Aldosterone: a new culprit in CKD

Prof. Dr. Adrian Covic
Parhon University Hospital
Iasi, Romania
Aldosterone: a new culprit in CKD

- **Some basic pathophysiology**
- **Is ALDO an inflammatory mediator?**
  - ALDO and the heart: experimental evidence
  - ALDO and the kidney: experimental evidence
  - ALDO antagonists and nephroprotection
  - Is ALDO antagonism mandatory for heart failure patients with CKD?
  - ALDO antagonism in dialysis patients?
- Perspectives of aldosterone blockade
Deleterious Effects of Aldosterone

Renin-Angiotensin Activation  

Potassium

Aldosterone

K⁺ loss  Na⁺ retention  Mg⁺⁺ loss  ↑ PAI-1  TGFβ₁  ROS  EGFR  Endothelial Dysfunction  ↓ Vascular compliance  

Proinflammatory effects on Cox-2 and osteopontin

Myocardial fibrosis and remodeling

Hypertension

Renal failure

Progression of renal disease, heart failure, and endothelial dysfunction
Eplerenone Prevents Vascular Inflammatory Lesions in All/Salt Hypertensive Rats

**perivascular inflammatory response**

**fibrinoid necrosis**

Spironolactone Prevents Diabetic Nephropathy through an Anti-Inflammatory Mechanism in Type 2 Diabetic Rats

Sang-Youb Han JASN 2006
Sometimes humans are not rats...

CKD and proteinuria:
linear correlation between
mineralocorticoid receptor /
serum aldosterone
and
inflammatory markers /
renal scarring

*Circulation* 2005, 112:1435
ALDOSTERONE – Rho kinase pathway

Fasudil - specific Rho-kinase inhibitor

Sun et al., *J Am Soc Nephrol* 2006

![Images of tissue sections](A-C and D-F)

- **A:** Vehicle
- **B:** Aldosterone
- **C:** Aldosterone + fasudil
- **D:** Vehicle
- **E:** Aldosterone
- **F:** Aldosterone + fasudil

**G:** Tubulointerstitial fibrosis score (0 to 3+)

- Vehicle: 0
- Aldosterone: 3
- Aldosterone + fasudil: 1

**H:** Proteinaceous casts in tubuli (0 to 4+)

- Vehicle: 0
- Aldosterone: 3
- Aldosterone + fasudil: 1
Aldosterone: a new culprit in CKD

ALDO ANTAGONISTS and the kidney: experimental evidence – ‘proof of concept’

1) Prevention of kidney injury
2) Regression of established kidney damage
First, ‘old’ but classical data
Eplerenone Prevents Proteinuria and Protects Against Renal Injury

Saline-Drinking SHRSP

SBP (mm Hg)

Renovascular Lesions (lesioned vessels/100 glomeruli)
P < 0.001

Urinary Protein Excretion (mg/day)
P < 0.001

Effect of combining ACE inhibition with aldosterone blockade on proteinuria and renal damage in experimental nephrosis

AB Kramer\textsuperscript{1,2}, FF van der Meulen\textsuperscript{1}, I Hamming\textsuperscript{1}, H van Goor\textsuperscript{1} and G Navis\textsuperscript{2}
Figure 2 | Markers of tubular damage at termination; graphs represent mean and SD. (a) OPN mRNA (qPCR), (b) OPN protein expression (computer-assisted morphometry), (c) Kim-1 mRNA (qPCR), and (d) Kim-1 protein expression (computer-assisted morphometry). Mean and SD are given.
Dual blockade of aldosterone and angiotensin II additively suppresses TGF-β and NADPH oxidase in the hypertensive kidney

Maristela Lika Onozato¹, Akihiro Tojo¹, Naohiko Kobayashi², Atsuo Goto¹, Hiroaki Matsuoka² and Toshiro Fujita¹

Table 1. Blood pressure, serum creatinine and potassium and renal oxidative products

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DSHF</th>
<th>DSHF+ACEI</th>
<th>DSHF+Epl</th>
<th>DSHF+ACEI+Epl</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>132 ± 3</td>
<td>245 ± 5**</td>
<td>180 ± 4††</td>
<td>243 ± 5**, †</td>
<td>177 ± 5*, ††</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.21 ± 0.01</td>
<td>0.46 ± 0.04**</td>
<td>0.24 ± 0.01**, †</td>
<td>0.27 ± 0.02**, †</td>
<td>0.15 ± 0.01††</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.32 ± 0.10</td>
<td>4.40 ± 0.24</td>
<td>4.36 ± 0.20</td>
<td>4.68 ± 0.15</td>
<td>4.42 ± 0.23</td>
</tr>
<tr>
<td>Urinary LPO (nmol/mg Cr)</td>
<td>1.49 ± 0.08</td>
<td>1.93 ± 0.18*</td>
<td>1.39 ± 0.20††</td>
<td>0.67 ± 0.15††</td>
<td>0.49 ± 0.17††</td>
</tr>
<tr>
<td>Glomerular LPO Staining score</td>
<td>0.16 ± 0.03</td>
<td>1.13 ± 0.09**</td>
<td>0.30 ± 0.05**, †</td>
<td>0.76 ± 0.05**, ††</td>
<td>0.23 ± 0.04††</td>
</tr>
<tr>
<td>Renal 4-HNE (Arbitrary unit)</td>
<td>0.71 ± 0.05</td>
<td>0.88 ± 0.04*</td>
<td>0.71 ± 0.05†</td>
<td>0.80 ± 0.06</td>
<td>0.67 ± 0.04†</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; LPO, lipid peroxidation products; 4-HNE, 4-Hydroxy-2-nonenal.
*P < 0.05; **P < 0.005 vs Control; †P < 0.05; ††P < 0.005 vs DSHF; ††P < 0.005 vs DSHF+ACEI+Epl.
Fig. 1. Urinary albumin excretion (A), Glomerulosclerosis score (B), Representative morphological changes (C) by PAS staining. DSHF indicates Dahl salt-sensitive rats fed with 8% NaCl from 6-week until 18-week-old, DSHF + ACEI, DSHF rats treated with trandolapril from 11-week to 18-week-old, DSHF + Epl, DSHF rats treated with eplerenone from 11-week to 18-week-old, DSHF + ACEI + Epl, DSHF treated with trandolapril and eplerenone from 11-week to 18-week-old. *P < 0.05, **P < 0.005 vs Control, †P < 0.05, ††P < 0.005, †††P < 0.0001 vs DSHF, ††P < 0.05, †††P < 0.005 vs DSHF + ACEI + Epl. The bar indicates 100 μm.
Effect of spironolactone and captopril on kidney NO synthetase


Renocortical mRNA expression of vasoactive factors during spironolactone protective effect in chronic cyclosporine nephrotoxicity

Jazmin M. Pérez-Rojas, et al

“...Our results suggest that aldosterone contributes to renal vasoconstriction observed in CsA nephrotoxicity and that renoprotection conferred by spironolactone was related to modification of renocortical vasoactive pathways expression...

Finally, our data point to spironolactone as a potential treatment to reduce CsA nephrotoxicity in transplant patients...”
Regression of Existing Glomerulosclerosis by Inhibition of Aldosterone

Jean Claude Aldigier, Talerngsak Kanjanbuch, Li-Jun Ma, Nancy J. Brown, and Agnes B. Fogo

treatment protocols.
Regression of Existing Glomerulosclerosis by Inhibition of Aldosterone

Jean Claude Aldigier, Taleredsak Kanjanbuch, Li-Jun Ma, Nancy J. Brown, and Agnes B. Fogo
<table>
<thead>
<tr>
<th>Study</th>
<th>Animal Model</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greene et al, 1996&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Remnant kidney rats</td>
<td>Losartan + enalapril + aldosterone infusion</td>
<td>Proteinuria and glomerulosclerosis</td>
<td>● ↑ Proteinuria</td>
</tr>
<tr>
<td>Rocha et al, 1998&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Saline-dinking SHRSP</td>
<td>Spironolactone</td>
<td>Urine protein excretion, Survival</td>
<td>● ↓ Proteinuria, Protection against malignant nephrosclerotic and cerebrovascular lesions</td>
</tr>
<tr>
<td>Rocha et al, 1998&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Saline-dinking SHRSP</td>
<td>Eplerenone</td>
<td>Urine protein excretion, Renal injury, Urine protein excretion</td>
<td>● ↑ Proteinuria, No renal lesions</td>
</tr>
<tr>
<td>Rocha et al, 1999&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Saline-dinking SHRSP</td>
<td>Captopril + aldosterone infusion</td>
<td>Renal injury, Urine protein excretion</td>
<td>● ↑ Proteinuria, Severe renal lesions</td>
</tr>
<tr>
<td>Rocha et al, 2000&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Male L-NAME saline-drinking rats</td>
<td>Eplerenone or adenectomy</td>
<td>Myocardial necrosis, Development of sclerosis</td>
<td>● ↓ Renal damage</td>
</tr>
<tr>
<td>Brown et al, 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Male Sprague-Dawley rats with renal radiation injury</td>
<td>Spironolactone</td>
<td>Renal injury, inflammation, and fibrosis</td>
<td>● ↓ Development of sclerosis, ↓ PAI-1 expression</td>
</tr>
<tr>
<td>Blasi et al, 2003&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Unnephrecto-mized Sprague-Dawley rats given 1%NaCl + aldosterone infusion</td>
<td>Eplerenone</td>
<td>Renal injury, inflammation, and fibrosis</td>
<td>● ↓ Systemic osteopontin, ↓ Albuminuria</td>
</tr>
<tr>
<td>Feria et al, 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Male Wistar rats, low sodium diet</td>
<td>Csa + spironolactone</td>
<td>Ccr, blood CsA, renal arteriolopathy, TGF-β1, collagen I, collagen IV, fibronectin, EFG mRNA levels</td>
<td>● Prevented fall in renal function, Prevented TGF-β1, collagen I, and fibronectin up-regulation, Reduced arteriolopathy and tubulo-interstitial fibrosis, ↓ Proteinnuria, ↓ Tubulo-interstitial damage index</td>
</tr>
<tr>
<td>Zhou et al, 2004&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Male L-NAME/SHR rats</td>
<td>Eplerenone</td>
<td>Renal and glomerular hemodynamics, and renal function</td>
<td>● Improved glomerular and arteriolar injuries</td>
</tr>
</tbody>
</table>

*Ccr = creatinine clearance; Csa = cyclosporin A; EGF = epidermal growth factor; IL-1beta = interleukin-1beta; IL-6 = interleukin-6; L-NAME = L-arginine methyl ester; MCP-1 = monocyte chemotactant protein-1; OPN = osteopontin; PAI-1 = plasminogen activator inhibitor-1; SHR = spontaneously hypertensive rats; SHRSP = stroke-prone spontaneously hypertensive rats; TGF-β1 = transforming growth factor-β1.*
Let’s move to humans…

**Figure 3** This slide shows the regression line between baseline plasma aldosterone levels and proteinuria in the 165 patients included in the study ($r = 0.766$, $P < 0.0001$).
And let’s not forget classic things, that support a role for aldosterone

Conn (1964) - 154 cases of primary hyperaldosteronism

**Primary aldosteronism:**
- Plasma renin < 5pU/ml;
- Plasma aldosterone ≥15ng/dl;
- P aldosterone/P renin >3.0

N = 154:
→ 85% with heavy proteinuria
→ severe HTN + hyperkalemia
…and…

Prevalence of Primary Aldosteronism in Subjects with Resistant Hypertension

<table>
<thead>
<tr>
<th>City</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>17%</td>
</tr>
<tr>
<td>Birmingham</td>
<td>20%</td>
</tr>
<tr>
<td>Oslo</td>
<td>22%</td>
</tr>
<tr>
<td>Prague</td>
<td>19%</td>
</tr>
</tbody>
</table>

Seattle (n=90)  Birmingham (n=88)  Oslo (n=90)  Prague (n=402)
Aldosterone: a new culprit in CKD

• Some basic pathophysiology
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• ALDO and the heart: experimental evidence
• ALDO and the kidney: experimental evidence
• **ALDO antagonists and nephroprotection**
  • Is ALDO antagonism mandatory for heart failure patients with CKD?
  • ALDO antagonism in dialysis patients?
  • Perspectives of aldosterone blockade
A first proposal of using Spironolactone to limit renal injury

- 8 pts with CKD and proteinuria > 1g/24h, despite ACE-I
- 25 mg spironolactone was added
- mean proteinuria ↓ from 3.81 to 1.75 g/24 g (54% reduction)
- no significant ↓ in BP or creatinine clearance
Type 1 DM with macroalbuminuria

RANDOMIZED, DOUBLE-MASKED, PLACEBO CONTROLLED, CROSSOVER TRIAL

TX PERIODS - TWO MONTHS

SPIRONO ADDED TO USUAL ANTI-HTA TX, INCLUDING A RAS-BLOCKING AGENT INDUCED A 30% REDUCTION IN ALBUMINURIA FROM A MEAN OF 831 (624-1106) MG/24 HRS

SCHJOEDT ET AL, KIDNEY INT 2005
Type 2 DM with macroalbuminuria

The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study


<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>16</th>
<th>36</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>152 ± 12</td>
<td>128 ± 4</td>
<td>Ci</td>
<td>127</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sp</td>
<td>128</td>
<td>129</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>93 ± 7</td>
<td>81 ± 3</td>
<td>Ci</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sp</td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>536</td>
<td>452</td>
<td>Ci</td>
<td>349</td>
<td>302</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sp</td>
<td>272*</td>
<td>216*</td>
</tr>
<tr>
<td>sCr (µmol/l)</td>
<td>115 ± 11</td>
<td>121 ± 12</td>
<td>Ci</td>
<td>126</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sp</td>
<td>117</td>
<td>119</td>
</tr>
</tbody>
</table>

Ci, cilazapril; Sp, spironolactone.

*P = 0.02 for the difference between spironolactone and cilazapril;
**P = 0.01 for the difference between ACR at weeks 36 and 60.
...and, by the way...

P-Aldosterone - Independently Associated With the Metabolic Syndrome

Bochud M et al. Hypertension 2006;48:239-245
Non-DM CKD

- 42 CKD pts already on ACE-I and/or ARB

  Spironolactone 25 mg ↓ proteinuria
  from 2.09 to 1.32 after 2 weeks
  and to 1.05 g/24h after 8 weeks

- significant increase in serum K levels
  (from 4.4 mEq/L at baseline to 4.8 mEq/L after 8 weeks of treatment; P < 0.01).
Proteinuria levels in all 42 patients at baseline; during treatment with spironolactone, 25 mg/d; and 4 weeks after discontinuation of the drug.
Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease

S Bianchi¹, R Bigazzi¹ and VM Campese²

¹Unità Operativa Nefrologia, Spedali Riuniti, Livorno, Italy and ²Division of Nephrology, Keck School of Medicine, USC, Los Angeles, California, USA
Figure 1 | This slide shows the percent reduction of proteinuria from baseline in patients treated with spironolactone (25 mg/day) in addition to conventional therapy divided on the basis of their eGFR (< or > 60 ml/min/1.73 m²). *P < 0.001 vs basal proteinuria; *P < 0.05 vs patients with eGFR < 60 ml/min; @P < 0.01 vs patients with eGFR < 60 ml/min.
Figure 2 | This slide shows the percent decline in eGFR in patients treated with spironolactone and those treated with conventional therapy. Patients were followed for 1 year. *$P < 0.001$ vs basal eGFR, **$P < 0.0001$ vs basal eGFR.
## P-uria decrease predicts renal outcomes?

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>F/U (yrs)</th>
<th>GFR (mls/min)</th>
<th>Max. change in P-uria</th>
<th>Significance of P-uria decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>3.4</td>
<td>58</td>
<td>-35% (losartan)</td>
<td>↓50% = ↓45% in ESRD</td>
</tr>
<tr>
<td>AASK</td>
<td>4</td>
<td>46</td>
<td>-20% (ramipril)</td>
<td>Predicts 5-yr ESRD</td>
</tr>
<tr>
<td>COOPERATE</td>
<td>3</td>
<td>51</td>
<td>-75.6% (losartan + trandolapril)</td>
<td>Greatest ↓ in P-uria = slowest decline in GFR</td>
</tr>
<tr>
<td>IDNT</td>
<td>2.6</td>
<td>59</td>
<td>-33% (irbesartan)</td>
<td>↓50% = &gt; ↓50% endpoint</td>
</tr>
</tbody>
</table>
Some important practical questions

The benefit of Spironolactone lies on:
1. its diuretic effect or

2. Its ability to modulate non-volume-mediated effects of ALDOSTERONE?
DM with nephrotic P-uria

- Schjoedt KJ et al *KI* 2006, 70: 536-542
- N = 20 DM, randomized cross-over, double masked trial

- Spironolactone *on top of usual antiHTA Tx* (including maximal ACEI/ARB) induced a 32% reduction in albuminuria from a mean of 3718 mg/24 hrs
Other important practical questions

Which patients benefit the most?

1) With aldosterone escape
   YES – Sato et al Hypertension 2003

2) Regardless of the baseline plasma aldosterone and PRA
   NO – Schjoedt et al KI 2006
Spironolactone (25 mg) with ACE-I for 24 weeks in early diabetic nephropathy


Aldosterone escape is observed in 40% of patients with type 2 DM and early nephropathy treated by ACE inhibitors.
Two (final) essential questions:

1) What is more efficient:  
   \[ \text{ACE-I + ARB or ACE-I + SPIRONO?} \]

2) Triple therapy (\text{ACE-I + ARB + SPIRONO}) is even better?
Double-Blind, Placebo-Controlled Study on the Effect of the Aldosterone Receptor Antagonist Spironolactone in Patients Who Have Persistent Proteinuria and Are on Long-Term Angiotensin-Converting Enzyme Inhibitor Therapy, with or without an Angiotensin II Receptor Blocker

Anastasia Chrysostomou, Eugenia Pedagogos, Lachlan MacGregor, and Gavin J. Becker
Royal Melbourne Hospital, Parkville, Victoria, Australia

Epstein et al. Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes.


<table>
<thead>
<tr>
<th>Group</th>
<th>Completed</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>80 (87.9%)</td>
<td>11 (12.1%)</td>
</tr>
<tr>
<td>EPL50</td>
<td>83 (91.2%)</td>
<td>8 (8.8%)</td>
</tr>
<tr>
<td>EPL100</td>
<td>77 (89.5%)</td>
<td>9 (10.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>PBO</th>
<th>EPL50</th>
<th>EPL100</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE:</td>
<td>5 (5.5%)</td>
<td>2 (2.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AE &gt;7d*:</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>↑ K*:</td>
<td>2 (2.2%)</td>
<td>4 (4.4%)</td>
<td>7 (8.1%)</td>
</tr>
<tr>
<td>TRT failure:</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Protocol violation:</td>
<td>2 (2.2%)</td>
<td>0 (0.0%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Consent withdrawn:</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Lost to follow-up:</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>
Epstein et al. Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes.

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• ALDO and the kidney: experimental evidence
• ALDO antagonists and nephroprotection
• *Is ALDO antagonism mandatory for heart failure patients with CKD?*
• ALDO antagonism in dialysis patients?
• Perspectives of aldosterone blockade
Just as a reminder…
reducing proteinuria may save your kidneys AND your heart
The landmark study...

The New England Journal of Medicine

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

Bertram Pitt, M.D., Faiez Zannad, M.D., Willem J. Remme, M.D., Robert Cody, M.D., Alain Castaigne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D., for the Randomized Aldactone Evaluation Study Investigators*
Aldosterone-Induced Myocardial Fibrosis and Perivascular Cuffing

Normal Rat

Aldosterone-Infused Rat

a: coronary artery

Spironolactone (25 mg) with ACE-I for 24 weeks in early diabetic nephropathy
Aldosterone-to-renin ratio, arterial stiffness, and the response to aldosterone antagonism in essential hypertension.


- 24 untreated patients (mean age 51 yrs)
- randomization in a cross-over design to 50 mg of spironolactone or 2.5 mg of bendroflumetrazide for 4 weeks with washout period of 1 month
- both drugs significantly reduced brachial BP, but only spironolactone reduced (P < .001) PWV and AIx
- Aldosterone antagonism has BP-independent effects on arterial stiffness.
However:
The RALES effect... Juurlink et al, *NEJM* 2004

*Figure 3.* Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.
Safety

Please...
Speak up loud...
You ARE reluctant because you are concerned / worried about safety
Aldosterone: a new culprit in CKD

Editorial Review

Is it time for spironolactone therapy in dialysis patients?

Adrian Covic¹, Paul Gusbeth-Tatomir¹ and David J. A. Goldsmith²
Effect of Spironolactone on Blood Pressure and the Renin-Angiotensin-Aldosterone System in Oligo-Anuric Hemodialysis Patients

Evan Gross, MD, Marcos Rothstein, MD, Susan Dombek, RN, and Henrikas Irmantas Juknis, MD

*Am J Kidney Dis* 2005

- randomized, double-blind, placebo-controlled, cross-over study

- 50 mg spironolactone or placebo twice daily for 2 wks + 3 wks of wash-out + 2 wks of cross-over
What about CAPD?

Even less experience as with HD…

- One case presentation (Hausmann et al, _NDT_ 2002) - significant improvement of heart failure, no hyper-K, but gynecomastia


→ no hyperkalemia during 24 month of FUP
Safety

What about Eplerenone?
## Eplerenone: Tolerability

### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Eplerenone n = 220</th>
<th>Spironolactone n = 119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impotence</td>
<td>0</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>2 (0.8%)</td>
<td>16 (13.6%)</td>
</tr>
<tr>
<td>Menstrual irregularities</td>
<td>0</td>
<td>11 (9.3%)</td>
</tr>
<tr>
<td>Female breast pain</td>
<td>0</td>
<td>19 (16.1%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1 (0.5%)</td>
<td>7 (5.9%)</td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>9 (4.1%)</td>
<td>10 (8.4%)</td>
</tr>
</tbody>
</table>
Percent of Patients Withdrawn Due to Potassium Elevations*

* >5.5 mmol/L on 2 consecutive occasions

Epstein et al. Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes. 
Table 1 Worsening of renal failure and onset of hyperkalemia in patients with chronic kidney disease treated with the aldosterone antagonist spironolactone.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of patients with diabetes</th>
<th>Mean baseline GFR (ml/min)</th>
<th>Mean baseline serum creatinine level (mg/dl)(^a)</th>
<th>Spironolactone dose (mg/day)</th>
<th>Duration of treatment (months)</th>
<th>Number of patients with plasma potassium level 5.0–5.4 mmol/l</th>
<th>Number of patients with plasma potassium level ≥5.5 mmol/l</th>
<th>ARF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysostomou et al. (2001)(^50)</td>
<td>8</td>
<td>5</td>
<td>81 ± 48</td>
<td>NA</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sato et al. (2003)(^51)</td>
<td>13</td>
<td>13</td>
<td>NA</td>
<td>0.89 ± 0.30</td>
<td>25</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rachmani et al. (2004)(^52)</td>
<td>46</td>
<td>46</td>
<td>NA</td>
<td>0.91 ± 0.03</td>
<td>100</td>
<td>12</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sato et al. (2005)(^53)</td>
<td>32</td>
<td>17</td>
<td>NA</td>
<td>0.88 ± 0.25(^b)</td>
<td>25</td>
<td>3</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bianchi et al. (2005)(^54)</td>
<td>42</td>
<td>0</td>
<td>56.8 ± 4.7</td>
<td>NA</td>
<td>25</td>
<td>2</td>
<td>0</td>
<td>5(^d)</td>
<td>0</td>
</tr>
<tr>
<td>Schjoedt et al. (2005)(^55)</td>
<td>22</td>
<td>22</td>
<td>~80</td>
<td>NA</td>
<td>25</td>
<td>2+2(^e)</td>
<td>2</td>
<td>1</td>
<td>1(^f)</td>
</tr>
<tr>
<td>Schjoedt et al. (2006)(^56)</td>
<td>20</td>
<td>20</td>
<td>~64</td>
<td>NA</td>
<td>25</td>
<td>2+2(^e)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Takebayashi et al. (2006)(^57)</td>
<td>37</td>
<td>37</td>
<td>NA</td>
<td>0.74 ± 0.17</td>
<td>50</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)To convert creatinine values from mg/dl to µmol/l, multiply by 88.4. \(^b\)Diabetics. \(^c\)Nondiabetics. \(^d\)Patients with GFR below 60 ml/min. \(^e\)Crossover trial design. \(^f\)Reversible increase in plasma creatinine of 33%. Abbreviations: ARF, acute renal failure; GFR, glomerular filtration rate; NA, not applicable.
Perspectives (I)

• If spironolactone (added to ACE inhibition) is effective in retarding the progression of CKD remains to be validated in large clinical trials.

• An interesting end-point will be also the impact of aldosterone blockade on CVD in pre-dialysis patients.

• An interesting issue is also the effect of spironolactone on the prevention/progression of chronic allograft dysfunction in renal transplant patients.
Perspectives (II)

• A large-scale trial of low-dose spironolactone in dialysis patients is less probable, but mandatory.

• It is likely, based on *extrapolations* from the general population, that spironolactone may have a significant (or even more pronounced) effect on abnormal cardiac remodeling, and therefore on cardiovascular hazard, compared to non-renal populations.

• The issue of safety of spironolactone in dialysis is far from being solved and should be examined in larger trials, for longer periods, with and without concomitant ACE-I
Perspectives (III)

• Based on current knowledge, we can conclude that at least in selected dialysis patients, low dose aldosterone blockade may be safe.

• However, peculiar situations like dehydration, dietary incompliance, hyperglycaemia etc may add an additional hazard for hyperkalaemia.

• Concomitant use of bowel chelation of potassium with resins may be beneficial in addition to spironolactone, but has never been properly studied.
Book your places for the 6th RFA, 2008

Constantin Brancusi
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Study Patients</th>
<th>No. of Pts</th>
<th>Intervention</th>
<th>Length</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al, 2002</td>
<td>Randomized, double-blind</td>
<td>Type 2 diabetics w/ mild to-moderate hypertension and microalbuminuria</td>
<td>215</td>
<td>EPL 200 mg/d vs ENAL 40 mg/d vs EPL 200 mg/d + ENAL 10 mg/d</td>
<td>24 wk</td>
<td>Change in UACR</td>
<td>↓ UACR</td>
</tr>
<tr>
<td>Epstein et al, 2006</td>
<td>Randomized, double-blind, placebo-controlled, parallel group</td>
<td>Type 2 diabetics</td>
<td>268</td>
<td>EPL 50 mg/d vs EPL 100 mg/d vs placebo, all in addition to enalapril 20 mg/d</td>
<td>12 wk</td>
<td>Change in UACR</td>
<td>↓ UACR</td>
</tr>
<tr>
<td>Rachmani et al, 2004</td>
<td>Randomized, prospective</td>
<td>Female type 2 diabetics</td>
<td>46</td>
<td>Cilazapril 5 mg/day or SPL 100 mg/day in addition to baseline atenolol and HCTZ</td>
<td>24 wk</td>
<td>Change in ACR</td>
<td>↓ ACR</td>
</tr>
<tr>
<td>Rossing et al, 2005</td>
<td>Randomized, double-masked, placebo-controlled crossover</td>
<td>Type 2 diabetics w/nephropathy</td>
<td>20</td>
<td>SPL 25 mg/d in addition to baseline diuretics and maximally recommended doses of ACEI/ARBs</td>
<td>28-wk periods</td>
<td>Change in albuminuria</td>
<td>Albuminuria</td>
</tr>
<tr>
<td>Schjoedt et al, 2005</td>
<td>Randomized, double-masked, placebo-controlled crossover</td>
<td>Caucasian type 1 diabetics w/persistent microalbuminuria</td>
<td>20</td>
<td>SPL 25 mg/d in addition to baseline ACEI/ARB and diuretics</td>
<td>2 mo</td>
<td>Change in albuminuria (24-hr urine)</td>
<td>↓ Albuminuria</td>
</tr>
<tr>
<td>Sato et al, 2005</td>
<td>Prospective, open-label, uncontrolled</td>
<td>Chronic renal disease w/ proteinuria persistently &gt;0.5 g/d</td>
<td>32</td>
<td>SPL 25 mg/d added to baseline candesartan</td>
<td>12 wk</td>
<td>Change in proteinuria (urine protein)</td>
<td>↓ Proteinuria</td>
</tr>
<tr>
<td>Bianchi et al, 2005</td>
<td>Prospective, open-label, uncontrolled</td>
<td>CKD (eGFR* 20-138 mL/min)</td>
<td>42</td>
<td>SPL 25 mg/d added to baseline ACEI/ARB</td>
<td>8 wk</td>
<td>Change in proteinuria (urine protein)</td>
<td>↓ Proteinuria</td>
</tr>
<tr>
<td>Chrysostomou et al, 2006</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Persistent proteinuria &gt;1.5 g/d</td>
<td>41</td>
<td>Ramipril 5 mg/d vs ramipril 5 mg/d + irbesartan 150 mg/d vs ramipril 5 mg/d + spironolactone 25 mg/d vs ramipril 5 mg/d + spironolactone 150 mg/d + spironolactone 25 mg/d</td>
<td>3 mo</td>
<td>Change in proteinuria (urine protein)</td>
<td>↓ Proteinuria (there was a greater reduction in proteinuria in the 2 treatment regimens that incorporated spironolactone)</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin/creatinine ratio; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ENAL = enalapril; EPL = eplerenone; HCTZ = hydrochlorothiazide; Lgth = length of study; Pts = patients; SPL = spironolactone; UACR = urinary albumin/creatinine ratio.

*Estimated using Modification of Diet in Renal Disease (MDRD) formula.