Training course: All About Clinical Trials
Stockholm, 13 December 2019

Clinical Trial Parade: What’s next - Upcoming and Ongoing Clinical Trials: Diabetes

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Chair, ESC Working Group on Cardiovascular Pharmacotherapy 2018-2020
Feldkirch, A, Bern, CH, Triesen, FL
Conflict of Interest

National PI: ODYSSEY OUTCOMES
Lecture Honoraria, Research Grants, Advisory Boards for:
NovoNordisk, Merck, MSD, Pfizer, Sanofi-Aventis, AstraZeneca, Bayer, Takeda, Daiichi-Sankyo, Novartis, Amgen, Boehringer Ingelheim, BMS, Abbott, Janssen-Cilag, Genericon
Long-term consequences of Diabetes mellitus

• Microangiopathy:
  • Glucose-dependent
  • Retinopathy
  • Neuropathy
  • Nephropathy

• Macroangiopathy – Atherosclerosis
  • Coronary Artery Disease
  • Peripheral Artery Disease
  • Cerebrovascular Disease
Session Objectives

- Why diabetes in Cardiology?
- Fields of Innovation
- Late breaking trials in 2018 & 2019
- Class effects or not?
Considerations helping to determine whether there is a class effect or not?

- The drug
- The population
- Look at placebo outcome
- Entry criteria
- Trial size (power)
- Trial duration (safety)

...COMPARABLE?
Baseline criteria of recent CVOTs in T2D

Rates of **baseline established CVD** varied substantially between CVOTs, which may have affected outcomes.

Prior CV history used to define CVD also differed between CVOTs, with varying combinations of the following in inclusion criteria:

- Cardiovascular disease
- Myocardial infarction
- Acute coronary syndrome
- Coronary heart disease
- Chronic kidney disease
- Peripheral vascular disease
- CV risk factor
- Age
- Time since event
- Number of risk factors

**CVOTs**: EMPA-REG OUTCOME®, ELIXA, EXAMINE, TECOS, SUSTAIN™-6, LEADER®, SAVOR, EXSCEL, CANVAS/CANVAS-R

**Rates of Baseline CVD**:
- EMPA-REG OUTCOME® (empagliflozin): 100%
- ELIXA (lixisenatide): 83%
- EXAMINE (alogliptin) TECOS (sitagliptin): 81%
- SUSTAIN™-6 (semaglutide *): 78%
- LEADER® (liraglutide): 73%
- SAVOR (saxagliptin): 73%
- EXSCEL (exanatide): 65%
- CANVAS/CANVAS-R (canagliflozin): 65%

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*not currently licensed*
Session Objectives

• Why diabetes in Cardiology?
• Fields of Innovation
• Late breaking trials in 2018 & 2019
✓ Class effects or not?
FDA and EMA Demands for CV Safety Data

- **1961**: UGDP trial: tolbutamide discontinued due to increased CV mortality vs other treatment groups

- **2005**: Muraglitazar found to potentially increase CV risk during FDA assessment
- **2007**: Rosiglitazone associated with increased risk for MI and CV-related death

- **2008**: ACCORD trial: intensive glucose lowering was associated with increased all-cause mortality
  - HR 1.22 (95% CI 1.01, 1.46); p=0.04

- **2008**: New FDA requirements

- **2012**: New EMA requirements
  - New diabetes drugs should demonstrate CV safety with meta-analysis and a CV outcomes trial (CVOT)

- **Sponsor withdrew application**
- **Withdrawn in the EU**
- **Use restricted in US**

*In 2013, FDA panel voted to reduce safety restrictions on rosiglitazone

References:
- FDA guidance 2008; EMA scientific guidelines 2012.
✓ Why diabetes in Cardiology?
• Fields of Innovation
• Late breaking trials in 2018 & 2019
• Class effects or not?
Fields of Innovation

• GLP1 Receptor Agonists
• DPP4 Inhibitors
• SGLT2 Inhibitors
Fields of Innovation

- GLP1 Receptor Agonists
- DPP4 Inhibitors
- SGLT2 Inhibitors
Published Trials With GLP1 Receptor Agonists

<table>
<thead>
<tr>
<th>Study</th>
<th>SUSTAIN-6</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>EXSCEL</th>
</tr>
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<tbody>
<tr>
<td>Intervention</td>
<td>Semaglutid</td>
<td>Liraglutid</td>
<td>Lixisenatid</td>
<td>Exenatid</td>
</tr>
<tr>
<td></td>
<td>vs. Placebo</td>
<td>vs. Placebo</td>
<td>vs. Placebo</td>
<td>vs. Placebo</td>
</tr>
<tr>
<td>CV Outcome</td>
<td>Positive</td>
<td>Positive</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td>Population</td>
<td>High risk</td>
<td>High risk</td>
<td>ACS</td>
<td>T2DM</td>
</tr>
<tr>
<td>Patient number</td>
<td>3297</td>
<td>9340</td>
<td>6060</td>
<td>14752</td>
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<tr>
<td>Baseline HbA1c</td>
<td>8.7</td>
<td>8.7</td>
<td>7.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Follow-up</td>
<td>25 Mo</td>
<td>46 Mo</td>
<td>25 Mo</td>
<td>38 Mo</td>
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<tr>
<td>ΔHbA1c</td>
<td>-0.7/1.0%</td>
<td>-0.4%</td>
<td>-0.3%</td>
<td>-0.53%</td>
</tr>
<tr>
<td>ΔWeight</td>
<td>-2.9/4.3 kg</td>
<td>-2.3 kg</td>
<td>-0.6 kg</td>
<td>-1.27 kg</td>
</tr>
</tbody>
</table>

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators

To be Concise

Liraglutide + usual care

versus placebo + usual care
LEADER: Cardiovascular Mortality

Fields of Innovation

- GLP1 Receptor Agonists
- DPP4 Inhibitors
- SGLT2 Inhibitors
Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes
The CAROLINA Randomized Clinical Clinical Trial

Julio Rosenstock, MD; Steven E. Kahn, MB, ChB; Odd Erik Johansen, MD, PhD; Bernard Zinman, MD; Mark A. Espeland, PhD; Hans J. Woele, MD; Egon Pfarr, MSc; Annette Keller, MSc, PhD; Michaela Mattheus, MSc; David Baanstra, MSc, MBA; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHS; Nikolaus Marx, MD; for the CAROLINA Investigators
Type 2 diabetes is associated with increased cardiovascular risk. In placebo-controlled cardiovascular safety trials, the dipeptidyl peptidase-4 inhibitor linagliptin demonstrated noninferiority, but it has not been tested against an active comparator.

This trial assessed cardiovascular outcomes of linagliptin vs glimepiride (sulfonylurea) in patients with relatively early type 2 diabetes and risk factors for or established atherosclerotic cardiovascular disease.
CAROLINA: Results

Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.

OUTCOME:

Linagliptin = Glimepiride = Standard therapy (not placebo!).

# Three Published DPP4 Inhibitor Trials

<table>
<thead>
<tr>
<th>SAVOR-TIMI 53</th>
<th>EXAMINE</th>
<th>TECOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Saxagliptin/placebo</td>
<td>Alogliptin/placebo</td>
</tr>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>History of or multiple risk factors for CVD within 15–90 days before randomization</td>
<td>ACS CVD</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>3P-MACE</td>
<td>3P-MACE</td>
</tr>
<tr>
<td><strong>Key secondary outcome</strong></td>
<td>Expanded MACE</td>
<td>Expanded MACE</td>
</tr>
<tr>
<td><strong>Target no. of events</strong></td>
<td>650</td>
<td>650</td>
</tr>
<tr>
<td><strong>Median follow-up (y)</strong></td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>Completed</td>
<td>Completed</td>
</tr>
</tbody>
</table>

*Non-Inferiority Met*  
*No CVD Benefit*

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk
The CARMELINA Randomized Clinical Trial

Julio Rosenstock, MD; Vlado Perkovic, MBBS, PhD; Odd Erik Johansen, MD, PhD; Mark E. Cooper, MBBS, PhD; Steven E. Kahn, MB, ChB; Nikolaus Marx, MD; John H. Alexander, MD, MHRSc; Michael Pencina, PhD; Robert D. Toto, MD; Christoph Wanner, MD; Bernard Zinman, MD; Hans Juergen Woeber, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schmidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHRSc; for the CARMELINA Investigators
Time to first occurrence of 4P-MACE

3P-MACE + hospitalization for unstable angina

HR 1.00
(95% CI 0.88, 1.13)
p<0.0001 for non-inferiority
p=0.9898 for superiority

Patients with event (%)

No. of patients
Placebo, n 3,485 3,335 3,217 2,600 1,909 1,265 740 244
Linagliptin, n 3,494 3,365 3,233 2,609 1,949 1,288 767 266

Session Objectives

• Why diabetes in Cardiology?
• Fields of Innovation
✓ Late breaking trials in 2018 & 2019
• Class effects or not?
Fields of Innovation

- GLP1 Receptor Agonists
- DPP4 Inhibitors
- SGLT2 Inhibitors
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
Empagliflozin + usual care versus placebo + usual care
EMPAREG-OUTCOME Primary EP

EMPAREG-OUTCOME CV Death

EMPAREG-OUTCOME Total Mortality

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4687</td>
<td>2333</td>
</tr>
<tr>
<td>6</td>
<td>4651</td>
<td>2303</td>
</tr>
<tr>
<td>12</td>
<td>4608</td>
<td>2280</td>
</tr>
<tr>
<td>18</td>
<td>4556</td>
<td>2243</td>
</tr>
<tr>
<td>24</td>
<td>4128</td>
<td>2012</td>
</tr>
<tr>
<td>30</td>
<td>3079</td>
<td>1503</td>
</tr>
<tr>
<td>36</td>
<td>2617</td>
<td>1281</td>
</tr>
<tr>
<td>42</td>
<td>1722</td>
<td>825</td>
</tr>
<tr>
<td>48</td>
<td>414</td>
<td>177</td>
</tr>
</tbody>
</table>

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure in patients with T2DM (possibly through glucose-independent mechanisms).

More data regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced EF are needed - regardless of the presence or absence of T2DM.

DAPA-HF: Methods

- Phase 3, placebo-controlled trial
- 4744 patients with New York Heart Association class II, III, or IV heart failure and an EF of 40% or less
- Either dapagliflozin (10 mg once daily) or placebo, in addition to recommended therapy.
- Primary outcome: composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

DAPA-HF: Results

DAPA-HF: Primary Outcome in Subgroups

**Table: Dapagliflozin vs Placebo**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin (N=2373)</th>
<th>Placebo (N=2371)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>186/2373</td>
<td>160/2371</td>
<td>0.74 (0.65–0.85)</td>
</tr>
<tr>
<td>Age ≤45 yr</td>
<td>162/2522</td>
<td>160/2371</td>
<td>0.79 (0.61–1.00)</td>
</tr>
<tr>
<td>&gt;45 yr</td>
<td>224/1841</td>
<td>166/1372</td>
<td>0.77 (0.60–0.98)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>307/1099</td>
<td>406/1416</td>
<td>0.77 (0.61–0.99)</td>
</tr>
<tr>
<td>Female</td>
<td>27/124</td>
<td>96/917</td>
<td>0.79 (0.53–1.20)</td>
</tr>
</tbody>
</table>

**Type 2 diabetes at baseline**

- **Yes**
  - Dapagliflozin: 215/1075
  - Placebo: 271/1064
  - Hazard Ratio: 0.75 (0.63–0.90)
- **No**
  - Dapagliflozin: 171/1298
  - Placebo: 231/1307
  - Hazard Ratio: 0.73 (0.60–0.88)

Among patients with heart failure and a reduced EF: risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than placebo, regardless of the presence of diabetes.
Session Objectives

• Why diabetes in Cardiology?
  ✓ Fields of Innovation
  ✓ Late breaking trials in 2018 & 2019
• Class effects or not?
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

## Other Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin (N=8582)</th>
<th>Placebo (N=8578)</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>417 (4.9)</td>
<td>496 (5.8)</td>
<td>0.83 (0.73–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>MACE</td>
<td>756 (8.8)</td>
<td>803 (9.4)</td>
<td>0.93 (0.84–1.03)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥40% decrease in eGFR to ≤60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause</td>
<td>370 (4.3)</td>
<td>480 (5.6)</td>
<td>0.76 (0.67–0.87)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>529 (6.2)</td>
<td>570 (6.6)</td>
<td>0.93 (0.82–1.04)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>212 (2.5)</td>
<td>286 (3.3)</td>
<td>0.73 (0.61–0.88)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>393 (4.6)</td>
<td>441 (5.1)</td>
<td>0.89 (0.77–1.01)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>235 (2.7)</td>
<td>231 (2.7)</td>
<td>1.01 (0.84–1.21)</td>
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<tr>
<td>Death from cardiovascular cause</td>
<td>245 (2.9)</td>
<td>249 (2.9)</td>
<td>0.98 (0.82–1.17)</td>
<td></td>
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<tr>
<td>Death from noncardiovascular cause</td>
<td>211 (2.5)</td>
<td>238 (2.8)</td>
<td>0.88 (0.73–1.06)</td>
<td></td>
</tr>
<tr>
<td>≥40% decrease in eGFR to ≤60 ml/min/1.73 m², ESRD, or death from renal cause</td>
<td>127 (1.5)</td>
<td>238 (2.8)</td>
<td>0.53 (0.43–0.66)</td>
<td></td>
</tr>
</tbody>
</table>

Wiviott SD et al.; NEJM 2019; 380; 347-357.
A Synopsis of Recent Diabetes Outcome Trials

Significantly improved, neutral, significantly worse

<table>
<thead>
<tr>
<th>Class →</th>
<th>SGLT-2 Inhibitors</th>
<th>GLP-1 Receptor agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>EMPA-REG (pooled)</td>
<td>ELIXA</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>Lixisenatide</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Liraglutide</td>
<td>Alogliptin</td>
</tr>
<tr>
<td>3pt MACE</td>
<td></td>
<td>Semaglutide</td>
<td><strong>Victoza®</strong></td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td>Exenatide</td>
<td><strong>Jardiance®</strong></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
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</tr>
<tr>
<td>Nonfatal stroke</td>
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<td></td>
<td></td>
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<tr>
<td>Heart Failure hospitalization</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Overall mortality</td>
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</table>

Benefit in CAD: Empagliflozin* and Liraglutid
Benefit in Heart Failure: Empagliflozin*

Training course: All About Clinical Trials
Stockholm, 13 December 2019

Clinical Trials - What's next - Upcoming and Ongoing Clinical Trials: Diabetes

Heinz Drexel, MD, FESC, FAHA, FRCP (Ed);
Chair, ESC Working Group on Cardiovascular Pharmacotherapy 2018-2020