EMPA-REG Results: Implications for CVD Prevention in Type 2 Diabetes Therapy

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Metabolic Basis of Increased Atherosclerosis: Diabetes & Beyond

• Metabolic substrates
  – Glucose
  – Fatty acids
  – Lipoproteins
• ↑ Inflammation
• ↑ Oxidation/Glycoxidation
• ↑ Endothelial dysfunction
• Pro-thrombotic state
  – ↑ thrombosis
  – ↓ fibrinolysis
Metabolic Basis of Increased Atherosclerosis: Diabetes & Beyond

- Metabolic substrates
  - Glucose
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  - Lipoproteins
- ↑ Inflammation
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- Pro-thrombotic state
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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Describe the mechanism of action of the SGLT2 inhibitors.
2. Review the main findings of the EMPA-REG OUTCOME trial.
3. Discuss the implications that the EMPA-REG OUTCOME trial has for CVD risk reduction in diabetes treatment.
SGLT2 Inhibition Reduces Renal Glucose Reabsorption


*not approved in U.S.
**Placebo-corrected change from baseline in HbA1c**

![Graph showing placebo-corrected change from baseline in HbA1c](chart)

Pooled results for 22 dapagliflozin, 11 empagliflozin, 9 canagliflozin, 7 ipragliflozin and 3 luseogliflozin studies with ≥12 weeks duration from published and gray literature sources through June 30, 2014 (search strategy adapted from Vasilakou et al. Ann Intern Med. 2013;159:262-274). Results are presented for the group allocated to the highest, most common dose across studies. SGLT2: sodium glucose cotransporter 2, CI: confidence interval, HbA1c: haemoglobin A1c.

Courtesy, A. Tsapas MD, Aristotle Univ, Thessaloniki, Greece


**EMPAP-REG OUTCOME® Trial design**

- **Study medication was given in addition to standard of care.**
- **Primary outcome: 3-point MACE**
- **Analysis: Placebo vs. pooled empagliflozin groups**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>63.2 (8.8)</td>
<td>63.0 (8.6)</td>
<td>63.2 (8.6)</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>30.7 (5.2)</td>
<td>30.6 (5.2)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td><em><em>eGFR</em>, mL/min/1.73m²</em>*</td>
<td>73.8 (21.1)</td>
<td>74.3 (21.8)</td>
<td>74.0 (21.4)</td>
</tr>
<tr>
<td><strong>&lt;60 mL/min/1.73m²</strong></td>
<td>607 (26.0%)</td>
<td>605 (25.8%)</td>
<td>607 (25.9%)</td>
</tr>
</tbody>
</table>

#### Glucose-lowering medication

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>992 (42.5)</td>
<td>985 (42.0)</td>
<td>1029 (43.9)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>101 (4.3)</td>
<td>96 (4.1)</td>
<td>102 (4.4)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

* According to approved EU label, empagliflozin should not be initiated in patients with eGFR < 60 ml/min/1.73m²

* Based on MDRD, Modification of Diet in Renal Disease equation

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### Baseline characteristics

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<tr>
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<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any CVD</strong></td>
<td>2307 (98.9%)</td>
<td>2333 (99.5%)</td>
<td>2324 (99.2%)</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>1763 (75.6%)</td>
<td>1782 (76.0%)</td>
<td>1763 (75.3%)</td>
</tr>
<tr>
<td><strong>History of MI</strong></td>
<td>1083 (46.4%)</td>
<td>1107 (47.2%)</td>
<td>1083 (46.2%)</td>
</tr>
<tr>
<td><strong>History of stroke</strong></td>
<td>553 (23.7%)</td>
<td>535 (22.8%)</td>
<td>549 (23.4%)</td>
</tr>
<tr>
<td><strong>Anti-hypertensive therapy</strong></td>
<td>2221 (95.2%)</td>
<td>2227 (95.0%)</td>
<td>2219 (94.7%)</td>
</tr>
<tr>
<td><strong>ACE inhibitors/ARBs</strong></td>
<td>1868 (80.1%)</td>
<td>1896 (80.9%)</td>
<td>1902 (81.2%)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>988 (42.3%)</td>
<td>1036 (44.2%)</td>
<td>1011 (43.2%)</td>
</tr>
<tr>
<td><strong>Lipid-lowering drugs</strong></td>
<td>1864 (79.9%)</td>
<td>1926 (82.1%)</td>
<td>1894 (80.9%)</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>1773 (76.0%)</td>
<td>1827 (77.9%)</td>
<td>1803 (77.0%)</td>
</tr>
<tr>
<td><strong>Anti-coagulants and anti-platelets</strong></td>
<td>2090 (89.6%)</td>
<td>2098 (89.5%)</td>
<td>2064 (88.1%)</td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid</strong></td>
<td>1927 (82.6%)</td>
<td>1939 (82.7%)</td>
<td>1937 (82.7%)</td>
</tr>
</tbody>
</table>

Data are n (%) in patients treated with ≥1 dose of study drug

* Based on narrow standardised MedDRA query “cardiac failure”

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EMPA-REG: Treatment and Observation Times

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Pooled Empagliflozin (n=4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>2.6 (1.8-3.40) years</td>
<td>2.6 (2.0-3.4) years</td>
</tr>
<tr>
<td><strong>Observation:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3.1 (2.2-3.5) Years</td>
<td>3.2 (2.2-3.6) years</td>
</tr>
</tbody>
</table>

Zinman B et al, NEJM 373:2117, 2015

HbA1c

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements


All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat/X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements)

Diastolic blood pressure

Adjusted mean (SE) diastolic blood pressure (mmHg)

Week

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

2232
2235 2235 2199
2174 2125 2095 2072 1853 1556 1327 1189 1034 790
518
199

2200 2204 2171 1492 1274 1126 981 735 450
171

2250 2251 2197 2169 2129 2102 2086
1878
1571
1212
1070
842
528
216

247 2221 2197 2169 2129 2102 2086
1878
1571
1212
1070
842
528
216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat). X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements.


Primary outcome:
3-point MACE

HR 0.86
(95.02% CI 0.74, 0.99)

p=0.0382*

N=7020

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

* Two-sided tests for superiority were conducted (statistical significance was indicated if p<0.0498)
CV death

HR 0.62
(95% CI 0.49, 0.77)

p<0.0001

Cumulative incidence function: HR, hazard ratio


CV death, MI and stroke

<table>
<thead>
<tr>
<th>Patients with event/analysed</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

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

*95.02% CI

**CV death, MI and stroke**

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<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


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**Hospitalization for heart failure**

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

N=7020

Cumulative incidence function. HR, hazard ratio

Hospitalization for heart failure in patients with vs. without heart failure at baseline

HR 0.59
(95% CI 0.43, 0.82)
N=6314

HR 0.75
(95% CI 0.48, 1.19)
N=706

Patients without heart failure at baseline

Patients with heart failure at baseline

Interaction P=NS


All-cause mortality

HR 0.68
(95% CI 0.57, 0.82)
p<0.0001

Kaplan-Meier estimate. HR, hazard ratio

Predefined AEs of special interest

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<tbody>
<tr>
<td></td>
<td>Rate/100pt-years</td>
<td>n (%)</td>
<td>Rate/100pt-years</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>0.02</td>
<td>1 (&lt;0.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8.21</td>
<td>423 (18.1)</td>
<td>8.02</td>
</tr>
<tr>
<td>Complicated UTI</td>
<td>0.71</td>
<td>41 (1.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Genital infection</td>
<td>0.73</td>
<td>42 (1.8)</td>
<td>153 (6.5)</td>
</tr>
<tr>
<td>Confirmed hypoglycemia AEs</td>
<td>–</td>
<td>650 (27.9)</td>
<td>–</td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>1.91</td>
<td>108 (4.6)</td>
<td>1.35</td>
</tr>
<tr>
<td>Decreased renal function (including AKI)</td>
<td>2.77</td>
<td>155 (6.6)</td>
<td>2.07</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>2.04</td>
<td>115 (4.9)</td>
<td>1.97</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>3.59</td>
<td>197 (8.4)</td>
<td>2.75</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>1.61</td>
<td>91 (3.9)</td>
<td>1.57</td>
</tr>
<tr>
<td>Venous thrombotic events</td>
<td>0.35</td>
<td>20 (0.9)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Treated set (patients randomised and treated with at least one dose of study drug)

What was the underlying reason(s) for the dramatic benefit on CV outcomes observed in EMPA-REG?

**SGLT2 Inhibitors: Risks & Benefits**

**BENEFITS**
- Insulin-independent glucose lowering effect (irrespective of DM duration)
- Low hypoglycemia rates
- Modest ↓ weight
- Modest ↓ BP
- ↓ uric acid
- ↓ Albuminuria
- Small ↓ TGs

**RISKS**
- DKA
- Genital mycotic infections
- ? UTIs
- Polyuria / Dehydration
- Reversible ↓ GFR
- Small ↑ Hgb/Hct
- Small ↑ LDL-C
- ? Fractures

* Prior to CV outcomes trial(s)

*not approved for weight loss, BMI, WC, BP, TG, albuminuria reduction; or to increase HDL-C

---

**Large CV Outcomes Trials in Diabetes (Non-Insulin)**

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELI A</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>16,500</td>
<td>6,000</td>
<td>6,000</td>
<td>5,400</td>
<td>8,300</td>
</tr>
<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>NCT01986881</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>7,500</td>
<td>4,300</td>
<td>22,200</td>
<td>3,900</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>
**EMPA-REG: Impact on Diabetes Therapy**

**SUMMARY**

1. SGLT2-i’s exert their glucose-lowering effect through the augmentation of urinary glucose excretion and are associated with modest weight loss and BP reduction.

2. Risks include DKA, GU infections, & polyuria/dehydration.

3. In the first SGLT2-i CV outcome trial (OT), empagliflozin ↓’d 3-pt MACE (CV death) & HF hospitalizations.

4. The drug also had a significant benefits on renal outcomes.

5. The mechanisms behind these effects are not clear.

6. Other CVOT’s with other SGLT2-i’s are currently underway.

7. Guidelines writers will need to consider these findings when developing future T2DM treatment algorithms.

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Thank You!