Heart failure and SGLT2 inhibitors: With or without diabetes?

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow.
Diabetes and heart failure

- Heart failure is one of the most common cardiovascular complications of diabetes. Diabetes is very common in heart failure.
- Heart failure is the most disabling and deadly complication of diabetes – patients with both conditions do especially badly.
- (Do treatments for heart failure work as well in patients with diabetes as they do in those without?)
- Treatments for diabetes may increase or decrease the risk of developing heart failure.
- What is the effect of glucose-lowering therapy in patients with established heart failure?
Prevalence of diabetes in HF

- Registers/administrative data/observational cohorts
- Clinical trials
HFrEF: Prevalence of diabetes
HFpEF: Prevalence of diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-Preserved</td>
<td>28%</td>
</tr>
<tr>
<td>I-Preserve</td>
<td>27%</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>32%</td>
</tr>
<tr>
<td>PARAGON-HF</td>
<td>43%</td>
</tr>
</tbody>
</table>

* TOPCAT – Americas 45%
PARADIGM-HF: Dys-glycaemia in heart failure

8274 patients with HF-REF randomized in PARADIGM-HF. Diabetes = investigator reported diagnosis. Undiagnosed diabetes = no diagnosis of diabetes and HbA1c ≥ 6.5%. Pre-diabetes = no diabetes and HbA1c 6.0-<6.5% (caveat: single HbA1c measurement)
CHARM programme: Dysglycemia (biomarker subgroup USA & Canada)

HFrEF (n=1578)
- Normoglycemic: 35%
- Prediabetes: 26%
- Undiagnosed diabetes: 16%
- Diabetes: 22%

HFpEF (n=1072)
- Normoglycemic: 40%
- Prediabetes: 22%
- Undiagnosed diabetes: 18%
- Diabetes: 20%
New onset diabetes in heart failure (CHARM)
Diabetes and heart failure

- Heart failure is one of the most common cardiovascular complications of diabetes/diabetes is very common in heart failure.
- Heart failure is the most disabling and deadly complication of diabetes – patients with both conditions do especially badly.
- (Do treatments for heart failure work as well in patients with diabetes as they do in those without?)
- Treatments for diabetes may increase or decrease the risk of developing heart failure.
- What is the effect of glucose-lowering therapy in patients with established heart failure?
PARADIGM-HF: Dys-glycaemia in heart failure

8274 patients with HF-REF randomized in PARADIGM-HF. Diabetes = investigator reported diagnosis. Undiagnosed diabetes = no diagnosis of diabetes and HbA1c ≥ 6.5%. Pre-diabetes = no diabetes and HbA1c 6.0-<6.5% *(caveat: single HbA1c measurement)*
PARADIGM-HF: Outcome according to glycaemic status at baseline

Primary composite outcome

Log rank
P <0.001

Diabetes
Pre-diabetes
Normal
Diabetes and heart failure

- Heart failure is one of the most common cardiovascular complications of diabetes/diabetes is very common in heart failure.

- Heart failure is the most disabling and deadly complication of diabetes – patients with both conditions do especially badly.

- *(Do treatments for heart failure work as well in patients with diabetes as they do in those without?)*

- Treatments for diabetes may increase or decrease the risk of developing heart failure.

- What is the effect of glucose-lowering therapy in patients with established heart failure?
## Summary of CV effects of treatments for diabetes in recent trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary MACE</th>
<th>All-cause death</th>
<th>CV death</th>
<th>MI</th>
<th>stroke</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Saxagliptin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>• Sitagliptin</td>
<td>-</td>
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<tr>
<td>• Alogliptin</td>
<td>-</td>
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<tr>
<td><strong>SGLT-2 inhibitors</strong></td>
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</tr>
<tr>
<td>• Empagliflozin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>• Canagliflozin</td>
<td>↓</td>
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<td><strong>GLP-1 RA</strong></td>
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<tr>
<td>• Liraglutide</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>• Semaglutide</td>
<td>↓</td>
<td>-</td>
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<td>-</td>
<td>→</td>
</tr>
<tr>
<td>• Exenatide</td>
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<tr>
<td>• Lixisenatide</td>
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</tr>
</tbody>
</table>
SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?
EMPA-REG OUTCOME

7,020 patients with T2DM and CV disease

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

### EMPA-REG OUTCOME: Primary endpoint

<table>
<thead>
<tr>
<th>Event/Analysed Outcome</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</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>
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<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>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>

*Significant difference

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The key findings in EMPA-REG OUTCOME

Cardiovascular mortality

Heart failure Hospitalization

Major completed SGLT-2 inhibitor trials

**EMPA-REG Outcome**

7,020 patients with T2DM and CV disease

**CANVAS Program**

CANVAS n=4,330 and CANVAS-R n=5812: ≥30 years with atherothrombotic CV disease or ≥50 years with ≥2 CV risk factors

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Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators


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**Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes**

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

*The New England Journal of Medicine*
**CANVAS compared with EMPA-REG OUTCOME**

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>CANVAS Program</td>
</tr>
<tr>
<td>CV death</td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td></td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Progression to macroalbuminuria*</td>
<td></td>
</tr>
<tr>
<td>Renal composite*</td>
<td></td>
</tr>
</tbody>
</table>

*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.*

[Hazard ratio graph with endpoints compared](http://www.georgeinstitute.org/sites/default/files/canvas-study-results-ada-2017.pdf)
**SGLT-2 inhibitors: Large mortality/morbidity trials in type 2 diabetes (excluding CKD and HF trials)**

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG</th>
<th>CANVAS (-R)</th>
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<td>NCT01032629</td>
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<td>NCT01986881</td>
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<td>SGLT2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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<tr>
<td>Patients</td>
<td>CVD</td>
<td>CV risk factors</td>
<td>CV risk factors</td>
<td>CVD</td>
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<td>/CVD</td>
<td>/CVD</td>
<td></td>
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<tr>
<td>Number of</td>
<td>7020</td>
<td>4430</td>
<td>17276</td>
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<tr>
<td>patients</td>
<td></td>
<td>5812</td>
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<tr>
<td>Results</td>
<td>Completed</td>
<td>Completed</td>
<td>2018</td>
<td>2019</td>
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</table>
SGLT-2 inhibitors: Key questions

- What type of heart failure prevented?
- What is the mechanism of benefit?
- Can they be used to treat established (prevalent) heart failure (as opposed to preventing incident heart failure)?
SGLT-2 inhibitors: Key questions

- What type of heart failure prevented?
- What is the mechanism of benefit?
- Can they be used to treat established (prevalent) heart failure (as opposed to preventing incident heart failure)?
Anti-diabetes drugs and prevention of CV events

- "Metabolic" effect
- Diuretic/hemodynamic effect

Months  Years  Decades

Decrease in CV events

adapted from Tanaka A, Node K. J Cardiol. 2017 Mar; 69(3): 501-507
SGLT2 inhibitors: How do they work?

"The metabolodiuretic promise of SGLT2 inhibition: The search for the sweet spot in heart failure"

- Na+/H+ exchanger
- CaMKII/RyR2 activity
- ATP
- Myocardial Energetics
- β-hydroxybutyrate (ketone body)
- Afterload
- LV wall stress
- Diuresis
- Natruresis
- Glycosuria
- Proteinuria
- Afferent arteriole
- Effluent arteriole
- Afferent arteriolar dilatation
- Decrease in afferent arteriolar pressure
- Na⁺/glucose cotransport
- SGLT2 Inhibitors cause effluent arteriolar constriction

Adapted from Verma, McMurray & Cherney JAMA Cardiol. 2017; 2:939-940
SGLT2 inhibition: Vascular function and central haemodynamics

- double-blind, crossover RCT.
- 76 patients aged 18–75 years with T2DM diagnosed type 2 diabetes mellitus were randomized to
- 6 weeks empagliflozin 25 mg qd/6 weeks placebo
- central systolic pressure and central pulse pressure, radial artery waveforms were recorded by the SphygmoCor System
- Ambulatory BP/derived central aortic pressure (Mobilograph)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central systolic pressure</td>
<td>114 ± 12</td>
<td>119 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central pulse pressure</td>
<td>39.5 ± 9.9</td>
<td>42.2 ± 11</td>
<td>0.012</td>
</tr>
<tr>
<td>Forward wave amplitude</td>
<td>27.2 ± 5.4</td>
<td>29.1 ± 6.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Reflected wave amplitude</td>
<td>19.1 ± 5.7</td>
<td>20.4 ± 6.1</td>
<td>0.026</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h central systolic pressure</td>
<td>117 ± 9.0</td>
<td>119 ± 8.7</td>
<td>0.059</td>
</tr>
<tr>
<td>24-h central diastolic pressure</td>
<td>79.0 ± 6.9</td>
<td>80.7 ± 7.2</td>
<td>0.011</td>
</tr>
<tr>
<td>24-h pulse wave velocity</td>
<td>8.76 ± 1.0</td>
<td>8.81 ± 1.0</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Striepe et al Circulation. 2017;136:1167–1169
Effect of canagliflozin on cardiac biomarkers in older individuals with T2DM (change from BL)

**NT-pro BNP**

<table>
<thead>
<tr>
<th>Time point (wk)</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>187</td>
<td>402</td>
</tr>
<tr>
<td>52</td>
<td>165</td>
<td>389</td>
</tr>
<tr>
<td>104</td>
<td>155</td>
<td>341</td>
</tr>
</tbody>
</table>

Median percent change (±SE) from baseline in NT-proBNP:
- Placebo: -15.0% (-27.4, -3.3)*
- Canagliflozin: -16.1% (-28.8, -3.8)*
- Canagliflozin: -26.8% (-42.3, -10.7)**

**hsTnI**

<table>
<thead>
<tr>
<th>Time point (wk)</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>172</td>
<td>343</td>
</tr>
<tr>
<td>52</td>
<td>145</td>
<td>328</td>
</tr>
<tr>
<td>104</td>
<td>140</td>
<td>293</td>
</tr>
</tbody>
</table>

Median percent change (±SE) from baseline in hsTnI:
- Placebo: -8.3% (-14.0, -2.5)**
- Canagliflozin: -11.9% (-18.0, -5.6)**
- Canagliflozin: -10.0% (-17.3, -2.6)**

*Januzzi et al J Am Coll Cardiol 2017;70:704–12*
Outcomes in HFrEF (BEST) according to microvascular complications status

CV death or heart failure hospitalization

- Diabetes + complications
- Diabetes + No complications
- No diabetes

Years after randomization

0.00 0.20 0.40 0.60 0.80 1.00
SGLT-2 inhibitors: Key questions

- What type of heart failure prevented?
- What is the mechanism of benefit?
- Can they be used to treat established (prevalent) heart failure (as opposed to preventing incident heart failure)?
Outcomes according to baseline HF in existing SGLT2i trials

CV death or heart failure hospitalisation

**EMPRA-REG**
- No HF: HR 0.63 (95% CI 0.51 – 0.78)
- HF: HR 0.72 (95% CI 0.50 – 1.04)

**CANVAS**
- No HF: HR 0.87 (95% CI 0.72 – 1.06)
- HF: HR 0.61 (95% CI 0.46 – 0.80)

*Fitchett et al. Eur Heart J. 2016;37:1526–1534*
*Figtree et al ACC presentation 11 March 2018*
New diabetes trials according to background cardiovascular disease (excluding CKD & IGT trials)

**COMPLETED trials**

- EXSCEL
- LEADER, SUSTAIN-6
- SAVOR-TIMI 53
- CANVAS
- DEVOTE

**ONGOING trials**

- CV risk factors
  - REWIND, PIONEER-6
  - CARMELINA, CAROLINA
  - DECLARE-TIMI 58

- Atherothrombotic CV disease
  - TECOS
  - EMPA-REG
  - HARMONY VERTIS

- Acute coronary syndrome
  - ELIXA
  - EXAMINE

- Heart failure
  - Dapa-HF & DELIVER
  - EMPEROR Red. & Pres.
  - SOLOIST-WHF

**GLP-1 RA**
- DPP-4 i
- SGLT-2 i
- insulin
Phase 3 mortality/morbidity trials with SGLT2 inhibitors in HFrEF

**EMPEROR-Reduced**¹

- **Hypothesis:** Empagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HFrEF (patients with *and* without diabetes)
- **Population:** 2850 patients; symptomatic HF; EF ≤40%; EF 36-40%/NT-proBNP ≥2500 pg/ml; 31-35%/≥1000 pg/ml; ≤30% ≥600 pg/ml; eGFR ≥20 ml/min/1.73 m²; SBP ≥100 mmHg
- **Primary endpoint:** CV death or HF hospitalization

**Dapa-HF**²

- **Hypothesis:** Dapagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HFrEF (patients with *and* without diabetes)
- **Population:** 4500 patients; symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml; eGFR ≥30 ml/min/1.73 m²; SBP ≥95 mmHg
- **Primary endpoint:** CV death or worsening HF event

¹NCT03057977 ²NCT03036124
Phase 3 mortality/morbidity trials with SGLT2 inhibitors in HFpEF

**EMPEROR-Preserved**

- **Hypothesis:** Empagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with and without diabetes)
- **Population:** 4126 patients; symptomatic HF; EF >40%; NT pro BNP >300 pg/ml (> 900 pg/ml for patients with AF); structural heart disease or HF hospitalisation in prior 12 months.
- **Primary endpoint:** CV death or HF hospitalization

**DELIVER**

- **Hypothesis:** Dapagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with and without diabetes)
- **Population:** 4500 patients; symptomatic HF: outpatient/inpatient/recently discharged; EF >40%; structural heart disease; NT-proBNP ≥300 pg/ml; eGFR ≥30 ml/min/1.73 m²; SBP ≥95 mmHg
- **Primary endpoint:** CV death or worsening HF event

1NCT03057951  2NCT03619213
SOLOIST-WHF
Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening HF

- 4000 patients with T2DM and chronic HF treated with a loop diuretic (>3 months).
- Hospitalised or urgent visit for worsening heart failure
- BNP ≥150 pg/mL (≥450 pg/mL if AF) or NT pro BNP ≥600 pg/mL (≥1800 pg/mL if AF).
- Any LVEF.
- Randomised as in-patient or within 3 days of discharge.
- Placebo or SGLT1/2 inhibitor sotagliflozin.
- CV death or HF hospitalisation in patients with LVEF <50% (and in all patients).

https://clinicaltrials.gov/ct2/show/NCT03521934
NCT03521934
Large Phase III mortality/morbidity outcome trials in heart failure

- Ambulatory
  - Dapa-HF
  - EMPEROR-R
- Hospitalised
  - HFpEF
  - DELIVER
- SOLOIST-WHF

HFrEF

HFpEF
HF in diabetes with nephropathy
# SGLT-2 inhibitors: Large mortality/morbidity trials in CKD*

<table>
<thead>
<tr>
<th></th>
<th>CREDENCE</th>
<th>Dapa-CKD</th>
<th>SCORED</th>
<th>EMPA-Kidney</th>
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<tr>
<td><strong>SGLT2-i</strong></td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>sotagliflozin+</td>
<td>empagliflozin</td>
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<tr>
<td><strong>Comparator</strong></td>
<td>placebo</td>
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<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Type 2 DM GFR ≥30 &lt;90 &amp; UACR &gt;300 ≤5000mg/g</td>
<td>Type 2 DM and no DM GFR ≥25 ≤75 &amp; UACR ≥200 ≤5000mg/g</td>
<td>Type 2 DM CV risk factors GFR ≥25 ≤60</td>
<td>Type 2 DM and no DM GFR ≥20 &lt;45 GFR ≥45 &lt;90 &amp; UACR ≥200 mg/g</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>4,461</td>
<td>~4000</td>
<td>10,500</td>
<td>~5000</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>2019</td>
<td>2020</td>
<td>2022</td>
<td>2022</td>
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*SGLT-1/2 inhibitor
# SGLT-2 inhibitors: Large mortality/morbidity trials in CKD*

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</tr>
<tr>
<td>No. of patients</td>
<td>4,461</td>
<td>~4000</td>
<td>10,500</td>
<td>~5000</td>
</tr>
<tr>
<td>Results</td>
<td>2019</td>
<td>2020</td>
<td>2022</td>
<td>2022</td>
</tr>
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</table>

*SGLT-1/2 inhibitor

Stoped early for efficacy
Diabetes and heart failure: Summary and conclusions

• There is enormous overlap between diabetes and heart failure - 75% or more of patients with heart failure have diabetes or pre-diabetic dysglycemia (why?)

• Heart failure patients with diabetes (and pre-diabetic dysglycemia) have much worse outcomes than those without diabetes (why?)

• Treatments for diabetes may increase or decrease the risk of developing heart failure (incident heart failure) – exciting new findings with SGLT-2 inhibitors.

• We need to examine the effect of glucose-lowering therapies in patients with established heart failure (prevalent heart failure) – they may not be the same as in patients without heart failure. Not just patients with diabetes – pre-diabetic dysglycemia too?