Heart failure & diabetes: What is the goal of treatment?

John McMurray, MD
Glasgow, United Kingdom
HFpEF and diabetes: What are the goals of treatment?

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow.
Heart failure and type 2 diabetes

- Prevention of heart failure – where we are today
- Treatment of heart failure – the next step
Heart failure and type 2 diabetes

**Prevention of heart failure – where we are today**

- “Old” glucose lowering therapies (biguanides, sulfonylureas, insulins): No idea whether they reduce risk of heart failure or any other CV event (*insulin safe?*).
Do NOT believe non-randomized, observational analyses of outcomes related to treatment!

**EDITORIAL COMMENT**

Only Trials Tell the Truth About Treatment Effects*

John J.V. McMurray, MD

**CLINICAL REVIEW**

Controversies in cardiovascular medicine

Association is not causation: treatment effects cannot be estimated from observational data in heart failure

Christopher J. Rush, Ross T. Campbell, Pardeep S. Jhund, Mark C. Petrie, and John J.V. McMurray*

**THE LANCET**

Real-world studies no substitute for RCTs in establishing efficacy

We live in the real world, so it is reasonable to expect that data collected from the real world should help identify effective therapies. Indeed, rapid increases in the availability of registries, electronic health records, and insurance claims, and the ability to access, process, link, and classify data, mean that there is more information available than ever before. However, observational studies suffer from confounding. For example, the presence of a particular risk factor may be a consequence of a patient’s treatment rather than the cause. The E value can quantify the vulnerability of an observed relationship to unaccounted for confounders.9

*Hertzl C Gerstein, John McMurray, Rory R Holman
Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON L8S 4K1, Canada (HCG); University of Glasgow, BHF Cardiovascular Research Centre, Glasgow, UK (JM); and Diabetes Trials Unit, University of Oxford, Oxford, UK (RRH)

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Heart failure and type 2 diabetes

• Prevention of heart failure – where we are today

  – “Old” glucose lowering therapies (biguanides, sulfonylureas, insulins): No idea whether they reduce risk of heart failure.

  – DPP-4 inhibitors don’t reduce the risk of any CV event (yet are the most widely prescribed of the “new” glucose lowering drugs - *paradox!* )
Updated meta-analysis of DPP-4 inhibitor trials

CV death/MI/stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>1.00 (0.89, 1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>EXAMINE²,³</td>
<td>0.96 (n/a, 1.16)</td>
<td>0.32*</td>
</tr>
<tr>
<td>TECOS⁴</td>
<td>0.99 (0.89, 1.10)</td>
<td>0.84</td>
</tr>
<tr>
<td>CARMELINA®</td>
<td>1.02 (0.89, 1.17)</td>
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HF hospitalization

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.27 (1.07, 1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>1.19 (0.89, 1.59)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.83, 1.20)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>0.90 (0.74, 1.08)</td>
<td>0.2635</td>
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</tbody>
</table>

Favors DPP-4 inhibitor  Favors placebo

3P-MACE, 3-point major adverse CV events (CV death, non-fatal MI, non-fatal stroke); CV, cardiovascular

*One-sided p-value

Heart failure and type 2 diabetes

**Prevention of heart failure – where we are today**

- "Old" glucose lowering therapies (biguanides, sulfonylureas, insulins): No idea whether they reduce risk of heart failure or any other CV event (insulin safe?).

- DPP-4 inhibitors don’t reduce the risk of any CV event (yet are the most widely prescribed of the “new” glucose lowering drugs!)

- SGLT2 inhibitors (definitely) and GLP-1 RAs (probably) reduce incident heart failure events
# SGLT-2 inhibitors: Large mortality/morbidity trials in type 2 diabetes (excluding CKD and HF trials)

<table>
<thead>
<tr>
<th>SGLT2-i</th>
<th>EMPA-REG</th>
<th>CANVAS (-R)</th>
<th>DECLARE</th>
<th>VERTIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCT01131676</td>
<td>NCT01032629</td>
<td>NCT01730534</td>
<td>NCT01986881</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 enrolled</td>
<td>CVD</td>
<td>CV risk factors /CVD</td>
<td>CV risk factors /CVD</td>
<td>CVD</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7020</td>
<td>4430 5812</td>
<td>17276</td>
<td>~8000</td>
</tr>
<tr>
<td>Results</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>2019?</td>
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</table>
Large SGTLT2 inhibitor RCTs: Effect on heart failure hospitalization

<table>
<thead>
<tr>
<th>Patients with atherosclerotic CV disease</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>19.7</td>
<td>30.9</td>
<td>0.66 (0.55-0.79)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>21.0</td>
<td>32.8</td>
<td>0.77 (0.65-0.92)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>19.9</td>
<td>36.4</td>
<td>0.83 (0.71-0.98)</td>
</tr>
<tr>
<td>Fixed effects model for atherosclerotic cardiovascular disease (p&lt;0.0001)</td>
<td></td>
<td></td>
<td>0.76 (0.69-0.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>8.9</td>
<td>30.2</td>
<td>0.83 (0.58-1.19)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7.0</td>
<td>69.8</td>
<td>0.84 (0.67-1.04)</td>
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<tr>
<td>Fixed effects model for multiple risk factors (p=0.0634)</td>
<td></td>
<td></td>
<td>0.84 (0.69-1.01)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>CREDENCE NCT02065791</th>
<th>Dapa-CKD NCT03036150</th>
<th>SCORED NCT03315143</th>
<th>EMPA-Kidney NCT03594110</th>
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</thead>
<tbody>
<tr>
<td><strong>SGLT2-i</strong></td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>sotagliflozin+</td>
<td>empagliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<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>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>2020</td>
<td>2022</td>
</tr>
</tbody>
</table>
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy


CV death death or HF hospitalization: HR 0.69 (0.57, 0.83), P<0.001

- CV death: HR 0.78 (0.61, 1.00), P=0.05
- Hospitalization for HF: HR 0.61 (0.47, 0.80), P<0.001
Summary of effect of GLP-1 RAs on HF in recent trials in T2DM

Comparison of New Glucose-Lowering Drugs on Risk of Heart Failure in Type 2 Diabetes
A Network Meta-Analysis

Caroline K. Kramer, MD, PhD,1,2b Chang Ye, MSc,3 Sara Campbell, MD,4 Ravi Retnakaran, MD,2,5c

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample size</th>
<th>Favors GLP-1 agonist</th>
<th>Favors Placebo</th>
<th>RR (95%CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>2015</td>
<td>6068</td>
<td></td>
<td></td>
<td>0.96 (0.75, 1.23)</td>
<td>19.54</td>
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<tr>
<td>LEADER</td>
<td>2016</td>
<td>9340</td>
<td></td>
<td></td>
<td>0.68 (0.74, 1.05)</td>
<td>36.76</td>
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<tr>
<td>SUSTAIN-6</td>
<td>2016</td>
<td>3297</td>
<td></td>
<td></td>
<td>1.09 (0.76, 1.57)</td>
<td>8.79</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>2017</td>
<td>14752</td>
<td></td>
<td></td>
<td>0.95 (0.79, 1.14)</td>
<td>34.91</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.94 (0.64, 1.04)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

JACC HF 2018;6:823–30
# Major GLP-1 RA CV outcome trials

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Semaglutide</th>
<th>Exenatide</th>
<th>ITCA 650/exenatide</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>~14000</td>
<td>~4000</td>
<td>~9400</td>
<td>~9600</td>
</tr>
<tr>
<td>Excluded therapy</td>
<td>DPP-4i pramlintide</td>
<td>DPP-4i pramlintide</td>
<td>DPP-4i pramlintide</td>
<td>-</td>
<td>?</td>
<td>GLP-1 agonists</td>
<td>-</td>
</tr>
<tr>
<td>Patients</td>
<td>ACS</td>
<td>CVD/CV risk factors (RF)</td>
<td>CVD/subclinical CVD</td>
<td>CVD/CVRF</td>
<td>CVD</td>
<td>CVD</td>
<td>CVD/subclinical CVD/CVRF</td>
</tr>
</tbody>
</table>

1 primary endpoint: cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalisation due to unstable angina pectoris. 2-6 primary endpoint: major adverse CV events (CV death, nonfatal MI, nonfatal stroke). ACS, acute coronary syndrome. Source: 1. NCT01147250. 2. NCT01179048. 3. NCT01720446. 4. NCT01144338. 5. NCT01455896. 6. NCT02465515. 7. NCT01394952.
Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D’Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators*

Lancet. 2018; 392:1519-1529
Primary Outcome:
Time to CV Death, MI or Stroke (MACE)

Cumulative Incidence (%)

- Placebo (428 events)
- Albiglutide (338 events)

HR: 0.78 (95% CI 0.68, 0.90)
Non-inferiority p<0.0001
Superiority p=0.0006

Event rate per 100 person-years
Placebo 5.87
Albiglutide 4.57

People at risk
Placebo 4,732 4,460 3,074 1,030
Albiglutide 4,731 4,503 3,148 1,064
## Major GLP-1 RA CV outcome trials

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Comparator</th>
<th>No. of patients</th>
<th>Trial initiation/completion</th>
<th>Excluded therapy</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Lixisenatide</td>
<td>Placebo</td>
<td>6068</td>
<td>June 2010 April 2015</td>
<td>DPP-4i pramlintide</td>
<td>ACS</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Placebo</td>
<td>9340</td>
<td>Sept. 2010 Oct. 2015</td>
<td>DPP-4i pramlintide</td>
<td>CVD/CV risk factors (RF)</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Placebo</td>
<td>3297</td>
<td>Feb. 2013 Jan. 2016</td>
<td>DPP-4i pramlintide</td>
<td>CVD/subclinical CVD</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Placebo</td>
<td>~14000</td>
<td>June 2010 April 2018</td>
<td>-</td>
<td>CVD/CVRF</td>
</tr>
<tr>
<td>ITCA 650/exenatide</td>
<td>Placebo</td>
<td>~4000</td>
<td>March 2013 July 2018</td>
<td>?</td>
<td>CVD</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Placebo</td>
<td>~9400</td>
<td>June 2015 Aug. 2019</td>
<td>GLP-1 agonists</td>
<td>CVD</td>
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<tr>
<td>Dulaglutide</td>
<td>Placebo</td>
<td>~9600</td>
<td>July 2011 April 2019</td>
<td>-</td>
<td>CVD</td>
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</tbody>
</table>

1 primary endpoint: cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalisation due to unstable angina pectoris. 2-6 primary endpoint: major adverse CV events (CV death, nonfatal MI, nonfatal stroke). ACS, acute coronary syndrome. Source: 1. NCT01147250. 2. NCT01179048. 3. NCT01720446. 4. NCT01144338. 5. NCT01455896. 6. NCT02465515. 7. NCT01394952.
Oral semaglutide: PIONEER-6
Peptide InnOvatioN for Early DiabEtesTreatment

- 3183 patients with T2DM
- Age ≥50 yr and CV disease or ≥60 yr and CV risk factors
- Primary end point: CV death, MI or stroke (MACE)
- Key secondary: primary endpoint, plus unstable angina or hospitalization for heart failure (and analysis of components)

**Company Announcement**

Oral semaglutide demonstrates a favourable cardiovascular safety profile and a significant reduction in cardiovascular death and all-cause mortality in people with type 2 diabetes in the PIONEER 6 trial

Bagsværd, Denmark, 23 November 2018 - Novo Nordisk today announced the headline results from the last global phase 3a trial, PIONEER 6, for oral semaglutide, an investigational GLP-1 analogue taken once daily as a tablet. This double-blinded trial investigated the cardiovascular safety of oral semaglutide 14 mg compared with placebo,
More GLP-1 receptor agonist trials

• **Semaglutide oral:** SOUL (n~9,600): T2DM and CV or renal disease.
• **Semaglutide oral:** SELECT (n~17,500): *obese/overweight* and CV disease (diabetes excluded).
• **Semaglutide sc weekly:** FLOW (n~3160): T2DM and CKD. eGFR decline ≥50%, ESRD or renal/CV death.
• **Semaglutide sc weekly:** FOCUS (n~1500): T2DM ≥10 yr and retinopathy - ETDRS level of 10-75. Eye outcomes.
• **Liraglutide sc daily:** LAMP (n~1708): T2DM minor stroke/high-risk TIA. Outcome: 90-day new stroke events.
• **Efpeglenatide sc weekly:** AMPLITUDE-O (n=4,000): T2DM CV disease or men ≥50 yr/women ≥55 yr with eGFR ≥25 and <60 mL/min and ≥1 CV risk factor.
More GLP-1 receptor agonist trials

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What type of heart failure?

HFrEF or HFpEF?

Normal  HFrEF  HFpEF
Heart failure and type 2 diabetes

- Prevention of heart failure – where we are today
- Treatment of heart failure – the next step

It is wrong to assume that a drug that prevents/delays the development of HF will be beneficial in patients with established HF. Consider CCBs for hypertension or statins for CHD.
Heart failure and type 2 diabetes

- **Prevention of heart failure** – where we are today
- **Treatment of heart failure** – the next step
  - It is wrong to assume that a drug that prevents/delays the development of HF will be beneficial in patients with established HF
  - Consider CCBs for hypertension or statins for CHD
Goals of treating patients with heart failure and type 2 diabetes

• Prevent progression of HF – worsening symptoms/QoL & functional capacity; hospital admission; death

• Prevent progressive deterioration in renal function

• Prevent (other) “microvascular” complications of diabetes

• (Prevent progression from pre-diabetes to diabetes)
Goals of treating patients with heart failure and type 2 diabetes

- Prevent progression of HF – worsening symptoms/QoL & functional capacity; hospital admission; death
- Prevent progressive deterioration in renal function
- Prevent (other) “microvascular” complications of diabetes
- (Prevent progression from pre-diabetes to diabetes)
DPP-4 inhibitors and GLP-1 RAs in patients with established heart failure

- **DPP-4 inhibitors**: Very little evidence on way or other, especially in HFpEF. In HFrEF, increase in ventricular volumes with vildagliptin (VIVIDD). Subgroups from “prevention trials” showed no effect, good or bad, in patients with baseline HF (poorly defined phenotype).

- **GLP-1 RAs**: Very little evidence on way or other, especially in HFpEF. GLP-1 RAs increase heart rate. In HFrEF, two small trials showed trends to worse outcomes (FIGHT and LIVE). Subgroups from “prevention trials” showed no effect, good or bad, in patients with baseline HF (poorly defined phenotype).
SGLT2 inhibitor trials and outcomes according to baseline heart failure status

CV death or HF hospitalization

<table>
<thead>
<tr>
<th>Patients with history of heart failure</th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n/N) Placebo (n/N)</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>462/706  244/706</td>
<td>124</td>
<td>63.6  85.5</td>
<td>23.6</td>
<td>0.72 (0.50-1.04)</td>
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<tr>
<td>CANVAS Program</td>
<td>803/1461 658/1461</td>
<td>203</td>
<td>35.4  55.8</td>
<td>34.1</td>
<td>0.61 (0.46-0.80)</td>
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<td>DECLARE-TIMI 58</td>
<td>852/1724 872/1724</td>
<td>314</td>
<td>45.1  55.5</td>
<td>42.4</td>
<td>0.79 (0.63-0.99)</td>
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<tr>
<td>Fixed effects model for history of heart failure (p&lt;0.0001)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with NO history of heart failure</th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n/N) Placebo (n/N)</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
<td>Treatment Placebo</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4225/6314 2089/6314</td>
<td>339</td>
<td>15.5  24.9</td>
<td>30.0</td>
<td>0.63 (0.51-0.78)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>4992/8681 3689/8681</td>
<td>449</td>
<td>13.6  15.2</td>
<td>32.4</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7730/15436 7706/15436</td>
<td>599</td>
<td>8.9   10.5</td>
<td>37.6</td>
<td>0.84 (0.72-0.99)</td>
</tr>
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<td>Fixed effects model for no history of heart failure (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase 3 mortality/morbidity trials with SGLT2 inhibitors in HFpEF

Both trials include patients with and without T2DM

**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:** ~6000 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

**DELLIVER**

- **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 or in-patient/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

1 NCT03057951 2 NCT03619213
Why patients with *and* without type 2 diabetes?

- SGLT2 inhibitors may have benefits unrelated to glucose-lowering.
- Even if benefits are due to glucose lowering, most patients with HF have diabetes or pre-diabetes.
SGLT2 inhibitors: How do they work?

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

Additional effects on:
- Apidokines?
- Inflammation?
- Fibrosis?

Adapted from Verma, McMurray & Cherney JAMA Cardiol. 2017; 2:939-940
Why patients with *and without* type 2 diabetes?

- SGLT2 inhibitors may have benefits unrelated to glucose-lowering.
- Even if benefits are due to glucose lowering, most patients with HF have diabetes or pre-diabetes.
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: 20%
- Diabetes: 18%
**Aim:** To evaluate the effect of empagliflozin 10 mg versus placebo on exercise ability using the 6MWT in patients with HF with *reduced* or *preserved* ejection fraction.

**Population:** Chronic HF (HFrEF or HFpEF), with/without T2D.
DETERMINE trials
Dapagliflozin Effect on Exercise capacity using a 6-MINute walk test in patients with heart failure

DETERMINE-Preserved and DETERMINE-Reduced

HFpEF 400 patients
- Dapagliflozin 10 mg
- Placebo

HFrEF 300 patients
- Dapagliflozin 10 mg
- Placebo

**Primary endpoint:**
Change from baseline in 6MWD at Week 16

**Key Secondary endpoint:**
Change from baseline in the KCCQ-TSS at Week 16 (total symptom score)
Large Phase III mortality/morbidity outcome trials with SGLT2 (or SGLT1/2) inhibitors in heart failure
Goals of treating patients with heart failure and type 2 diabetes

- Prevent progression of HF – worsening symptoms/QoL & functional capacity; hospital admission; death
- Prevent progressive deterioration in renal function
- Prevent (other) “microvascular” complications of diabetes
- (Prevent progression from pre-diabetes to diabetes)
Patients with diabetes: Change in eGFR: PARADIGM-HF

Effects of GLP-1 RAs and SGLT2 inhibitors on “hard” renal outcomes* in type 2 diabetes

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- Prevent progressive deterioration in renal function
- Prevent (other) “microvascular” complications of diabetes
- (Prevent progression from pre-diabetes to diabetes)
TOPCAT: Outcomes in diabetes with and without “microvascular complications”

The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction

Pratik B. Sandesara, Wesley T. O’Neal, Heval M. Kelli, Ayman Samman-Tahhan, Muhammad Hammadah, Arshed A. Quyyumi, and Laurence S. Sperling

Sandesara et al Diabetes Care. 2018;41:150-155
Goals of treating patients with heart failure and type 2 diabetes

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- Prevent progressive deterioration in renal function
- Prevent (other) “microvascular” complications of diabetes
- (Prevent progression from pre-diabetes to diabetes)
Summary and conclusions

• Exciting times with new glucose-lowering therapies!
• Overwhelming evidence that SGLT2 inhibitors reduce the risk of heart failure hospitalization in patients with type 2 diabetes.
• Can they be used to treat (as well as prevent) heart failure?
• Are they of benefit even in heart failure patients without diabetes? We will find out shortly in HFrEF but will have to wait a bit longer for the results of the HFpEF trials.
• Don’t know about the safety of DDP-4 inhibitors or GLP-1 Ras in HFrEF or HFpEF.