Understanding Diabetes Kidney Disease: What are the best options for clinical management?

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Bangkok 30.7.2016
Outline of the talk

• The consequences of diabetic kidney disease
• The prevalence of diabetic kidney disease
• Importance of blood glucose control
• Treatment of diabetic kidney disease
• How can we achieve optimal glucose control without causing harm (hypoglycemia)?
• Why does empagliflozin work so well?
• Take home messages
The consequences of diabetic kidney disease (DKD)
Kidney disease and increased mortality risk in type 2 diabetes

The dashed line indicates mortality in persons without diabetes or kidney disease (the reference group). The numbers above bars indicate excess mortality above the reference group.

ADVANCE: Cardiovascular events

Cardiovascular risk is greatest when both diabetes and CKD are present.

Among patients with diabetes and CKD, the rate of cardiovascular events is more than twice that among patients with diabetes only.

Impaired kidney function may directly contribute to adverse outcomes

- Hypertension
- Oxidative stress
- Insulin resistance
- Arterial calcification
- Inflammation/immunity
- Accumulation of uraemic toxins
- Left ventricular hypertrophy
- Endothelial dysfunction
- Activation of the RAAS
- Activation of the SNS
- Anaemia

RAAS = renin-angiotensin aldosterone system; SNS = sympathetic nervous system
Changes in numbers of ESRD cases due to diabetes in the US over 25 years

Number of people initiating treatment for ESRD 1980-2006

Rates Per Million Population

U.S. Renal Data System, USRDS 2008 Annual Data Report

Changes in numbers of ESRD cases due to diabetes in the US over 25 years
Declining renal function also increases risk of severe hypoglycaemia

Increased risk most dramatic in patients with renal dysfunction and type 2 diabetes

Around 74% of sulphonylurea-induced severe hypoglycaemic events (loss of consciousness) occurs in patients with reduced renal function

The prevalence of diabetic kidney disease
Global perspective

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

Prevalence of diabetic kidney disease in the US

- De Boer et al. *JAMA* 2011;305:2532-2539.

![Graph showing the prevalence of diabetic kidney disease from 1988-1994, 1999-2004, and 2005-2008.](image)
Importance of blood glucose control
Intensive glucose control reduces risk of MICROALBUMINURIA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD^8,14</td>
<td>0.88 (0.80-0.96)</td>
</tr>
<tr>
<td>ADVANCE^12</td>
<td>0.92 (0.86-0.98)</td>
</tr>
<tr>
<td>Kumamoto^4,15</td>
<td>0.44 (0.16-1.17)</td>
</tr>
<tr>
<td>UKPDS 33^16</td>
<td>0.88 (0.75-1.04)</td>
</tr>
<tr>
<td>UKPDS 34^17</td>
<td>1.00 (0.77-1.30)</td>
</tr>
<tr>
<td>VADT^11</td>
<td>0.74 (0.51-1.07)</td>
</tr>
<tr>
<td>VA Feasibility Trial^5</td>
<td>0.26 (0.13-0.52)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>0.86 (0.76-0.96)</strong></td>
</tr>
</tbody>
</table>

Favors Intensive | Favors Standard
Intensive glucose control reduces risk of MACROALBUMINURIA

![Risk ratio graph showing the impact of intensive glucose control on macroalbuminuria risk across various studies.](image-url)
Intensive glucose lowering and ESRD
The ADVANCE trial

Standard management
Intensive glucose control

HR = 0.35
(CI 0.15-0.83)

p = 0.012

Zoungas et al. Kidney International 2012
Treatment of diabetic kidney disease – “five finger rule”
Treatment - “Five finger rule”

- Try to achieve optimal glucose control
  - HbA$_1c$ target <7% (or individualized target)
- Stop smoking
- Lowering of blood pressure
  - RR target < 140/90
  - RR target < 130/80 if proteinuric (of 1 g)
- Use ACE-inhibitors and/or AR blockers
- Consider lipid-lowering treatment
How can we achieve good glycemic control with benefits but without causing harm (hypoglycemia)?
1. DPP-4 inhibitors
# Efficacy of DPP-4 inhibitors in monotherapy trials

Placebo-corrected, adjusted mean change from baseline HbA$_{1c}$

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Baseline HbA$_{1c}$</th>
<th>Linagliptin$^1$</th>
<th>Linagliptin$^1$</th>
<th>Saxagliptin$^2$</th>
<th>Saxagliptin$^2$</th>
<th>Sitagliptin$^3$</th>
<th>Sitagliptin$^3$</th>
<th>Vildagliptin$^4$</th>
<th>Vildagliptin$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 mg QD 8.1%</td>
<td>5 mg QD 8.0%</td>
<td>5 mg QD ≥7% to ≤10%</td>
<td>5 mg QD 8.0%</td>
<td>100 mg QD 8.0%</td>
<td>100 mg QD 8.0%</td>
<td>50 mg BID 8.6%</td>
<td>50 mg BID 8.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.6%</td>
<td>-0.7%</td>
<td>-0.4%</td>
<td>-0.6%</td>
<td>-0.6%</td>
<td>-0.6%</td>
<td>-0.5%</td>
<td>-0.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>p-value$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>147</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>272</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>69</td>
<td>=0.0059</td>
</tr>
<tr>
<td>103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>193</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>229</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>79</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* 18 weeks treatment duration, 24 weeks otherwise
† Between group difference versus placebo

Sources:
1- 3, US PI for linagliptin, saxagliptin, sitagliptin
4. EU SmPC for vildagliptin
Linagliptin is the first DPP-4 inhibitor that is primarily excreted by bile and gut\(^1\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Share of renal excretion(^2), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linagliptin</td>
<td>5</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>87</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>85</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>75</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>60–71</td>
</tr>
</tbody>
</table>

1. Of currently globally approved DPP-4 inhibitors.
2. Including metabolites and unchanged drug; excretion after single dose administration of C14 labeled drug.

Pharmacokinetics of DPP4 inhibitors in patients with renal impairment

**Linagliptin**

- No dosage adjustment required in renal impairment
- Fold increase in exposure relative to normal renal function:
  - Normal (n = 6)
  - Mild (n = 6)
  - Moderate (n = 6)
  - Severe (n = 6)
  - ESRD (n = 6)

- Creatinine clearance* (mL/min):
  - Normal >80
  - Mild 50 to ≤80
  - Moderate 30 to ≤50
  - Severe <30
  - ESRD <30 on HD

**Saxagliptin** (5-hydroxy saxagliptin metabolite)†

- Fold increase in exposure relative to normal renal function:
  - Normal (n = 8)
  - Mild (n = 8)
  - Moderate (n = 8)
  - Severe (n = 8)
  - ESRD on HD (n = 8)

- Creatinine clearance* (mL/min):
  - Normal >80
  - Mild 50 to ≤80
  - Moderate 30 to ≤50
  - Severe <30

**Sitagliptin**

- Fold increase in exposure relative to normal renal function:
  - Normal (n = 6)
  - Mild (n = 6)
  - Moderate (n = 6)
  - Severe (n = 6)
  - ESRD (n = 6)

- Creatinine clearance* (mL/min):
  - Normal >80
  - Mild 50 to ≤80
  - Moderate 30 to ≤50
  - Severe <30 on HD

**Vildagliptin** (LAY151 metabolite)‡

- Fold increase in exposure relative to normal renal function:
  - Normal
  - Mild
  - Moderate
  - Severe
  - ESRD

- Renal impairment status

ESRD, end-stage renal disease; HD, haemodialysis.

*Estimated creatinine clearance values were calculated using the Cockcroft–Gault formula; †90% confidence intervals not available; ‡Patient numbers, 90% CI and definitions of RI according to creatinine clearance not available for vildagliptin.

Pooled analysis suggests that linagliptin reduces albuminuria.

24 weeks' treatment
Meta-analysis: effect of linagliptin on albuminuria in humans*

**Adjusted mean change in albuminuria, % (24 weeks)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>55</td>
<td>162</td>
</tr>
<tr>
<td>-28%</td>
<td>-6</td>
<td>-32</td>
</tr>
<tr>
<td><strong>p = 0.0357</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>-47% to</td>
<td>-2%</td>
</tr>
</tbody>
</table>

Baseline UACR, mg/g, median (range)

- **Placebo**: 80.5 (30.9–1538.2)
- **Linagliptin**: 73.8 (30.1–2534.4)

-28% in albuminuria versus placebo after 24 weeks' treatment on top of recommended standard treatment for diabetic nephropathy

1. Inclusion criteria: stable ACE/ARB background; albuminuria 30–3000 mg/g creatinine; GFR > 30.

*MARLINA-T2D™ (1218.89) will aim to demonstrate albuminuria-lowering evidence for linagliptin.

Effects of linagliptin on albuminuria in Type 2 diabetes (The MARLINA-T2D Trial)

Figure 6: (A) Adjusted* geometric mean for time-weighted average of percentage change from baseline in UACR over 24 weeks†, FAS (LOCF) – key secondary efficacy endpoint; (B) Adjusted* geometric mean ratio of relative change from baseline in UACR over time, FAS (LOCF)

A. Linagliptin (n=178) Placebo (n=173) Placebo-adjusted

- Linagliptin: -5.1
- Placebo: -6.0

95% CI: -15, 3
p=0.1954

B. Linagliptin (n=178)
(gMean baseline UACR: 120.5 mg/gCr)
- Placebo (n=173)
(gMean baseline UACR: 132.2 mg/gCr)

*ANCOVA model includes baseline HbA1c and baseline log10 (UACR) as linear covariates and treatment as fixed effect
†Area under the curve (AUC) for UACR at a given week was divided by AUC for UACR at baseline; calculated per patient from UACR values at baseline and Weeks 6, 12, 18, and 24. The measures were summed over all days up to the scheduled visit date and divided by the number of days on treatment at scheduled visit date. AUC per patient was then normalized to 1 day

Groop et al. ADA 2016 (poster)
Effects of linagliptin on albuminuria in Type 2 diabetes (The MARLINA-T2D Trial)

Figure 8: Distribution of UACR change from baseline at Week 24 by UACR response categories (FAS OC-ROC)

<table>
<thead>
<tr>
<th>UACR response categories</th>
<th>Linaglaptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20% reduction</td>
<td>32.2% (56/174)</td>
<td>43.9% (79/180)</td>
</tr>
<tr>
<td>10% to 20% reduction</td>
<td>9.4% (17/180)</td>
<td>6.3% (11/174)</td>
</tr>
<tr>
<td>&lt;10% reduction</td>
<td>4.4% (8/180)</td>
<td>10.3% (18/174)</td>
</tr>
<tr>
<td>Increase</td>
<td>37.2% (67/180)</td>
<td>46.6% (81/174)</td>
</tr>
</tbody>
</table>

Odds ratio*: 1.67
95% CI: 1.04, 2.68; p=0.0351

*Logistic regression was performed on the proportion of UACR responders at Week 24. UACR responders were defined as patients from the FAS who had a UACR reduction of >20% at Week 24 relative to baseline; UACR non-responders were those who had a UACR increase or no change at Week 24 relative to baseline. Patients with UACR reduction ≤20% relative to baseline were excluded from the analysis, as well as those with missing UACR values at Week 24 (linagliptin, n=9 [5.0%]; placebo, n=8 [4.6%]). Patients with UACR value at Week 24 on rescue therapy (OC-ROC) were included in the analysis. The model includes treatment as factor and continuous baseline HbA1c and continuous baseline log10 (UACR) as covariates.

Analysis by responder categories showed a 70% higher rate of achieving a meaningful response (>20% decrease in UACR from baseline) in the linagliptin arm compared with the placebo arm (Figure 8).

Groop et al. ADA 2016 (poster)
CARMELINA will evaluate CV and renal safety of linagliptin in T2D at high CV and renal risk

Inclusion criteria
1. T2D with HbA₁c ≥ 6.5% and ≤ 10.0%
2. Stable background antidiabetic medication, excluding GLP1, DPP4, SGLT2
3. High risk of CV events

Linagliptin 5 mg versus Placebo
N = 8300; approximate 4-year follow-up

Primary CV endpoint: time to first occurrence of primary composite endpoint
1. CV death (including fatal stroke and fatal MI)
2. Non-fatal MI
3. Non-fatal stroke
4. Hospitalization for unstable angina pectoris

Renal endpoint: time to first occurrence of the composite endpoint
1. Renal death
2. Sustained ESRD
3. Sustained decrease of ≥ 50% eGFR

This study addresses the CV safety requirements from the FDA, as well as investigating the potential renal effects of the drug.
Overview of CVOTs of glucose-lowering drugs

Timings represent estimated completion dates as per ClinicalTrials.gov.
Adapted from Johansen. World J Diabetes 2015;6:1092–96.(references 1–19 expanded in slide notes)
2. GLP-1 agonists
# Microvascular event definitions

<table>
<thead>
<tr>
<th>Event type</th>
<th>Event definition – one or more of the below</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong></td>
<td>• New onset of persistent macroalbuminuria</td>
</tr>
<tr>
<td></td>
<td>• Persistent doubling of serum creatinine</td>
</tr>
<tr>
<td></td>
<td>• Need for continuous renal replacement therapy</td>
</tr>
<tr>
<td></td>
<td>• Death due to renal disease</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>• Need for retinal photocoagulation or treatment with intravitreal agents</td>
</tr>
<tr>
<td></td>
<td>• Vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Diabetes-related blindness</td>
</tr>
</tbody>
</table>
## Basal renal function

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Liraglutide (N=4668)</th>
<th>Placebo (N=4672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function (eGFR ≥90 mL/min/1.73 m²)</td>
<td>1620 (34.7)</td>
<td>1655 (35.4)</td>
</tr>
<tr>
<td>Mild impairment (eGFR 60–89 mL/min/1.73 m²)</td>
<td>1932 (41.4)</td>
<td>1975 (42.3)</td>
</tr>
<tr>
<td>Moderate impairment (eGFR 30–59 mL/min/1.73 m²)</td>
<td>999 (21.4)</td>
<td>935 (20.0)</td>
</tr>
<tr>
<td>Severe impairment (eGFR &lt;30 mL/min/1.73 m²)</td>
<td>117 (2.5)</td>
<td>107 (2.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Liraglutide (N=4668)</th>
<th>Placebo (N=4672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>915 (19.6)</td>
<td>1007 (21.6)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>257 (5.5)</td>
<td>264 (5.7)</td>
</tr>
</tbody>
</table>

Full analysis set. Data are means ± standard deviations or number of patients (percentage of either liraglutide-treated or placebo-treated group). Percentage data refer to proportion of patients. eGFR: estimated glomerular filtration rate.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Time to first renal event
Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

Marso et al. NEJM 2016
3. SGLT2-inhibitors
A pre-specified objective was to examine the effects of empagliflozin, on top of standard care, on the progression of renal disease in patients with T2D and high CV risk.

Pre-specified renal endpoints:

- New or worsening nephropathy, defined as:
  - Progression to macroalbuminuria
  - Doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m²)
  - Initiation of renal replacement therapy
  - Death due to renal disease
- The composite of new or worsening nephropathy, or CV death
- The individual components of new or worsening nephropathy
- New onset of albuminuria in patients with normoalbuminuria at baseline

Empagliflozin is not indicated for CV risk reduction or kidney disease.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; T2D, type 2 diabetes.
New onset or worsening nephropathy

Empagliflozin is not indicated for CV risk reduction or kidney disease. Kaplan-Meier estimate. Treated set (≥1 dose of study drug)

*Nominal p-value. CI, confidence interval; CV, cardiovascular; HR, hazard ratio

Wanner C et al. NEJM 2016
New onset or worsening nephropathy

Empagliflozin is not indicated for CV risk reduction or kidney disease. Kaplan-Meier estimate. Treated set (≥1 dose of study drug)

*Nominal p-value. CI, confidence interval; CV, cardiovascular; HR, hazard ratio

Wanner C et al. NEJM 2016
New onset or worsening nephropathy in patients with prevalent kidney disease* (eGFR < 60 ml/min and/or ACR > 300 mg/g)

Empagliflozin is not indicated for CV risk reduction or kidney disease. Kaplan–Meier estimates in patients with prevalent kidney disease treated with ≥1 dose of study drug; HRs are based on Cox regression analyses; Post hoc analyses. *Defined as eGFR (MDRD) < 60 ml/min/1.73 m$^2$ and/or macroalbuminuria (urine albumin-to-creatinine ratio > 300 mg/g) at baseline; †Nominal p-value. CI, confidence interval; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HR, hazard ratio.

Wanner et al. NEJM 2016
Doubling of serum creatinine*, initiation of renal replacement therapy or death due to renal disease

Empagliflozin is not indicated for CV risk reduction or kidney disease. Kaplan–Meier estimate; Treated set. Post hoc analyses.

*Accompanied by eGFR (MDRD) ≤45 ml/min/1.73m²; †Nominal p-value. CI, confidence interval; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HR, hazard ratio.

Wanner et al. NEJM 2016
Renal outcomes summary

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>New or worsening of nephropathy or CV death</td>
<td>675/170 (16.2%)</td>
<td>497/2102 (23.6%)</td>
<td>0.61 (0.55, 0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset or worsening of nephropathy</td>
<td>525/124 (12.7%)</td>
<td>388/2161 (18.8%)</td>
<td>0.61 (0.53, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>459/491 (11.2%)</td>
<td>330/2033 (16.2%)</td>
<td>0.62 (0.54, 0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine†</td>
<td>70/4645 (1.5%)</td>
<td>60/2323 (2.6%)</td>
<td>0.56 (0.39, 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>13/4687 (0.3%)</td>
<td>14/2333 (0.6%)</td>
<td>0.45 (0.21, 0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of serum creatinine†, initiation of renal replacement therapy or death due to renal disease</td>
<td>81/4645 (1.7%)</td>
<td>71/2323 (3.1%)</td>
<td>0.54 (0.40, 0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset of albuminuria in patients with normoalbuminuria at baseline‡</td>
<td>1430/2779 (51.5%)</td>
<td>703/1374 (51.2%)</td>
<td>0.95 (0.87, 1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Empagliflozin is not indicated for CV risk reduction or kidney disease
*Nominal p-values; †Accompanied by eGFR (MDRD) ≤45 ml/min/1.73 m²; ‡UACR <30 mg/g
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio;
MDRD, Modification of Diet in Renal Disease; UACR, urine albumin-to-creatinine ratio

Wanner et al. NEJM 2016
Empagliflozin is not indicated for CV risk reduction or kidney disease. Pre-specified mixed model repeated measures analysis in all patients treated with ≥1 dose of study drug (OC-AD). All participants in the study were able to reach the study visit at week 94 and patient numbers declined thereafter based on study design.

*Wanner et al. NEJM 2016*
Doubling of serum creatinine

ESRD

Hospitalisation for heart failure

All cause mortality

RENAAL (losartan vs placebo)

- Doubling of serum creatinine: 0.75 vs 1.02
- ESRD: 0.72 vs 1.02
- Hospitalisation for heart failure: 0.68 vs 1.02
- All cause mortality: 0.1 vs 1.4

- 21.6% vs 26.0%
- 19.6% vs 25.5%
- 21% vs 20.3%
- 21% vs 20.3%
Doubling of serum creatinine

ESRD

Hospitalisation for heart failure

All cause mortality
Doubling of serum creatinine

ESRD

Hospitalisation for heart failure

All cause mortality
Why does empagliflozin work so well?
# Renal Protection with SGLT2 Inhibition

<table>
<thead>
<tr>
<th>Indirect effects</th>
<th>Direct effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved glycemic control</td>
<td>Prevent hyperfiltration</td>
</tr>
<tr>
<td></td>
<td>- ↓ intraglomerular pressure</td>
</tr>
<tr>
<td></td>
<td>- ↓ proteinuria</td>
</tr>
<tr>
<td>↓ Insulin levels</td>
<td>Prevent glomerular and tubulointerstitial injury</td>
</tr>
<tr>
<td>Improved insulin sensitivity</td>
<td>↓ Toxicity of glucose</td>
</tr>
<tr>
<td></td>
<td>- ↓ inflammation, ROS</td>
</tr>
<tr>
<td>↓ Weight</td>
<td></td>
</tr>
<tr>
<td>↓ Blood pressure</td>
<td></td>
</tr>
<tr>
<td>↓ Uric acid levels</td>
<td></td>
</tr>
</tbody>
</table>

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Thomas et al. Ther Adv Endo Metab 2014;5:53-61  
Glomerular hypertension causes glomerular damage and progressive nephron loss

- Glomerular hypertension in single nephrons causes:
  - inflammation
  - fibrosis
  - sclerosis

The single nephron hypothesis - Adaptive response due to loss in total amount of single nephrons

Kanzaki et al. *Hypertension Res* 2015;38:633
Glomerular hypertension causes glomerular damage and progressive nephron loss

- Eventually single nephrons are lost
- Remaining nephrons adapt, increasing filtration by glomerular hypertension
- Vicious cycle of progressive CKD

The single nephron hypothesis - Adaptive response due to loss in total amount of single nephrons

Kanzaki et al. Hypertension Res 2015;38:633
Empagliflozin attenuates glomerular hyperfiltration

Type 1 diabetes patients with hyperfiltration. Mean GFR recorded at baseline and after 8 weeks treatment with empagliflozin 25 mg QD

Empagliflozin reduces intra-glomerular pressure

△~6–8 mmHg ↓

Intra-glomerular pressure recorded at baseline and after 8 weeks treatment with empagliflozin

<table>
<thead>
<tr>
<th>Glomerular pressure T1D-H (mmHg)</th>
<th>Baseline</th>
<th>EMPA</th>
<th>p value</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycaemia (mmHg)</td>
<td>67.4 ± 5.4</td>
<td>61.0 ± 5.2</td>
<td>&lt;0.0001</td>
<td>9.5%</td>
</tr>
<tr>
<td>Hyperglycaemia (mmHg)</td>
<td>69.3 ± 6.5</td>
<td>61.6 ± 6.3</td>
<td>&lt;0.0001</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

Skrtic M et al. Diabetologia 2014;57:2599
Reduced hyperfiltration was mediated by effects on renal blood flow and vascular resistance

- Reduced renal blood flow (RBF) & increased renal vascular resistance (RVR) after empagliflozin treatment are consistent with afferent arteriole vasoconstriction.

**Patients with type 1 diabetes and hyperfiltration at baseline. RBV and RVR recorded in euglycaemic state.**

RBF, renal blood flow; RVR, renal vascular resistance

The “Tubular Hypothesis”

(A) Normal physiology

- SGLT-2
- Afferent arteriole
- Normal GFR
- Macula densa
- Na+/glucose reabsorption

(B) Hyperfiltration in early stages of diabetic nephropathy

- Afferent vasodilation
- Elevated GFR
- Increased Na+/glucose reabsorption
- Decreased Na+ delivery to macula densa

(C) SGLT-2 inhibition reduces hyperfiltration via TGF

- Afferent vasoconstriction
- Normalization of GFR
- SGLT-2 inhibition in proximal tubule
- Increased Na+ delivery to macula densa

Glycosuria Natriuresis

Heerspink and Cherney et al. Circulation 2016
Empagliflozin effect on glomerular hyperfiltration shows similar magnitude as ACE inhibitor.

Sochett, Cherney, Miller et al. JASN, 2006
Cherney, Perkins et al. Circulation 2014;129:587
Implications for clinical practice
Cardiovascular mortality

RRR = 37% (21 to 51)
ARR = 3.5%
NNT 29 (for 4.5 years)

Cardiovascular mortality

RRR = 38% (23 to 51)
ARR = 2.1%
NNT 45 (for 2.6 years)

Zinman et al NEJM 2015
Heart Outcomes Prevention Evaluation (HOPE) Study

Heart Outcomes Prevention Evaluation (HOPE) Study

Take home messages

• Diabetic kidney disease is a common complication

• ... and the consequences are grim

• Optimal glucose control reduces the risk of diabetic kidney disease

• Newer oral antidiabetic drugs such as linagliptin and empagliflozin on top of standard care provide great glucose-lowering efficacy without risk of hypoglycemia

• Empagliflozin reduces not only risk of CV death, all-cause mortality and hospitalization for heart failure but also the progression of diabetic kidney disease