinuria greater than 300 to 1000 mg/d. We suggest that practitioners use discretion in patients with CKD and proteinuria and base the blood pressure target on individualized risk–benefit assessment and the patient's tolerance and preferences. Treatment to a lower target may require greater vigilance to monitor for and avoid possible symptoms and adverse events from hypotension.
What agent will you use?

- A. ARB
- B. Diuretic; thiazide v loop
- C. Uptitrate alpha blocker
- D. Aldosterone antagonist
- E. Other?
Prevention of progression CKD

Combination anti hypertensives; ACE/ dihydropyridine
The Lancet, April 2010
Prevention of progression CKD

Combination anti hypertensives;

? ACE/ ARB
Dual RAS Therapy Not on Target, but Fully Alive

Renal protection in diabetes: lessons from ONTARGET®

Have we fallen off target with concerns surrounding dual RAAS blockade?

Michael R. Lattanzio¹ and Matthew R. Weir¹

¹Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA
CONFUSION
It can be a life long Journey
OnTarget, albuminuria and mortality

Doubling of albuminuria associated with 47% increased mortality
Halving of albuminuria associated with 15% reduced mortality

P< 0.001

Baseline value
Doubling of urinary albumin excretion
Halving of urinary albumin excretion

P<0.025

Schmeider ESH Abstract July 2010
• **ON TARGET**; no benefit - renal or cardiovascular

• **TRANSCEND**;
  – significant towards harm in the normoalbuminemic group
  – trend towards benefit in the micro/ macroalbuminuria
The safety of combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers in elderly.

Figure 2: Kaplan–Meier curves for primary outcome (doubling of serum creatinine, development of end-stage renal failure or death from any cause) among the 24 800 patients for whom serum creatinine was measured before and after the start of treatment. Numbers in parentheses are the number of patients who had at least one of the three outcome events. Hazard ratio 2.36 (95% confidence interval 1.51 to 3.71).
Development of ESKD and progression of micro to macroalbuminurina were reduced significantly with ACE v placebo and ARB v placebo, but not with combined ACE/ARB v monotherapy
Prevention of progression CKD
Aldosterone Antagonists
Aldosterone Antagonists for Preventing the Progression of Chronic Kidney Disease: A Systematic Review and Meta-analysis

Sankar D. Navaneethan,* Sagar U. Nigwekar,† Ashwini R. Sehgal,§ and Giovanni F.M. Strippoli††**

*Department of Nephrology and Hypertension, Glickman Institute of Urological and Kidney Diseases, Cleveland Clinic, Cleveland, Ohio; †Department of Medicine, Rochester General Hospital, Rochester, New York; ‡Division of Nephrology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio; §Department of Pharmacology and Clinical Epidemiology, Mario Negri Sud Consortium, S. Maria Imbaro, Italy; ††Damerum Corporate Medical Scientific Office, Lund Sweden; ††Cochrane Renal Group, Sydney, Australia; **School of Public Health, University of Sydney, Sydney, Australia
Aldo antagonist +ACEi/ARB
Vs ACEi /ARB alone

Proteinuria Change in GFR Incidence of hyperkalaemia

Spironolactone Eplerenone Total

Navaneethan et al, Clinical JASN 2009
Follow-up; 2 weeks

- Bumetanide commenced 1 mg tds
- Significant diuresis, 3 kg weight loss, peripheral oedema improved
- BP in GP rooms; 155 /80
- Creatinine 272. Urinary PCR 90.

“ I brought in those films you asked to look at”...
**Plasma aldosterone/ renins; performed off ACE/ beta blockade/ diuretic/ calcium channel blockers 10/7. On Prazosin 5 mg tds.**

<table>
<thead>
<tr>
<th>SEND AWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred Institution</td>
</tr>
<tr>
<td>Test(s) Requested</td>
</tr>
<tr>
<td>Date Sent</td>
</tr>
</tbody>
</table>

**COMMENT:**

Plasma aldosterone is again high. Plasma renin activity is low. Plasma aldosterone/PRA ratio is again high, indicating high probability of primary hyperaldosteronism.

- **Plasma Renin Activity result**: < 0.1 ng/mL/h
- **Aldosterone result**: 922 pg/mL
• 24 hr urinary aldosterone; 30 micrograms/ 24 hrs
• Adrenal vein sampling; Aldosterone levels are all high. Ratios for LAV and RAV all higher than low IVC/ SRV ratios suggesting patient has Bilateral Adrenal Hyperplasia (R > L)

• 24 hr urinary catecholamines/ plasma metanephrines normal studies
• Interval 3 month MR left adrenal lesion ; consistent with an adrenal haematoma
Summary

1. Multiagent hypertension
2. Primary hyperaldosteronism
   - Bilateral adrenal hyperplasia
3. Proteinuric CKD Stage 4 (approx 700 mg)
   - No biopsy
   - Presumed hypertensive small vessel ischaemic nephropathy +/- diabetic glomerulosclerosis +/- secondary FSGS
4. Adrenal haematoma (Probable)
Discussion

• Aldosterone antagonism?
Serum creatinine

Aldactone commenced

Aldactone ceased
Update

• March 2011- partial left laparoscopic adrenalectomy
• Macro; adrenal haematoma complicating underlying adrenal adenoma; pathology pending
• 2 weeks post surgery; BP 125/65. Loop diuretic ceased. Creatinine 310 (eGFR 17 mls/min) stable.
• Attending renal education sessions.
Hypothetical; Needs CABG

• ? Role of preoperative cessation RAAS blockade
Medications at presentation

- Metoprolol 50 mg bd
- Prazosin 2.5 mg bd
- Ramipril 10 mg po mane
- Lercanidipine 20 mg po nocte
- Aspirin 100 mg po daily
- Atorvastatin 20 mg po nocte
- Lantus bd
RAAS blockade in coronary artery surgery:

- Retrospective cohort study of 10,023 pts
- Pre operative RAAS blockade associated with doubling of the risk of death, increased need for inotropic support and incidence of renal dysfunction

Miceli, JACCC, 2009
RAAS blockade in non cardiac surgery:

- Prospective observational study of 65,043
- Patients undergoing perioperative therapy with ACEi or ARBs *in combination with diuretic* showed:
  - More periods with SBP less than 70mmHg
  - Periods with greater than 50% decrease in SBP
  - Increased vasopressor requirement

*Kheterpal et al, J Cardiothor and Vasc Anaesthesias, 2008*
Thankyou