Outcomes of SGLT2i in Diabetic Kidney Disease: Is it all diabetes?

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Renal Outcomes of SGLT2i trials

Is it only DKD?
Empagliflozin slowed the decline eGFR over 192 weeks

Empagliflozin

Placebo

Empagliflozin is not indicated for the treatment of CKD
Effect of SGLT 2 inhibitors on eGFR

Direct comparison of trials should be interpreted with caution due to differences in study design, populations and methodology.
UNIFORM

Proportion of GFR Declines

Rate of GFR Decline

- Control Group
  Symmetrical distribution of GFR declines. Mean GFR decline <0.

- Intervention Group
  Uniform treatment effect: Same treatment effect in patients with fast vs slow GFR declines.

PROPORTIONAL

Proportion of GFR Declines

Rate of GFR Decline

- Control Group
  Symmetrical distribution of GFR declines. Mean GFR decline <0.

- Intervention Group
  Proportional treatment effect: Larger treatment effect in patients with fast vs slow declines.
Distribution of individual eGFR slopes in the overall population
From baseline to follow-up

Empagliflozin is not indicated for the treatment of CKD

*Adjusted mean (95% CI)

Thomas MC et al. American Society of Nephrology ASN, New Orleans 2017. TH-OR035
Distribution of individual eGFR slopes in the overall population
From baseline to follow-up

Empagliflozin is not indicated for the treatment of CKD
*Adjusted mean (95% CI)
Thomas MG et al. American Society of Nephrology ASN, New Orleans 2017. TH-OR035
Empagliflozin is not indicated for the treatment of CKD

Thomas MC et al. American Society of Nephrology ASN, New Orleans 2017. TH-OR035
Distribution of individual eGFR slopes in the overall population
From baseline to follow-up

Empagliflozin is not indicated for the treatment of CKD
Thomas MC et al. American Society of Nephrology ASN, New Orleans 2017. TH-OR035
# Risk comparison for sustained absolute decline in eGFR of 30%, 40%, 50% or ≥57% from baseline

<table>
<thead>
<tr>
<th>Sustained decline in eGFR from baseline of:</th>
<th>n with event (%)</th>
<th>Empagliflozin (n=4645)</th>
<th>Placebo (n=2323)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>260 (5.6)</td>
<td>159 (6.8)</td>
<td>0.78 (0.64, 0.95)</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>40%</td>
<td>89 (1.9)</td>
<td>76 (3.3)</td>
<td>0.55 (0.40, 0.75)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50%</td>
<td>31 (0.7)</td>
<td>33 (1.4)</td>
<td>0.44 (0.27, 0.73)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>≥57%</td>
<td>16 (0.3)</td>
<td>25 (1.1)</td>
<td>0.30 (0.16, 0.57)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Empagliflozin is not indicated for the treatment of CKD

Wanner C et al. ASN, 2016; Chicago
Did people without DKD also benefit from empagliflozin?

From baseline to follow-up

Empagliflozin is not indicated for the treatment of CKD

Thomas MC et al. American Society of Nephrology ASN, New Orleans 2017. TH-OR035
No hyperfunction – just closer to normal?

Change in eGFR (ml/min/1.73m²/year)

Diabetes

No Diabetes

Unadjusted Δ = 1.3
Adjusted Δ = 1.8

Warren et al. Diabetes Care 2018;41:1646
Empagliflozin is not indicated for the treatment of CKD
Cherney D et al. Lancet Diabetes Endocrinol 2017;5:610
eGFR over time in patient with nephrotic syndrome

Mixed-model repeated-measures analysis in patients treated with ≥1 dose of study drug who had a baseline and post-baseline measurement. eGFR, estimated glomerular filtration rate.
### Composite of doubling of serum creatinine,* initiation of renal replacement therapy or death due to renal disease

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>4645</td>
<td>2323</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Urine albumin-to-creatinine ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mg/g</td>
<td>2766</td>
<td>1376</td>
<td></td>
</tr>
<tr>
<td>≥30 to 300 mg/g</td>
<td>1325</td>
<td>671</td>
<td></td>
</tr>
<tr>
<td>&gt;300 mg/g</td>
<td>504</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated glomerular filtration rate</strong></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>≥90 ml/min/1.73 m²</td>
<td>1043</td>
<td>486</td>
<td></td>
</tr>
<tr>
<td>60 to &lt;90 ml/min/1.73 m²</td>
<td>2406</td>
<td>1232</td>
<td></td>
</tr>
<tr>
<td>45 to &lt;60 ml/min/1.73 m²</td>
<td>822</td>
<td>416</td>
<td></td>
</tr>
<tr>
<td>&lt;45 ml/min/1.73 m²</td>
<td>374</td>
<td>189</td>
<td></td>
</tr>
</tbody>
</table>

Empagliflozin is not indicated for the treatment of CKD

*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m²

If protecting kidneys with normoalbuminuria...
If protecting kidneys with normal renal function...

Is it even treating DKD?

Is it preventing renal hyper-functioning?
Is it preventing hypoxia & AKI?
Only in RAASi-responsive disease?
Glomerular hyperfiltration: vasodilatation of afferent arteriole, vasoconstriction of efferent arteriole, increase in GFR and intraglomerular capillary pressure

A reduction in GFR is seen in healthy controls

Ferrannini E et al. Diabetes (2017)
Survival to stage 4 CKD (eGFR <30 mL/min/1.73 m²) in patients with diabetes according to the number of AKI episodes.
Reduced risk of Acute Renal Failure

Late benefits
(Unlike mortality/CHF?)
CVD-REAL Nordic: Dapagliflozin was associated with lower risk of hospitalisation for kidney disease compared with DPP-4 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>DPP-4 inhibitors</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>Rate / 100 p-ys</td>
<td>Number of events</td>
<td>Rate / 100 p-ys</td>
</tr>
<tr>
<td>Hospitalisation for kidney disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52</td>
<td>0.64</td>
<td>417</td>
<td>1.64</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>77</td>
<td>0.95</td>
<td>375</td>
<td>1.47</td>
</tr>
<tr>
<td>All-cause death</td>
<td>106</td>
<td>1.04</td>
<td>468</td>
<td>1.44</td>
</tr>
</tbody>
</table>

<sup>a</sup>Any hospitalisation with main diagnosis for chronic, acute or unspecified kidney disease
CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; p-y, person-year
SGLT2 inhibitor trials primarily focused on CKD/DKD

<table>
<thead>
<tr>
<th></th>
<th>CREDENCE¹⁻³</th>
<th>Dapa-CKD⁴</th>
<th>EMPA-KIDNEY⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study drug</strong></td>
<td>Canagliflozin vs placebo</td>
<td>Dapagliflozin vs placebo</td>
<td>Empagliflozin vs placebo</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>DKD including</td>
<td>CKD including</td>
<td>CKD including</td>
</tr>
<tr>
<td></td>
<td>✓ T2D</td>
<td>✓ T2D</td>
<td>✓ T2D</td>
</tr>
<tr>
<td></td>
<td>x Non-DM</td>
<td>✓ Non-DM</td>
<td>✓ Non-DM</td>
</tr>
<tr>
<td></td>
<td>x T1D</td>
<td>x T1D</td>
<td>✓ T1D</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>4401</td>
<td>4000</td>
<td>~5000</td>
</tr>
<tr>
<td><strong>Key inclusion criteria</strong></td>
<td>eGFR ≥30 to &lt;90 ml/min/1.73 m² and UACR &gt;300 mg/g</td>
<td>eGFR ≥25 to ≤75 ml/min/1.73 m² and UACR ≥200–≤5000 mg/g</td>
<td>eGFR ≥20 to &lt;45 ml/min/1.73 m² or eGFR ≥45 to &lt;90 ml/min/1.73 m² and UACR ≥200 mg/g</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>Composite of ESKD, doubling of serum creatinine, or renal or CV death</td>
<td>Composite of ≥50% sustained decline in eGFR or reaching ESKD, or renal or CV death</td>
<td>Composite of a sustained decline in eGFR to ≥10 ml/min/1.73 m², ≥40% sustained decline in eGFR or reaching ESKD, or renal death</td>
</tr>
</tbody>
</table>
| **Secondary endpoints** | • Composite of CV death or HHF  
• All-cause mortality | • Composite of CV death or HHF  
• All-cause mortality | • Composite of CV death or HHF  
• All-cause hospitalisation  
• All-cause mortality |
| **Start date**    | February 2014 | February 2017 | November 2018 |
| **Expected completion date** | June 2019* | November 2020 | June 2022 |

*The IDMC of the trial has recommended to stop the trial early based on the achievement of pre-specified efficacy criteria at the time of a planned interim analysis³.*