Heart Failure Management in T2 DM
A Practical Approach

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Faculty Disclosure

Faculty: David Fitchett MD,, FRCP(C)
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Relationships with financial sponsors:
CME and Consultation honoraria: Boehringer Ingelheim, Lilly, Astra Zeneca, Novartis, Merck
EMPA Reg Outcome steering committee
DSMB: Sustain 6 and PIONEER 6

Potential for conflict(s) of interest:
Jannsen, Merck, Novartis, AstraZeneca, Servier, Novo Nordisk, Lilly and BI
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Mitigating Potential Bias

• All the recommendations involving clinical medicine are based on evidence that is accepted within the profession.
• All scientific research referred to, reported, or used is in the support or justification of patient care.
• Recommendations conform to the generally accepted standards.
• Independent content validation.
• The presentation will mitigate potential bias by ensuring that data and recommendations are presented in a fair and balanced way.
• Potential bias will be mitigated by presenting a full range of products that can be used in this therapeutic area.
• Information of the history, development, funding, and the sponsoring organizations of the disclosure presented will be discussed.
Diabetes and Heart Failure (HF)

“Heart failure in patients with diabetes is frequent, forgotten and often fatal”

Bell
Central Role of T2 DM in Heart Failure
Age Associated Prevalence of Heart Failure in Diabetic and Non-Diabetic Individuals

Nichols et al Diabetes Care 2004;27:1879
5 Year Survival with Diabetes with and without Heart Failure

**Diabetes increases risk of hospitalization or death due to heart failure**

HFrEF: adjusted HR 1.60
95% CI 1.44–1.77; \( p < 0.0001 \)

HFpEF: adjusted HR 2.0
95% CI 1.70–2.36; \( p < 0.0001 \)

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Heart Failure has a Greater Impact on CV Mortality than MI / Stroke

<table>
<thead>
<tr>
<th></th>
<th>Incidence per 100 patient-yrs</th>
<th>CV mortality (%) After event</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure (HF admission + Investigator reported HF)</td>
<td>3.7</td>
<td>24.2%</td>
<td>61</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.9</td>
<td>21.5%</td>
<td>26</td>
</tr>
</tbody>
</table>

Placebo group of EMPA REG Outcome
3000 Patients with DM and CV Disease
Observed 3 years

Fitchett et al Eur Heart J 2016;
HF was the first manifestation of T2D-related CV disease more often than MI or stroke

Cohort study of patients (n=34,198) with T2D and incidence of CV disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>% event as first CV event</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>16.2%</td>
</tr>
<tr>
<td>HF*</td>
<td>14.1%</td>
</tr>
<tr>
<td>NFMI</td>
<td>11.5%</td>
</tr>
<tr>
<td>CVA</td>
<td>10.3%</td>
</tr>
<tr>
<td>CV death</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

*Heart failure post MI was not included in this definition of HF

CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.
Left ventricular dysfunction occurs in the absence of atherosclerosis

- 68% of patients with T2D had evidence of LV dysfunction 5 years after T2D diagnosis\(^1\)
- Multicentre study evaluating clinical and echocardiographic characteristics of individuals with T2D (n=386)
- Patients had no evidence of inducible ischaemia by stress testing at baseline
- This suggests the earliest defect in the diabetic heart is that of diastolic dysfunction, not atherothrombosis\(^2\)

LV, left ventricular; LVD, LV dysfunction; T2D, type 2 diabetes.
HF remains under-diagnosed in patients with T2D, A high index of suspicion is required

The prevalence of undiagnosed HF was higher:
- With increasing age
- In females
- In patients with BMI ≥30 kg/m²
- In patients with dyspnea
- In patients complaining of fatigue
- In patients with hypertension

Cross-sectional study
605 subjects with T2 DM and no history of HF
ESC Criteria for HF: Judged by expert panel
Echocardiogram: Evidence of diastolic or systolic dysfunction

Unrecognised Heart Failure
- 4.8%
- 22.9%
- 27.7%
95% CI 24-31%

Unrecognised LV dysfunction
- 0.7%
- 25.1%
- 25.8%
95% CI 22-28%

Boonman de Winter et al  Diabetologia 2012;55:2154-62
Cardiovascular Outcomes Have Improved in Diabetes: Heart Failure Remains the Largest CVD Problem

Burns et al Diab Care 2018;42:293-302
Management of Patient with (or at risk for) HF with Diabetes

- Prevention
- Symptomatic
- Guideline recommended treatment to improve survival and prevent HF decompensation
- Diabetes management with agents that
  - reduce risk of HF decompensation
  - Improve survival / Reduce hospital admissions
Heart Failure with Reduced Ejection Fraction

The Building Blocks of Therapy

- Transplant
- VAD
- CRT
- ICD
- Beta Blocker
- ACE Inhibitor
- ARB
- MRA
- Hydralazine / IDN
- Digoxin
- CABG
- LCZ 696
- Ivabradine
- IV Iron

All treatments are equally effective in patients with and without diabetes.
Guideline management of HFpEF focuses on treatment of comorbidities

T2D, hypertension, coronary artery disease, and obesity

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalisation in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

LOE B: date derived from single study or non-randomized studies; LOE C: limited patient population evaluated (case study, consensus).

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; AF, atrial fibrillation; CAD, coronary artery disease; COR, class of recommendation; GDMT, guidelines-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LOE, level of evidence; T2D, type 2 diabetes.

Risk of Heart Failure Related to A1C

Lack of Intensive Glycemic Control on Heart Failure Admission or Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of events (yearly event rate, %)</th>
<th>$\Delta HbA_{1c}$ (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>More intensive: 152 (0.90) Less intensive: 124 (0.75)</td>
<td>-1.01</td>
<td>1.18 (0.93–1.49)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>More intensive: 220 (0.83) Less intensive: 231 (0.88)</td>
<td>-0.72</td>
<td>0.95 (0.79–1.14)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>More intensive: 8 (0.06) Less intensive: 6 (0.11)</td>
<td>-0.66</td>
<td>0.55 (0.19–1.60)</td>
</tr>
<tr>
<td>VADT</td>
<td>More intensive: 79 (1.80) Less intensive: 85 (1.94)</td>
<td>-1.16</td>
<td>0.92 (0.68–1.25)</td>
</tr>
<tr>
<td>Overall</td>
<td>More intensive: 459 Less intensive: 446</td>
<td>-0.88</td>
<td>1.00 (0.86–1.16)</td>
</tr>
</tbody>
</table>

$(Q=3.59, p=0.31, I^2=16.4\%)$
# Glucose Lowering: Impact on Heart Failure

<table>
<thead>
<tr>
<th>Glycemic Agent / Control</th>
<th>benefit</th>
<th>0 neutral</th>
<th>↑ harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td>0</td>
<td></td>
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<tr>
<td>Metformin</td>
<td>? ↓</td>
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<tr>
<td>Sulphonylurea / Glinide</td>
<td>? ↑</td>
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<td>TZD</td>
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<td>↑</td>
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<tr>
<td>DPP4 i</td>
<td></td>
<td>0 (saxagliptin ↑)</td>
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<tr>
<td>GLP1 agonist</td>
<td></td>
<td>0</td>
<td></td>
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<tr>
<td>SGLT2 inhibitor</td>
<td></td>
<td>↓</td>
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</tbody>
</table>
Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial

David Fitchett¹*, Bernard Zinman²³, Christoph Wanner⁴, John M. Lachin⁵, Stefan Hantel⁶, Afshin Salsali⁷, Odd Erik Johansen⁸, Hans J. Woerle⁹, Uli C. Broedl⁹, and Silvio E. Inzucchi¹⁰, on behalf of the EMPA-REG OUTCOME® trial investigators

http://dx.doi.org/10.1093/eurheartj/ehv728
Baseline Characteristics (n= 7034)

- Age 63.1 (9% > 75 yrs)
- Male 72%
- Current / ex smoker 46%
- Diabetes > 10yrs 57%
- eGFR 74 ml/min/1.73m²
  - 26% 30-60 ml/min/1.73m²
- Coronary disease 75%
- Prior MI 47%
- Multivessel CAD 47%
- CABG 25%
- Stroke 23%
- Heart failure 10.5%

Hospitalisation for heart failure

Cumulative incidence function. HR, hazard ratio
Heart failure Hospitalisation and Cardiovascular Mortality

HR 0.66
(95% CI 0.55–0.79)
p<0.001

No. of patients
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634 395
Placebo 2333 2271 2226 2173 1932 1424 1202 775 168
Effects of empagliflozin on various presentations of heart failure

<table>
<thead>
<tr>
<th>Patients with event/analysed (%)</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjudicated HHF</td>
<td>126/4687 (2.7)</td>
<td>95/2333 (4.1)</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td>Investigator-reported heart failure*</td>
<td>204/4687 (4.4)</td>
<td>143/2333 (6.1)</td>
<td>0.70 (0.56, 0.87)</td>
</tr>
<tr>
<td>Introduction of loop diuretics</td>
<td>340/3962 (8.6)</td>
<td>262/1969 (13.3)</td>
<td>0.62 (0.53, 0.73)</td>
</tr>
</tbody>
</table>

Favours empagliflozin
Favours placebo

Cox regression analysis in patients treated with ≥1 dose of study drug.
*Investigator-reported heart failure was based on the narrow standardised MedDRA query ‘cardiac failure’.
HHF, hospitalisation for heart failure.
Fitchett D et al. ESC 2016 Clinical Trial Update (2237)
Hospitalization for HF in patients with HF vs without HF at baseline

HR 0.59  
(95% CI 0.43, 0.82)

HR 0.75  
(95% CI 0.48, 1.19)

Patients hospitalized for heart failure (%)  
Placebo  
Empagliflozin

Cox regression analysis. CI, confidence interval; HR, hazard ratio  
Inzucchi SE. AHA 2015. Oral presentation
Reduction of CV Mortality in Overall Population and in Patients with ‘HF Burden’

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Empagliflozin</th>
<th>HR (95% CI)</th>
<th>CV deaths (%)</th>
<th>Absolute Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>137 / 2333 (5.9%)</td>
<td>172 / 4687 (3.7%)</td>
<td>0.62 (0.49, 0.77)</td>
<td>100%</td>
<td>2.2%</td>
</tr>
<tr>
<td>HF Burden (HFH, HFBL, HFI)</td>
<td>54 / 353 (15.3%)</td>
<td>63/605 (10.4%)</td>
<td>0.67 (0.47, 0.97)</td>
<td>37.9%</td>
<td>4.9%</td>
</tr>
<tr>
<td>No HF burden</td>
<td>83/1980 (4.1%)</td>
<td>109/4082 (2.7%)</td>
<td>0.63 (0.48, 0.84)</td>
<td>62.1%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

44% reduction of CV deaths by Empagliflozin in HF burden patients (15% of population)
### EMPA REG, CANVAS, DECLARE Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Patients enrolled</th>
<th>FU Yrs</th>
<th>MACE ARR</th>
<th>p</th>
<th>Mortality ARR</th>
<th>p</th>
<th>CV mortality /HF ARR</th>
<th>p</th>
<th>HF Hosp ARR</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>EMPA REG</strong></td>
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<tr>
<td>Empagliflozin</td>
<td>CVD</td>
<td>3</td>
<td>1.6%</td>
<td>0.04</td>
<td>2.6%</td>
<td>&lt;0.001</td>
<td>1.04%</td>
<td></td>
<td>1.4%</td>
<td>&lt;0.002</td>
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<td>14%</td>
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<td>32%</td>
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<td>34%</td>
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<tr>
<td><strong>CANVAS</strong></td>
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<tr>
<td>Canagliflozin</td>
<td>CVD + 30% High risk</td>
<td>3.2</td>
<td>1.5%</td>
<td>0.02</td>
<td>0.7%</td>
<td>ns</td>
<td>4.5%</td>
<td></td>
<td>1.0%</td>
<td>&lt;0.05</td>
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<td></td>
<td></td>
<td></td>
<td>14%</td>
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<td>13%</td>
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<td><strong>DECLARE</strong></td>
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<tr>
<td>Dapagliflozin</td>
<td>CVD + 60% High risk</td>
<td>4.3</td>
<td>0.6%</td>
<td>ns</td>
<td>0.4%</td>
<td>ns</td>
<td>1.0%</td>
<td>0.005</td>
<td>0.92%</td>
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<td>17%</td>
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</table>

ARR Absolute risk reduction, RRR Relative risk reduction, HFH Heart failure hospitalisation
## CV Benefits of SGLT2 Inhibition in patients with Established CVD vs Risk Factors only

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Established ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>0.80</td>
<td>(0.71-0.91)</td>
<td>1.02</td>
<td>(0.80-1.30)</td>
</tr>
<tr>
<td>Non fatal MI</td>
<td>0.85</td>
<td>(0.76-0.95)</td>
<td>0.99</td>
<td>(0.79-1.24)</td>
</tr>
<tr>
<td>Non fatal Stroke</td>
<td>0.97</td>
<td>(0.86-1.10)</td>
<td>1.01</td>
<td>(0.80-1.28)</td>
</tr>
<tr>
<td>Heart Failure Hospitalisation</td>
<td>0.71</td>
<td>(0.62-0.82)</td>
<td>0.64</td>
<td>(0.48-0.85)</td>
</tr>
<tr>
<td>CV Death / HFH</td>
<td>0.76</td>
<td>(0.69-0.84)</td>
<td>0.84</td>
<td>(0.69-1.01)</td>
</tr>
</tbody>
</table>

Zelniker et al Lancet 2018
Empagliflozin was associated with a reduced risk of HHF† in routine clinical practice compared with DPP-4i.

HR 0.56
(95% CI 0.43, 0.73)
p<0.0001

1Broad definition HHF data shown  
1:1 propensity score-matched cohorts; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure  
Patorno E et al. AHA 2018; poster 1112
**HHF in EMPRISE**  
Suggests Patients with and without CVD Benefit from EMPAGLIFLOZIN

<table>
<thead>
<tr>
<th>Study</th>
<th>Empagliflozin</th>
<th>Comparator</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPRISE</strong> (empagliflozin vs DPP-4i in Real World Setting)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td>83/17,539 (0.5)</td>
<td>10.5</td>
<td>150/17,539 (0.9)</td>
</tr>
<tr>
<td>Without CVD</td>
<td>17/13,243</td>
<td>2.8</td>
<td>47/13,243</td>
</tr>
<tr>
<td>With CVD</td>
<td>63/4,217</td>
<td>35.2</td>
<td>120/4,217</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. †Broad definition HHF data shown

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure; MI, myocardial infarction; PY, patient-years; RCT, randomised controlled trial; RWE, real-world evidence;

Impact of SGLT2i on CV Outcomes by the presence or absence of established CVD

Cardiorenal efficacy of SGLT2i

Renal protection

Hospitalisation for heart failure

Major adverse cardiovascular events

Secondary prevention population
SGLT2i prevent heart failure and renal disease, and reduce atherosclerotic events (major adverse cardiovascular events)

Diabetes and established cardiovascular disease

Primary prevention population
SGLT2i prevent heart failure and renal disease but may not reduce major adverse cardiovascular events

Diabetes and multiple risk factors

Verma et al Lancet 2018
Recent guidelines recognise empagliflozin for the prevention or delay of heart failure in T2D

- ESC Heart Failure Association position statement – February 2018

Prevention of heart failure by type 2 antidiabetic drugs (p12)

“A significant breakthrough in contemporary cardiology was the finding that some T2DM drugs are associated with a lower risk of HF hospitalization in patients with CV disease or at high risk of CV disease.”

Three large RCTs that assessed CV safety of the sodium–glucose co-transporter type 2 (SGLT2) inhibitors, empagliflozin and canagliflozin, have shown a significant reduction in HF hospitalization with both drugs”

Empagliflozin is not indicated for the treatment of heart failure
CV, cardiovascular; HF, heart failure; RCT, randomised controlled trial; T2DM, type 2 diabetes
Seferovic PM et al. Eur J Heart Failure 2018;20:853
Consider SGLT2i in patients with Multiple CV Risk Factors

ADA /EASD Guidelines 2018

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY) IF HbA1c ABOVE TARGET PROCEED AS BELOW

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/ OR

GLP-1 RA with proven CVD benefit

SGLT2i with proven CVD benefit, if eGFR adequate

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVD 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

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
- SU

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

TO AVOID CLINICAL INERTIA REASSES AND MODIFY TREATMENT REGULARLY (3-4 MONTHS)
Heart Failure Risk Assessed by ABC Heart Failure Risk Score

ABC Heart failure Score

Parameters

- Age
- Coronary heart disease
- SBP
- Heart rate
- ECG LVH
- Smoking
- Albumin level
- Fasting glucose
- Creatinine

Butler et al Circ HF 2008;1:125

Heart Failure Hospitalisation / CV Mortality

ABC HF Risk
- <10%
- 10-20%
- >20%

Heart Failure / CV Mortality Risk /1000

Butler et al Circ HF 2008;1:125

Fitchett et al Eur Heart J 2018;39:313
EMPEROR-Reduced and EMPEROR-Preserved Heart Failure Outcome Trials

1. EMPEROR-Reduced
   - HF with Reduced Ejection Fraction (HFrEF)
     - T2D and non-T2D
     - Event driven trial
     - 2850 pts

2. EMPEROR-Preserved
   - HF with Preserved Ejection Fraction (HFpEF)
     - T2D and non-T2D
     - Event driven trial
     - 4126 pts

1. NCT03057977 2. NCT03057951 www.clinicaltrials.gov
Take Home Messages

- SGLT2 inhibitors in patients with established CVD
  - All reduce HF / CV mortality, HFH, CKD
  - Empagliflozin reduces CV mortality

- SGLT2 inhibitors in patients with T2 DM with CVD risk factors reduce heart failure and stabilise CKD

- SGLT2 inhibitors should be more widely used in patients with both established CVD and with CV risk factors only, to prevent heart failure and stabilise renal function