Update on SGT2 Inhibition in Type 2 Diabetes

A Closer Look at EMPA REG OUTCOMES

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University of Toronto
Update on SGLT2 Inhibition and CV Outcomes

- Summary of EMPA REG Result
- How does it compare to other CVD prevention trials
- Can we believe the results?
- What is the mechanism? Does it matter?
- Is the benefit a class effect?
- Would the same benefits be seen in a lower risk population?
- Can the results of EMPA Reg be extrapolated to the Asian population?
- Are the adverse effects seen with other SGLT2i seen with Empagliflozin?
- Comparison of Liraglutide and Empagliflozin CV outcome trials
Primary outcome: 3-point MACE
Cardiovascular Mortality, Non-fatal MI, Non-fatal Stroke

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

* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)
### CV death, MI and stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687 – 282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687 – 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 – 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 – 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

CV death

Cumulative incidence function.
CI, confidence interval; 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
Renal Outcomes with Empagliflozin

- Slows progression of CKD
  - Preserves eGFR
  - Reduces
    - Development of albuminuria
    - Doubling of creatine
    - Need for dialysis

HR = 0.58
95% CI 0.47-0.71
What does EMPA-REG Outcomes Trial tell us?

1. Empagliflozin meets CVD safety standards set by regulators
   – Can be used safely in wide range of patients for glycemic control

2. Empagliflozin in patients with established CVD reduces CV mortality, heart failure outcomes and progression of chronic kidney disease
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin\(^1\) for 5.4 years

- High CV risk
- 5% diabetes, 26% hypertension

Ramipril\(^2\) for 5 years

- High CV risk
- 38% diabetes, 46% hypertension

Empagliflozin for 3 years

- T2DM with high CV risk
- 92% hypertension

Pre-ACEi/ARB era

- >80% ACEi/ARB

Pre-statin era

- <29% statin

Discussion

• Are the results too good to be true?
• Is it a class effect?
• What is the mechanism?
Is the Mortality Benefit With Empagliflozin in Type 2 Diabetes Mellitus Too Good To Be True?

Sanjay Kaul, MD

CIRCULATION 2016;134:94-96
Strengths of EMPA REG OUTCOME Trial

• The mortality benefit is large and clinically important
  – 2.6% absolute and 32% relative risk reduction
• The mortality risk reduction is statistically robust
  – P<0.001 for both all cause and CVD mortality
• The mortality benefit is based on a large number of events
  – 463 all cause and 309 CV deaths
• A consistent benefit is seen with both doses.
  – All cause mortality 10mg RRR 30%, 25 mg RRR 33%
  – CV mortality 10mg RRR 35%, 25mg RRR 41%
### Evaluating Strength of Evidence of Cardiovascular Outcomes in EMPA-REG OUTCOME Using Bayes Factor

<table>
<thead>
<tr>
<th>End Point</th>
<th>P Value (z Score)</th>
<th>Minimum Bayes Factor</th>
<th>Decrease in Probability of Null Hypothesis, %</th>
<th>Strength of Evidence</th>
<th>Effect Size, HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Point MACE</td>
<td>0.038 (2.02)</td>
<td>0.131</td>
<td>From: 95 to 54</td>
<td>Moderate</td>
<td>0.86</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>From: 75 to 28</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>From: 50 to 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.0001 (3.94)</td>
<td>0.0006</td>
<td>From: 95 to 0.49</td>
<td>Very strong</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From: 75 to 0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From: 50 to 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.0001 (3.87)</td>
<td>0.0004</td>
<td>From: 95 to 0.38</td>
<td>Very Strong</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From: 75 to 0.13</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>From: 50 to 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.0017 (2.93)</td>
<td>0.0137</td>
<td>From: 95 to 11</td>
<td>Strong</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From: 75 to 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From: 50 to 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is the CV / Renal Benefit of SGLT2 Inhibitors a Class Effect?

Uncertain

• Different SGLT2/ SGLT1 specificity
  – Empagliflozin 5000
  – Dapagliflozin 1400
  – Canagliflozin 160

• Limited value of meta-analyses

• ? Different safety profile
Meta-analysis of SGLT2 Trials and CV Outcomes

<table>
<thead>
<tr>
<th></th>
<th>SGLT2 inhibitor (n/N)</th>
<th>Control (n/N)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>104/6396</td>
<td>62/3403</td>
<td>1.02 (0.74–1.42)</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>73/5936</td>
<td>62/3403</td>
<td>0.67 (0.48–0.94)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>Ipragliflozin</td>
<td>7/628</td>
<td>10/368</td>
<td>0.41 (0.16–1.07)</td>
</tr>
<tr>
<td>(I²=43%)</td>
<td></td>
<td></td>
<td>0.84 (0.75–0.95)</td>
</tr>
<tr>
<td><strong>MACE plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>130/6395</td>
<td>71/3327</td>
<td>0.95 (0.72–1.27)</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>97/5936</td>
<td>81/3403</td>
<td>0.69 (0.51–0.92)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>621/7082</td>
<td>359/3547</td>
<td>0.87 (0.77–0.98)</td>
</tr>
<tr>
<td>(I²=24%)</td>
<td></td>
<td></td>
<td>0.85 (0.77–0.95)</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>21/6396</td>
<td>16/3327</td>
<td>0.68 (0.36–1.31)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.50–0.78)</td>
</tr>
<tr>
<td>(I²=0%)</td>
<td></td>
<td></td>
<td>0.63 (0.51–0.77)</td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>45/6396</td>
<td>27/3327</td>
<td>0.87 (0.54–1.39)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.88 (0.70–1.09)</td>
</tr>
<tr>
<td>(I²=0%)</td>
<td></td>
<td></td>
<td>0.88 (0.72–1.07)</td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>47/6396</td>
<td>16/3327</td>
<td>1.53 (0.87–2.69)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.93–1.67)</td>
</tr>
</tbody>
</table>

Wu et al  Lancet Diab Endo 2016;4:411-6
### Meta-analysis of SGLT2 Trials and Adverse Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Data from regulatory submissions</th>
<th>Data from scientific reports</th>
<th>Relative risk (95% CI)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>1419/19835</td>
<td>1852/17096</td>
<td>1.15 (1.06-1.26)</td>
<td>0</td>
</tr>
<tr>
<td>Genital infection</td>
<td>1243/19835</td>
<td>1419/19702</td>
<td>4.75 (4.00-5.63)</td>
<td>59%*</td>
</tr>
<tr>
<td>Cancer</td>
<td>253/25071</td>
<td>13/1865</td>
<td>1.07 (0.85-1.34)</td>
<td>0</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>301/19120</td>
<td>254/8469</td>
<td>0.99 (0.82-1.21)</td>
<td>29%</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>505/19835</td>
<td>438/14402</td>
<td>1.53 (1.27-1.83)</td>
<td>40%</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>26/13375</td>
<td>30/4687</td>
<td>1.54 (0.63-3.79)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2283/18147</td>
<td>3204/19260</td>
<td>1.00 (0.94-1.07)</td>
<td>67%*</td>
</tr>
<tr>
<td>Acidosis</td>
<td>1/1630</td>
<td>4/4687</td>
<td>0.57 (0.02-14.10)</td>
<td>NA</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>145/20973</td>
<td>292/7075</td>
<td>1.21 (0.91-1.62)</td>
<td>10%</td>
</tr>
</tbody>
</table>

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Wu et al. Lancet Diab Endo 2016;4:411-6
Other Adverse Outcomes

• Amputations
  – CANVAS: Increased rate of toe amputations
  – No cause found
  – Not observed with empagliflozin or dapagliflozin
  – EMA: a class effect cannot be excluded at the moment

• DKA
  – No increase in clinical trials
  – Post marketing events occur infrequently
  – Causality of SGLT2 I uncertain
  – Awareness of possible diagnosis of normoglycemic DKA
Mechanisms of Benefit of Empagliflozin

EMPA REG OUTCOME was a clinical trial and not a mechanistic study

• Should not limit application of drug

• Many drugs have unclear mechanisms of benefit
  – Metformin: reduction of blood glucose and CV events
  – Liraglutide and reduction of CV mortality
  – Saccubitril / Valsartan : Reduction of CV mortality
EMPA-REG OUTCOME®: Explaining Findings
Should We Even Attempt to Explain an ‘Unexpected’ Outcome?

Mortality Benefit

- Large prompt effect on CVD and HF
  - Consistent with previous HF trials
    - EPHESUS, PARADIGM (RAAS)

- Time to onset too rapid
  - BP differential too small (4 mmHg)
  - No stroke benefit
  - Inconsistent with previous trials (ACCORD-BP)

- Too rapid an onset

- Weight contrast too small (1-2 kg)
  - No outcome benefit shown with weight loss previously (LOOK AHEAD)

- Volume Depletion/antiarrhythmic

- Glycemic control
  - Glycemic differential too small (0.3%)
  - Inconsistent with previous trials

- Time to onset too rapid
  - BP differential too small (4 mmHg)
  - No stroke benefit
  - Inconsistent with previous trials (ACCORD-BP)

- Weight contrast too small (1-2 kg)
  - No outcome benefit shown with weight loss previously (LOOK AHEAD)
Change of Hematocrit with Empagliflozin
Possible Mechanism of the Cardiovascular Benefit of Empagliflozin

**Circulation**
- \( \downarrow \) Intravascular/ECF volume
- \( \uparrow \) Haematocrit (thus, haemoconcentration)
- \( \downarrow \) Systolic blood pressure

**Kidney: SGLT2 inhibition**
- \( \uparrow \) Urinary glucose loss
- \( \uparrow \) Urinary sodium loss + Diuresis
- \( \uparrow \) Glucose and sodium reabsorption in proximal tubule (improved tubular glomerular feedback)
- Improved renal function

**Heart (+ lungs)**
- \( \downarrow \) Cardiac afterload
- \( \downarrow \) Cardiac pre-load
- \( \uparrow \) Myocardial oxygen supply
- \( \pm \) Improved cardiac metabolism?
- \( \Rightarrow \) Improvement in systolic and diastolic dysfunction
- \( \downarrow \) Likelihood of pulmonary congestion
- \( \Rightarrow \) Lower risk of HFH
- \( \Rightarrow \) Lower risk of fatal arrhythmias

Sattar et al Diabetologia 2016 In Press
Mediation Analysis

1. Initial inquiry into potential mechanisms suggests that ↑ hematocrit (↓ plasma volume?) may be a key but partial factor in the drug’s effect.

2. In contrast, changes in glucose, BP, lipids and weight appear to have little or no effect.

3. Unable to assess the alternative metabolic pathways proposed by some experts.

Presented at ADA New Orleans 2016
Does Diuresis Reduce CV Mortality?

• Diuretic Clinical Trials
  – Hypertension
    • Magnitude of BP lowering more important than agent
    • Diuretics probably most effective first line agent to prevent CVD morbidity and mortality
    • Stroke and CHF more reduced than mortality
    • MACE benefits seen with > 3 years diuretic treatment
  – Heart Failure
    • No loop diuretic trials
    • MRAs
      – Early MACE / mortality / heat failure benefit
Early Mortality Benefit of Mineralocorticoid Inhibitors

**RALES**  
Spironolactone in HFrEF

**EMPHASIS:**  
Eplerenone in HFrEF and Mild symptoms

### Survival

- **HR 0.70 (95% CI 0.60-0.82)**

![Survival Curve](Image)


### Heart failure Death or Hospitalisation for HF

- **Hazard ratio, 0.63 (95% CI, 0.54–0.74)**

  - Placebo
  - Eplerenone

![Hospitalization Curve](Image)

Changes in Myocardial Fuel Metabolism with SGLT2 Inhibitors

T2DM Heart
- ↑ Fat Oxidation
- ↓ Glucose Oxidation
- ↓ P/O Ratio
- ↓ Cardiac Work Efficiency

Myocardial Contractility

With SGLT2i Treatment

↓ Fat Oxidation
- ↑ Glucose Oxidation
- ↑ BHOB Ox
- ↑ P/O Ratio
- ↑ Cardiac Work Efficiency

Myocardial Contractility

↑ Incidence/Progression of Heart Failure

↓ Incidence/Progression of Heart Failure

Mudaliar et al  Diabetes Care 2016;39:1115
Is the Reduction of CV Mortality mainly in Patients with Heart Failure?

• High CV mortality in patients with HF
  – Baseline HF 11.1% vs No HF <sub>BL</sub> 5.3%
  – HH Hospitalisation 24.5% vs No HF <sub>H</sub> 5.3%
# Impact of Empagliflozin on CV Mortality in Patients with Heart Failure

<table>
<thead>
<tr>
<th>HF subgroup</th>
<th>Placebo</th>
<th>Empagliflozin</th>
<th>P-value</th>
<th>HR (95% CI)</th>
<th>% of all CV deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF at Baseline N=706 (HF&lt;sub&gt;BL&lt;/sub&gt;)</td>
<td>27/244 (11.1%)</td>
<td>38/462 (8.2%)</td>
<td>0.167</td>
<td>0.71 (0.43, 1.16)</td>
<td>21.0%</td>
</tr>
<tr>
<td>HF Hospital Adm N=221 (HHF)</td>
<td>23/95 (24.2%)</td>
<td>18/126 (14.3%)</td>
<td>0.182</td>
<td>0.65 (0.35, 1.22)</td>
<td>13.3%</td>
</tr>
<tr>
<td>HF Inv reported N=347 (HF&lt;sub&gt;AE&lt;/sub&gt;)</td>
<td>38/143 (26.6%)</td>
<td>36/204 (17.6%)</td>
<td>0.180</td>
<td>0.73 (0.46, 1.16)</td>
<td>23.9%</td>
</tr>
<tr>
<td>HF&lt;sub&gt;BL&lt;/sub&gt;, HHF or HF&lt;sub&gt;AE&lt;/sub&gt; (N=958)</td>
<td>54/353 (15.3%)</td>
<td>63/605 (10.4%)</td>
<td>0.034</td>
<td>0.67 (0.47, 0.97)</td>
<td>37.9%</td>
</tr>
</tbody>
</table>

Empa Reg: 137 / 2333 (5.9%) 172/4687 (3.7%) <0.001 0.62 (0.49-0.77) 100%
Is the Reduction of CV Mortality in Patients with Heart Failure?

- HF related CV deaths 38% of total CV deaths yet in only 15% of population
- Reduction of CV deaths in the 958 HF patients by empagliflozin accounts for almost half (44%) of reduced CV mortality in the overall 7020 patients

**Conclusions**

Reduction of mortality with empagliflozin occurs in patients with and without HF

Large proportion of benefit in patients with heart failure signal
Stroke and Empagliflozin

Stroke rates

- Placebo 3.0% (69/2333)  Empagliflozin 3.5% (164/4687)
- HR 1.18 (95% CI 0.89-1.56)

Ischemic stroke
Placebo 2.7%  Empagliflozin 3.2%

Haemorrhagic stroke
Placebo 0.3%  Empagliflozin 0.2%
Stroke Rates with Empagliflozin

All Strokes

Censored at 90 days after last treatment

HR 1.18
(95% CI 0.89, 1.56)
p=0.26

HR 1.08
(95% CI 0.81, 1.45)
p=0.60
# Stroke and Empagliflozin Sensitivity Analysis

## Patients with event/analysed (%)

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal or non-fatal stroke</strong></td>
<td></td>
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<tr>
<td>Modified intent-to-treat analysis*</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treated set</td>
<td>164/4687 (3.5)</td>
<td>69/2333 (3.0)</td>
<td>1.18</td>
<td>(0.89, 1.56)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated set + 90 days†</td>
<td>146/4687 (3.1)</td>
<td>66/2333 (2.8)</td>
<td>1.08</td>
<td>(0.81, 1.45)</td>
<td>0.60</td>
</tr>
<tr>
<td>Treated set + 30 days†</td>
<td>143/4687 (3.1)</td>
<td>66/2333 (2.8)</td>
<td>1.06</td>
<td>(0.79, 1.41)</td>
<td>0.71</td>
</tr>
<tr>
<td>Treated set + 7 days†</td>
<td>139/4687 (3.0)</td>
<td>62/2333 (2.7)</td>
<td>1.09</td>
<td>(0.81, 1.48)</td>
<td>0.55</td>
</tr>
<tr>
<td>On-treatment set‡</td>
<td>141/4607 (3.1)</td>
<td>66/2308 (2.9)</td>
<td>1.04</td>
<td>(0.78, 1.40)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

## Timing of Stroke

- **> 90 days after stopping treatment**
  - Empa 18
  - Placebo 3
- **> 1 year after stopping treatment**
  - Empa 13
  - Placebo 1
Stroke and Empagliflozin
Conclusions

• Stroke not significantly increased by empagliflozin
• Mortality benefit greatly exceeds any possible small risk of stroke
  Impact on 1000 patients treated for 3 years
  – Mortality  25 less deaths
  – Stroke   Possibly 6 increased events
• No association with
  – Increase in hematocrit
  – Volume depletion symptoms
• Excess of strokes occurs long after treatment discontinued
  – Why was treatment discontinued in these patients
  – ? Increased atrial fibrillation
Would the same benefits be seen in a lower risk population?

- Unknown

- But empagliflozin effective glucose lowering agent with
  - weight loss and
  - very low risk for hypoglycemia and
  - excellent safety profile in high risk CV patients
  - may have CVD benefit in lower risk population
Can the results of EMPA REG Outcome be Extrapolated to an Asian Population

### CV Mortality

<table>
<thead>
<tr>
<th>Region</th>
<th>Empa</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>80/1926</td>
<td>56/959</td>
<td>0.72 (0.51, 1.01)</td>
</tr>
<tr>
<td>N Am Australia</td>
<td>40/932</td>
<td>25/462</td>
<td>0.81 (0.49, 1.33)</td>
</tr>
<tr>
<td>Latin America</td>
<td>22/721</td>
<td>24/360</td>
<td>0.43 (0.24, 0.77)</td>
</tr>
<tr>
<td>Africa</td>
<td>12/211</td>
<td>7/102</td>
<td>0.80 (0.31, 2.03)</td>
</tr>
<tr>
<td>Asia (19%)</td>
<td>18/897</td>
<td>25/450</td>
<td>0.35 (0.19, 0.65)</td>
</tr>
<tr>
<td>EMPA REG</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
</tbody>
</table>
LEADER vs EMPA REG Outcomes
Comparison of CV Mortality

Hazard ratio 0.78 (95%CI 0.66-0.93)
P=0.007

## Comparison of LEADER and EMPA-REG

<table>
<thead>
<tr>
<th></th>
<th>LEADER</th>
<th>EMPA REG Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Known CVD or High risk</td>
<td>Known CVD</td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
<td>3.8 years</td>
<td>3 years</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Triple MACE</td>
<td>Triple MACE</td>
</tr>
<tr>
<td><strong>Major impact</strong></td>
<td>CV death (↓ 22%) MI Stroke ns</td>
<td>CV Death (↓ 38%) MI, Stroke ns</td>
</tr>
<tr>
<td><strong>NNT mortality (3yrs)</strong></td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td><strong>Time to benefit</strong></td>
<td>&gt; 12 months</td>
<td>Very early (&lt; 3 months)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>No significant impact</td>
<td>Reduced 35%</td>
</tr>
<tr>
<td><strong>Renal benefit</strong></td>
<td>? impact on progression of renal disease</td>
<td>Slows progression of renal disease</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>? Increased pancreatic Ca</td>
<td>No increase detected</td>
</tr>
</tbody>
</table>
## Comparison of Liraglutide and Empagliflozin

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents</strong></td>
<td>Daily injectable</td>
<td>Oral medication</td>
</tr>
<tr>
<td><strong>Efficacy A1C lowering</strong></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>GI 2.5%</td>
<td>Genital infections 0.5%</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>~$10 / day</td>
<td>~$2.50/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT for all cause mortality /3 years</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Cost / life saved</td>
<td>$1,400,000</td>
<td>$120,000</td>
</tr>
</tbody>
</table>
Prevention of Cardiovascular Disease?
Pharmacological Management of Type 2 Diabetes

4. In people with clinical cardiovascular disease in whom glycemic targets are not met, an SGLT2 inhibitor with demonstrated cardiovascular outcome benefit should be added to antihyperglycemic therapy to reduce the risk for cardiovascular and all-cause mortality (Grade A, Level 1A for empagliflozin)
## Recommendations for the Prevention of Heart Failure or Death

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

2016 ESC Guidelines for the Diagnosis and treatment of on Acute & Chronic Heart Failure
In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.
Empagliflozin is a Cardiovascular Drug with a Side Effect of Reducing blood Glucose

• What is the role of medical specialists in diabetes management?
• Should cardiologists prescribe / recommend empagliflozin?
Diabetes and Coronary Heart Disease
Prevalence Depends on Perspective

Cardiologist
Diabetes in Patients with CAD
50%

Diabetologist
CAD in Patients with Diabetes
15%
Who sees the most patients who will benefit from Empagliflozin or Liraglutide for CVD risk Reduction?

• **GPs**
  - General population > 20 yrs old ~10% have diabetes
  - Of the patients with diabetes ~10-20% have CVD
  - ~1-2% of patients are potentially candidates

• **Diabetologists / Endocrinologists**
  - All have DM 90% T2 DM
  - ~20% have CVD
  - 15-20% have GFR < 30
  - 10-15% of patients are potential candidates

• **Cardiologists**
  - 40-50% of patients have T2 DM
  - 95% have CVD
  - 10% have CKD
  - 40% of patients are potential candidates
Role of Cardiologist in Glucose Control in 2016

- To identify patients with diabetes
- To monitor glycemic control to targets
- To optimise choice of glucose lowering drugs to reduce cardio-renal adverse outcomes
  - Use agents with proven CV benefit
    - Empagliflizin, Liraglutide
  - Use agents with proven CV safety
    - Metformin, Saxagliptin, Sitagliptin, Alogliptin, Lixisenatide
  - Avoid agents with CV safety concerns or no adequate data
    - Sulphonylureas, TZDs (for HF)
- Either prescribe optimal glucose lowering agent
- Or Recommend primary diabetes care MD makes changes
Conclusions

- Benefits of empagliflozin in high CVD risk t2 DM patients is large and real
- Mortality reduction in patients with and without HF signal
- Stroke not significantly increased. Any increase greatly overwhelmed by reduction of mortality
- Mechanism of benefit speculative: should not influence application
- Adverse outcomes infrequent: need for vigilance