Clinical trials in T2DM & CVD: Review of key outcomes with GLP-1 RA and SGLT2i

Eduard Montanya, MD
Barcelona, Spain

Cardio Diabetes Master Class
November 16 - 17, 2018 - Dubai, UAE
Clinical trials in T2DM & CVD: Review of key outcomes with GLP-1 RA and SGLT2i

Eduard Montanya, MD, PhD
Hospital Universitari Bellvitge
IDIBELL
CIBERDEM
University of Barcelona
Cardiovascular risk with new therapies

Requirement to demonstrate that new antidiabetic therapies to treat type 2 diabetes are not associated with an unacceptable increase in cardiovascular risk

FDA, U.S. Food and Drug Administration
Contemporary CVOTs in diabetes

Clinical Trials.gov. Accessed 08 October 2018
CVOTs in diabetes: GLP1-RA and SGLT-2i

ClinicalTrials.gov. Accessed 08 October 2018
SGLT-2i CVOTs
CVOTs in diabetes: SGLT-2i

- **EMPA-REG OUTCOME** (Empagliflozin, SGLT-2i)
  - n=7000; duration up to 5 yrs
  - Q3 2015 – RESULTS

- **CANVAS** (Canagliflozin, SGLT-2i)
  - n=4418; duration 4+ yrs
  - Q2 2017 – RESULTS

- **CANVAS-R** (Canagliflozin, SGLT-2i)
  - n=5826; duration ~3 yrs
  - Q2 2017 – RESULTS

- **DECLARE-TIMI 58** (Dapagliflozin, SGLT-2i)
  - n=17,276; duration ~6 yrs
  - Q3 2018 – RESULTS

- **CREDENCE (cardio-renal)** (Canagliflozin, SGLT-2i)
  - n=4464; duration ~5.5 yrs
  - Q3 2018 – CANCELLED (+ve efficacy)

- **VERTIS CV** (Ertugliflozin, SGLT-2i)
  - n=8000; duration ~6 yrs
  - Completion Q3 2019

- **SOLOIST-WHF** (Sotagliflozin, SGLT-1i & SGLT-2i)
  - n=4000; duration ~2.7 yrs
  - Completion Q1 2021

- **SCORED** (Sotagliflozin, SGLT-1i & SGLT-2i)
  - n=10,500*; duration ~4.5 yrs
  - Completion Q1 2022

- **AMPLITUDE-O** (Efpeglenatide, OW GLP-1RA)
  - n=4000*; duration ~3 yrs
  - Completion Q2 2021

- **VERTIS CV** (Ertugliflozin, SGLT-2i)
  - n=5826; duration ~3 yrs
  - Q2 2017 – RESULTS

- **CREDENCE (cardio-renal)** (Canagliflozin, SGLT-2i)
  - n=4464; duration ~5.5 yrs
  - Q3 2018 – CANCELLED (+ve efficacy)

- **VERTIS CV** (Ertugliflozin, SGLT-2i)
  - n=4464; duration ~5.5 yrs
  - Q3 2018 – CANCELLED (+ve efficacy)

- **SOLOIST-WHF** (Sotagliflozin, SGLT-1i & SGLT-2i)
  - n=4000; duration ~2.7 yrs
  - Completion Q1 2021

- **SCORED** (Sotagliflozin, SGLT-1i & SGLT-2i)
  - n=10,500*; duration ~4.5 yrs
  - Completion Q1 2022
## Comparison of SGLT-2 inhibitors: HbA$_{1c}$

<table>
<thead>
<tr>
<th>Study</th>
<th>Dapagliflozin (Dapa)$^1$ 52-week data</th>
<th>Canagliflozin (Cana)$^2$ 52-week data</th>
<th>Empagliflozin (Empa)$^3$ 24-week data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study arm</td>
<td>Dapa (5 mg) n=137</td>
<td>Dapa 10 mg n=135</td>
<td>Placebo n=137</td>
</tr>
<tr>
<td>Baseline HbA$_{1c}$ (%)</td>
<td>8.2</td>
<td>7.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Change in HbA$_{1c}$ from baseline (%)</td>
<td>-0.7</td>
<td>-0.8</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

**EMPA-REG, CANVAS and DECLARE population and design**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Baseline Age, years</th>
<th>Diabetes duration, years</th>
<th>BMI, kg/m²</th>
<th>HbA₁ᵦ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS</td>
<td>63</td>
<td>14</td>
<td>32.0</td>
<td>8.2</td>
</tr>
<tr>
<td>EMPA-REG</td>
<td>63</td>
<td>NR</td>
<td>30.6</td>
<td>8.1</td>
</tr>
<tr>
<td>DECLARE</td>
<td>64</td>
<td>12</td>
<td>32.1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Event-driven</th>
<th>Time-driven</th>
<th>Median duration of follow-up, years</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG</td>
<td>✓</td>
<td>×</td>
<td>3.1</td>
<td>7,028</td>
</tr>
<tr>
<td>CANVAS</td>
<td>✓</td>
<td>×</td>
<td>2.4</td>
<td>10,142</td>
</tr>
<tr>
<td>DECLARE</td>
<td>✓</td>
<td>×</td>
<td>4.2</td>
<td>17.160</td>
</tr>
</tbody>
</table>
CVD and Non-CVD proportion in CVOTs of SGLT-2i

- **EMPA-REG**
  - CVD: 7,020 pt's
  - non-CVD: 0 pt's

- **CANVAS**
  - CVD: 6,656 pt's
  - Non-CVD: 3,486 pt's
  - Total: 10,142 pt's

- **DECLARE**
  - CVD: 6,971 pt's
  - Non-CVD: 10,189 pt's
  - Total: 17,160 pt's
Empagliflozin: EMPA-REG results

The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke,
Canagliflozin: CANVAS results

The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, Neal et al. N Eng J Med 2017; DOI: 10.1056/NEJMoa1611925.

Canagliflozin: Placebo

HR: 0.86 [0.75; 0.97] 95% CI, p<0.0001 for non-inferiority, p=0.0158 for superiority

Participants with an event (%)

Hospitalization for HF 0.67 (0.52-0.87)
CV death or hospitalization for HF 0.78 (0.67-0.91)
All-cause mortality 0.87 (0.74-1.01)

Primary cardiovascular outcome
CV death 0.87 (0.72-1.06)
Non-fatal MI 0.85 (0.69-1.05)
Non-fatal stroke 0.90 (0.71-1.15)
Dapagliflozin: DECLARE-TIMI 58 Results

**Cardiovascular Death or Hospitalization for Heart Failure**

- Hazard ratio, 0.83 (95% CI, 0.73–0.95)
- P=0.005 for superiority

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>8578</td>
<td>8485</td>
<td>8387</td>
</tr>
<tr>
<td>8325</td>
<td>8259</td>
<td>8127</td>
</tr>
<tr>
<td>8003</td>
<td>7880</td>
<td>7367</td>
</tr>
<tr>
<td>7367</td>
<td>5362</td>
<td>5362</td>
</tr>
</tbody>
</table>

**MACE**

- Hazard ratio, 0.93 (95% CI, 0.84–1.03)
- P=0.17 for superiority

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>8578</td>
<td>8433</td>
<td>8281</td>
</tr>
<tr>
<td>8129</td>
<td>7969</td>
<td>7805</td>
</tr>
<tr>
<td>7805</td>
<td>7649</td>
<td>7137</td>
</tr>
<tr>
<td>7137</td>
<td>5158</td>
<td>5158</td>
</tr>
</tbody>
</table>

## Dapagliflozin: DECLARE-TIMI 58 Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>0.83 (0.73–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>MACE</td>
<td>0.93 (0.84–1.03)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause</td>
<td>0.76 (0.67–0.87)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.93 (0.82–1.04)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.73 (0.61–0.88)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.89 (0.77–1.01)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.01 (0.84–1.21)</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>0.98 (0.82–1.17)</td>
<td></td>
</tr>
<tr>
<td>Death from noncardiovascular cause</td>
<td>0.88 (0.73–1.06)</td>
<td></td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 ml/min/1.73 m², ESRD, or death from renal cause</td>
<td>0.53 (0.43–0.66)</td>
<td></td>
</tr>
</tbody>
</table>

GLP-1RA CVOTs
CVOTs in diabetes: GLP1-RA

- **ELIXA** (Lixisenatide; GLP-1RA)
  - n=6068; follow-up ~2 yrs
  - Q1 2015 – RESULTS

- **FREEDOM** (ITCA 650, GLP-1RA in DUROS)
  - n=4000; duration ~2 yrs
  - Q2 2016 – TOPLINE RESULTS

- **LEADER** (Liraglutide, GLP-1RA)
  - n=9340; duration 3.5–5 yrs
  - Q2 2016 – RESULTS

- **SUSTAIN 6** (Semaglutide, OW GLP-1RA)
  - n=3297; duration ~2.8 yrs
  - Q3 2016 – RESULTS

- **EXSCHEL** (Exenatide ER, OW GLP-1RA)
  - n=14,752; follow-up ~3 yrs
  - Q3 2017 – RESULTS

- **REWIND** (Dulaglutide, OW GLP-1RA)
  - n=9622; duration ~6.5 yrs
  - Q4 2018 COMPLETED

- **HARMONY OUTCOMES** (Albiglutide, OW GLP-1RA)
  - n=9574; duration ~4 yrs
  - Q3 2018 – RESULTS

- **PIONEER 6** (Oral semaglutide, GLP-1RA)
  - n=3176; duration ~1.5 yrs
  - Completion Q4 2018

- **AMPLITUDE-O** (Efpeglenatide, OW GLP-1RA)
  - n=4000*; duration ~3 yrs
  - Completion Q2 2021

- **SUSTAIN 6** (Semaglutide, OW GLP-1RA)
  - n=3297; duration ~2.8 yrs
  - Q3 2016 – RESULTS

- **EXSCHEL** (Exenatide ER, OW GLP-1RA)
  - n=14,752; follow-up ~3 yrs
  - Q3 2017 – RESULTS

- **REWIND** (Dulaglutide, OW GLP-1RA)
  - n=9622; duration ~6.5 yrs
  - Q4 2018 COMPLETED

- **HARMONY OUTCOMES** (Albiglutide, OW GLP-1RA)
  - n=9574; duration ~4 yrs
  - Q3 2018 – RESULTS

- **PIONEER 6** (Oral semaglutide, GLP-1RA)
  - n=3176; duration ~1.5 yrs
  - Completion Q4 2018

- **AMPLITUDE-O** (Efpeglenatide, OW GLP-1RA)
  - n=4000*; duration ~3 yrs
  - Completion Q2 2021

ClinicalTrials.gov. Accessed 08 October 2018
GLP-1RA therapies are not all the same

- Long-acting vs short-acting
- Large vs small molecules
- GLP-1-based vs exendin-based

| Molecular mass (kDa) |
|----------------------|---|
|                      | 0 |
|                      | 10 |
|                      | 20 |
|                      | 30 |
|                      | 40 |
|                      | 50 |
|                      | 60 |
|                      | 70 |
|                      | 80 |
|                      | 90 |
|                      | 100 |
Long-acting and short-acting GLP-1RAs

GLP-1RA, glucagon-like peptide-1 receptor agonist
Large versus small GLP-1RA molecules

GLP-1 based versus exendin based GLP-1RAs

Exenatide\textsuperscript{1–3}

Liraglutide\textsuperscript{4}

Dulaglutide\textsuperscript{5}

Lixisenatide\textsuperscript{6–8}

Semaglutide\textsuperscript{9}

Albiglutide\textsuperscript{10}

\(\sim 50\%\) amino-acid homology to human GLP-1

97\% amino-acid homology to human GLP-1

90\% amino-acid homology to human GLP-1

97\% amino-acid homology to human GLP-1

94\% amino-acid homology to human GLP-1

97\% amino-acid homology to human GLP-1

\textbf{Fc, fragment crystallisable; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; IgG4, immunoglobulin G4}

### GLP-1RA CVOTs. Patient population

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>Dulaglutide</th>
<th>Lixisenatide</th>
<th>Exenatide</th>
<th>Semaglutide</th>
<th>Liraglutide</th>
<th>Albiglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>1.5 mg /week</td>
<td>20 µg* /day</td>
<td>2.0 mg /week</td>
<td>0.5 or 1 mg /week</td>
<td>1.2 or 1.8 mg /day</td>
<td>30 mg† /week</td>
</tr>
<tr>
<td><strong>Mean age, years</strong></td>
<td>66</td>
<td>60</td>
<td>63</td>
<td>65</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Gender, % female</strong></td>
<td>46</td>
<td>31</td>
<td>38</td>
<td>39</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td><strong>Diabetes duration, years</strong></td>
<td>10.0</td>
<td>9.3</td>
<td>12</td>
<td>13.9</td>
<td>12.8</td>
<td>14</td>
</tr>
<tr>
<td><strong>Prior CVD, %</strong></td>
<td>31</td>
<td>100</td>
<td>73</td>
<td>59</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td><strong>Mean BMI, kg/m²</strong></td>
<td>32</td>
<td>30</td>
<td>32</td>
<td>33</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td><strong>Mean HbA₁c %</strong></td>
<td>7.3</td>
<td>7.7</td>
<td>8.0</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>
Lixisenatide: ELIXA results

The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for unstable angina.

HR: 0.91 (95% CI: 0.83; 1.00)

Events: exenatide 839/7356; placebo 905/7396

p < 0.001 for non-inferiority
p = 0.061 for superiority

Primary endpoint
CV Death
Non-fatal MI
Non-fatal Stroke

→ Favours exenatide OW
← Favours placebo

p-value
0.096
0.622
0.095

Exenatide once weekly: EXSCEL results

Liraglutide: LEADER results

HR: 0.87 [0.78; 0.97] \(_{95\% \text{ CI}}\)  
\(p<0.001\) for non-inferiority,  
\(p=0.01\) for superiority

Patients with an event (%)  

Months from randomisation

- **Primary endpoint**:  
  - CV Death: 0.007  
  - Non-fatal MI: 0.11  
  - Non-fatal stroke: 0.30

- Favours placebo ➔  
  - Favours liraglutide ←
Semaglutide: SUSTAIN-6 results

HR: 0.74 [0.58; 0.95]_{95\% CI},
\( p < 0.001 \) for non-inferiority,
\( p = 0.02 \) for superiority (not pre-specified)

Albiglutide: HARMONY outcomes

**HR: 0.78**

(95% CI: 0.68; 0.90)
Event rate per 100 person-years: albiglutide 4.57; placebo 5.87

\( p<0.0001 \) for non-inferiority

\( p=0.0006 \) for superiority

Time to first occurrence of CV death, MI or stroke

### HARMONY OUTCOMES

Secondary endpoints and all-cause death

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Albiglutide (N=4731)</th>
<th>Placebo (N=4732)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE (primary outcome)</td>
<td>338</td>
<td>428</td>
<td>0.78 (0.68; 0.90)</td>
<td>&lt;0.0001, 0.0006</td>
</tr>
<tr>
<td>4-point MACE*</td>
<td>373</td>
<td>468</td>
<td>0.78 (0.69; 0.90)</td>
<td>0.0005</td>
</tr>
<tr>
<td>CV death</td>
<td>122</td>
<td>130</td>
<td>0.93 (0.73; 1.19)</td>
<td>0.578</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>181</td>
<td>240</td>
<td>0.75 (0.61; 0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke</td>
<td>94</td>
<td>108</td>
<td>0.86 (0.66; 1.14)</td>
<td>0.300</td>
</tr>
<tr>
<td>CV death or hospitalisation for HF</td>
<td>188</td>
<td>218</td>
<td>0.85 (0.70; 1.04)</td>
<td>0.113</td>
</tr>
<tr>
<td>All-cause death</td>
<td>196</td>
<td>205</td>
<td>0.95 (0.79; 1.16)</td>
<td>0.644</td>
</tr>
</tbody>
</table>

*CV death, myocardial infarction, stroke and urgent revascularisation for unstable angina; Hernandez AF et al. Lancet 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-X [Epub ahead of print]
**Dulaglutide: REWIND**

“Dulaglutide **significantly reduced major adverse cardiovascular events (MACE)**, a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial”

<table>
<thead>
<tr>
<th></th>
<th>REWIND&lt;sup&gt;1&lt;/sup&gt; (N=9901)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>1.5 mg /week</td>
</tr>
<tr>
<td><strong>Mean age, years</strong></td>
<td>66</td>
</tr>
<tr>
<td><strong>Gender, % female</strong></td>
<td>46</td>
</tr>
<tr>
<td><strong>Diabetes duration, years</strong></td>
<td>10.0</td>
</tr>
<tr>
<td><strong>Prior CVD, %</strong></td>
<td>31</td>
</tr>
<tr>
<td><strong>Mean BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>32</td>
</tr>
<tr>
<td><strong>Mean HbA&lt;sub&gt;1c&lt;/sub&gt;, %</strong></td>
<td>7.3</td>
</tr>
</tbody>
</table>

• SGLT2 inhibitors have shown CV safety

• Empagliflozin and canagliflozin have shown reduction in risk of MACE in patients with ACVD (secondary prevention). SGLT-2i have not shown reduction in MACE in patients with multiple risk factors (primary risk factors)

• CV death and death from any cause reduced by liraglutide

• SGLT-2i prevent hospitalization for heart failure, both in patients with and without established ACVD

SGLT-2i have a more robust and consistent effect on prevention of heart failure (and renal outcomes) than on atherosclerotic cardiovascular events
• GLP-1RAs inhibitors have shown CV safety

• GLP-1RAs liraglutide, semaglutide, albiglutide, and dulaglutide have shown CV benefit with MACE reduction in patients with ACVD (secondary prevention).

• CV death and death from any cause reduced by liraglutide

• Results suggest that GLP-1RA may have also CV benefit in patients with multiple risk factors (primary prevention).

GLP-1RA with proven CV efficacy have a more robust and consistent effect on prevention of atherosclerotic events, with more modest effects on renal outcomes, and safety on heart failure.