SGLT2-inhibition:
A New Strategy to Protect the Heart and the Kidney?

Hiddo Lambers Heerspink
Department of Clinical Pharmacy and Pharmacology
University Medical Center Groningen
The Netherlands

Disclosures: Consultancy for Abbvie, Astellas, Astra Zeneca, Boehringer Ingelheim, Janssen, Merck, ZS-Pharma. All honoraria paid to institution
Mortality is more frequent present in diabetes and kidney disease than those without.

Percentages indicate absolute excess mortality above the reference group (individuals with no diabetes or kidney disease)

*No diabetes and no kidney disease; GFR, glomerular filtration rate; T2D, type 2 diabetes

Potential approaches and trials testing additive renal (cardiovascular) protection (on top of ACEi or ARB)

- ACEi+ARB
  - (VA NEPHRON-D; prematurely stopped for safety; renal)
- ACEi + ARB
  - (HALT-PKD; no effect; renal)
- ACEi/ARB + DRI
  - (ALTITUDE; prematurely stopped for safety; CV/renal)
- Low Protein Diet
  - (MDRD; completed, no additive effect?)
- Erythropoietin
  - (TREAT; completed; no effect CV/renal)
- GAG’s
  - (SUN-Overt; prematurely stopped; no effect renal)
- GAG’s
  - (SUN-Micro; completed; no effect renal)
- ET-A (Avosentan)
  - (ASCEND; prematurely stopped for safety; renal)
- Statins
  - (SHARP; completed; no renal effect?; CV/renal)
- Pentoxifylline
  - (PREDIAN; completed; eGFR protection)
- Nrf2 (Bardoxolone)
  - (BEACON; stopped for safety; renal/CV outcome)
- Carbon Absorption (AST-120)
  - (CAP-KD; completed no effect; renal outcome)
- Nrf2 (Bardoxolone)
  - (Japanese study; ongoing; renal outcome)
- ET-A (Atrasentan)
  - (SONAR; ongoing; renal outcome)
- SGLT2 (canagliflozin)
  - (CREDENCE; starting; renal/CV outcome)
- SGLT2 (empagliflozin)
  - (EMPA-REG; completed; CV and renal protection)
- Uric acid (allopurinol)
  - (PERL; ongoing; renal outcome)
- GLP-1 mimetic (Liraglutide)
  - (LEADER; ongoing; CV and renal outcome)
- DPP-4 (Linagliptin)
  - (CARMELENA; ongoing; CV and renal)
- Pyridorin
  - (PIONEER; ongoing, renal outcome)
- AngII/NEPi (LCZ696)
  - (?)
- Prostacyclin (Beraprost)
  - (CASSIOPEIR; ongoing; renal outcome; ASN submission)
- MCA (spironolactone)
  - (PRIORITY; ongoing; renal outcome)
- MCA (fineronone)
  - (FIGARO and FIDELIO-DKD; ongoing; renal/CV outcome)
The kidney plays an important role in glucose production and utilization

The kidney contributes to glucose homeostasis through processes of:
1. Glucose release (gluconeogenesis)
2. Glucose utilisation for energy needs
3. Glucose filtration and reabsorption

De Fronzo et al. Nat Rev Nephrol 2017;1:11
The role of SGLT2 inhibitors in glucose reabsorption

- By inhibiting SGLT2, these drugs remove excess glucose in the urine and lower HbA1c.¹
- SGLT-2 inhibitors act on natriuretic mechanisms and are associated with a decrease in intracellular Na⁺ concentration & Na⁺/K ATPase activity

SGLT2 Mediates Glucose Reabsorption in the Kidney

SGLT2: Major transporter of glucose in the kidney

- Co-transport Na+ and glucose at 2:1 stoichiometry
- Responsible for majority of renal glucose reabsorption in the proximal tubule

SGLT2 inhibitors decrease the glucose excretion threshold

![Graph showing urinary glucose excretion (mg/min) against blood glucose (mg/dL) for Canagliflozin 100mg and Untreated conditions.](image)

*Polidori D et al. Con Endocrinol Metab 2013;98:E867-E871*
SGLT2 decreases HbA1c on top of other diabetic medications

Add-on Combinations with

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy (DIA3005) N = 584</th>
<th>Metformin (DIA3006) N = 1284</th>
<th>SU (DIA3008) N = 127</th>
<th>Met/SU (DIA3002) N = 469</th>
<th>Met/Pio (DIA3012) N = 342</th>
<th>Insulin (DIA3008) N = 1718</th>
<th>Current Therapy in Older Subjects (DIA3010) N = 714</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BL Mean HbA1c (%)</strong></td>
<td>8.0</td>
<td>7.9</td>
<td>8.4</td>
<td>8.1</td>
<td>7.9</td>
<td>8.3</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Placebo-subtracted LS Mean Change in HbA1c (%) (95% CI)</strong></td>
<td><strong>3005</strong></td>
<td><strong>3006</strong></td>
<td><strong>3008SU</strong></td>
<td><strong>3002</strong></td>
<td><strong>3012</strong></td>
<td><strong>3008INS</strong></td>
<td><strong>3010</strong></td>
</tr>
</tbody>
</table>

All at 26 weeks except 18 weeks DIA3008 Insulin, SU sub-studies

* p<0.001

Based on ANCOVA models, data prior to rescue (LOCF)
EMPAREG: Empagliflozin is cardioprotective in patients with type 2 diabetes and established CV disease

**Primary CV endpoint**

- HR 0.86 (95% CI 0.74, 0.99); p=0.04*

**CV death endpoint**

- HR 0.62 (95% CI 0.49, 0.77); p<0.001*

- Patients were randomly assigned to empa 10 mg, empa 25 mg or placebo. Shown are the combined 10 and 25 mg doses versus placebo.

EMPAREG: Empagliflozin is cardioprotective in patients with type 2 diabetes and established CV disease

<table>
<thead>
<tr>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>95/4687</td>
<td>126/2333</td>
</tr>
</tbody>
</table>

What could be the mechanisms of clinical benefit?

- Clinical benefit of SGLT2 inhibitors could be explained by:
  1. Metabolic effects
     - Improved β-cell function/ tissue insulin sensitivity
     - Decrease in β-cell glucotoxicity
     - Body weight loss
       - effects on visceral
       - subcutaneous fat
  2. Diuretic / Natriuretic effects
  3. Renal effects
SGLT2 inhibitors: Proximal tubular diuretics?

3 days cum Na excretion (mmol)

Body weight change (kg)

Hematocrit (%) change

Heerspink et al. World Congress Nephrology 2011
Dapagliflozin diuretic effects: lower plasma volume, body weight, and 24-hr blood pressure

- Dapagliflozin reduces plasma volume compared to placebo or HCTZ as measured by $^{51}$Cr Albumin
- Reductions in body weight during the initial 4 weeks paralleled reductions in body weight during HCTZ

Abbreviations: HCTZ, hydrochlorothiazide, SBP, systolic blood pressure

<table>
<thead>
<tr>
<th>Cardiovascular events</th>
<th>RR (95% CI)</th>
<th>Favors diuretic</th>
<th>Favors Placebo</th>
<th>Favors Empa</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-type</td>
<td>0.67 (0.56 – 0.81)</td>
<td></td>
<td></td>
<td>0.86 (0.74 – 0.99)</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.67 (0.60 – 0.75)</td>
<td></td>
<td></td>
<td>1.24 (0.92 – 1.67)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td></td>
<td></td>
<td></td>
<td>0.65 (0.50 – 0.85)</td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.52 (0.38 – 0.69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.68 (0.57 – 0.80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td>0.68 (0.57 – 0.82)</td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.36 (0.16 – 0.84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.47 (0.36 – 0.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.86 (0.75 – 1.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.84 (0.74 – 0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Olde Egberink et al. Hypertension 2015
What could be the mechanisms of clinical benefit?

- Clinical benefit of SGLT2 inhibitors could be explained by:
  1. Metabolic effects
  2. Diuretic / Natriuretic effects
  3. Renal effects
     - Restore tubulo-glomerular feedback
     - Reduction Intraglomerular Pressure
     - Reduction Albuminuria
High intraglomerular pressure causes renal damage

**Normal Glomerulus**

- Afferent arteriole
- Normal endothelium
- Efferent arteriole
- Podocytes

**Glomerular Hypertension**

- Dilated afferent arteriole
- Loss of podocyte integrity
- Constricted efferent arteriole
- Damaged endothelium
- Focal glomerulosclerosis
Acute reduction in GFR during RAAS inhibition associated with subsequent stable renal function

**RENAAL**: Type 2 diabetes and nephropathy randomized to losartan 100 mg/d or placebo.

**Holtkamp et al. Kidney Int 2011**:

**ALTITUDE**: Selection of patients with type 2 diabetes and nephropathy randomized to aliskiren 300 mg/d or placebo on top of ACEI or ARB.

**Heerspink et al. Lancet Diabetes & Endocrinology 2016**
Initial fall in eGFR is associated with less renal function decline during prolonged follow-up

Tertiles of initial fall in eGFR

-8.6  
-2.4  
+4.2  
-8.6  
-2.4  
+4.2

Long-term eGFR slope (ml/min/1.73m²/year)

-3.77  
-4.10  
-4.82  
-3.64  
-3.85  
-4.40

p=0.009

Unadjusted analysis

p=0.049

Adjusted analysis

Holtkamp et al. Kidney Int 2011
SGLT2 inhibitors restore tubulo-glomerular feedback

GFR, glomerular filtration rate; SGLT, sodium–glucose cotransporter; TGF, tubuloglomerular feedback
SGLT2 inhibitors decrease RPF and GFR

**Type 1 diabetes**

<table>
<thead>
<tr>
<th>Mean RBV (ml/min/1.73 m²)</th>
<th>Mean GFR (ml/min/1.73 m²)</th>
<th>T1D-H (Euglycemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1641</td>
<td>172.0</td>
<td>139.0</td>
</tr>
<tr>
<td>1156</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type 2 diabetes**

<table>
<thead>
<tr>
<th>Mean GFR (ml/min/1.73 m²)</th>
<th>baseline</th>
<th>week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heerspink et al. DOM 2013: 15:853-62
EMPAREG: Empagliflozin slows eGFR decline over time

### Adjusted Mean (SE) eGFR (ml/min/1.73 m²)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empa 10 mg</th>
<th>Empa 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2223</td>
<td>2322</td>
<td>2322</td>
</tr>
<tr>
<td>4</td>
<td>2295</td>
<td>2290</td>
<td>2288</td>
</tr>
<tr>
<td>12</td>
<td>2267</td>
<td>2264</td>
<td>2269</td>
</tr>
<tr>
<td>28</td>
<td>2205</td>
<td>2235</td>
<td>2216</td>
</tr>
<tr>
<td>52</td>
<td>2121</td>
<td>2162</td>
<td>2156</td>
</tr>
<tr>
<td>80</td>
<td>2064</td>
<td>2114</td>
<td>2111</td>
</tr>
<tr>
<td>108</td>
<td>1927</td>
<td>2012</td>
<td>2006</td>
</tr>
<tr>
<td>122</td>
<td>1981</td>
<td>2064</td>
<td>2067</td>
</tr>
<tr>
<td>150</td>
<td>1763</td>
<td>1839</td>
<td>1871</td>
</tr>
<tr>
<td>164</td>
<td>1479</td>
<td>1540</td>
<td>1563</td>
</tr>
<tr>
<td>178</td>
<td>1262</td>
<td>1314</td>
<td>1340</td>
</tr>
<tr>
<td>192</td>
<td>1123</td>
<td>1180</td>
<td>1207</td>
</tr>
<tr>
<td>206</td>
<td>977</td>
<td>1024</td>
<td>1063</td>
</tr>
<tr>
<td></td>
<td>731</td>
<td>785</td>
<td>838</td>
</tr>
<tr>
<td></td>
<td>448</td>
<td>513</td>
<td>524</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>193</td>
<td>216</td>
</tr>
</tbody>
</table>

EMPAREG: Empagliflozin reduces renal risk in patients with type 2 diabetes and established CV disease

In patients with eGFR (MDRD) <60 mL/min/1.73 m² and/or macroalbuminuria (UACR >300 mg/g) at baseline, **empagliflozin reduced the risk of incident or worsening nephropathy**

HR 0.58
(95% CI 0.47, 0.71)

*P* < 0.001

**Cumulative probability of event (%)**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>998</td>
<td>507</td>
</tr>
<tr>
<td>6</td>
<td>952</td>
<td>462</td>
</tr>
<tr>
<td>12</td>
<td>895</td>
<td>425</td>
</tr>
<tr>
<td>18</td>
<td>836</td>
<td>377</td>
</tr>
<tr>
<td>24</td>
<td>694</td>
<td>302</td>
</tr>
<tr>
<td>30</td>
<td>516</td>
<td>206</td>
</tr>
<tr>
<td>36</td>
<td>420</td>
<td>172</td>
</tr>
<tr>
<td>42</td>
<td>273</td>
<td>102</td>
</tr>
<tr>
<td>48</td>
<td>69</td>
<td>23</td>
</tr>
</tbody>
</table>

EMPAREG: Empagliflozin reduces renal risk

<table>
<thead>
<tr>
<th>Event/Medication</th>
<th>N With Event/N Patients</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset/worsening of nephropathy</td>
<td>525/4124</td>
<td>388/2061</td>
<td>0.61</td>
<td>(0.53, 0.70)</td>
<td>&gt;0.0001</td>
<td></td>
</tr>
<tr>
<td>New onset macroalbuminuria</td>
<td>459/4091</td>
<td>330/2033</td>
<td>0.62</td>
<td>(0.54, 0.72)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Doubling of serum-creatinine*</td>
<td>70/4645</td>
<td>60/2323</td>
<td>0.56</td>
<td>(0.39, 0.79)</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>13/4687</td>
<td>14/2333</td>
<td>0.45</td>
<td>(0.21, 0.97)</td>
<td>0.0409</td>
<td></td>
</tr>
</tbody>
</table>

* Accompanied by estimated glomerular filtration rate (MDRD) ≤45 mL/min/1.73 m².

RAAS and SGLT2 inhibitors reduce intraglomerular pressure through different mechanisms

SGLT2i ↑ tubuloglomerular feedback, ↑ afferent arteriole tone and ↓ intraglomerular pressure

Initial ↓ in eGFR followed by stabilization ↓ albuminuria

Renal Protection (to be determined)

ACEi and ARB ↓ efferent arteriole tone and ↓ intraglomerular pressure

Initial ↓ in eGFR followed by stabilization ↓ albuminuria

Renal Protection

Increased intraglomerular pressure and hyperfiltration are key steps in the progression of diabetic kidney disease
Empagliflozin had a **protective effect against** acute renal failure and acute kidney injury vs placebo.

- **Empagliflozin** had a protective effect against acute renal failure and acute kidney injury vs placebo.

Cl, confidence interval; HR, hazard ratio;
Wanner C, et al. Presented at the 52nd EASD Annual Meeting 2016. Munich, Germany; 16th September 2016; OP S44.3
IMPROVE: Dapagliflozin consistently reduces albuminuria in type 2 diabetes and micro/macroalbuminuria

Petrykiv S. et.al. Submitted
Summary of Product Characteristics

Dapagliflozin

Use in patients with renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m²), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension.

Canagliflozin

Renal impairment
For patients with an eGFR 60 mL/min/1.73 m² to < 90 mL/min/1.73 m² or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m² or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).
Glycemic effects of dapagliflozin is blunted in patients with renal impairment

Excludes data after rescue. Adj., adjusted; BL, baseline; CI, confidence interval.

Petrykiv S. et.al. CJASN provisionally accepted
Albuminuria lowering effect persists in patients with renal impairment

<table>
<thead>
<tr>
<th>eGFR subgroup (mL/min/1.73 m²)</th>
<th>Mean UACR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
</tr>
<tr>
<td>≥45–&lt;60, n</td>
<td>211 (370)</td>
</tr>
<tr>
<td>≥60–&lt;90, n</td>
<td>206 (350)</td>
</tr>
<tr>
<td>≥90, n</td>
<td>170 (248)</td>
</tr>
</tbody>
</table>

UACR ≥30 mg/g at baseline

Petrykiv S. et al. CJASN provisionally accepted
Clinical implications: Individualize treatment

In patient with longstanding diabetes and established atherosclerotic cardiovascular disease empagliflozin or liraglutide should be considered as they have shown to reduce cardiovascular events.

ADA standard of care guideline; Diabetes Care 2017; Supplement 1; S1-S135
Conclusions

• SGLT2 inhibitors form a new class of oral glucose lowering agents
• These drugs have multiple pleiotropic effects
• The alleged renoprotective effects are mediated by
  ▪ Restoring tubulo-glomerular feedback,
  ▪ Inducing natriuresis/diuresis
  ▪ Lowering renal glucotoxicity
• Glucose lowering efficacy in patients with CKD is diminished but albuminuria, blood pressure, body weight lowering effects persists
• Hard outcome outcome trials are needed to definitely proof the renoprotective effects
The “incretin effect” is reduced or absent in type 2 diabetes patients.

- A dysfunctional incretin system is part of the pathogenesis of type 2 diabetes.
- Enhancement of incretin action was pursued as an interesting therapeutic solution.


Jørgensen MB. *Kidney Week* 2016. TH-PO445