Heart Failure and SGLT2 inhibition: Understanding the mechanism for potential benefit

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## CV death, MI and stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

*95.02% CI
Hospitalisation for heart failure

**HR 0.65**
(95% CI 0.50, 0.85)
*p=0.0017*

Cumulative incidence function. HR, hazard ratio

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Months</th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4687</td>
<td>2333</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4614</td>
<td>2271</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4523</td>
<td>2226</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4427</td>
<td>2173</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3988</td>
<td>1932</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2950</td>
<td>1424</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>2487</td>
<td>1202</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td></td>
<td>775</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td></td>
<td>168</td>
</tr>
</tbody>
</table>
Mechanism of action: thoughts changed

- Schools of thought
- Before versus after trial
- Expectations vs reality
- Unexpected findings
Empagliflozin modulates several factors related to CV risk

Adapted from Inzucchi SE, Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) timepoints with reasonable amount of data available for pre-scheduled measurements.
Post trial – Not athero-thrombotic

• Too fast

• ↓ HFH CVD death BUT not MI or CVA suggests:
  – vascular actions so ↓ cardiac pre- and after-load
  – renal actions leading to ↓ extracellular fluid volume and cardiac pre-load
  – cardiac metabolism better? enhancing diastolic and systolic function
Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

**CIRCULATION**

↓ Intravascular /ECF volume

↑ Haematocrit (thus, haemoconcentration)

↓ Systolic blood pressure

**KIDNEY: SGLT2 inhibition**

↑ Urinary glucose loss

↑ Urinary sodium loss + Diuresis (+ calorie loss, weight reduction?)

↓ glucose and sodium reabsorption in proximal tubule

(Improved tubular glomerular feedback)

**HEART (+Lungs)**

↓ Cardiac afterload

↓ Cardiac pre-load

↑ Myocardial oxygen supply

+/− Improved cardiac metabolism?

⇒ Improvement in systolic and diastolic dysfunction

↓ Likelihood of pulmonary congestion,

⇒ Lower risk of HFH

⇒ Lower risk of fatal arrhythmias

Sodium homeostasis: tubulo-glomerular feedback

- Afferent arteriolar constriction
- Proximal tubular sodium reabsorption
- Adenosine release
- Furosemide: increased distal tubular sodium concentration
Cardiac (patho-)physiology
BP reduction is extremely effective in reducing the risk of developing HF

Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis


www.thelancet.com  Published online December 23, 2015
BP reduction is extremely effective in reducing the risk of developing HF

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mm Hg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>137319</td>
<td>0.80 (0.77-0.83)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>136986</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>136682</td>
<td>0.73 (0.68-0.77)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>43</td>
<td>3284</td>
<td>115411</td>
<td>0.72 (0.67-0.78)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>39888</td>
<td>0.95 (0.84-1.07)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>138298</td>
<td>0.87 (0.84-0.91)</td>
</tr>
</tbody>
</table>

RR per 10 mm Hg reduction in systolic blood pressure
Favours intervention  Favours control
How much BP reduction?

Mean BP difference 6.3/2.8mmHg
Do only patients with a very high BP benefit?

**SPRINT**
- BP 139.7/78.1 mmHg
- Heart failure – HR 0.62 (0.45, 0.84); P=0.002

**EMPA-REG**
- BP 135.5/76.7 mmHg
- Heart failure – HR 0.65 (0.50, 0.85); P=0.002
Are diabetes patients at elevated HF / fatal MI risk?

<table>
<thead>
<tr>
<th>Vascular Outcome</th>
<th>Number of cases</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>26,505</td>
<td>2.00 (1.83–2.19)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05–2.60)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</td>
</tr>
</tbody>
</table>

**Stroke subtypes**

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Number of cases</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95–2.65)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19–2.05)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59–2.13)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51–1.98)</td>
</tr>
</tbody>
</table>

Hazard ratios for vascular outcomes DM vs. no DM
Paradigm: many reasons for \( \uparrow \) HF risk in diabetes

**Atherothrombosis**
- Smoking
- Dyslipidaemia
- Hypertension
- Hyperglycaemia
  - Microvascular damage

**Heart failure / CVD death risks emerge over time**
- Hypertension
- Renal disease
- Obesity
  + some diabetes drugs
- Hyperglycaemia
  - Myocardial effects
- CHD

Body Volume changes
Emerging concept

HF & related outcomes

Non-fatal MI + CVA

SGLT2 Inhibitors

Statins

Pioglitazone (IRIS)

Metformin

BP Reduction

NB: different weight gain, other risks
Remaining questions

- **More than diuretic effect?**
  - glucose, weight, better renal effect? Likely yes

- **Will other SGLT2 inh. show same?**
  - time will tell but likely yes – trials on the go
Conclusion: Empa haemodynamic / renal benefits in groups at ↑ heart failure risk

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