Effective Treatment Strategies to Delay the Progression of Renal Disease and Vascular Disease in CKD

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Renin Angiotensin Aldosterone System

Renin \rightarrow \text{Angiotensinogen} \rightarrow \text{Ang I} \rightarrow \text{Ang II} \rightarrow \text{AT}_1 \text{ Receptor} \rightarrow \text{ACE}
Renin Angiotensin System and End-Organ Damage

Angiotensin II

Brain

Vasoconstriction
Vascular inflammation and hypertrophy
Endothelial dysfunction

Atherosclerosis

Vessels

Left ventricular hypertrophy
Fibrosis
Remodeling
Apoptosis

Heart

Kidney

Glomerular capillary pressure
Proteinuria
Aldosterone release
Glomerular sclerosis

↑ Glomerular capillary pressure
↑ Proteinuria
↑ Aldosterone release

Stroke

Hypertension

Heart Failure
Myocardial Infarction

Death

Renal Failure

Willenheimer et al, Eur Heart J 1999
Dahlof B, J Hum Hypertens 1995
Fyhrquist F, J Hum Hypertens 1995

Anderson S, Exp Nephrol 1996
Booz GW et al, Heart Fail Rev 1998
The Role of Angiotensin II in Endothelial Dysfunction and Atherosclerosis

NADH = nicotinamide adenine dinucleotide; EC = endothelial cell.

Activation of NADH Oxidase in EC

- $\uparrow$ $O_2^-$ Generation
- $O_2^-$
- ↓ NO

Interference With Endothelium-Dependent Vasodilation

Angiotensin II

- $\uparrow$ LOX-1 Receptors
- $\uparrow$ Uptake of Oxidized LDL

Oxidized LDL

- Accumulation of Lipids in Plaques

EC Injury

- Formation of Foam Cells

$\uparrow$ LDL Oxidation and Uptake by Macrophages
Blockade of the Renin Angiotensin System

Feedback Loop
- Increased PRA, Ang I and Ang II

Renin

Angiotensinogen

AT₁ Receptor

ARBS

Ang II

Ang I

ACE
Strategies to achieve RAAS inhibition

- Sodium restriction and/or diuretics to enhance RAAS blockade
- ACEI vs. ARB?
- Supramaximal doses of ACEI/ARB
- Combination of therapy for RAAS blockade
- Vitamin D receptor activation
Sodium restriction and/or diuretics

- Effect of RAAS blockade is blunted by a high salt diet
- Sodium restriction or diuretic therapy may restore the efficacy of ACEI/ARB and contribute to renoprotection through BP control and proteinuria reduction

ACEI vs. ARB

- Are ARBs more effective at suppressing RAAS?
- Are any theoretical differences clinically relevant?
Increase the dose of ACEI/ARB

- Maximal renal benefit from ACEI/ARB may require higher dosages than those needed to normalize BP
- Clinical trials showed better proteinuria reduction with supramaximal doses of ACEI/ARB
- Few studies examined clinical end points

Week 6: -13.95% (64 mg), -18.45% (128 mg)

Week 30: -16.91% (64 mg), **-33.05% (128 mg)**
Combination therapy for RAAS blockade

- The redundancy of the RAAS makes suppression difficult
- Combining agents acting at different sites of the RAAS may result in more complete suppression
- The addition of candesartan 16 mg daily to maximal recommended doses of ACEI in patients with Type 2 diabetes and nephropathy enhanced the reduction in albuminuria independent of changes in BP (Rossing 2003).
Combination therapy for RAAS blockade

- Direct renin inhibitors (DRI) may provide superior blockade of RAAS
- Aliskiren has been shown to have equivalent BP lowering effects compared to ARB and ACEI
- The AVOID study showed reduction in proteinuria after adding aliskiren to maximal recommended dose of losartan in patients with hypertension and type 2 diabetes with nephropathy
- Clinical trials examining the effects of aliskiren added to ACEI/ARB on hard clinical end points are underway

Study Design: Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

N=599 patients with HTN/type 2 DM/albuminuria*

Open-label

Patients screened
n=301
n=298

Double-blind

Losartan 100 mg od + optimal hypertensive therapy

3 to 4 months
3 months
3 months

Primary endpoint: difference in proteinuria between treatment groups at 24 weeks.

*UACR >300 mg/g; or UACR >200 mg/g in patients receiving therapy targeted at blockade of the RAAS. All patients must have had a urinary albumin to creatinine ratio ≤3500 mg/g.

Primary Endpoint: Difference in UACR at 24 weeks

- At week 24, the difference in proteinuria between the groups was 20%.

Mean Blood Pressure at Baseline and End of Study

- No difference in mean BP was seen between aliskiren and placebo.

Vitamin D receptor activation

- Observational studies have suggested an association between lower 25OHD levels and higher proteinuria/higher incidence of ESRD
- Treatment with active vitamin D has been associated with a trend towards lower incidence of ESRD

Ravani et al, Kidney International 2009; 75:88–95
Kovesdy et al, Arch Intern Med 2008;168:397-403
25OH vitamin D levels and albuminuria

25OH vitamin D levels and albuminuria

25OHD levels and outcomes in CKD

## Risk of various end points for calcitriol treated vs. non-treated CKD patients

<table>
<thead>
<tr>
<th>Level of adjustment</th>
<th>Death before ESRD</th>
<th>Composite of Death before ESRD or ESRD</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.53 (0.37-0.77)</td>
<td>0.72 (0.56-0.92)</td>
<td>0.95 (0.67-1.34)</td>
</tr>
<tr>
<td>Age, race, BMI, SBP, DBP, smoking status, comorbidity index, diabetes mellitus, use of calcium containing phosphate binders and use of sevelamer</td>
<td>0.47 (0.32-0.69)</td>
<td>0.55 (0.42-0.72)</td>
<td>0.67 (0.46-0.97)</td>
</tr>
<tr>
<td>Model 2 plus PTH, estimated GFR, calcium, phosphorus, albumin, cholesterol, hemoglobin, WBC count, percent lymphocytes in WBC and 24 hour urine protein</td>
<td>0.35 (0.23-0.54)</td>
<td>0.46 (0.35-0.61)</td>
<td>0.75 (0.50-1.12)</td>
</tr>
</tbody>
</table>

Vitamin D receptor activation

- The biological actions of vitamin D receptor activation provided plausible explanations for the observed associations
Cellular action of calcitriol and the vitamin D receptor (VDR)

Calcitriol

Calcitriol, vitamin D receptor; 
VDRE, vitamin D response element; 
RXR, retinoid x receptor.

Vitamin D receptor activation

- Observational studies and biologic plausibility cannot prove cause-and-effect
- A number of small clinical trials suggested that active vitamin D therapy alone or in combination can induce lowering of proteinuria

Effect of Paricalcitol on albuminuria in CKD stage 3 patients

Effect of paricalcitol on spot UProt/creat in nondiabetic proteinuric patients

Effect of oral calcitriol on proteinuria and blood pressure in IgA nephropathy on top of ACEi/ARB treatment


Proteinuria (g/g-Cr)

Blood pressure (mmHg)

Systolic

Diastolic

p<0.004
Additive antiproteinuric effect of paricalcitol on top of ACEI/ARB

Independent of a number of factors, including age, sex, race, DM, HTN
Adjustment for urine specific gravity increased the adjusted odds of reduction of protein from 3.2 to 4.0

VITAL Study Question and Design

Does treatment with paricalcitol capsules reduce albuminuria in subjects with type 2 diabetic nephropathy receiving treatment with ACE inhibitors and/or ARBs?

Double-blind, placebo controlled, multicenter study

<table>
<thead>
<tr>
<th>Screening Phase</th>
<th>Treatment Phase</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks</td>
<td>Paricalcitol 2 μg/day + concomitant therapy</td>
<td>30 days</td>
</tr>
<tr>
<td>Baseline</td>
<td>Paricalcitol 1 μg/day + concomitant therapy</td>
<td>60 days</td>
</tr>
<tr>
<td>Matched placebo</td>
<td>Matched placebo + concomitant therapy</td>
<td>Week 24</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 281</td>
<td></td>
</tr>
</tbody>
</table>
Primary Endpoint: Effect of paricalcitol on UACR

Percent geometric mean change from baseline to the last on-treatment UACR for combined doses compared to placebo

\[ P = 0.071 \]
Secondary Endpoint: Effect of paricalcitol doses on UACR

Percent geometric mean change from baseline to the last on-treatment UACR for individual dose groups compared to placebo

% Geometric Mean Change

Placebo  Paricalcitol 1 µg  Paricalcitol 2 µg

$P = 0.229$  $P = 0.053$

*De Zeeuw et al; submitted*
Secondary Endpoint: Paricalcitol 2 µg/day reduces 24-hour urinary albumin excretion

De Zeeuw et al; submitted
Post-hoc Endpoint: Dietary sodium intake modulates the UACR effect of paricalcitol 2 μg/day

De Zeeuw et al; submitted
Tertiary Endpoint: paricalcitol 2 μg/day reversibly reduces UACR over time (repeated measures 24 wks)

$P = 0.014$ for paricalcitol 2 μg vs. placebo over 24 weeks

De Zeeuw et al; submitted
Tertiary Endpoint: paricalcitol 2 μg/day reversibly reduces eGFR over time (repeated measures 24 wks)

De Zeeuw et al; submitted
De Zeeuw et al; submitted
Conclusions

- RAAS inhibition continues to be the cornerstone of renal and vascular protection.
- Various strategies can be used to enhance RAAS inhibition, but the clinical utility of these approaches has not been thoroughly tested.
- Vitamin D therapy can emerge as a novel treatment for RAAS inhibition that is devoid of the side effects that may inhibit the use of ACEI/ARB.
The diagram illustrates the renin-angiotensin-aldosterone system (RAAS). It starts with the renin gene, which produces renin. Renin converts angiotensinogen to angiotensin I (Ang I), which is then converted to angiotensin II (Ang II) by ACE enzyme. Ang II binds to the AT1 receptor, leading to vasoconstriction and thirst. The system is regulated by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which block the conversion of Ang I to Ang II. Vitamin D and its analogs also play a role in regulating renin secretion.
Role of VDR in albuminuria, glomerulosclerosis

VDR and renal morphology, RAS activation

VDR and intrarenal inflammation

VDRA and intrarenal RAS expression

VDRA and TGFβ, nephrin

Selective Vitamin D Receptor (VDR) Activator for Albuminuria Lowering (VITAL) Study in Type 2 Diabetic Nephropathy

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¹University Medical Center Groningen, Netherlands; ²Indiana University School of Medicine, United States; ³Abbott Labs, United States; ⁴Washington University School of Medicine, United States; ⁵University Hospital of Copenhagen, Denmark; ⁶Mario Negri Institute for Pharmacological Research, Italy; ⁷University of Heidelberg, Germany
Eligibility Criteria

Key Inclusion Criteria
- Diagnosed with type 2 diabetes on medication for at least 12 months
- Received a stable dose of ACE-inhibitor or ARB for ≥3 months
- eGFR (simplified MDRD) between 15 to 90 mL/min/1.73m²
- Urinary albumin creatinine ratio (UACR) between 100 to 3000 mg/g creatinine on 3 consecutive first morning void urine samples
- PTH between 35 to 500 pg/mL

Key Exclusion Criteria
- VDR activator therapy within 6 months of screening
- Poorly controlled hypertension (SBP ≥160 mm Hg and/or DBP ≥100 mm Hg)
- History of allergic reaction to paricalcitol or similar drugs
- Primary glomerulonephritis or secondary nephritis
- Acute renal failure within 12 weeks of the Screening Phase
VITAL Study Endpoints

Primary Endpoint (ITT population)
• Percent geometric mean change from baseline to the last on-treatment UACR, comparing the combined paricalcitol dose groups (1 µg/day and 2 µg/day) with placebo

Secondary Endpoints (ITT population)
For the individual paricalcitol doses:
• Percent geometric mean change from baseline to the last on-treatment measurement in 24 hour urine albumin
• Proportion of subjects achieving at least a 15% reduction in the last on-treatment UACR from baseline

Tertiary Endpoints (ITT population)
• Change in UACR and eGFR repeated measures analysis
• Change in UACR and eGFR to the 30-day and 60-day post-treatment
<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 93)</th>
<th>Paricalcitol 1 µg (n = 93)</th>
<th>Paricalcitol 2 µg (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean ± SD</strong></td>
<td>64 ± 11</td>
<td>64 ± 10</td>
<td>65 ± 10</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>33 (35)</td>
<td>27 (29)</td>
<td>26 (27)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 (77)</td>
<td>63 (68)</td>
<td>66 (70)</td>
</tr>
<tr>
<td>Black</td>
<td>11 (12)</td>
<td>15 (16)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (11)</td>
<td>14 (15)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Blood pressure, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, (mm Hg)</td>
<td>142 ± 17</td>
<td>142 ± 18</td>
<td>141 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure, (mmHg)</td>
<td>73 ± 12</td>
<td>73 ± 12</td>
<td>73 ± 9</td>
</tr>
<tr>
<td><strong>Urinary Indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UACR(^a) (mg/g creatinine),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median [Q1,Q3]</td>
<td>642 [263,1128]</td>
<td>626 [288,1225]</td>
<td>597 [246,1172]</td>
</tr>
<tr>
<td>24-hour urinary albumin, (mg/d),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median [Q1,Q3]</td>
<td>705 [238,1534]</td>
<td>564 [307,1724]</td>
<td>819 [290,1447]</td>
</tr>
<tr>
<td>Serum creat. (mg/dL), mean ±SD</td>
<td>2.0 ± 1</td>
<td>1.9 ± 1</td>
<td>1.9 ± 1</td>
</tr>
<tr>
<td>eGFR(^b) (ml/min/1.73 m), mean ±SD</td>
<td>39 ± 17</td>
<td>40 ± 15</td>
<td>42 ± 18</td>
</tr>
</tbody>
</table>

\(^a\)UACR=urinary albumin:creatinine ratio  
\(^b\)eGFR=estimated glomerular filtration rate
Secondary Endpoint: paricalcitol 2 µg/day increases the percentage of subjects with > 15% reduction in UACR

De Zeeuw et al; submitted
## Safety

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 93)</th>
<th>Paricalcitol 1 µg (n = 93)</th>
<th>Paricalcitol 2 µg (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia (2 consecutive Ca &gt;10.5 mg/dL)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>58 (62%)</td>
<td>59 (63%)</td>
<td>63 (66%)</td>
</tr>
<tr>
<td>Any Serious Adverse Event</td>
<td>12 (13%)</td>
<td>13 (14%)</td>
<td>19 (20%)</td>
</tr>
<tr>
<td>Any Adverse Event Leading to Discontinuation of Study</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>11 (12%)*</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

*P-value = 0.018

_De Zeeuw et al; submitted_
Conclusions

- Paricalcitol 2 µg/day lowers albuminuria in patients with diabetic nephropathy who are on stable RAAS blockade.

- Paricalcitol 2 µg/day is most effective during high sodium intake (thus complementing the effect of RAAS blockade which is maximal during low sodium intake)

- Paricalcitol was found to be generally safe and tolerable and was associated with a low incidence of hypercalcemia in this study.

- The albuminuria-lowering effect of paricalcitol 2 µg/day was associated with a reversible fall in eGFR and systolic blood pressure (renoprotective?)

- Selective VDR activation with paricalcitol may be a novel approach to lowering the risk of kidney disease progression when used on top of ACE inhibitor or ARB therapy.
A post-hoc analysis of RENAAL showed that the risk of ESRD depended on albuminuria reduction and also showed dependence on the residual level of albuminuria, even in patients who reached the current SBP target.
