CKD PROGRESSION AND MANAGEMENT
a. Diffuse and nodular mesangial expansion in a type 1 diabetic

b. Persistence of diffuse and nodular mesangial expansion 5 years after successful PTA

c. Marked reduction of mesangial expansion 10 years after successful PTA
Summary

1. CKD progression
2. Blockade of vasoconstrictor peptide action;
   - The Renin-Angiotensin System
   - Endothelin
3. Inhibition of TGF beta
4. Inhibition of inflammation-oxidative stress;
5. Other strategies;
   - Tyrosine Kinase Receptors of Growth Factors
   - Stabilization of the Extracellular Matrix
   - AGE/RAGE
   - Pirfenidone and tranilast
Summary

1. **CKD progression**

2. **Blockade of vasoconstrictor peptide action;**
   - The Renin-Angiotensin System
   - Endothelin

3. **Inhibition of TGF beta**

4. **Inhibition of inflammation-oxidative stress;**

5. **Other strategies;**
   - Tyrosine Kinase Receptors of Growth Factors
   - Stabilization of the Extracellular Matrix
   - AGE/RAGE
   - Pirfenidone and tranilast
Definition of CKD

KDOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2005

Table 11. Definition of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by <em>either</em>:</td>
</tr>
<tr>
<td>• Pathological abnormalities; or</td>
</tr>
<tr>
<td>• Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests</td>
</tr>
<tr>
<td>2. GFR &lt;60 mL/min/1.73 m² for ≥3 months, with or without kidney damage</td>
</tr>
</tbody>
</table>

Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.
<table>
<thead>
<tr>
<th>Stage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GFR (ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Normal or increased GFR with other evidence of kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Moderate decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>3A</td>
<td>45–59</td>
<td>Moderate decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>3B</td>
<td>30–44</td>
<td>Severe decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Established renal failure</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15</td>
<td>Established renal failure</td>
</tr>
</tbody>
</table>

Stages of chronic kidney disease

Stage 3 CKD should be split into two subcategories

• 3A: GFR 45–59 ml/min/1.73 m²
• 3B: GFR 30–44 ml/min/1.73 m²

Critics:

• Existing classification of five stages for CKD may not be sufficiently sophisticated for clinical needs
• Is neither staged according to age, nor according to level of proteinuria
• the loss of GFR may be a feature of ageing and that many people classified as stage 3 CKD are merely exhibiting a normal ageing process.
The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report

Andrew S. Levey¹, Paul E. de Jong², Josef Coresh³, Meguid El Nahas⁴, Brad C. Astor³, Kunihiro Matsushita³, Ron T. Gansevoort², Bertram L. Kasiske⁵ and Kai-Uwe Eckardt⁶

¹Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA; ²Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ³Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; ⁴Sheffield Kidney Institute, University of Sheffield, Sheffield, UK; ⁵Hennepin County Medical Center, Minneapolis, Minnesota, USA and ⁶Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany

| Summary of relative risks from categorical meta-analysis (dipstick included) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| (−, ±, +, ≥+)   | ACR <10         | ACR 10-29       | ACR 30-299      | ACR ≥300        |
| eGFR > 105      | 1.1             | 1.5             | 2.2             | 5.0             |
| eGFR 90-105     | 1.4             | 1.5             | 3.1             |                 |
| eGFR 75-90      | 1.3             | 1.5             | 2.3             |                 |
| eGFR 60-75      | 1.4             | 1.8             | 2.7             |                 |
| eGFR 45-60      | 1.7             | 2.2             | 3.6             |                 |
| eGFR 30-45      | 2.3             | 3.3             | 4.9             |                 |
| eGFR 15-30      | 4.7             | 6.6             |                 |                 |

<table>
<thead>
<tr>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;10</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR 10-29</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR 30-299</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR ≥300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;10</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR 10-29</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR 30-299</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>eGFR ≥300</td>
</tr>
</tbody>
</table>

AS Levey et al., Kidney Int. 2010
Renal functional decline in healthy adults

Annual change in creatinine clearance in the Baltimore Longitudinal Study of Aging by age

Glomerular filtration rates (by inulin clearance) by age

Renal function decline in adults with renal disease

Macroalbuminuria is a better risk marker - the PREVEND study

The decline in GFR was significantly less in those with impaired renal function compared with the general population (−0.2 vs. −2.3 ml/min/1.73 m², p<0.01)

eGFR less than 60 mL/min/1.73 m² and ACR 1.1 mg/mmol (10 mg/g) or more are independent predictors of all-cause mortality and cardiovascular mortality in the general population.

Chronic Kidney Disease Prognosis Consortium*, Lancet 2010
Summary

1. CKD progression

2. Blockade of vasoconstrictor peptide action;
   - The Renin-Angiotensin System
   - Endothelin

3. Inhibition of TGF beta

4. Inhibition of inflammation-oxidative stress;

5. Other strategies
The renin–angiotensin system (RAS)

Angiotensin II
Ang II strongly induces TGF-β production - in vivo

Ang II treatment of rat mesangial cells in culture increase TGF-beta, matrix components (biglycan, fibronectin), and collagen type I in a time- and dose-dependent manner

Angiotensin AT1 receptor blockers are renoprotective

Losartan led to significant improvement in renal outcomes that was beyond that attributable to blood-pressure control in patients with type 2 diabetes and nephropathy

Brenner, NEJM 2001
## ARA II vs PLACEBO on proteinuria

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment, n</th>
<th>Comparator, n</th>
<th>Ratio of Means (95% CI)</th>
<th>Ratio of Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy with ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator: placebo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Andersen et al., 2000 (39)</td>
<td>16</td>
<td>16</td>
<td>-</td>
<td>0.56 (0.39-1.26)</td>
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<tr>
<td>Handa et al., 2004 (40)</td>
<td>34</td>
<td>30</td>
<td>-</td>
<td>0.74 (0.66-0.98)</td>
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<tr>
<td>Jacobsen et al., 2003 (41)</td>
<td>18</td>
<td>18</td>
<td>-</td>
<td>0.36 (0.29-0.45)</td>
</tr>
<tr>
<td>Li et al., 2006 (42)</td>
<td>54</td>
<td>55</td>
<td>-</td>
<td>0.54 (0.39-0.74)</td>
</tr>
<tr>
<td>Rossing et al., 2003 (44)</td>
<td>23</td>
<td>23</td>
<td>-</td>
<td>0.48 (0.41-0.56)</td>
</tr>
<tr>
<td>Sasso et al., 2002 (45) (hypertensive)</td>
<td>64</td>
<td>64</td>
<td>-</td>
<td>0.73 (0.66-0.80)</td>
</tr>
<tr>
<td>Sasso et al., 2002 (45) (normotensive)</td>
<td>60</td>
<td>60</td>
<td>-</td>
<td>0.69 (0.62-0.77)</td>
</tr>
<tr>
<td>Zandbergen et al., 2003 (46)</td>
<td>71</td>
<td>71</td>
<td>-</td>
<td>0.53 (0.42-0.67)</td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
<td>337</td>
<td>-</td>
<td>0.57 (0.47-0.68)</td>
</tr>
</tbody>
</table>

### Proteinuria at 1-4 mo


<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment, n</th>
<th>Comparator, n</th>
<th>Ratio of Means (95% CI)</th>
<th>Ratio of Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy with ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator: placebo</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Atkins et al., 2005 (29)</td>
<td>437</td>
<td>437</td>
<td>-</td>
<td>0.70 (0.63-0.78)</td>
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<tr>
<td>de Zeeuw et al., 2004 (3)</td>
<td>751</td>
<td>762</td>
<td>-</td>
<td>0.69 (0.63-0.76)</td>
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<tr>
<td>Ishihitsu et al., 2005 (22)</td>
<td>22</td>
<td>22</td>
<td>-</td>
<td>0.75 (0.69-0.81)</td>
</tr>
<tr>
<td>Li et al., 2006 (42)</td>
<td>54</td>
<td>55</td>
<td>-</td>
<td>0.65 (0.42-1.00)</td>
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<tr>
<td>Muirhead et al., 1999 (43)</td>
<td>31</td>
<td>28</td>
<td>-</td>
<td>0.65 (0.43-1.00)</td>
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<tr>
<td>Parving et al., 2001 (6)</td>
<td>194</td>
<td>201</td>
<td>-</td>
<td>0.63 (0.60-0.67)</td>
</tr>
<tr>
<td>Total</td>
<td>1489</td>
<td>1505</td>
<td>-</td>
<td>0.66 (0.63-0.69)</td>
</tr>
</tbody>
</table>

### Proteinuria at 5-12 mo

# ACEI + ARB vs ACEI – effect on proteinuria

## Reduction in proteinuria at 1-4 months

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment, Comparator</th>
<th>Ratio of Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, n</td>
<td>Comparator, n</td>
<td>Rate of Means</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator: ACE inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal, 2009 (65)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Berger et al., 2002 (70)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Campbell et al., 2003 (49)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Ernaud et al., 2005 (51)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Ferrari et al., 2002 (52)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Horita et al., 2004 (53)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Jacobsen et al., 2003 (41)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Jacobsen et al., 2003 (72)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Jacobsen et al., 2002 (71)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Kim et al., 2003 (21)</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Kim et al., 2002 (20)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Luo et al., 2002 (66)</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Matos et al., 2005 (56)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Renke et al., 2004 (59)</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Resing et al., 2003 (74)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Resing et al., 2002 (73)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Russo et al., 2001 (60)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Rutkowski et al., 2004 (61)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Segura et al., 2003 (63)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Song et al., 2006 (65)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Tütüncü et al., 2001 (66)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>417</td>
<td>418</td>
</tr>
</tbody>
</table>

## Reduction in proteinuria at 5-12 months

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment, n</th>
<th>Comparator, n</th>
<th>Ratio of Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, n</td>
<td>Comparator, n</td>
<td>Rate of Means</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator: ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horita et al., 2004 (53)</td>
<td>11</td>
<td>10</td>
<td>0.64 (0.59-0.65)</td>
</tr>
<tr>
<td>Luo et al., 2002 (55)</td>
<td>16</td>
<td>14</td>
<td>0.55 (0.23-1.29)</td>
</tr>
<tr>
<td>Mogensen et al., 2000 (58)</td>
<td>67</td>
<td>64</td>
<td>0.82 (0.56-1.20)</td>
</tr>
<tr>
<td>Renke et al., 2004 (59)</td>
<td>16</td>
<td>18</td>
<td>1.31 (0.77-2.26)</td>
</tr>
<tr>
<td>Segura et al., 2003 (63)</td>
<td>12</td>
<td>12</td>
<td>0.49 (0.24-0.99)</td>
</tr>
<tr>
<td>Sengui et al., 2006 (64)</td>
<td>47</td>
<td>48</td>
<td>0.76 (0.66-0.92)</td>
</tr>
<tr>
<td>Tütüncü et al., 2001 (66)</td>
<td>10</td>
<td>12</td>
<td>1.15 (0.46-2.99)</td>
</tr>
<tr>
<td>Total</td>
<td>179</td>
<td>178</td>
<td>0.82 (0.67-1.01)</td>
</tr>
</tbody>
</table>

Kunz et al, Annals Int Med 2008
Are Two Better Than One?

**ACE-I + AT₁-RA in Patients with CKD**

Fig 4. Change in estimated GFR when an ARB is added to ACE-inhibitor therapy.

MacKinnon AJKD 2006
Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial


<table>
<thead>
<tr>
<th></th>
<th>Ramipril gMean (95% CI)</th>
<th>Telmisartan gMean (95% CI)</th>
<th>Ramipril+telmisartan gMean (95% CI)</th>
<th>Telmisartan vs ramipril p</th>
<th>Telmisartan+ramipril vs ramipril p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACR, Baseline</td>
<td>0.83 (0.78-0.84)</td>
<td>0.83 (0.80-0.86)</td>
<td>0.81 (0.78-0.84)</td>
<td>0.246</td>
<td>0.923</td>
</tr>
<tr>
<td>2-year ratio to baseline</td>
<td>1.17 (1.13-1.20)</td>
<td>1.08 (1.05-1.12)</td>
<td>1.05 (1.02-1.08)</td>
<td>0.0013</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Final ratio to baseline</td>
<td>1.32 (1.27-1.37)</td>
<td>1.25 (1.20-1.29)</td>
<td>1.22 (1.17-1.26)</td>
<td>0.033</td>
<td>0.0028</td>
</tr>
<tr>
<td>LO ratio to baseline</td>
<td>1.31 (1.26-1.35)</td>
<td>1.24 (1.20-1.28)</td>
<td>1.21 (1.17-1.25)</td>
<td>0.027</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

GFR declined least with ramipril/telmisartan compared to combination therapy

MAU / Proteinuria “best”; BP reduction effect “best”: -2.4 mmHg SBP
But overall outcome same; renal outcome worst of all
Minireview

Dual RAS Therapy Not on Target, but Fully Alive

H.J. Lambers Heerspink  D. de Zeeuw
Renin and Renal Fibrosis

Nguyen, Curr Opin Nephrol Hypertens 2007
Renin can induce an increase of TGF-β1 expression in rat mesangial cells, which in turn upregulates the expression of other profibrotic molecules PAI1, fibronectin and collagen I

Huang, Kidney INT 2006
Renin inhibitors (aliskiren) - a promising approach against renal fibrosis and disease progression

Pilz, Hypertension, 2005
Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Randomization
Open-label Double-blind
Forced titration at week 12
All doses were administered once daily

Losartan 100 mg and optimal antihypertensive therapy
Placebo
Aliskiren 150 mg
12–14 weeks
24 (endpoint)

Geometric Mean Change in Urinary Albumin-Creatinine Rate [%]

Geometric Mean Change in Urinary Albumin Excretion Rate [%]

Mean Systolic Blood Pressure (mmHg)

Mean Diastolic Blood Pressure (mmHg)
Aldosterone and Renal Fibrosis

- Angiotensin II
- Low salt intake
- Dyslipidemia
- Hyperglycemia

↑ Aldosterone

ACTIVATION

- Inflammation: ROS, MCP-1, IL-6, IL-1β
- Growth factors: CTGF, TGF-1β
- Extracellular matrix: Collagen (I, IV), PAI-1
- Cell proliferation: Fibroblast growth, Fibroblast proliferation

Glomerulosclerosis/
Tubulo-interstitial fibrosis

Renal scarring
Spironolactone causes regression of established glomerulosclerosis after subtotal nephrectomy

Mineralocorticoid blockade: less glomerulosclerosis and collagen IV expression

<table>
<thead>
<tr>
<th>Groups</th>
<th>Glomerulosclerosis index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=10/group)</td>
<td>0.14 ± 0.07</td>
</tr>
<tr>
<td>SNX (n=10/group)</td>
<td>1.72 ± 0.48*</td>
</tr>
<tr>
<td>SNX + Q (n=10/group)</td>
<td>1.03 ± 0.20*,#</td>
</tr>
<tr>
<td>SNX + S (n=10/group)</td>
<td>1.31 ± 0.20*</td>
</tr>
<tr>
<td>SNX + Q + S (n=10/group)</td>
<td>0.69 ± 0.21*,#</td>
</tr>
<tr>
<td>SNX + HRH (n=6/group)</td>
<td>1.20 ± 0.14*</td>
</tr>
<tr>
<td>ANOVA</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Hamar, NDT 2009

![Images of glomerular expression of collagen IV](image-url)

Quinapril
Spironolactone
combination Q+S
Thiazide+ Reserpin+ Hydralazin

negative control
Are Two Better Than One? ACE-I + SPIRONO in Patients with CKD
**INTENSIVE:**

1) RAS inhibitors (ACE inhibitors plus ARBs) +

2) spironolactone,

3) statin
Urine protein excretion over time
Changes in eGFR over time

* p<0.05 vs conventional therapy
** p<0.01 vs conventional therapy
Vasopeptidase inhibitors block both ACE and neutral endopeptidase and retarded fibrosis.

Therapy with AVE7688 in patients with CKD might have a profound nephroprotective effect in regards to reduction of profibrotic factors, being the major players in progression of CKD.

an animal model of Alport syndrome

Gross, Kidney INT 2005
CKD

- Poor sunlight exposure
- Decreased skin synthesis of VD3
- Dietary restriction of VD-rich food
- Urine loss of 25(OH)D3 and DBP
- Loss of renal mass and/or ↓ GFR
- Defective 25D uptake by the failing kidney
- Decreased renal 1α-OHase activity.
- Increased serum FGF-23
- Uremic toxicity over 1,25VD synthesis and over function of VD-VDR complex

Vitamin D Deficiency
 [25(OH)D and 1,25(OH)D Deficiency]

- Metabolic Bone Disease
- Atherogenesis
  - Antithrombin
  - Thrombomodulin
  - Tissue Factor
- Insulin Resistance
  - Metabolic Syndrome
  - Obesity
- RAAS Activation
- Immune Dysfunction

- Vascular Calcification
- Hypertension
  - LV Hypertrophy
  - LV Dysfunction
- Proteinuria
  - Renal inflammation
  - Glomerulosclerosis
- Chronic Inflammation

- Progression of CKD-ESRD
  - Major Cardiovascular Outcomes
    (Heart Failure, AMI, Stroke, PAD)

- High Morbidity
- High Mortality
Vitamin D Receptor Attenuates Renal Fibrosis

VDR-null mice developed more severe renal damage in the obstructed kidney, with marked tubular atrophy and interstitial fibrosis.

Zhang, JASN 2010
VDR Activity is a Negative Endocrine Regulator of the Renin-angiotensin System

*a* /+/+  -/-

Renin mRNA

<table>
<thead>
<tr>
<th></th>
<th>+/+</th>
<th>-/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>*</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
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<td></td>
</tr>
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<td>0.5</td>
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*b* +/+  -/-

Ang II (pg/ml)

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<thead>
<tr>
<th></th>
<th>+/+</th>
<th>-/-</th>
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<tbody>
<tr>
<td>600</td>
<td>*</td>
<td>400</td>
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<td>300</td>
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<td>200</td>
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<td>100</td>
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</tbody>
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c
d

Ang II = angiotensin II; CaBP = calcium-binding protein; V = vehicle; 36B4 = human cDNA clone


*P < 0.001 vs. wild-type mice

Ang II = angiotensin II; CaBP = calcium-binding protein; V = vehicle; 36B4 = human cDNA clone

Studiul VITAL

Faza de Screening | Faza de tratament | Perioada de urmărire

Paricalcitol 2 $\mu g$* QD + terapie concomitentă

Paricalcitol 1 $\mu g$* QD + terapie concomitentă

Placebo corespunzător + terapie concomitentă

3 săptămâni

30 zile

60 zile

Înțial

Săptămâna 24

Trei probe din prima urină de dimineață. Colectate în:
Ziua 1, Săptămâna 4, 8, 12, 16, 20 și 24

*Capsule orale
### VITAL Primary Study Results

**Primary Endpoint**
- Placebo: p=0.071
- Combined: p=0.053

**Secondary Endpoint**
- Paricalcitol 1 μg: p=0.229
- Paricalcitol 2 μg: p=0.053
Change in UACR by Sodium Tertile
Post-hoc Analysis

Sodium Excretion Tertile

- <121 mmol/24-h
  - Placebo: p=0.999
  - 1 μg Paricalcitol: p=0.999
  - 2 μg Paricalcitol: p=0.999

- 121-178 mmol/24-h
  - Placebo: p=0.810
  - 1 μg Paricalcitol: p=0.324
  - 2 μg Paricalcitol: p=0.047

- >178 mmol/24-h
  - Placebo: p=0.944
  - 1 μg Paricalcitol: p=0.005
  - 2 μg Paricalcitol: p=0.005

(n = 27) (n = 28) (n = 31) (n = 29) (n = 31) (n = 32) (n = 31) (n = 31) (n = 29)

Endothelin – important mediator of vascular and renal fibrosis

A part of this fibrosis was attributed to abnormal collagen I presence
Summary

1. CKD progression

2. Blockade of vasoconstrictor peptide action;
   - The Renin-Angiotensin System
   - Endothelin

3. Inhibition of TGF beta

4. Inhibition of inflammation-oxidative stress;

5. Other strategies;
TGF β 1 - a key effect in the induction of renal fibrosis

Administration of anti TGF-β 1 suppresses the increased production of extracellular matrix and dramatically attenuates the histological manifestation of the disease

Border, Nature 1990
TGF-β signalling and its modulation
BMP-7 was shown to reduce renal interstitial fibrosis in two genetic mouse models.
BMP-7 prevents renal fibrogenesis better (?) than ACE-I
The plant alkaloid halofuginone inhibit Smad-3 and ameliorated renal fibrosis

Effect of halofuginone on proteinuria and collagen content in 5/6 nephrectomized rats.
HGF counteracts the profibrotic action of TGF-1 by intercepting Smad signaling through different mechanisms in various types of kidney cells.

Liu, Y. Am J Physiol Renal Physiol 2004
HGF markedly blocks TGF-β1-mediated myofibroblastic activation of renal interstitial fibroblasts
Glycosaminoglycan (GAG) Therapy

GAGs reduced extracellular matrix deposition and TGF-β overexpression induced by high concentration of glucose in mesangial cells in a rat model of streptozocin-induced diabetic nephropathy

Ceol, JASN 2000
Oral Sulodexide Reduces Albuminuria in Diabetic Patients: The Di.N.A.S. Randomized Trial

Gambaro G et al. JASN 2002
Sulodexide can reduce the early, but not late, kidney disease in radiation nephropathy in rats.

Rossini, NDT 2010
Keryx Biopharmaceuticals, Inc. announced top-line results from its SUN-MICRO Phase 3 clinical trial of Sulonex (sulodexide) for the treatment of diabetic nephropathy. The Company announced that this Phase 3 clinical trial failed to meet the primary objective of the study, which was to increase the proportion of patients that achieve therapeutic success at 6 months as compared to placebo over background therapy of maximal doses of ACE-inhibitors or ARBs. Therapeutic success was defined as (i) conversion from microalbuminuria to normoalbuminuria, as measured by albumin/creatinine ratio (ACR), with at least a 25% reduction in ACR relative to baseline ACR, or (ii) a 50% reduction in ACR relative to baseline ACR. In addition, in reviewing the mean changes in ACR over time, Sulonex and placebo appeared to be similar.
Summary

1. **CKD progression**
2. **Blockade of vasoconstrictor peptide action;**
   - The Renin-Angiotensin System
   - Endothelin
3. **Inhibition of TGF beta**
4. **Inhibition of inflammation-oxidative stress;**
5. **Other strategies;**
   - Tyrosine Kinase Receptors of Growth Factors
   - Stabilization of the Extracellular Matrix
   - AGE/RAGE
   - Pirfenidone and tranilast
Treatment with corticosteroids has been used in some fibrotic nephropathies (IgA) with relative success.

Glomerular and interstitial lesions of IgA nephropathy might be reversible to a considerable degree after corticosteroids.
Treatment with ICAM-1 antibody protect the rats kidney from the development of fibrosis in the anti MBG model of nephropathy.

Anti-rat ICAM-1 glomerular abnormalities was absent in day 14.

None-treated rats
This rats had diffuse fibrocellular crescents, glomerular sclerosis, and tubulointerstitial damage.
Nitric oxide
The PDE-5 inhibitor, sildenafil, prevented the development of fibrosis.

Rodriguez-Iturbe, Kidney Int 2005
...but it was ineffective in reversing established lesions

![Graph showing glomerulosclerosis index over time and treatment groups.](image)

*Rodriguez-Iturbe, Kidney Int 2005*
Antiproteinuric Effect of Pentoxifylline in Patients with Type 2 Diabetes

Navarro, JASN 2005

Pentoxifylline Attenuates Tubulointerstitial Fibrosis

Lin, JASN 2005
Pentoxifylline ameliorates proteinuria through suppression of renal monocyte chemoattractant protein-1 in patients with proteinuric primary glomerular diseases.
Pentoxifylline may slow the estimated GFR decrease in high-risk patients

The PTX group had a slower rate of decrease in kidney function than the placebo group

Perkins, AJKD 2009
Uric Acid in Hypertension and Renal Disease: The Chicken or the Egg?
Mehmet Kanbay, Yalcin Solak, Ekrem Dogan, Miguel A. Lanasa, Adrian Covic
Is the reverse true?

Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions

Mehmet Kanbay · Adem Ozkara · Yusuf Seloiki · Bunyamin Isik · Faruk Turgut · Nuket Baybek · Ebru Uz · Ali Akcay · Ramazan Yigitoglu · Adrian Covic

Received: 26 April 2007/ Accepted: 19 June 2007/Published online: 15 August 2007
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Abstract

Background Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease. However, there is no data about the effect of lowering uric acid level on hypertension, materials and methods Forty-eight hyperuricemic and 21 normouricemic patients were included in the study. Hyperuricemic patients received 300 mg/day allopurinol for three months. All patients’ serum creatinine level, 24-h urine protein level, glomerular
Allopurinol Increases Glomerular Filtration Rate

and helps preserve kidney function during 12 months of therapy compared with controls

Kanbay, Covic, Int Urol Nephrol, 2007
Summary

1. **CKD progression**

2. **Blockade of vasoconstrictor peptide action**;
   - *The Renin-Angiotensin System*
   - *Endothelin*

3. **Inhibition of TGF beta**

4. **Inhibition of inflammation-oxidative stress**;

5. **Other strategies**;
   - *Tyrosine Kinase Receptors of Growth Factors*
   - *AGE/RAGE*
   - *Bicarbonate*
EGF receptor-tyrosine kinase inhibitors prevent inhibition of abnormal increase in collagen I gene expression, decrease proteinuria and creatinemia, and prevent the development of renal vascular and glomerular fibrosis.
1. AGE can directly change the structure and function of basement membrane proteins

1. AGEs can induce specific cellular responses by interacting with the receptor for AGE (RAGE), a process contributing to TGF-beta and CTGF production
Administration of a single dose of soluble RAGE could inhibit mesangial matrix expansion and albuminuria in experimental diabetes.

Wendt, Am J Pathol 2003
Placebo vs Pimagedine

• Doubling S-Cr.: 26% vs 20% - P = 0.099
• 36-mo. decrease in GFR: 9.8 vs 6.3 ml/min – P = 0.05
Bicarbonate Supplementation Slows Progression of CKD

Ione de Brito-Ashurst, JASN 2009
Amelioration of metabolic acidosis reduces urine parameters of kidney injury including tubulointerstitial injury, and slows eGFR decline with better GFR preservation.

Phisitkul, Kidney Int 2010
**Polypill and the Future of Medicine**

**The Potential:**

- **50% Reduction All-Cause Mortality**
- **50% Reduction CHD, CVD, and Cancer-specific Mortality**
- **88% Reduction in MIs**
- **80% Reduction in Strokes**
- **11 Added Years of Life**