Understanding the mechanisms of SGLT2 inhibition in heart failure and diabetes

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Novo Nordisk, Sanofi 
Grants: Boehringer Ingelheim
EMPA-REG OUTCOME® trial overview

- **Study medication was given on top of standard of care**
  - Glucose-lowering medication was to remain unchanged for the first 12 weeks

- **Key inclusion criteria**
  - Type 2 diabetes
  - High CV risk
  - BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 ml/min/1.73 m² (MDRD)
  - Average Age 63, HbA1c 8.07%, ~1/4 eGFR<60

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eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease.
Empagliflozin modulates several factors related to CV risk – most expected MI and CVA benefits

- BP
- Arterial stiffness
- Albuminuria
- Glucose
- Insulin
- Uric acid
- LDL-C
- HDL-C
- Triglycerides
- Oxidative stress
- Weight
- Visceral adiposity
- Sympathetic nervous system activity

Adapted from Inzucchi SE, Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100
### CV death, MI and stroke – an unexpected pattern of effects

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>1.24</td>
<td>(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
CV death

HR 0.62
(95% CI 0.49, 0.77)
\( p < 0.0001 \)

Cumulative incidence function. HR, hazard ratio
Hospitalisation for heart failure

**HR 0.65**

(95% CI 0.50, 0.85)

*p*=0.0017

Cumulative incidence function. HR, hazard ratio
# CV Outcomes: Relative Risk Reductions

Blue Boxes Imply Significant Outcomes; This is Not a Head-to-Head Comparison

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EMPA-REG OUTCOME</th>
<th>Pooled CANVAS Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P-MACE</td>
<td>14%</td>
<td>14%*</td>
</tr>
<tr>
<td></td>
<td>(HR 0.86, 95%CI 0.74-0.99)</td>
<td>(HR 0.86, 95%CI 0.75-0.97)</td>
</tr>
<tr>
<td>4P-MACE</td>
<td>HR 0.89, p=0.08</td>
<td>N/a</td>
</tr>
<tr>
<td>CV Death</td>
<td>38%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>(HR 0.62, p &lt;0.001)</td>
<td>(HR 0.87, 95%CI 0.72-1.06)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>32%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>(HR 0.68, p &lt;0.001)</td>
<td>(HR 0.87, 95%CI 0.74-1.01)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>(HR 0.87, 95%CI 0.7-1.09)</td>
<td>(HR 0.85, 95%CI 0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>HR 1.24</td>
<td>HR 0.90</td>
</tr>
<tr>
<td></td>
<td>(95%CI 0.92-1.67)</td>
<td>(95%CI 0.71-1.15)</td>
</tr>
<tr>
<td>HHF or CV Death</td>
<td>34%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>(HR 0.66, 95%CI 0.55-0.79)</td>
<td>(HR 0.78, 95%CI 0.67-0.91)</td>
</tr>
</tbody>
</table>

* Analysis not powered to detect superiority for 3P MACE

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Post trial - Mechanism of action thoughts differ

• Athero-thrombosis?
• No, too fast, less HFH & CVD death (but no clear MI or CVA reduction) suggests
  • vascular / renal actions?
  • Or cardiac metabolism?
    » Ketone hypothesis

Glucosuria via SGLT2i
no hypo

Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium glucose cotransporters SGLT2 and SGLT1.

SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to glucosuria with low risk of hypoglycemia.

Glucosuria
Loss of calories
BP reduction

Butler et al (2017) EJHF
Don’t forget sodium in SGLT2

- **SGLT2**
- **SODIUM**
B

Hyperfiltration in early stages of diabetic nephropathy

C

SGLT-2 inhibition reduces hyperfiltration via TGF
SGLT2-inhibition and RAS-blockade

Actions:

**SGLT2 inhibition**

Afferent vasomodulation (constriction)

**RAAS blockade**

Efferent vasodilation

Clinical implications:

- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection suggested

- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection proven in clinical trials

Adapted from: Cherney D et al. Circulation 2014;129:587
Preservation of Renal Function with Empagliflozin
45% Lesser Events of ‘Decline in eGFR (by ≥40%) Over Time’

**Ketone hypothesis**

- SGLT2 inhibitors increase ketone synthesis
  - Ferrannini et al (2016) Diabetes Care
- In Diabetes – switch in cardiac use from FFAs to glucose – impairs cardiac function
- Ketones more energy efficient fuel for failing heart
- BUT others not yet convinced
  - Lopaschuk and Verma (2016) Cell Metabolism
  - Empagaflozins fuel hypothesis: not too soon
EMPA-REG: effect on Hematocrit level - early and sustained

Change in HCT
• Consistent with ~ 7% decrease in plasma volume
• Similar change over range of renal function

Table 2—Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the change from baseline in each variable

<table>
<thead>
<tr>
<th></th>
<th>HR for CV death with empagliflozin vs. placebo (95% CI)</th>
<th>Percentage mediation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.615 (0.491, 0.770)</td>
<td></td>
</tr>
<tr>
<td>Adjusted for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.624 (0.496, 0.785)</td>
<td>3.0</td>
</tr>
<tr>
<td>FPG</td>
<td>0.665 (0.529, 0.837)</td>
<td>16.1</td>
</tr>
<tr>
<td>SBP</td>
<td>0.593 (0.473, 0.743)</td>
<td>−7.5</td>
</tr>
<tr>
<td>DBP</td>
<td>0.614 (0.490, 0.769)</td>
<td>−0.3</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.621 (0.495, 0.780)</td>
<td>2.0</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.596 (0.475, 0.748)</td>
<td>−6.5</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.636 (0.506, 0.799)</td>
<td>6.9</td>
</tr>
<tr>
<td>logTG</td>
<td>0.604 (0.482, 0.758)</td>
<td>−3.7</td>
</tr>
<tr>
<td>FFAs</td>
<td>0.586 (0.463, 0.741)</td>
<td>−9.9</td>
</tr>
<tr>
<td>logUACR</td>
<td>0.649 (0.518, 0.815)</td>
<td>11.1</td>
</tr>
<tr>
<td>eGFR (MDRD)</td>
<td>0.631 (0.504, 0.790)</td>
<td>5.3</td>
</tr>
<tr>
<td>eGFR (CKD-EPI)</td>
<td>0.632 (0.505, 0.791)</td>
<td>5.6</td>
</tr>
<tr>
<td>Weight</td>
<td>0.579 (0.461, 0.727)</td>
<td>−12.4</td>
</tr>
<tr>
<td>BMI</td>
<td>0.578 (0.460, 0.726)</td>
<td>−12.8</td>
</tr>
<tr>
<td>WC</td>
<td>0.598 (0.477, 0.750)</td>
<td>−5.8</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.791 (0.626, 1.000)</td>
<td>51.8</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.780 (0.619, 0.983)</td>
<td>48.9</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.696 (0.555, 0.873)</td>
<td>25.5</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.693 (0.553, 0.869)</td>
<td>24.6</td>
</tr>
</tbody>
</table>
An early hypothesis – fluid-directed from Glasgow team

- SGLT2 inhibition
  ↓ Glucose and sodium reabsorption in proximal tubule
  ↓ Nephron hyperfiltration

- Generalized decongestion

- Urinary glucose & sodium

- Cardiac afterload/pre-load
- Systolic & diastolic dysfunction
- Heart failure hospitalization
- Fatal arrhythmias

Slow renal dysfunction

Several differences from other agents

- **Loop and Thiazides** – naturesis only
- **Vaptans** – aquaresis
- **SGLT2i** – both glucose and sodium loss -
  - Initial reduction in excess body sodium?
    - Haemodynamic benefits?
    - Cellular benefits in cardiomyocytes?
- **SGLT2i** – no change osmolality/serum K+, uric acid down, not up, glucose down, not up
  - Diabetes-directed diuretic?
  - Butler et al (2017) EJHF
EMPA/CANVAS trials led to “a rethink on diabetes to CVD pathways”

- T2DM
- Obesity

Traditional focus
- Lipids
- Glucose
- BP
- Thrombotic tendency

Novel Insights
- Insulin
- Renal SGLT2
- Glomerular hyperfiltration
- Tubuloglomerular feedback
- Other mechanisms?

Accelerated Atherogenesis
- Na⁺ & glucose retention
- Intravascular volume increase
- Volume Status/Hemodynamic & Glomerular stress

MI, CVA, PAD
- Heart Failure
- Kidney disease

Sattar N, McGuire D. Circulation (In press)
Summary – SGLT2i mechanism

• SGLT2i renal Na+/ glu effects & ensuring haemoconcentration likely key mechanism for HF benefits
  • More data needed to confirm
• Trials on go in HF per se

• New understanding of link of T2 diabetes to HF?