SGLT2 inhibition in cardiology: What a cardiologist needs to know

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What works for CVD prevention in diabetes

What works?

- **Statins / BP reduction / Smoking cessation**

- **Glucose lowering?**
  - Slow burn modest effect which takes time?
  - Further trials confirm this
  - And via less microvascular (end-point) damage?
    - Again takes time
Background: Estimated future years of life lost due to diabetes with and without MI or stroke.
Adults with type 2 diabetes
HbA1c 7–10%*
ALL with Established CVD
  • Prior MI, CAD, stroke, UA or occlusive PAD

Screening (n=11531) → Randomised and treated (n=7020)

Placebo (n=2333)
  - Empagliflozin ▼ 10 mg (n=2345)
  - Empagliflozin 25 mg (n=2342)

HbA1c

Adjusted mean (SE) HbA1c (%)

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<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
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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.
Primary outcome:
3-point MACE (fatal and non-fatal MI and stroke)

HR 0.86
(95.02% CI 0.74, 0.99)
\( p=0.0382^* \)

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.

* Two-sided tests for superiority were conducted (statistical significance was indicated if \( p\leq0.0498 \)
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
EMPAGLIFLOZIN benefit?

- **Schools of thought**

- **Before trial results** – mix of risk factors improvements some surrogate of unknown benefit
  - Uric acid
  - Oxidative stress etc
  - Lipid changes – mixed

- **After trials results**
  - Focus shifted
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
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 actions** so less cardiac pre- and after-load
  - **renal actions** so less extracellular fluid volume and cardiac pre-load
  - Improved **cardiac metabolism**, enhancing diastolic and systolic function

The cardio-renal axis is critical in heart failure (SGLT2i thus exciting)
Figure. Cardioprotective Effect of Sodium-Glucose Cotransporter 2 (SGLT2) on Sodium-Hydrogen Exchange in the Heart and Kidneys

Blockade of the sodium-hydrogen exchanger by SGLT2 inhibitors

Decreased cardiac injury
Decreased cardiac wall stress

- Increased sodium excretion
- Decreased body weight
- Decreased blood pressure
- Hemoconcentration

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Packer, M et al. JAMA Cardiol. 2017

Butler et al (2017) EJHF
SGLT2-inhibition and RAS-blockade

**Actions:**
- **SGLT2 inhibition**
  - Afferent vasomodulation (constriction)

**Clinical implications:**
- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection suggested

**RAAS blockade**
- Efferent vasodilation

**Clinical implications:**
- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection proven in clinical trials

Adapted from: Cherney D et al. Circulation 2014;129:587
The cardio-renal axis is critical in heart failure (SGLT2i thus exciting)

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

**↑** Urinary glucose & sodium

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

*Sattar et al (2016) Diabetologia*
Preservation of Renal Function with Empagliflozin
45% Lesser Events of ‘Decline in eGFR (by ≥40%) Over Time’

HR 0.55
(95% CI 0.40, 0.75)
p=0.0001

Clinical implications of EMPAREG

- **Proven benefit in patients with DM + CVD**
  - To lower CVD mortality
  - HF benefit? New trials in play
  - Renal benefits? – new trials in play

- **What about DM without CVD?**
  - Not clear but SGLT2i used earlier in course of disease by many
  - Who to treat? DM plus high CVD risk?
  - High NTproBNP levels? Need new studies
Patient with established cardiovascular (CV) disease but no prior Type 2 diabetes mellitus (T2DM): Cardiologist to perform routine, systematic measurement of HbA1c to evaluate presence of T2DM

And/or

Eligible patients with CV disease and prior T2DM

Consider recommending treatments if no contraindication:

- **SGLT2 inhibitor: empagliflozin**
  - Decreased CV mortality and decreased heart failure hospitalizations
  - + Decreased blood glucose
  - + Promotes weight loss
  - + Renal benefits

- **GLP-1 receptor agonist: liraglutide**
  - Decreased CV mortality
  - + Decreased blood glucose
  - + Promotes weight loss
  - + Potential renal benefits

Refer to primary care physician or endocrinologist

Follow CV and T2DM progress in tandem

New trial data? CANVAS

- Clinical impression mixed:
- MACE & HFH /renal benefits similar - reassuring
- CVD and All Cause death not significant
  - Not clear why different
  - Amputation and Fracture risk significant
  - CVA less in CANVAS
# CV Outcomes: Relative Risk Reductions

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

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

* Analysis not powered to detect superiority for 3P MACE

What to make of it? Chance, diff populations or real differences

- Difference in (some) results, a Statistical chance?
  - Amputations & CVD death, or
- Baseline population differences, EMPA vs CANVA?
  - More CVD (all vs 2/3), slightly lower BMI & HbA1c,
  - More Asians ~8%, more males (lower BMI?)
- Or, Real drug differences? If so, why?
  - H2H trials to look at risk factor /fluid shifts?
- NO ONE KNOWS FOR SURE
- Take results at face value
Safety issues

Prohibit Use of SGLT2-i therapy, in:

• Moderate to Severe CKD (eGFR <45mL/min/1.73 m²)
• Pregnant and breast-feeding women: Risk not known
• Acute stressful states (severe medical / surgical considerations)

Observe Caution in:

• Risk of volume depletion (frail elderly, concomitant loop diuretics, predisposition to dehydration / renal impairment)
• Complicated UTIs: temporary discontinuation recommended
• History of recurrent UTIs: Risk of UTI
• Conditions of fasting: Risk of starvation and precipitation of eu-DKA
• Patients with already elevated haematocrit

Conclusions

- EMPAREG outcome / SGLT2 inhibitors
- Patients with T2DM and CVD: important CVD / HFH / renal benefits
- Generally safe on current trial data / results guideline changing – help lower CVD mortality
  - Rarely achieved
  - New understanding of mechanisms of death in T2DM+CVD
- Ongoing trials in high risk populations