New Treatments of Diabetic Nephropathy

Hassan Argani MD
Professor of nephrology
<table>
<thead>
<tr>
<th>Parameter</th>
<th>CKD 3 and 4</th>
<th>CKD 5 and Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb-A1C</td>
<td>&gt;6.5-7.5%</td>
<td>&gt;7.0-8.0%</td>
</tr>
<tr>
<td>Preferred agents</td>
<td>Meglitinides, sulfonylureas, insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>130/80 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Preferred agents</td>
<td>ACE/ARBs</td>
<td>?</td>
</tr>
<tr>
<td><strong>Lipid Treatment</strong></td>
<td>&lt;100 mg/dl</td>
<td>?</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred agents</td>
<td>Statins</td>
<td>?</td>
</tr>
<tr>
<td><strong>Anemia Treatment</strong></td>
<td>11.0-12.0 g/dl</td>
<td>11.0-12.0 g/dl (avoid &gt;13)</td>
</tr>
<tr>
<td>Hb level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred agents</td>
<td>Iron/ESA</td>
<td>Iron/ESA</td>
</tr>
<tr>
<td><strong>Vitamin D Supplements</strong></td>
<td>Vitamin D₃/1,25-OH D₃</td>
<td>1,25-OH D₃/vitamin D₃</td>
</tr>
<tr>
<td><strong>Supportive Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>++</td>
<td>NP</td>
</tr>
<tr>
<td>Hypoglycemia awareness</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Exercise (daily/weekly)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Foot care</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Prevention of falls</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Diabetic Nephropathy
Clinical outcomes of patients with DNP randomized to Clopidogrel plus aspirin versus aspirin alone (CHARISMA Trial)
Clinical outcomes of patients with DNP randomized to Clopidogrel plus aspirin versus aspirin alone (CHARISMA Trial)

The presence of DNP make ineffective many cardio-protective drugs such as Clopidogrel.
Nephrotic Syndrome in Diabetic Kidney Disease: An Evaluation and Update of the Definition

Nicholas Stoycheff, MD, MS,¹ Lesley A. Stevens, MD, MS,¹ Christopher H. Schmid, PhD,² Hocine Tighiouart, MS,² Julia Lewis, MD,³ Robert C. Atkins, MD,⁴ and Andrew S. Levey, MD¹

What about control of diabetes?

**Type 1 Diabetes**
- DCCT trial
  - Basal-bolus/insulin pump versus BD insulin
  - Reduction in incidence and progression of albuminuria
  - Followed up for 22 years – 50% reduction in incidence of impaired GFR

**Type 2 Diabetes**
- UKPDS/ACCORD/ADVANCE
- Intensive v standard glycaemic control
- Probably some benefit in reduction in DN but less impressive than for T1DM
Prevention Glycemic control with an HbA1c of ≤7%.

**Good Glycemic Control (Lower A1C) Reduces Complications**

<table>
<thead>
<tr>
<th>A1C</th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>76%</td>
<td>69%</td>
<td>17-21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>57%</td>
<td>-</td>
<td>16%*</td>
</tr>
</tbody>
</table>

Be careful about metabolic memory

Hypoglycemia & Variability contributes to glycemic variability and possibly to long-term complications through inflammatory mediators which persist for hours after the hypoglycemic event itself.
With good blood sugar control, microalbuminuria seldom arises.

---

**Graph:**

- **Y-axis:** Frequency of microalbuminuria (%)
- **X-axis:** Years
- **Legend:**
  - Blue line: Conventional treatment
  - Pink line: Intensive treatment

The graph shows the comparison between conventional treatment and intensive treatment over 9 years. The frequency of microalbuminuria increases over time for both treatments, but the intensive treatment shows a significantly lower frequency compared to conventional treatment.
The relation between the level of albuminuria and ESRD is very similar for all different studied conditions.

Short-term change in albuminuria during RAAS blockade is associated with long-term renal risk change protection.


Decreased albuminuria is promising.
Meta-analysis of clinical trials showing the drug effect on albuminuria correlated with the drug effect on renal outcome.

Diabetes

Normoalbuminuria → Microalbuminuria → Overt nephropathy (macroalbuminuria) → End-stage renal disease → Death

Pre-diabetes

BENEDICT (n=1,204) ROADMAP (n=4,447) RASS (n=285)

ADVANCE (n=11,140)

IRMA-2 (n=590) INNOVATION (n=527)

RENAAL (n=1,513) IDNT (n=1,715) ORIENT (n=577)
## FDA approved drugs that lower albuminuria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Comment</th>
</tr>
</thead>
</table>
| ACEI  | Hypertension                                    | All ACEIs lower albuminuria. Prospective trials in non-diabetic populations and patients with type 1 diabetes have shown renoprotective effects.  
                                              |  
| ARB   | Hypertension                                    | All ARBs lower albuminuria. The ARBs losartan and irbesartan have received an indication for the treatment of nephropathy in patients with type 2 diabetes.  
                                              |  
| Aliskiren | Hypertension                                 | Aliskiren lowers albuminuria but a hard outcome trial in patients with type 2 diabetes at cardio-renal risk did not show renal benefit.  
                                              |  
| MRA   | Congestive heart failure, hypertension, edematous conditions | Spironolactone and eplerenone lower albuminuria but increase risk of hyperkalemia. No hard renal outcome data are available. |  
| Linagliptin | Hyperglycemia                              | Linagliptin belongs to the dipeptidyl peptidase 4 inhibitors. Hard renal outcome trials are ongoing.                                                                                               |
| Canagliflozin | Hyperglycemia                           | Canagliflozin belongs to the sodium-glucose co-transporter inhibitors. Hard renal outcome trials are ongoing.                                                                                      |
| NSAIDs | Pain and inflammatory diseases                  | NSAIDs decrease albuminuria but are not often used in CKD patients.                                                                                                                                 |
| Pentoxifylline | Treatment of intermittent claudication         | No hard outcome data available.                                                                                                                                                                     |

Why we need new drugs for treating of DNP?

1. The global prevalence of DM is increasing and Diabetic nephropathy is a potentially life-threatening complication of DM that affects approximately one-third of all diabetic individuals and is the leading cause of ESRD.

2. More complete inhibition of the RAAS system, have halted for safety concerns:
   - ALTITUDE trial ➔ Combining ACEi or ARB + aliskiren ➔ Terminated for renal complications, Hyperkalemia and Stroke
   - NEPHRON-D trial ➔ Combining ACEi + ARB ➔ Induced acute loss of renal function and severe hyperkalemia.

3. New favourable treatments were ineffective for progression of DNP
   - BEACON Phase III ➔ Bardoxolone methyl ➔ Halted because of increased risk of CHF, MI and nonfatal stroke.
   - ASCEND trial ➔ Endothelin receptor antagonist ➔ halted because of fluid overload and heart failure.
Clinical Trials of Potential New Therapeutic Agents for Diabetic Nephropathy
## On-target and off-target effects of various drugs used in the management of DNP (Old Therapies With New Insights)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>On-target parameter</th>
<th>Off-target parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS intervention</td>
<td>Blood pressure ↓</td>
<td>Albuminuria ↓; K+ ↑; Uric acid ↓ (losartan)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Blood pressure ↓</td>
<td>K+↓; Uric acid ↑</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glucose ↓</td>
<td>VCAM ↓; ICAM ↓</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Glucose ↓</td>
<td>Blood pressure ↓; Albuminuria ↓</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Glucose ↓</td>
<td>Blood pressure ↓; Body weight ↓; Uric acid ↓; albuminuria ↓</td>
</tr>
<tr>
<td>Statins</td>
<td>LDL-cholesterol ↓</td>
<td>C-reactive protein ↓; albuminuria ↓</td>
</tr>
<tr>
<td>Vitamin D receptor activators</td>
<td>PTH ↓</td>
<td>Albuminuria ↓; Blood pressure ↓</td>
</tr>
<tr>
<td>Erythropoetin stimulating agents</td>
<td>Hb ↑</td>
<td>Blood pressure ↑</td>
</tr>
</tbody>
</table>
Advanced Glycation End Product Inhibitors
Aminoguanidine
Pyridoxamine.

Aldose Reductase Inhibitor.

Antioxidants as Therapeutics.

Anti-Inflammatory Drugs as Therapeutics.
Aspirin and Cyclooxygenase-2 Inhibitors
Pentoxifylline
Chemokine C-C Motif ligand 2 Inhibitor: (CCL2).

Anti-Extracellular Matrix Production.
Mineralocorticoid Antagonist.
Vitamin D.

Endogenous Protective Factors
Protein Kinase C Activation
Insulin
VEGF-A
Activated Protein C
Glucagon like Peptide-1.
The endocrine pathway for the actions of GLP-1

↑ Insulin secretion

↑ Insulin-sensitivity

↑ Beta cells mass

↓ Acid secretion

↑ Gastric emptying time.

↓ Glucagon secretion.

Physiol Rev 87: 1409–1439, 2007
Exenatide
Incretin mimic

Liraglutide
GLP-1 receptor activators

Incretins: GLP-1, GIP

GLP-1 receptors

Stimulate insulin release

Inhibit glucagon release

Lowering of blood glucose

DPP-4 enzyme inactivates incretins

DPP-4 inhibitors (drugs) block DPP-4

Sitagliptin
Linagliptin
The dipeptidyl peptidase inhibitor linagliptin and the angiotensin II receptor blocker telmisartan show renal benefit by different pathways in rats with 5/6 nephrectomy

Oleg Tsuprykov¹,², Ryotaro Ando³,⁴, Christoph Reichetzeder¹,², Karoline von Websky¹,², Viktoria Antonenko¹,², Yuliya Sharkovska⁵, Lyubov Chaykovska⁶, Jan Rahnenführer¹,², Ahmed A. Hasan¹, Harald Tammen⁷, Markus Alter²,⁸, Thomas Klein⁹, Seiji Ueda³, Sho-ichi Yamagishi⁴, Seiya Okuda³,⁴ and Berthold Hocher¹,¹⁰,¹¹

¹Institute of Nutritional Sciences, University of Potsdam, Potsdam, Germany; ²Center for Cardiovascular Research, Charité - Universitätsmedizin Berlin, Berlin, Germany; ³Division of Nephrology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; ⁴Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan; ⁵Institute of Vegetative Anatomy, Charité - Universitätsmedizin Berlin, Berlin, Germany; ⁶Department of Cardiovascular Surgery, University Hospital Zurich, Zurich, Switzerland; ⁷PXBioVision GmbH, Hannover, Germany; ⁸Department of Nephrology and Endocrinology, Charité - Universitätsmedizin Berlin, Berlin, Germany; ⁹Boehringer Ingelheim Pharma GMBH & Co. KG, Biberach, Germany; ¹⁰Institute for Laboratory Medicine, IFLB, Berlin, Germany; and ¹¹Department of Basic Medicine, Medical college of Hunan Normal University, Changsha, China

Dipeptidyl peptidase (DPP)-4 inhibitors delay chronic kidney disease (CKD) progression in experimental diabetic nephropathy in a glucose-independent manner. Here we compared the effects of the DPP-4 inhibitor linagliptin versus telmisartan in preventing CKD progression in reduction. Thus, linagliptin showed comparable efficacy to telmisartan in preventing CKD progression in non-diabetic rats with 5/6 nephrectomy. However, the underlying pathways seem to be different.

Kidney International (2016) 89, 1049–1061; http://dx.doi.org/10.1016/
Glucose reabsorption 18 gr/D

Gluconeogenesis 15-55 gr/D

Glucose Utilization 15-25 gr/D
RCTs found that Dapagliflozin may protect eGFR and decreases albuminuria.

Dapagliflozin: A novel insulin-independent approach to remove excess glucose.

TGF-B stimulate SGLT2 expression.

Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule.

Tubuloglomerular feedback and sodium glucose cotransporter 2

(a) Normal TGF
- Appropriate afferent arteriole tone
- Normal GFR
- Normal sodium/glucose reabsorption
- SGLT2

(b) Impaired TGF
- Elevated GFR
- Decreased Na⁺ delivery to macula densa
- Increased Na⁺/glucose reabsorption

(c) Restored TGF
- Glucosuria
- Increased Na⁺ delivery to macula densa
- SGLT2 inhibition in proximal tubule
- Normalization of GFR
- Afferent arteriole constriction

Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT2 inhibition reduces hyperfiltration via TGF
Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment

Paola Fioretto 1 · Bergur V. Stefansson 2 · Eva Johnsson 2 · Valerie A. Cain 3 · C. David Sjöström 2

Received: 18 February 2016 / Accepted: 20 May 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com
Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin–angiotensin blockers

H. J. L. Heerspink¹, E. Johnsson², I. Gause-Nilsson², V. A. Cain³ & C. D. Sjöström²

¹University of Groningen, University Medical Center, Groningen, The Netherlands
²AstraZeneca, Gothenburg, Mölndal, Sweden
³AstraZeneca, Wilmington, DE, USA
## Effects of SGLT-2 inhibitors in the management of T2DM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect of SGLT-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C</td>
<td>0.5% to 1.2% reduction (compared with placebo)</td>
</tr>
<tr>
<td>Glucose-lowering actions dependent on insulin secretion?</td>
<td>No</td>
</tr>
<tr>
<td>Weight</td>
<td>~2 kg weight loss, stabilizing over 6-12 months</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>~2-4/~1-2 mm Hg reduction</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>~5% increase</td>
</tr>
<tr>
<td>Plasma uric acid level</td>
<td>Reduction</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Reduction</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Increase (transient)</td>
</tr>
<tr>
<td>Microvascular outcomes</td>
<td>Effect unknown</td>
</tr>
</tbody>
</table>
Pathogenesis of Abnormal Angiogenesis in Diabetic Nephropathy

Diabetes

- Glomerular hypertension
- NO deficiency
- Uncoupling of VEGF with NO

VEGF induction

Abnormal angiogenesis

TGF-β expression
- Macrophage infiltration
- Glomerular hypertrophy
- Urinary Albumin excretion
NOx synthesis rate is decreased in Type 2 diabetic nephropathy.
The Effects of NO

**Favourable effects**

- Maintenance of vascular.
- Contribution to intestinal motility.
- Interaction with ascorbic acid in endothelial barrier tightening.
- Decrease expression of amyloid precursor protein.
- Improvement of erection in men with mild erectile dysfunction.
- Favourable action in the antiphospholipid syndrome.

**Unfavourable effects**

- Significant role, when produced in excess, in sepsis-related hypotension, shock and depression of cardiomyocyte contractility.
- Enhancement of invasion of bladder epithelial cells by uropathogenic E. coli.
- Involvement in tumor progression.
- Factor to paradoxically induce endothelial stress.
- Possible involvement in brain damage following subarachnoid hemorrhage.
Schematic pathway of NO synthesis:

1. Insulin
2. Akt
3. eNOS
4. NADPH oxidase
5. NO
6. 5'-GMP
7. cGMP
8. sGuanylylCyclase
9. ADMA
10. Anti-oxidants
11. B-blockers
12. CCB
13. ARB
14. Ang II
15. Glucose
16. L-Arg
17. L-Cit
18. O$_2$
19. ONOO$^-$
20. BH$_4$
21. SOD
22. H$_2$O$_2$
23. SOD
24. ACE-I
25. Ang I
26. Ang II
27. Aldosterone
28. Bradykinin
29. ARB

References:

Phosphodiesterase Type 5 Inhibition Reduces Albuminuria in Subjects with Overt Diabetic Nephropathy

Wim Scheele,* Susan Diamond,† Jeremy Gale,* Valerie Clerin,* Nihad Tamimi,† Vu Le,* Rosalind Walley,† Fernando Grover-Páez,§ Christelle Perros-Huguet,* Timothy Rolph,* and Meguid El Nahas‖
Urinary albumin to Cr ratio decreased with PDE-5 inhibitors

J Am Soc Nephrol, 2016: 27; 1-10
The role of epigenetic

Key epigenetic regulators, microRNAs and long noncoding RNAs could serve as new therapeutic targets for diabetic nephropathy

Emerging molecular mechanisms of diabetic nephropathy

MicroRNAs relevant to the pathogenesis of diabetic nephropathy

<table>
<thead>
<tr>
<th>microRNA</th>
<th>Animal model/cell type</th>
<th>Targets</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-21</td>
<td>OVE26 mice</td>
<td>Pten</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-21</td>
<td>db/db mice, MCs</td>
<td>Pten</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-21</td>
<td>KK-Ay mice</td>
<td>MMP-9, TIMP-1</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-21</td>
<td>db/db mice</td>
<td>Smad7</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-25</td>
<td>STZ rat, MCs</td>
<td>NADPH oxidase 4</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-29c</td>
<td>db/db mice, ECs, podocytes</td>
<td>Spry-1</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-29'</td>
<td>STZ Apo e−/− mice, STZ rats, PTEC, human HK-2 cells</td>
<td>Collagens</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-93</td>
<td>STZ mice, db/db mice, EC, podocytes</td>
<td>Vegf-A</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-192</td>
<td>STZ mice, db/db mice, MCs</td>
<td>Zeb1/Zeb2</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-192</td>
<td>STZ Apo e−/− mice, PTEC</td>
<td>Zeb1/Zeb2</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-200a</td>
<td>STZ Apo e−/− mice, PTEC</td>
<td>TGF-β2</td>
<td>Decrease</td>
</tr>
<tr>
<td>miR-200b/c</td>
<td>STZ mice, db/db mice, MCs</td>
<td>Zeb1</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-215</td>
<td>db/db mice</td>
<td>β-catenin-interacting protein 1</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-216a</td>
<td>STZ mice, db/db mice, MCs</td>
<td>Ybx1</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-216a/217</td>
<td>STZ mice, db/db mice, MCs</td>
<td>Pten</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-377</td>
<td>STZ mice, MCs</td>
<td>Pak1, Sod1/Sod2</td>
<td>Increase</td>
</tr>
<tr>
<td>miR-451</td>
<td>db/db mice</td>
<td>Ywhaz</td>
<td>Decrease</td>
</tr>
<tr>
<td>let-7</td>
<td>STZ Apo e−/− mice, MCs, PTECs</td>
<td>TGFR-1, collagens</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

MicroRNAs are gaining interest as sensitive, noninvasive and quantitative diagnostic biomarkers for DN, especially owing to stability in biofluids (such as urine and plasma).

Early detection of DNP

Early Treatment of DNP

The use of SGLT-2 inhibitors co-treated with RAAS inhibitors may favor an increase in angiotensin 1-7.
Neprilysin is a widespread enzyme responsible for degradation of natriuretic peptides, bradykinin, substance P. Neprilysin inhibitors (NEPi) lead to natriuresis, vasodilatation, reduced intraglomerular pressure and decreased proteinuria.

DKD reduces tubular ACE2 expression.

ACE2 activators and Neprilysin inhibitors: promising therapeutic targets to supplement conventional RAAS blockade in diabetic nephropathy.
<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic and non-diabetic chronic kidney diseases</td>
<td>Simvastatin plus ezetimibe vs. placebo</td>
<td>Major vascular event (MI, stroke, cardiac death, arterial revascularization)</td>
<td>17% reductions in major atherosclerotic events; non-significant 9% renal risk reduction</td>
</tr>
</tbody>
</table>

Loss of kidney function is less during statin therapy.

Cr clearance (ml/min/1.73 m²)

With statin therapy

Without statin therapy
**ASCEND Study:** $(n = 1300)$
Endothelin antagonist intervention + Top of RAAS blockade

<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes and nephropathy (serum creatinine 1.3 to 3.0 mg/ dl)</td>
<td>Avosentan vs. placebo. Clincal Trials.gov. Study of diabetic nephropathy with atrasentan (SONAR) is ongoing in 2016</td>
<td>Decreased cr, ESRD or death</td>
<td>Prematurely terminated due to increase in CHF events.</td>
</tr>
</tbody>
</table>

**SUN-Macro Study:** (n = 176)

Glycosaminoglycans intervention + Top of RAAS blockade

<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes and nephropathy (serum creatinine 1.3 to 3.0 mg/dl)</td>
<td>Sulodexide vs. placebo</td>
<td>DSCR, ESRD</td>
<td>Prematurely terminated due to futility</td>
</tr>
</tbody>
</table>

Sulodexide therapy for the treatment of diabetic nephropathy, a meta-analysis and literature review
Role of diabetes in CKD-associated oxidative stress

**Direct effect of hyperglycemia on ROS**

Uncoupled NOS, impairment of mitochondrial metabolism.

**Indirect effect of hyperglycemia on ROS**

Advanced glycation end products (AGEs), which raise intracellular ROS generation in mesangial cells.
Effects of oxidative stress in early diabetic nephropathy.

Glomerulus
- Endothelial cell dysfunction
- Mesangial cell injury
- Podocyte dysfunction
- Extracellular matrix deposition
- High TGF-B
- Glomerular apoptosis
- Microalbuminuria

Tubule
- Nitric oxide
- HIF-1a
- Tubular oxidant injury
- Tubular hypoxia
- Tubulo-interstitial fibrosis
- Tubular apoptosis
- Tubular proteinuria

Nature Reviews Endocrinology 7, 176-184 (March 2011)
Nrf2 antioxidant response pathway is the primary cellular defense against the cytotoxic effects of oxidative stress.
BARDOXOLOZONE METHYL; the most potent activators of Nrf2 known to date
**BEACON Study:** \( n = 2200 \)

Anti-inflammatory agents intervention + Top of RAAS blockade

<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
</table>
| Type 2 diabetes and nephropathy (eGFR 15 to 30 ml min) | Bardoxolone-methyl vs. placebo | Dialysis / cardiovascular death | Prematurely terminated due to increased mortality???

### PREDIAN Study: \( n = 169 \)

Pentoxifyllin: 1200 mg/d \( (n=82) \) compared with the control group \( (n=87) \) for 2 years. All patients received similar doses of RAS inhibitors.

<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes and nephropathy</td>
<td>Pentoxifylline vs. placebo</td>
<td>Rate of eGFR decline and protinuria</td>
<td>smaller decrease in eGFR and a greater reduction of residual albuminuria.</td>
</tr>
</tbody>
</table>

PTX when used as add-on therapy in patients with DKD on RAAS blockers leads to a greater reduction in albuminuria and reduced inflammation, and may decrease progression of renal disease.
**Pyridorin CSG study:** (n = 317)

<table>
<thead>
<tr>
<th>Population</th>
<th>Study treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes nephropathy (serum Cr 1.3–3.5 mg/dl and protein/creatinine &gt; 1200 mg/g)</td>
<td>Pyridorin (<strong>an AGE antagonist agent</strong>) vs. placebo</td>
<td>Rate of eGFR decline</td>
<td>No renal protection</td>
</tr>
</tbody>
</table>
High-dose thiamine therapy improves microalbuminuria in type 2 diabetic patients?

Diabetologia (2009) 52:208–212
Autophagy: A Novel Therapeutic Target for Diabetic Nephropathy

Shinji Kume¹, Daisuke Koya²

¹Department of Medicine, Shiga University of Medical Science, Otsu,
²Department of Diabetology & Endocrinology, Kanazawa Medical University, Kahoku, Japan

Diabetic nephropathy is a leading cause of end stage renal disease and its occurrence is increasing worldwide. The most effective treatment strategy for the condition is intensive treatment to strictly control glycemia and blood pressure using renin-angiotensin system inhibitors. However, a fraction of patients still go on to reach end stage renal disease even under such intensive care. New therapeutic targets for diabetic nephropathy are, therefore, urgently needed. Autophagy is a major catabolic pathway by which mammalian cells degrade macromolecules and organelles to maintain intracellular homeostasis. The accumulation of damaged proteins and organelles is associated with the pathogenesis of diabetic nephropathy. Autophagy in the kidney is activated under some stress conditions, such as oxidative stress and hypoxia in proximal tubular cells, and occurs even under normal conditions in podocytes. These and other accumulating findings have led to a hypothesis that autophagy is involved in the pathogenesis of diabetic nephropathy. Here, we review recent findings underpinning this hypothesis and discuss the advantages of targeting autophagy for the treatment of diabetic nephropathy.
Autophagy: self eating

1) Recycles intracellular energy resources in response to conditions of nutrient depletion.
2) Removes cytotoxic proteins and damaged organelles under various stress conditions.
mTOR-inhibitors Induces autophagy metformin and resveratrol

Diabetes Metab J 2015;39:451-460
Sirtuins and their functions

Mitochondrial biogenesis, ATP production, Anti-apoptosis, Anti-oxidative stress, cell survival

Effect of Allopurinol in Decreasing Proteinuria in Type 2 Diabetic Patients

Ali Momeni,1 Shahrzad Shahidi,2 Shiva Seirafian,3 Shahram Taheri,3 Soleiman Kheiri4

Mean serum levels of uric acid during the study

Mean 24-hour urine levels of protein during the study
Conclusion