Current and novel therapeutic approaches in diabetic nephropathy

Vladimir Tesar
Department of Nephrology, Charles University, Prague, Czech Republic
Structure of the lecture

1. Outcome of pts with diabetic nephropathy
2. RAS inhibition
3. Endothelin antagonists
4. Bardoxolone
5. Other putative targets
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### Causes of end-stage renal disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>35%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>20%</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>8%</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>
KDOQI guidelines for the diagnostics and treatment of DKD

In the secondary analysis of the SHARP study, pts with DN had compared to cystic kidney disease ↓ progression to ESRD, but ↑ mortality.
Albuminuria – predictor mortality in type 2 diabetes

![Graph showing patient survival percentages over time for different levels of albuminuria.]

- Normoalbuminuria (n=191)
- Microalbuminuria (n=86)
- Macroalbuminuria (n=51)^

5-year mortality:
- 3%
- 11%
- 25%
Albuminuria and the risk of ESRD (RENAAL study)  
(Eijkelkamp et al., J. Am. Soc. Nephrol., 2007; 18: 1540 - 1546)

1428 pts from the RENAAL study
Rezidual albuminuria and risk of ESRD (RENAAL study)
(Eijkelkamp et al., J. Am. Soc. Nephrol., 2007; 18: 1540 - 1546)

\[ RR = 5 \]
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Angiotensin II and the progression of chronic nephropathy

(Taal and Brenner, Kidney Int 2000; 57: 1803 - 1817)
Succinate, Krebs cycle intermediate, activates RAS

High glucose and renin release: the role of succinate and GPR91

Kidney International advance online publication, 22 September 2010;

János Peti-Peterdi
New pharmacological treatments for improving renal outcomes in diabetes

Anne-Emilie Decièves and Kumar Sharma

FOCUS ON DIABETIC NEPHROPATHY

Nat Rev. Nephrol. advance online publication 4 May 2010;

Diagram:
- Prorenin → Renin
- Renin inhibitors
- Angiotensinogen → Angiotensin I
- ACEIs
- ACE
- Angiotensin II
- Angiotensin-(1–7)
- ACE2
- AT1 receptor
- ARBs
- ERK1/2
- Hypertrophic and proliferative effects
- Vasoconstriction
- Cell proliferation
- Generation of ROS
- ECM accumulation
- Vasodilation
- ↓ Cell proliferation
- Angiotensin II antagonism
Cummulative incidence of doubling of serum creatinine in patients with type 1 diabetes

(Lewis et al., N Engl J Med 1993; 329: 1456 - 1462)
Incidence of overt DN in microalbuminuric pts with type 2 diabetes

(Parving et al., N Engl J Med 2001; 345: 870 - 878)
ACEI a ARB
in diabetic pts with CKD

a. progression from normoalbuminuria to microalbuminuria
   - EUCLID (1997) - lisinopril
   - BENEDICT (2004) - trandolapril
   - verapamil

b. progression from microalbuminuria to overt proteinuria
   - Ravid et al. (1993, 1996) - enalapril
   - IRMA (2001) - irbesartan
   - DETAIL (2004) - telmisartan vs. enalapril

c. progression of chronic kidney disease (decrease of GFR)
   - Lewis et al. (1993) - captopril
   - RENAAL (2001) - losartan
   - IDNT (2001) - irbesartan
Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial

Johannes F E Mann, Roland E Schmieder, Matthew McQueen, Leanne Dyal, Helmut Schumacher, Janice Pogue, Xingyu Wang, Aldo Maggioni, Andrzej Budaj, Suphachai Chaithiraphan, Kenneth Dickstein, Matyas Keltai, Kaj Metsärinne, Ali Otto, Alexander Parkhomenko, Leopoldo S Piegas, Tage L Svendsen, Koon K Tse, Salim Yusuf, on behalf of the ONTARGET investigators

Summary

Figure 2: Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end
Aliskiren decreased albuminuria in pts with type 2 diabetes on maximal dose of losartan.
ALTITUDE was preliminarily stopped - a trend to more endpoints in the aliskiren limb
Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Pts in the aliskiren limb ↑ hyperkalemia and hypotension

Table 3. Most Commonly Reported Adverse Events and Study-Drug Discontinuation.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Event Reported</th>
<th>P Value</th>
<th>Event Leading to Permanent Study-Drug Discontinuation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aliskiren (N = 4272)</td>
<td>Placebo (N = 4285)</td>
<td>Aliskiren (N = 4272)</td>
<td>Placebo (N = 4285)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1670 (39.1)</td>
<td>1244 (29.0)</td>
<td>&lt;0.001</td>
<td>205 (4.8)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>686 (16.1)</td>
<td>706 (16.5)</td>
<td>0.60</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>519 (12.1)</td>
<td>357 (8.3)</td>
<td>&lt;0.001</td>
<td>28 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>417 (9.8)</td>
<td>312 (7.3)</td>
<td>&lt;0.001</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>429 (10.0)</td>
<td>469 (10.9)</td>
<td>0.17</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>418 (9.8)</td>
<td>371 (8.7)</td>
<td>0.07</td>
<td>65 (1.5)</td>
</tr>
</tbody>
</table>
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Endothelin contributes to hypertension, atherosclerosis and CKD

Effect of endothelin-1 on vascular and renal cells, resulting in hypertension, atherosclerosis and chronic kidney disease
Endothelin-1 and the kidney – beyond BP

Neeraj Dhaun\(^1,3\), David J Webb\(^3\) and David C Kluth\(^1,2\)

A. Glomerular endothelium

B. Podocytes

C. Mesangial cells

D. Monocytes

IL-6, TGF-β, PDGF

Matrix deposition

Glomerular basement membrane

ET1

ET\(_A\) receptor

ET\(_B\) receptor

Nephrin
Endothelin, Kidney Disease, and Hypertension

(Hypertension. 2013;61:1142-1145.)

Joshua S. Speed, David M. Pollock
In rats with streptozotocine-induced diabetes, combination of lisinopril and avosentan induced ↓ albuminuria and almost completely eliminated glomerulosclerosis.
Albuminuria decreased by 9.7%, 44.3% and 49.3%, respectively, in pts with type 2 diabetes on placebo, 25 mg and 50 mg of avosentan.
The study was prematurely terminated because of higher incidence of hyperhydration and CHF in avosentan-treated patients.
Fluid retention was associated with dyspnoea and CHF

Table 5. Frequency of adverse events relating to fluid overload as reported by the clinical investigators on adverse event forms (not adjudicated)

<table>
<thead>
<tr>
<th>Signs of Fluid Overload (n [%])</th>
<th>Avosentan 25 mg (n = 455)</th>
<th>Avosentan 50 mg (n = 478)</th>
<th>Placebo (n = 459)</th>
<th>P Avosentan 25 mg versus Placebo</th>
<th>P Avosentan 50 mg versus Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>78 (17.1)</td>
<td>80 (16.7)</td>
<td>77 (16.7)</td>
<td>0.706</td>
<td>0.822</td>
</tr>
<tr>
<td>Other edema</td>
<td>42 (9.2)</td>
<td>55 (11.5)</td>
<td>25 (5.4)</td>
<td>0.053</td>
<td>0.006</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>28 (6.2)</td>
<td>26 (5.4)</td>
<td>5 (1.1)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>31 (6.8)</td>
<td>34 (7.1)</td>
<td>15 (3.3)</td>
<td>0.052</td>
<td>0.197</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>9 (2.0)</td>
<td>8 (1.7)</td>
<td>4 (0.9)</td>
<td>0.286</td>
<td>0.184</td>
</tr>
<tr>
<td>CHF</td>
<td>27 (5.9)</td>
<td>18 (3.8)</td>
<td>10 (2.2)</td>
<td>0.003</td>
<td>0.107</td>
</tr>
</tbody>
</table>
What are the differences between past trials with avosentan\textsuperscript{9,10} and this study? The authors come to the reasonable conclusion that the advantage of atrasentan is the higher selectivity for the ET\textsubscript{A} receptor, which may translate into reduced inhibition of ET\textsubscript{B} receptor–mediated sodium retention.\textsuperscript{12}
<table>
<thead>
<tr>
<th>Gene name</th>
<th>$\text{ET}_A$</th>
<th>$\text{ET}_B$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTNRA</td>
<td>$\text{EDNRB}$</td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>$\text{ET}-1 = \text{ET}-2 &gt; \text{ET}-3$</td>
<td>$\text{ET}-1 = \text{ET}-2 = \text{ET}-3$</td>
</tr>
<tr>
<td>Desensitization</td>
<td>slow</td>
<td>fast</td>
</tr>
<tr>
<td>Trafficking</td>
<td>endosomes for recycling</td>
<td>lysosomes for degradation</td>
</tr>
<tr>
<td>G protein-coupling</td>
<td>$G_q/G_{11}$ (also $G_i/o$, $G_{i2}$, $G_s$)</td>
<td>$G_q/G_{11}$, $G_s$, $G_q/G_{13}$, $G_{i2}$</td>
</tr>
<tr>
<td>Peptide agonists</td>
<td>–</td>
<td>Sarafotoxan $5\mu C$</td>
</tr>
<tr>
<td>Peptide antagonists</td>
<td>BQ123</td>
<td>BQ788</td>
</tr>
<tr>
<td></td>
<td>FR139317</td>
<td></td>
</tr>
<tr>
<td>Radiolabeled ligands</td>
<td>$[^{125}]\text{-PD151242}$</td>
<td>$[^{125}]\text{-BQ3020}$</td>
</tr>
<tr>
<td></td>
<td>$[^{3}H]\text{-BQ123}$</td>
<td></td>
</tr>
</tbody>
</table>

### Renal function

#### Vasculature
- cortical vasoconstriction
- conduit vessel vasoconstriction
- afferent arteriolar constriction
- efferent arteriolar constriction

#### Glomerulus
- mesangial cell contraction
- mesangial cell proliferation
- podocyte injury

#### Epithelium
- endothelial function not known

#### Inner medullary collecting duct
- extracellular matrix accumulation
- interstitial fibrosis

- natriuresis
Endothelin, Kidney Disease, and Hypertension

(Hypertension. 2013;61:1142-1145.)

Joshua S. Speed, David M. Pollock
Increased delivery of Na+ activates ET1 stimulation of ETB and NO inhibits ENaC
KEY POINTS

- There is increasing evidence that the endothelin system plays a pivotal role in hypertension and proteinuric kidney disease as well as in diabetic microvascular and macrovascular complications.

- On the basis of experimental evidence, endothelin receptor blockade, and, in particular, ET_\text{A} receptor blockade holds great promise in the treatment of proteinuric renal disease as well as diabetic nephropathy.

- Concomitant blockade of the ET_\text{B} receptor may not be beneficial and may lead to salt and water retention.

- Early clinical trials have been confounded by the selection of the study cohorts, dosing problems and questionable ET_\text{A}R selectivity.

- ET_\text{A} receptor antagonist may act synergistically with blockade of the renin–angiotensin system (RAS) in the treatment of diabetic microvascular and macrovascular complications.
Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy

Donald E. Kohan,* Yili Pritchett,† Mark Molitch,‡ Shihua Wen,‡ Tushar Garimella,‡ Paul Audhya,† and Dennis L. Andress†

Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy

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Blood pressure in atrasentan-treated patients

A

B

Placebo

0.25 mg Atrasentan

0.75 mg Atrasentan

1.75 mg Atrasentan

Placebo

0.25 mg Atrasentan

0.75 mg Atrasentan

1.75 mg Atrasentan

Systolic Blood Pressure, mm Hg

Diastolic Blood Pressure, mm Hg

Time, Weeks

Time, Weeks

P=0.033 for atrasentan 0.75 mg vs. placebo

P=0.017 for atrasentan 0.75 mg vs. placebo

P=0.062 for atrasentan 1.75 mg vs. placebo
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Albuminuria in atrasentan-treated patients

[Graph showing percent of geometric mean change from baseline in UACR and percent of subjects with ≥40% reduction in UACR across different treatment groups.]
Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy

Donald E. Kohan,* Yili Pritchett,† Mark Molitch,‡ Shihua Wen,† Tushar Garimella,† Paul Audhya,‡ and Dennis L. Andress†

Table 4. Treatment-emergent adverse events in study subjects

<table>
<thead>
<tr>
<th>Subjects Experiencing, N (%)</th>
<th>Placebo (n = 23)</th>
<th>Atrasentan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25 mg (n = 22)</td>
<td>0.75 mg (n = 22)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>13 (57%)</td>
<td>16 (73%)</td>
</tr>
<tr>
<td>Any adverse event at least possibly related to study drug</td>
<td>5 (22%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Any severe adverse event</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Any adverse event leading to discontinuation of study drug</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most commonly reported adverse effects</td>
<td>2 (9%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>peripheral edema</td>
<td>2 (9%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>dizziness</td>
<td>0</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>urinary tract infection</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>headache</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>cough</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>hypertension</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>0</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>hypotension</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^aP = 0.047\) versus placebo.
\(^bP = 0.016\) versus placebo.
\(^cReported\) in \(\geq 5\%) of subjects.
\(^dP = 0.007\) versus placebo.
Protocol Title: A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy

**SONAR: Study Of Diabetic Nephropathy with Atrasentan**

**Objectives:** The study objective is to evaluate the effect of atrasentan compared with placebo on time to doubling of serum creatinine or the onset of end stage renal disease (ESRD) in subjects with type 2 diabetes and nephropathy who are treated with the maximum tolerated labeled daily dose (MTLDD) of a Renin-Angiotensin System (RAS) inhibitor. In addition, the study will assess the effects of atrasentan compared with placebo on cardiovascular morbidity and mortality, urine albumin excretion, changes in estimated glomerular filtration rate (eGFR), as well as on the impact on quality of life in subjects with type 2 diabetes and nephropathy.

**Investigators:** Multicenter study

**Study Sites:** A sufficient number of sites globally will be selected in order to randomize approximately 4,148 subjects into the double-blind treatment period.

**Study Population:** Subjects that have type 2 diabetes with nephropathy (defined by an estimated glomerular filtration rate (eGFR) of 25 – 75 ml/min and a urinary albumin to creatinine ratio (UACR) ≥ 300 mg/g creatinine) who are being treated with the MTLDD of a RAS inhibitor.
Duration of Treatment: Estimated up to 48-month Double-Blind Treatment Period.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:
Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (needing chronic dialysis or renal transplantation or renal death).

Secondary Efficacy Endpoints:

- Change from baseline to Month 24 post-randomization visit on UACR.
- Time to a 30% eGFR reduction after 3 months post-randomization treatment.
- Time to cardio-renal composite endpoint: doubling of serum creatinine, ESRD, CV death, nonfatal myocardial infarction, nonfatal stroke.
- Time to the CV composite endpoint: CV death, nonfatal myocardial infarction and nonfatal stroke.
Endothelin antagonists ↓ proteinuria and should be renoprotective

SONAR study concentrates on renal endpoints

Fluid retention is mediated by ET\textsubscript{B} inhibition and is less expressed in pts treated with selective ETA antagonists

Despite that in the SONAR study great attention is paid to the fluid retention, its prevention, monitoring and treatment
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5. Other putative targets
bardoxxolone methyl inhibition of NFκB
Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

Pablo E. Pergola, M.D., Ph.D., Philip Raskin, M.D., Robert D. Toto, M.D.,
Colin J. Meyer, M.D., J. Warren Huff, J.D., Eric B. Grossman, M.D.,
Melissa Krauth, M.B.A., Stacey Ruiz, Ph.D., Paul Audhya, M.D.,
Heidi Christ-Schmidt, M.S.E., Janet Wittes, Ph.D., and David G. Warnock, M.D.,
for the BEAM Study Investigators*

This article (10.1056/NEJMoal105351) was published on June 24, 2011, at NEJM.org.

Bardoxolone increased GFR by 50%

A

![Graph showing the increase in GFR with Bardoxolone methyl compared to placebo.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Bardoxolone methyl, 25 mg</th>
<th>Bardoxolone methyl, 75 mg</th>
<th>Bardoxolone methyl, 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>0</td>
<td>57 56 55 53 54 54 53 52 53 51 53 52</td>
<td>57 53 52 52 52 51 51 49 49 47 48 48 48</td>
<td>57 55 51 51 53 52 52 51 48 50 50 48 48 48</td>
</tr>
</tbody>
</table>
Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

Bardoxolone decreased the risk of CKD progression

![Graph showing the decrease in risk of CKD progression with Bardoxolone methyl at different doses compared to placebo.](image)
Large phase III RCT with bardoxolone in pts with DN and CKD 4
BEACON

preliminarily stopped (10/2012) because of \[\uparrow\] fluid retention and heart failure

Further analyses necessary: probably no cardiotoxicity
sodium retention due to the stimulation of ENaC
because of the non-selective endothelin inhibition
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New pharmacological treatments for improving renal outcomes in diabetes

Anne-Emilie Declèves and Kumar Sharma

1. Obesity/insulin resistance
   - ROS
2. Glomerular alterations
3. Diabetic/hyperglycemia
   - ROS
   - AGEs
4. RAS inhibitors
   - ↑ PKC
5. ↑ Nox/ROS
6. Statins
7. ↑ TGF-β
   - Neutralizing antibody
8. CTGF
9. PAI-1
10. Renal hypertrophy
    - ↑ Glomerular volume
    - Vascular dysfunction
11. Pirfenidone
12. Mesangial and interstitial matrix EMT
In PREDIAN study 169 proteinuric type 2 diabetic pts were randomized to pentoxifylline or placebo (FU 2 years) all on RAS blockade, 90% on statins and aspirin

Table 1. Baseline characteristics of participants in the trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=87)</th>
<th>Pentoxifylline Group (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.5±9.5</td>
<td>70.2±8.9</td>
</tr>
<tr>
<td>Men (%)</td>
<td>46 (52.8)</td>
<td>45 (54.8)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known duration of diabetes (yr)</td>
<td>14.8±3.5</td>
<td>15.3±3.2</td>
</tr>
<tr>
<td>CKD stage 3, n (%)</td>
<td>63 (72.4)</td>
<td>53 (64.6)</td>
</tr>
<tr>
<td>CKD stage 4, n (%)</td>
<td>24 (27.5)</td>
<td>29 (35.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9±2.9</td>
<td>29.4±3.3</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>141.8±8.4</td>
<td>142.2±9.4</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>86.4±7.7</td>
<td>86.5±8.5</td>
</tr>
<tr>
<td><strong>Biochemical variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>7.2±0.7</td>
<td>7.3±0.7</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.5±0.8</td>
<td>4.3±1.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>2.4±0.6</td>
<td>2.3±0.6</td>
</tr>
<tr>
<td>HDL</td>
<td>1.1±0.3</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.8±0.9</td>
<td>1.8±0.7</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.3±1.3</td>
<td>4.3±1.3</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>37.6±11.9</td>
<td>37.1±12.4</td>
</tr>
<tr>
<td>UAE (mg/d)</td>
<td>1000 (600–1800)</td>
<td>1100 (689–2190)</td>
</tr>
<tr>
<td>UAE&gt;1 g/d, n (%)</td>
<td>43 (49.4)</td>
<td>49 (59.7)</td>
</tr>
<tr>
<td>Urinary TNF-α (ng/g)</td>
<td>16 (9.1–22)</td>
<td>16 (11–20.1)</td>
</tr>
</tbody>
</table>
Blood pressure control comparable in both limbs
Pentoxifylline significantly decreased the loss of GFR
Pentoxifylline decreased albuminuria and rate of loss of eGFR
In pts on 1200 mg of pirfenidone increase of GFR, higher dose of pirfenidone poorly tolerated (GI complaints)
MCP-1 (CCL2) is a key proinflammatory chemokine

- Inducers:
  - TNF-alpha
  - NF-kB
  - PDGF
  - Stress factors
- Pathologies:
  - Atherosclerosis
  - Ischemia
  - Angiogenesis & cancer progression
  - Autoimmune diseases
The only leukocyte receptor for MCP-1 is CCR2.

CCX140 is an oral antagonist of CCR2.
MCP-1 ↑ progression of DN
CCX140 ↑ insulin sensitivity in diabetic CCR2 knock-in mice
CCX140 decreases proteinuria in diabetic CCR2 knock-in mice

Diet-induced obesity

db/db mice
CCX140 antagonist CCX140-B provides renal and glycemic benefits in diabetic transgenic human CCR2 knock-in mice

CCX140 ↓ glomerular hypertrophy and ↑ podocyte number in diabetic CCR2 knock-in mice

A

B

glomerular volume number of podocytes

Vehicle CCX140-B

Vehicle CCX140-B

Vehicle CCX140-B

Vehicle CCX140-B
CCX140 in pts with diabetic nephropathy
(phase II study)

270 pts with ACR 100 – 3000 mg/g
and GFR>25 ml/min/m2
on stable doses of ACEI or (ARB),
randomized to CCX140 (5 mg or 10 mg), or a placebo,
once daily.

Interim analysis (12 weeks) September 20, 2013:

After 2 weeks 12% ↓ in UACR in 5 mg (p < 0.05);
8% ↓ in 10 mg, 1% ↑ in the placebo
The 12 week values -21%, -12%, -9%, respectively
CCX140 in pts with diabetic nephropathy  
(phase II study)

At 12 weeks UACR ↓ 27% (5 mg group), ↓ 33% (10 mg) vs. ↑ 2% placebo in a pre-specified subset of patients with baseline UACR > 800 mg/g and eGFR > 60 ml/min/m²

In the earlier study CCX140 (10 mg daily) ↓ plasma glucose and HBA1c compared to placebo in type 2D on metformin

↓ of HbA1c after 4 w of treatment in pts on 10 mg CCX140 compared to placebo confirmed also in this

52 – week data soon to be published in Lancet
Conclusions

In type 2 diabetes albuminuria increases the renal and cardiovascular risk

Antihypertensive medication should be based on the inhibition of renin-angiotensin-aldosterone system

Ongoing clinical studies should help to find new drugs with the potential to slow down or even halt the progression of chronic renal insufficiency with positive (or at least neutral) impact on CV outcome