ΣΔτ2 και ΚΔ Νόσος: Η σύγχρονη ταυτόχρονη παρέμβαση υπό το πρίσμα των τελευταίων κατευθυντήριων οδηγιών.

George Giannakoulas
Ass. Professor in Cardiology
Aristotle University of Thessaloniki
Disclaimer

- Honoraria for lectures and/or Advisory boards: Boehringer Ingelheim, Novartis, Servier, ELPEN Pharmaceuticals, Pfizer, Roche Diagnostics, Genesis Pharma
Cardiovascular disease –
A main killer in patients with diabetes

Cardiovascular disease
52%

People with diabetes and CV disease* die earlier than those without diabetes or CV disease

A 60-year-old male patient dies, on average, 12 years earlier with diabetes and CV disease, compared with no diabetes and CV disease*

*In this case, CV disease is represented by MI or stroke
CV, cardiovascular; MI, myocardial infarction
The Emerging Risk Factors Collaboration. JAMA 2015;314:52
### Personal Information

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>60</td>
</tr>
<tr>
<td>BMI</td>
<td>28 kg/m²</td>
</tr>
<tr>
<td>Smoker</td>
<td>Quitted 5 years ago</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>148/80 mmHg</td>
</tr>
<tr>
<td>Pulse</td>
<td>80 bpm</td>
</tr>
</tbody>
</table>

### Patient History

#### Medical History
- Hypertension - since ten years
- Type 2 diabetes - since nine years
  - HbA1c 8.2% (66 mmol/mol)
- Atrial fibrillation - since six years
  - CHA₂DS₂-VASc: 3
- Coronary artery disease – recent PCI
- Renal function
  - eGFR = 70 ml/min
- LDL-cholesterol = 120 mg/dl

#### Medications
- Lisinopril 20 mg o.d.
- Metformin 1000 mg b.i.d.
- Rosuvastatin 20 mg o.d.
- Bisoprolol 5 mg od
- Dabigatran 150 mg b.i.d. + Clopidogrel 75 mg o.d.

#### Presentation
- Post acute coronary syndrome - follow-up
### Personal Information

<p>| | |</p>
<table>
<thead>
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### Medical History

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  - CHA₂DS₂-VASc: 3
- Coronary artery disease – recent PCI
- Renal function
  - eGFR = 70 ml/min
- LDL-cholesterol = 120mg/dl

### Medications

- Lisinopril 20 mg o.d.
- **Amlodipine 5-10 mg o.d.**
- Metformin 1000 mg b.i.d.
- **Rosuvastatin 40 mg o.d. / Ezetimibe 10**
- Bisoprolol 10 mg od
- Dabigatran 150 mg b.i.d. + Clopidogrel 75 mg o.d.

### Presentation

- Post acute coronary syndrome - follow-up
**ESC guidelines – Ideal risk factor management**

**Glycaemic control (HbA$_{1c}$)**
- In general <7.0%
- On individual basis <6.5%-6.9%

**Antiplatelet therapy**
- Patients with CVD
- ASA 75-160 mg/d

**Blood pressure control**
- <140/85 mmHg
- Nephropathy: syst <130 mmHg

**Lipid control (LDL-C)**
- Very high risk <1.8 mmol/L
- High risk <2.5 mmol/L or –50%

**Lifestyle modification**

Glycaemic control – Evolution over time

- **<2008**
  - HbA1c – the lower the better

- **2008**
  - HbA1c – the lower the better but...
    - without weight gain, hypoglycaemia and side effects

- **2018**
  - Manage total cardiovascular risk by including glucose control with agents of proven safety and preventive efficacy
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin - canagliflozin.
HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

If HbA1c above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin
  - SU
Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load >180 g/day

SGLT1, sodium-glucose co-transporter-1; SGLT2, sodium-glucose co-transporter-2
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Reneard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David F. Pietz, M.D., Erich Bluemle, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattkeus, Dipl. Biomath., Therese Devins, Dr. P.H.,
Odd Erik Johanson, M.D., Ph.D., Hansj. Wöhrle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

The study evaluated the effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), on cardiovascular outcomes and mortality in patients with type 2 diabetes.
EMPA-REG OUTCOME® trial design

Screening (N=11,531) → Randomised and treated (n=7020) → Background glucose-lowering medication adjustment allowed to achieve glycaemic equipoise → Placebo (n=2333) → Empagliflozin 10 mg (n=2345) → Empagliflozin 25 mg (n=2342) → Pooled

3.1 years median observation time

- Study medication was given on top of standard of care
  - Glucose-lowering medication was to remain unchanged for the first 12 weeks
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

In EMPA-REG OUTCOME®, CV disease was broadly defined as CAD, PAD or a prior atherothrombotic event (e.g. MI, stroke)*

- >75% of patients had CAD at baseline, but not all had a prior atherothrombotic event

<table>
<thead>
<tr>
<th>Any CV disease risk factor, n (%)</th>
<th>Placebo (n=2333)</th>
<th>Pooled empagliflozin (n=4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASD</td>
<td>2307 (98.9)</td>
<td>4657 (99.4)</td>
</tr>
<tr>
<td>Multi-vessel CAD</td>
<td>1763 (75.6)</td>
<td>3545 (75.6)</td>
</tr>
<tr>
<td>History of MI</td>
<td>1100 (47.1)</td>
<td>2179 (46.5)</td>
</tr>
<tr>
<td>CABG</td>
<td>1083 (46.4)</td>
<td>2190 (46.7)</td>
</tr>
<tr>
<td>History of stroke†</td>
<td>563 (24.1)</td>
<td>1175 (25.1)</td>
</tr>
<tr>
<td>PAD</td>
<td>553 (23.7)</td>
<td>1084 (23.1)</td>
</tr>
<tr>
<td>Single-vessel CAD†</td>
<td>479 (20.5)</td>
<td>982 (21.0)</td>
</tr>
</tbody>
</table>

Patients treated with ≥1 dose of study drug
*CV disease defined as any of the components of history of MI, CABG, multi-vessel or single-vessel CAD
†Information was not available for one patient in the placebo group
CABG, coronary artery bypass graft; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease
Πόσοι ασθενείς με εξακριβωμένη ΚΔ νόσο δεν είχαν προηγούμενο αθηροθρομβωτικό συμβάν (ΕΜ και/ή εγκεφαλικό);

35% των ασθενών με ΚΔ νόσο δεν είχαν προηγούμενο αθηροθρομβωτικό συμβάν

Προηγούμενο αθηροθρομβωτικό συμβάν: ιστορικό ΕΜ και/ή εγκεφαλικού
ΚΔ, καρδιαγγειακό. ΕΜ, έμφραγμα του μυοκαρδίου
A closer look at CV risk entry criteria in EMPA-REG OUTCOME®

- At least one of the following criteria was required to be met:

1. **Prior atherothrombotic event**
   - MI or stroke

2. **Other vascular manifestation of CV disease**
   - **Coronary artery disease**
     - Multi-vessel disease or L main disease (≥50% luminal narrowing)
     - Single-vessel disease (≥50% luminal narrowing); plus
       - Provocable ischaemia
       - Unstable angina within 12 months prior
   - **Occlusive peripheral artery disease**
Προκαθορισμένες πρωτογενείς και κύριες δευτερογενείς εκβάσεις

• Πρωτογενής έκβαση

  3-point MACE:
  Χρόνος μέχρι την πρώτη εκδήλωση:
  – Καρδιαγγειακού Θανάτου,
  – μη-θανατηφόρου Εμφράγματος Μυοκαρδίου ή
  – μη-θανατηφόρου Αγγειακού Εγκεφαλικού Επεισοδίου

• Κύρια δευτερεύουσα έκβαση

  4-point MACE:
  Χρόνος μέχρι την πρώτη εκδήλωση:
  – Καρδιαγγειακού Θανάτου,
  – μη-θανατηφόρου Εμφράγματος Μυοκαρδίου,
  – μη-θανατηφόρου Αγγειακού Εγκεφαλικού Επεισοδίου ή
  – νοσηλείας για Ασταθή Στηθάγχη

MACE, Major Adverse Cardiovascular Event (Μείζον Καρδιαγγειακό Συμβάν)

Άλλες προκαθορισμένες εκβάσεις

• Καρδιαγγειακός θάνατος
• Μη-θανατηφόρο EM
• Μη-θανατηφόρο ΑΕΕ
• Νοσηλεία για Καρδιακή Ανεπάρκεια
• Θνησιμότητα κάθε αιτιολογίας

• Όλα τα ΚΔ και νευρολογικά συμβάντα, αξιολογήθηκαν από ανεξάρτητες, τυφλοποιημένες επιτροπές κλινικών συμβάντων

SGLT-2 inhibition
Summary of the impact of Empagliflozin

3P – MACE
ARR 1.6%
RRR 14%
P=0.04

- 3P-MACE: ↓14% P=0.04
- CV death: ↓38% P<0.0001
- All-cause mortality: ↓32% P<0.0001
- HHF: ↓35% P=0.0017
- Doubling of serum creatinine: ↓44% P<0.001

The effect of empagliflozin on **CV death** was consistent in patients with and without a history of atherothrombotic events (MI and/or stroke).
Data suggest the effect of empagliflozin on CV death was largely independent of baseline HbA1c in patients with T2D and established CV disease.

Cox regression analysis in patients treated with ≥1 dose of study drug. The subgroup with HbA1c ≥9% had a 95% CI that crossed unity.

** Patients with event, %

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3.7</td>
<td>5.9</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td>HbA1c at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.0%</td>
<td>2.4</td>
<td>7.9</td>
<td>0.30 (0.12, 0.80)</td>
</tr>
<tr>
<td>7.0% to &lt;8.0%</td>
<td>3.7</td>
<td>6.1</td>
<td>0.59 (0.42, 0.83)</td>
</tr>
<tr>
<td>8.0% to &lt;9.0%</td>
<td>3.7</td>
<td>5.4</td>
<td>0.67 (0.45, 0.99)</td>
</tr>
<tr>
<td>≥9.0%</td>
<td>4.2</td>
<td>5.5</td>
<td>0.76 (0.44, 1.31)</td>
</tr>
</tbody>
</table>

EMPA-REG OUTCOME® was not powered to show differences between subgroups.

Inzucchi S et al. ADA 2017; poster 1174-P.
The effect of empagliflozin on all-cause mortality was consistent in patients with and without a history of atherothrombotic events (MI and/or stroke)

<table>
<thead>
<tr>
<th>n event/N analysed (%)</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>269/4687 (5.7)</td>
<td>194/2333 (8.3)</td>
<td>0.68 (0.57, 0.82)</td>
<td>0.3808</td>
</tr>
<tr>
<td>Prior atherothrombotic event at baseline*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>190/3048 (6.2)</td>
<td>143/1518 (9.4)</td>
<td>0.65 (0.52, 0.80)</td>
<td>0.3808</td>
</tr>
<tr>
<td>No</td>
<td>79/1639 (4.8)</td>
<td>51/815 (6.3)</td>
<td>0.78 (0.55, 1.11)</td>
<td>0.3808</td>
</tr>
</tbody>
</table>

Cox regression analysis in patients treated with ≥1 dose of study drug. p-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple testing.

*Prior atherothrombotic event: history of MI and/or stroke

MI, myocardial infarction

Fitchett D. ACC 2018; oral presentation

Favours empagliflozin
Favours placebo
NNT – Achievements over time

1994

4S\textsuperscript{1} Simvastatin

Treatment for 5.4 years

30

2000

HOPE\textsuperscript{2} Ramipril

Treatment for 5 years

56

<29% statin

2015

EMPA-REG OUTCOME\textsuperscript{3} Empagliflozin

Treatment for 3 years

39

>80% ACEi/ARB

>75% statin

\textsuperscript{1}4S investigators. Lancet 1994;344:1383;
\textsuperscript{2}HOPE investigators. New Engl J Med 2000;342:145;
\textsuperscript{3}Zinman B et al. New Engl J Med 2015;373:2117
European guidelines
On the impact of empagliflozin

Empagliflozin
Demonstrated substantial reductions in cardiovascular death, total mortality and heart failure hospitalisations suggesting very early use in patients with diabetes and cardiovascular disease
### Personal Information

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<tbody>
<tr>
<td><strong>Sex</strong></td>
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</tr>
<tr>
<td><strong>Age</strong></td>
<td>61</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27 kg/m²</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>Quit 6 years ago</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>130/80 mmHg</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td>75 bpm</td>
</tr>
</tbody>
</table>

### Patient History

#### Medical History

- Hypertension - since 11 years
- Type 2 diabetes - since 10 years
  - HbA1c 6.9% (51 mmol/mol)
- Atrial fibrillation - since 16 years
  - CHA²DS²-VASc: 3
- Coronary artery disease - PCI 1 year ago
- Renal function
  - eGFR = 65 ml/min
- LDL-cholesterol
  - 1.8 mmol/L (65 mg/dl)

#### Medications

- Lisinopril 20 mg o.d.
- Amlodipine 5 mg o.d.
- Metformin 1000 mg b.i.d.
- Empagliflozin 10 mg o.d.
- Rosuvastatin 20 mg o.d. /Ezetimibe 10
- Bisoprolol 10 mg o.d.
- Dabigatran 150 mg b.i.d.

#### Presentation

- Breathless and tired
## Transthoracic echocardiogram

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal value</th>
<th>Measurement</th>
<th>Parameter</th>
<th>Normal value</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root</td>
<td>20 - 38 mm</td>
<td>39</td>
<td>Left ventricular end-diastolic diameter (LVEDD)</td>
<td>36 - 56 mm</td>
<td>50</td>
</tr>
<tr>
<td>Left atrium (LA)</td>
<td>19 - 39 mm</td>
<td>45</td>
<td>Left ventricular end-systolic diameter (LVESD)</td>
<td>25 - 37 mm</td>
<td></td>
</tr>
<tr>
<td>Right ventricle (RV)</td>
<td>7 - 25 mm</td>
<td></td>
<td>LV Shortening fraction</td>
<td>29 - 44 %</td>
<td></td>
</tr>
<tr>
<td>Interventricular septum (IVS)</td>
<td>7 - 11 mm</td>
<td>14</td>
<td>LV Ejection fraction</td>
<td>&gt; 55 %</td>
<td>54%</td>
</tr>
<tr>
<td>Posterior wall (PW)</td>
<td>7 - 11 mm</td>
<td>13</td>
<td>RWMAs : none</td>
<td>E/Em = 16</td>
<td></td>
</tr>
</tbody>
</table>

Aortic root : Mildly dilated
Ascending aorta: Mildly dilated (41 mm).
Aortic valve: Tricuspid aortic valve. Opens well. Mild calcification of the cusps
Left atrium: Moderately dilated (37 ml/m2)
Mitral valve: Normal in structure and function
Left ventricle: Normal LV size with mild concentric wall hypertrophy and preserved systolic function. Diastolic dysfunction. E/e’ = 16

Right ventricle: Normal in size and function
Right atrium: Mildly dilated
Pericardium : No pericardial effusion noted
Doppler Study: Mild mitral regurgitation. **Mild tricuspid regurgitation with estimated PASP 40 (35 +5)mmHg**
Work-up

NTproBNP 896 pg/dl
# Definition of heart failure

With preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>PFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
</tbody>
</table>
| 3         | 1. Elevated levels of natriuretic peptides.  
2. At least one additional criterion:  
   a. relevant structural heart disease (LVF and/or LAE);  
   b. diastolic dysfunction (for details see Section 4.3.2.). | 1. Elevated levels of natriuretic peptides.  
2. At least one additional criterion:  
   a. relevant structural heart disease (LVF and/or LAE);  
   b. diastolic dysfunction (for details see Section 4.3.2.). |
Cardiovascular Disease and Diabetes

T2DM = Type 2 diabetes Mellitus
Bell DSH. Diabetes Care 2003; 26:2433-41; Centers for Disease Control (CDC). www.cdc.gov
Treatment of Heart Failure in people with diabetes

• Builds on similar principles as in people without diabetes

• ACE-I, ARBs, beta-blockers and MRAs essential (HFrEF)
• Diuretics for symptom relief
• Ivabradine if SR and heart rate > 70 bpm (HFrEF)
• CRT and Heart Tx after careful consideration (HFrEF)
• Caution with glitazones
Empagliflozin improves outcome in patients with type 2 diabetes. Other hypoglycaemic agents have not been shown convincingly to reduce the risk of cardiovascular events and may increase the risk of heart failure.

Empagliflozin demonstrated substantial reductions in CV death and all-cause mortality, as well as in hospitalisation for HF suggesting use of an SGLT-2 inhibitor should come very early in the course of management of patients with diabetes and cardiovascular disease.
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)
$p=0.0017$
The effect of empagliflozin on HHF was consistent in patients with and without a history of atherothrombotic events (MI and/or stroke)

<table>
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<th>n event/N analysed (%)</th>
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<th>HR (95% CI)</th>
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<tr>
<td>All patients</td>
<td>126/4687 (2.7)</td>
<td>95/2333 (4.1)</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.5610</td>
</tr>
<tr>
<td>Prior atherothrombotic event at baseline*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94/3048 (3.1)</td>
<td>67/1518 (4.4)</td>
<td>0.68 (0.50, 0.94)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32/1639 (2.0)</td>
<td>28/815 (3.4)</td>
<td>0.57 (0.35, 0.95)</td>
<td></td>
</tr>
</tbody>
</table>

Cox regression analysis in patients treated with ≥1 dose of study drug. p-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple testing

*Prior atherothrombotic event: history of MI and/or stroke
HHF, hospitalisation for heart failure; MI, myocardial infarction
Fitchett D. ACC 2018; oral presentation
Data suggest the effect of empagliflozin on HHF was largely independent of baseline HbA1c in patients with T2D and established CV disease.

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<tbody>
<tr>
<td>All patients</td>
<td>2.7</td>
<td>4.1</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.8875</td>
</tr>
<tr>
<td>HbA1c at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.0%</td>
<td>3.4</td>
<td>5.5</td>
<td>0.56 (0.21, 1.48)</td>
<td></td>
</tr>
<tr>
<td>7.0% to &lt;8.0%</td>
<td>2.7</td>
<td>4.2</td>
<td>0.66 (0.44, 0.98)</td>
<td></td>
</tr>
<tr>
<td>8.0% to &lt;9.0%</td>
<td>2.0</td>
<td>3.4</td>
<td>0.56 (0.34, 0.95)</td>
<td></td>
</tr>
<tr>
<td>≥9.0%</td>
<td>3.6</td>
<td>4.7</td>
<td>0.76 (0.42, 1.37)</td>
<td></td>
</tr>
</tbody>
</table>

EMPARY-REG OUTCOME® was not powered to show differences between subgroups.

Cox regression analysis in patients treated with ≥1 dose of study drug. The subgroup with HbA1c <7% and ≥9% had a 95% CI that crossed unity.

CV, cardiovascular; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; T2D, type 2 diabetes.

Fitchett D et al. EASD 2017; poster 918
Reductions in HF, CV death and all-cause mortality were consistent in patients with and without HF at baseline\(^1\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HHF or CV death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>265/4687 (5.7)</td>
<td>198/2333 (8.5)</td>
<td>0.66 (0.55, 0.79)</td>
<td></td>
</tr>
<tr>
<td>HF at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>190/4225 (4.5)</td>
<td>149/2089 (7.1)</td>
<td>0.63 (0.51, 0.78)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75/462 (16.2)</td>
<td>49/244 (20.1)</td>
<td>0.72 (0.50, 1.04)</td>
<td></td>
</tr>
<tr>
<td><strong>HHF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>126/4687 (2.7)</td>
<td>95/2333 (4.1)</td>
<td>0.65 (0.50, 0.85)</td>
<td></td>
</tr>
<tr>
<td>HF at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78/4225 (1.8)</td>
<td>65/2089 (3.1)</td>
<td>0.59 (0.43, 0.82)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48/462 (10.4)</td>
<td>30/244 (12.3)</td>
<td>0.75 (0.48, 1.19)</td>
<td></td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>172/4687 (3.7)</td>
<td>137/2333 (5.9)</td>
<td>0.62 (0.49, 0.77)</td>
<td></td>
</tr>
<tr>
<td>HF at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>134/4225 (3.2)</td>
<td>110/2089 (5.3)</td>
<td>0.60 (0.47, 0.77)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38/462 (8.2)</td>
<td>27/244 (11.1)</td>
<td>0.71 (0.43, 1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>269/4687 (5.7)</td>
<td>194/2333 (8.3)</td>
<td>0.68 (0.57, 0.82)</td>
<td></td>
</tr>
<tr>
<td>HF at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>213/4225 (5.0)</td>
<td>159/2089 (7.6)</td>
<td>0.66 (0.51, 0.81)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56/462 (12.1)</td>
<td>35/244 (14.3)</td>
<td>0.79 (0.52, 1.20)</td>
<td></td>
</tr>
</tbody>
</table>

Empagliflozin is not indicated for the treatment of heart failure.

HHF, hospitalisation for heart failure

The effect of empagliflozin on HHF was consistent in patients with and without CVD

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Empagliflozin n event/N analysed (%)</th>
<th>Rate/1000 PY</th>
<th>Comparator n event/N analysed (%)</th>
<th>Rate/1000 PY</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPA-REG OUTCOME</strong>&lt;sup&gt;®1&lt;/sup&gt; (empagliflozin vs placebo)</td>
<td>126/4,687 (2.7)</td>
<td>9.4</td>
<td>95/2,333 (4.1)</td>
<td>14.5</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td><strong>EMPRISE</strong>&lt;sup&gt;2&lt;/sup&gt; (empagliflozin vs DPP-4i)</td>
<td>83/17,539 (0.5)</td>
<td>10.5</td>
<td>150/17,539 (0.9)</td>
<td>19.9</td>
<td>0.56 (0.43, 0.73)</td>
</tr>
<tr>
<td>Broad HHF</td>
<td>17/13,243 (2.8)</td>
<td>2.8</td>
<td>47/13,243 (8.3)</td>
<td>3.5</td>
<td>0.35 (0.20, 0.61)</td>
</tr>
<tr>
<td>Without CVD</td>
<td>63/4,217 (35.2)</td>
<td>35.2</td>
<td>120/4,217 (68.0)</td>
<td>5.3</td>
<td>0.53 (0.39, 0.72)</td>
</tr>
<tr>
<td>With CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Definitions of HHF vary between studies.

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure; PY, patient-years.

### Overview of major guidelines that include results from the EMPA-REG OUTCOME® trial

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Latest update</th>
<th>Recommendations on empagliflozin use in adult patients with T2D and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Diabetes Association</td>
<td>Jan 2018</td>
<td>To reduce the risk of MACE and CV mortality for patients with T2D and established atherosclerotic CVD</td>
</tr>
<tr>
<td>Diabetes Canada</td>
<td>Jan 2018</td>
<td>To reduce CV death in patients with T2D and established CVD</td>
</tr>
<tr>
<td>ESC European Society of Cardiology</td>
<td>Apr 2018</td>
<td>To reduce the risk of major CV events in adults with T2D with clinical CVD in whom glycaemic targets are not met</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC European Society of Cardiology</td>
<td>Aug 2016</td>
<td>To be considered early in the course of the disease to reduce CV and total mortality in patients with T2D and CVD</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC European Society of Cardiology</td>
<td>May 2016</td>
<td>To prevent or delay the onset of HF and prolong life in patients with T2D</td>
</tr>
<tr>
<td>Canadian Heart Failure Council</td>
<td>Nov 2017</td>
<td>To prevent HF-related outcomes in patients with T2D and established CVD</td>
</tr>
</tbody>
</table>
Rationale for exploring empagliflozin for the treatment of heart failure in patients without diabetes

Patients with HF have similar pathophysiological features as patients with diabetes\(^1,2\)

Glucosuria, natriuresis and metabolic effects of empagliflozin are seen in patients with and without diabetes\(^3-5\)

The CV benefits observed in EMPA-REG OUTCOME were largely independent of glucose levels\(^6\)

**Hypothesis:** Patients with HF without diabetes may benefit from empagliflozin

There is mechanistic rationale to investigate the CV outcomes of empagliflozin beyond T2D

---

# FUTURE TRIALS HF – primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Reduced (EF≤40%)</th>
<th>Preserved (EF&gt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPEROR</strong></td>
<td>Time to first event of adjudicated CV death or adjudicated HHF</td>
<td></td>
</tr>
<tr>
<td><strong>EMPERIAL</strong></td>
<td>Change from baseline to week 12 in exercise capacity (6MWT)</td>
<td></td>
</tr>
<tr>
<td><strong>EMPA VISION</strong></td>
<td>Change from baseline to Week 12 in PCr/ATP ratio in resting state measured by 31P-MRS</td>
<td></td>
</tr>
</tbody>
</table>
**Aim:** To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with reduced\(^1\) or preserved\(^2\) ejection fraction.

**Population:** T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)

---

**EMPEROR-Reduced\(^1\)**
- LVEF ≤40%
- Planned recruitment: 2850 patients
- Empagliflozin 10 mg qd + SoC*
- Placebo qd + SoC*
- Estimated follow-up ~38 months (event-driven)

**EMPEROR-Preserved\(^2\)**
- LVEF >40%
- Planned recruitment: 4126 patients
- Empagliflozin 10 mg qd + SoC*
- Placebo qd + SoC*
- Estimated follow-up ~38 months (event-driven)

---

*Guideline-directed medical therapy
HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SoC, standard of care
1. ClinicalTrials.gov NCT03057977; 2. ClinicalTrials.gov NCT03057951
The cardiovascular continuum

- Atherosclerosis
- Coronary artery disease
- LV hypertrophy
- Myocardial ischaemia
- Coronary thrombosis

Myocardial infarction

- Loss of myocardial tissue remodelling
- LV enlargement
- Heart failure
- Arrhythmias
- Ventricular fibrillation
- Sudden death
- Neurohormonal activation

Risk factors
- Smoking
- Obesity/overweight
- Hypertension
- Diabetes
- Dyslipidemia

Atrial fibrillation

End stage heart failure
- Death

HFpEF
HFrEF
Thank you
The effect of empagliflozin on \textbf{CV death} was consistent in patients with and without a history of atherothrombotic events (\textit{MI and/or stroke}).

Cox regression analysis in patients treated with ≥1 dose of study drug. \textit{p}-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple testing.

*Prior atherothrombotic event: history of MI and/or stroke

\textbf{CV}, cardiovascular; \textbf{MI}, myocardial infarction

\textbf{Fitchett D. ACC 2018; oral presentation}

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>\textit{p}-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{All patients}</td>
<td>172/4687 (3.7)</td>
<td>137/2333 (5.9)</td>
<td>0.62 (0.49, 0.77)</td>
<td></td>
</tr>
<tr>
<td>\textbf{Prior atherothrombotic event at baseline*}</td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Yes</td>
<td>131/3048 (4.3)</td>
<td>107/1518 (7.0)</td>
<td>0.60 (0.46, 0.77)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41/1639 (2.5)</td>
<td>30/815 (3.7)</td>
<td>0.69 (0.43, 1.10)</td>
<td></td>
</tr>
</tbody>
</table>
The effect of empagliflozin on **all-cause mortality** was consistent in patients with and without a history of atherothrombotic events (MI and/or stroke).

The effect of empagliflozin on **all-cause mortality** was consistent in patients with and without:

Cox regression analysis in patients treated with ≥1 dose of study drug. *p*-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple testing.

*Prior atherothrombotic event: history of MI and/or stroke

MI, myocardial infarction

Fitchett D. ACC 2018; oral presentation
The effect of empagliflozin on HHF was consistent in patients with and without a history of atherothrombotic events (MI and/or stroke).

Cox regression analysis in patients treated with ≥1 dose of study drug. \( p \)-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple testing.

*Prior atherothrombotic event: history of MI and/or stroke

HHF, hospitalisation for heart failure; MI, myocardial infarction

Fitchett D. ACC 2018; oral presentation