Farmaci antidiabetici ed endpoint cardiovascolari negli studi clinici

Paolo Falasca
UOC di Medicina interna
Ambulatorio di Endocrinologia e Diabetologia
Ospedale Frascati - Marino
Il dr. Paolo FALASCA dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Lifescan
- NovoNordisk
- Eli Lilly
- Takeda
- Boehringer Ingelheim
Over 50% of Diabetes-associated Deaths Are Attributable to CV Disease

Data source: USA Centers for Disease Control and Prevention National Vital Statistics Reports for total deaths in 2009 by primary cause of death, scaled to 2012 using the annual diabetes population growth rate from 2009 to 2012 for each age, sex, and race/ethnicity group.

CV, cardiovascular

ADA. Diabetes Care 2013;36:1033–1046
Cardiovascular Disease Complications of Type 2 Diabetes

~65% of deaths are due to CV disease

Coronary heart disease deaths ↑ 2- to 4-fold

Stroke risk ↑ 2- to 4-fold

Heart failure ↑ 2- to 5-fold

CV complications of Type 2 diabetes
Heart Failure: The frequent, forgotten and often fatal complication of diabetes

Table 1—Epidemiology of heart failure in diabetic patients

- HF is two times as common in diabetic men and five times as common in diabetic women as in age-matched nondiabetic subjects.
- About 12% of type 2 diabetic subjects have established HF.
- About 3.3% of type 2 diabetic subjects develop HF each year.
- Elderly diabetic subjects have a 1.3-fold greater risk of developing HF than nondiabetic subjects.
- Prevalence of HF in elderly diabetic subjects is 39%.
- 1% rise in HbA₁c is associated with a 15% increased risk of HF in elderly diabetic patients.
- Diabetic patients account for 25% of all patients enrolled in large HF trials.
Le prime 10 diagnosi in caso di ricovero ordinario in funzione del sesso (% ricoverati/diabetici con almeno un ricovero nell’anno)\(^7\)

![Bar chart showing the top 10 diagnoses in terms of gender.](chart.png)

Osservatorio ARNO Diabete
Il profilo assistenziale della popolazione con diabete

Rapporto 2015
Il ruolo del trattamento intensivo (vecchi trials)

I nuovi trials (SAVOR, TECOS, ELIXA)

I «game changer» (EMPA-REG, LEADER, SUSTAIN6)

Il futuro (CANVAS, EXCEL, DECLARE, etc)
Complex relationship between hyperglycaemia and CV risk

Current evidence does not support intensive glycaemic control for reducing CV risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Question</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>Does a intensive therapy targeting HbA1c &lt; 6.0% versus 7.0–7.9 % reduce CVD risk in middle-aged/older patients with high CV risk?</td>
<td>NO – Intensive glycaemic control had non-significant reduction in CV events (HR 0.9, p = 0.16); may increase mortality (HR 1.22, p = 0.04). Increased risk of hypoglycaemia</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Are micro- and macrovascular events reduced by intensive glucose control (HbA1c ≤ 6.5%) compared with standard therapy?</td>
<td>NO – Intensive glycaemic control had no effect on CV events (HR 0.94, p = 0.32), but did reduce microvascular events (HR 0.86, p &lt; 0.01). Increased risk of hypoglycaemia</td>
</tr>
<tr>
<td>VADT</td>
<td>Does intensive glycaemic control affect CVD risk compared with standard therapy in older male patients with T2DM?</td>
<td>NO – Intensive control has no impact on CV events (HR 0.88, p = 0.14). Increased risk of hypoglycaemia</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Does intensive glucose control with SU or insulin in newly diagnosed patients with T2DM provide any benefit?</td>
<td>YES – Early intensive glycemic control in newly diagnosed patients reduces long-term CV risk (myocardial infarction RR 0.85, p = 0.014)</td>
</tr>
</tbody>
</table>

### Intensive glycaemic control may reduce risk of myocardial infarction

A meta-analysis of ACCORD, ADVANCE, VADT and UKPDS suggests intensive glucose control reduces the risk of myocardial infarction by 15%.

**Study** | **Number of events (annual event rate, %)** | **Difference in HbA$_{1c}$ (%)** | **Favours intensive therapy** | **Favours less intensive therapy** | **Hazard ratio (95% CI)**
---|---|---|---|---|---
ACCORD | More intensive: 198 (1.18) | Less intensive: 245 (1.51) | –1.01 | | 0.77 (0.64, 0.93)
ADVANCE | More intensive: 310 (1.18) | Less intensive: 337 (1.28) | –0.72 | | 0.92 (0.79, 1.07)
UKPDS | More intensive: 150 (1.20) | Less intensive: 76 (1.40) | –0.66 | | 0.81 (0.62, 1.07)
VADT | More intensive: 72 (16.5) | Less intensive: 87 (1.99) | –1.16 | | 0.83 (0.61, 1.13)
Overall | More intensive: 730 | Less intensive: 745 | –0.88 | | 0.85 (0.76, 0.94)

History of glucose-lowering therapy and CV scares

1961 – UGDP study, tolbutamide increased CV mortality versus other treatment groups

Regulatory requirements for diabetes drugs:
1. Lower blood glucose levels
2. No obvious safety problems

Pharmaceutical industry did not have to investigate CV outcomes for new diabetes treatments/strategies – no outcome studies conducted

2005 – Muraglitazar found to increase CV risk during FDA assessment

2007 – Rosiglitazone associated with increased risk for myocardial infarction (meta-analysis, OR 1.43, p = 0.03)

2008 – ACCORD study, intensive glucose lowering was associated with increased mortality (hazard ratio 1.22, p = 0.04)

2013 – FDA panel vote to reduce safety restrictions on rosiglitazone

Regulatory requirements for outcome data for new diabetes drugs

Regulatory requirements for CV outcome data

FDA: Guidance for industry (Dec 2008)
Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies in Type 2 Diabetes

‘To establish the safety of a new antidiabetic drug to treat Type 2 Diabetes, the sponsors should demonstrate that the therapy will not result in an unacceptable increase in CV risk’

- Important CV events should be analysed
- High-risk population to be included
- Long term data required (≥ 2 years)
- Prospective adjudication of CV events by an independent committee

EMA: Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (Sept 2012 – final)

‘A fully powered cardiovascular safety assessment, e.g. based on a dedicated CV outcome study, should be submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/mechanism of action or has emerged from preclinical/clinical registration studies; e.g.,

- Increase in LDL
- Increase in triglycerides
- Increase in heart rate
- Increase in body weight
- Increase in incidence of MACE
- Increase in incidence of heart failure’

1. FDA Guidance for Industry.
2. EMA Guidelines.
Regulatory requirements for CV outcome data

**Submission with NDA:**
- Meta-analysis of important CV events across controlled Phase II and III studies to calculate the risk ratio
- If the upper bound of the two-sided 95% CI for the estimated risk ratio is:
  - $>1.8$: inadequate data to support approval
  - $1.3-1.8$,*: postmarketing CV trial(s) needed to show definitively $<1.3$
  - $<1.3$,*: postmarketing CV trial(s) generally not necessary
  * With a reassuring point estimate
- Studies included in the meta-analysis must be appropriately designed and include patients at higher CV risk so that sufficient endpoints are obtained to allow a meaningful estimate of risk

**Submission with MAA:**
- Integrated safety analysis (meta-analysis) with specific focus on CV safety
- A fully powered CV safety assessment, submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/mechanism of action or has emerged from preclinical/clinical registration studies
- Long-term CV outcome trials may be requested if there is an indication of increased risk

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Regulatory requirements for CV outcome data:
Meta-analysis* limits and outcome trial requirements

Increased risk

Safety

*Studies included in the meta-analysis must be appropriately designed and specifically include patients at higher risk of CV events to obtain sufficient endpoints to allow a meaningful estimate of risk.

CV safety trials are being conducted for each compound within the newer classes.
Ongoing CVOTs

- DPP4 inhibitors
- GLP1 receptor agonists
- SGLT2 inhibitors

Completed and ongoing CVOTs
Completed and ongoing CVOTs

DPP4 inhibitors

SGLT2 inhibitors

GLP1 receptor agonists
# Summary of CV outcomes trials with DPP4 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>SAVOR-TIMI 53&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EXAMINE&lt;sup&gt;2&lt;/sup&gt;</th>
<th>TECOS&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CAROLINA&lt;sup&gt;4&lt;/sup&gt;</th>
<th>CARMELINA&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Saxagliptin/placebo</td>
<td>Alogliptin/placebo</td>
<td>Sitagliptin/placebo</td>
<td>Linagliptin/glimepiride</td>
<td>Linagliptin/placebo</td>
</tr>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>History of or multiple risk factors for CVD</td>
<td>ACS within 15–90 days before randomisation</td>
<td>CVD</td>
<td>≥ 2 specified traditional CV risk factors or manifest CVD</td>
<td>High risk of CV events (e.g. albuminuria, prior CVD)</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>16,492</td>
<td>5380</td>
<td>14,671</td>
<td>6041</td>
<td>8300</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
</tr>
<tr>
<td><strong>Key secondary outcome</strong></td>
<td>Expanded MACE</td>
<td>4P-MACE</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>3P-MACE; renal composite</td>
</tr>
<tr>
<td><strong>Target no. of events</strong></td>
<td>1040&lt;sup&gt;6&lt;/sup&gt;</td>
<td>650</td>
<td>1300</td>
<td>631</td>
<td>625&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Median follow-up (y)</strong></td>
<td>2.1</td>
<td>1.5</td>
<td>3.0</td>
<td>6–7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>4&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Estimated completion</strong></td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>2018&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2018</td>
</tr>
</tbody>
</table>
Summary of completed DPP4 inhibitor CVOTS

**SAVOR-TIMI 53**
- **Primary endpoint**: CVD or CRFs
- **HbA1c**: 6.5–12.0%
- **n**: 16,492
- **Randomisation**: 2.1 year median follow-up
- **Saxagliptin** vs **Placebo**: Hazard ratio 1.00 (95% CI 0.89–1.12) p = 0.99

**EXAMINE**
- **Primary endpoint**: ACS
- **HbA1c**: 6.5–11.0%
- **n**: 5380
- **Randomisation**: 1.5 year median follow-up
- **Alogliptin** vs **Placebo**: Hazard ratio 0.96 (upper CI* 1.16) p = 0.32

**TECOS**
- **Primary endpoint**: CVD
- **HbA1c**: 6.5–8.0%
- **n**: 14,735
- **Randomisation**: 3.0 year median follow-up
- **Sitagliptin** vs **Placebo**: Hazard ratio 0.98 (95% CI 0.89–1.08) p = 0.65

*Upper boundary of 1-sided repeated CI.
SAVOR-TIMI 53 Saxagliptin and Cardiovascular Outcomes in T2DM Patients

<table>
<thead>
<tr>
<th>End Point</th>
<th>Saxagliptin (N=8280)</th>
<th>Placebo (N=8212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point</td>
<td>613 (7.3)</td>
<td>609 (7.2)</td>
<td>1.00 (0.89–1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point</td>
<td>1059 (12.8)</td>
<td>1034 (12.4)</td>
<td>1.02 (0.94–1.11)</td>
<td>0.66</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>420 (4.9)</td>
<td>378 (4.2)</td>
<td>1.11 (0.96–1.27)</td>
<td>0.15</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>269 (3.2)</td>
<td>260 (2.9)</td>
<td>1.03 (0.87–1.22)</td>
<td>0.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>265 (3.2)</td>
<td>278 (3.4)</td>
<td>0.95 (0.80–1.12)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>157 (1.9)</td>
<td>141 (1.7)</td>
<td>1.11 (0.88–1.39)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>97 (1.2)</td>
<td>81 (1.0)</td>
<td>1.19 (0.89–1.60)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>289 (3.5)</td>
<td>228 (2.8)</td>
<td>1.27 (1.07–1.51)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Hospitalization for coronary revascularization</td>
<td>423 (5.2)</td>
<td>459 (5.6)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.18</td>
</tr>
<tr>
<td>Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine &gt;6.0 mg/dl (530 μmol/liter)</td>
<td>194 (2.2)</td>
<td>178 (2.0)</td>
<td>1.08 (0.88–1.32)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hospitalization for hypoglycemia</td>
<td>53 (0.6)</td>
<td>43 (0.5)</td>
<td>1.22 (0.82–1.83)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

## EXAMINE events by history of HF

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients</th>
<th>History of heart failure at baseline</th>
<th>No history of heart failure at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alogliptin (n=2701)</td>
<td>Placebo (n=2679)</td>
<td>Alogliptin (n=771)</td>
</tr>
<tr>
<td>Cardiovascular death and hospital admission for heart failure</td>
<td>201 (7.4)</td>
<td>201 (7.5)</td>
<td>107 (13.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00 (0.82-1.21)</td>
<td>0.90 (0.70-1.17)</td>
<td>1.14 (0.85-1.54)</td>
</tr>
<tr>
<td>p value</td>
<td>0.976</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p&lt;sub&gt;interaction&lt;/sub&gt; for treatment and history of heart failure</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cardiovascular death*</td>
<td>112 (4.1)</td>
<td>130 (4.9)</td>
<td>55 (7.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.85 (0.66-1.10)</td>
<td>0.77 (0.54-1.09)</td>
<td>0.92 (0.64-1.32)</td>
</tr>
<tr>
<td>p value</td>
<td>0.212</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p&lt;sub&gt;interaction&lt;/sub&gt; for treatment and history of heart failure</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hospital admission for heart failure</td>
<td>106 (3.9)</td>
<td>89 (3.3)</td>
<td>63 (8.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.19 (0.90-1.58)</td>
<td>1.00 (0.71-1.42)</td>
<td>1.76 (1.07-2.90)</td>
</tr>
<tr>
<td>p value</td>
<td>0.220</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p&lt;sub&gt;interaction&lt;/sub&gt; for treatment and history of heart failure</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

**Table 4:** Risk of events assessed in the post-hoc analysis, by history of heart failure

Completed and ongoing CVOTs

DPP4 inhibitor

SGLT2 inhibitors

GLP1 receptor agonists
## Summary of CV outcomes trials with GLP1 receptor agonists

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Main inclusion criteria</th>
<th>No. of patients</th>
<th>Primary outcome</th>
<th>Key 2° outcome</th>
<th>Target no. of events</th>
<th>Estimated follow-up</th>
<th>Estimated completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA1,2</td>
<td>Lixisenatide/placebo&lt;br&gt;History of ACS</td>
<td>6068</td>
<td>4P-MACE</td>
<td>Expanded MACE</td>
<td>844</td>
<td>2.1 years median</td>
<td>Completed</td>
</tr>
<tr>
<td>LEADER6</td>
<td>Liraglutide/placebo&lt;br&gt;Vascular disease, or risk factors, or CRF, or CHF</td>
<td>9340</td>
<td>3P-MACE</td>
<td>Expanded MACE</td>
<td>&gt; 611</td>
<td>Up to ~5 years</td>
<td>Completed</td>
</tr>
<tr>
<td>SUSTAIN-6™4</td>
<td>Semaglutide/placebo&lt;br&gt;Evidence of CV disease</td>
<td>3297</td>
<td>3P-MACE</td>
<td>Expanded MACE</td>
<td>Not specified</td>
<td>Up to ~3 years</td>
<td>Completed</td>
</tr>
<tr>
<td>EXSCEL5</td>
<td>Exenatide ER*/placebo&lt;br&gt;No CV criteria specified</td>
<td>14,000</td>
<td>3P-MACE</td>
<td>All-cause mortality; HHF</td>
<td>Not specified</td>
<td>Up to ~7.5 years</td>
<td>Apr-18</td>
</tr>
<tr>
<td>REWIND6</td>
<td>Dulaglutide/placebo&lt;br&gt;Pre-existing vascular disease or ≥2 CV risk factors</td>
<td>9622</td>
<td>3P-MACE</td>
<td>Microvascular composite</td>
<td>Not specified</td>
<td>Up to ~6.5 years</td>
<td>Apr-19</td>
</tr>
<tr>
<td>HARMONY OUTCOMES7</td>
<td>Albiglutide/placebo&lt;br&gt;Established CVD</td>
<td>9400</td>
<td>3P-MACE</td>
<td>Expanded MACE</td>
<td>Not specified</td>
<td>3–5 years</td>
<td>May-19</td>
</tr>
</tbody>
</table>

*Once weekly.

ELIXA: Primary and Secondary Outcomes

CV Death, Nonfatal MI, or Nonfatal Stroke

- Lixisenatide 406/3034 = 13.4%
- Placebo 399/3034 = 13.2%

HR = 1.02
(0.89, 1.17)

Number at risk
- Placebo: 3034, 2759, 1566, 476
- Lixisenatide: 3034, 2785, 1558, 484

- Subgroup interactions were analysed, but none were significant

HF Hospitalization

- Lixisenatide 406/3034 = 13.4%
- Placebo 399/3034 = 13.2%

HR = 0.96
(0.75, 1.23)

LEADER: Primary Outcome

HR: 0.87
95% CI (0.78-0.97)
P < .001 for noninferiority
P = .01 for superiority

Patients With an Event

Months Since Randomization

No. at Risk
Liraglutide 4668 4593 4496 4400 4280 4172 4072 3982 1562 424
Placebo 4672 4588 4473 4352 4237 4123 4010 3914 1543 407

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

LEADER: CV Death

HR: 0.78
95% CI (0.66-0.93)
P = .007

LEADER: Hospitalization for HF

HR: 0.87
95% CI (0.73-1.05)
P = .14

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4668</td>
<td>4672</td>
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<tr>
<td>6</td>
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<td>12</td>
<td>4550</td>
<td>4540</td>
</tr>
<tr>
<td>18</td>
<td>4483</td>
<td>4464</td>
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<tr>
<td>24</td>
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<td>48</td>
<td>1662</td>
<td>1647</td>
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<tr>
<td>54</td>
<td>467</td>
<td>442</td>
</tr>
</tbody>
</table>

LEADER: Time to First Renal Event*

HR: 0.78
95% CI (0.67-0.92)
P = .003

Patients at risk

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4668</td>
<td>4672</td>
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<td>1613</td>
</tr>
<tr>
<td></td>
<td>454</td>
<td>433</td>
</tr>
</tbody>
</table>

*Macroalbuminuria, doubling of serum creatinine, ESRD, or renal death

Mann JF. ADA 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA.
GLP-1 RA CVOTs: A Comparison

**ELIXA**

CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

- **Placebo**
- **Lixisenatide**

<table>
<thead>
<tr>
<th>Time From Randomization (months)</th>
<th>Patients With an Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
</tr>
</tbody>
</table>

HR: 1.02  
95% CI (0.89, 1.17)  
P = .81 for superiority

**LEADER**

CV death, nonfatal MI, or nonfatal stroke

- **Placebo**
- **Liraglutide**

<table>
<thead>
<tr>
<th>Time From Randomization (months)</th>
<th>Patients With an Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
</tr>
</tbody>
</table>

HR: 0.87  
95% CI (0.78, 0.97)  
P = .01

**Number at risk**

- **Lixisenatide**
  - 3034  
  - 2759  
  - 1566  
  - 476

- **Placebo**
  - 3034  
  - 2785  
  - 1558  
  - 484

**Patients at risk**

- **Liraglutide**
  - 4668  
  - 4593  
  - 4496  
  - 4400  
  - 4280  
  - 4172  
  - 4072  
  - 3982  
  - 1562  
  - 424

- **Placebo**
  - 4672  
  - 4588  
  - 4473  
  - 4352  
  - 4237  
  - 4123  
  - 4010  
  - 3914  
  - 1543  
  - 407

---
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
Completed and ongoing CVOTs

DPP4 inhibitors

SGLT2 inhibitors

GLP1 receptor agonists
### Summary of CV outcome trials with SGLT2 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG OUTCOME®1</th>
<th>CANVAS²</th>
<th>CANVAS-R³</th>
<th>CREDENCE⁴</th>
<th>DECLARE-TIMI 58⁵</th>
<th>Ertugliflozin CVOT⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions</strong></td>
<td>Empagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Dapagliflozin/placebo</td>
<td>Ertugliflozin/placebo</td>
</tr>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>Est. vascular complications</td>
<td>Est. vascular complications or ≥ 2 CV risk factors</td>
<td>Est. vascular complications or ≥ 2 CV risk factors</td>
<td>Stage 2 or 3 CKD + macroalbuminuria</td>
<td>High risk for CV events</td>
<td>Est. vascular complications</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>7034</td>
<td>4339</td>
<td>5700</td>
<td>3627</td>
<td>17,150</td>
<td>3900</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>Progression of albuminuria</td>
<td>ESKD, S-creatinine doubling, renal/CV death</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
</tr>
<tr>
<td><strong>Key secondary outcome</strong></td>
<td>4P-MACE</td>
<td>Fasting insulin secretion, progression of albuminuria</td>
<td>Regression of albuminuria, change in eGFR</td>
<td>4P-MACE + HHF</td>
<td>4P-MACE + HHF + revascularisation</td>
<td>4P-MACE</td>
</tr>
<tr>
<td><strong>Target no. of events</strong></td>
<td>691</td>
<td>≥ 420</td>
<td>TBD</td>
<td>TBD</td>
<td>1390</td>
<td>TBD</td>
</tr>
<tr>
<td><strong>Estimated median FU</strong></td>
<td>~3 years</td>
<td>6–7 years</td>
<td>3 years</td>
<td>~4 years</td>
<td>4–5 years</td>
<td>5–7 years</td>
</tr>
<tr>
<td><strong>Estimated completion</strong></td>
<td>Completed</td>
<td>Apr 2017</td>
<td>2017</td>
<td>2019</td>
<td>2019</td>
<td>2021</td>
</tr>
</tbody>
</table>
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, myocardial infarction, or stroke; panel A), cumulative incidence of death from cardiovascular causes (panel B), the Kaplan-Meier estimate for death from any cause (panel C), and the cumulative incidence of hospitalization for heart failure (panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.
## EMPA-REG OUTCOME: Empagliflozin Improved CV Outcomes in Patients with T2DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with event / analyzed</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>0.74, 0.99*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>0.49, 0.77</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>0.70, 1.09</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>0.92, 1.67</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>126/4687</td>
<td>95/2333</td>
<td>0.65</td>
<td>0.50, 0.85</td>
</tr>
</tbody>
</table>
Primary End Point: 3P-MACE*

Cumulative incidence function. MACE=Major Adverse Cardiovascular Event; HR=hazard ratio.

* CV death, nonfatal MI, nonfatal stroke
† Two sided tests for superiority were conducted (statistics of significance was indicated if $P=0.0498$)
## 3P-MACE* and 4-P MACE

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-point MACE</strong></td>
<td>Empagliflozin</td>
<td>490/4687</td>
<td>0.86 (0.74, 0.99)*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>282/2333</td>
<td></td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>Empagliflozin</td>
<td>172/4687</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>137/2333</td>
<td></td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>Empagliflozin</td>
<td>213/4687</td>
<td>0.87 (0.70, 1.09)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>121/2333</td>
<td></td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
<td>Empagliflozin</td>
<td>150/4687</td>
<td>1.24 (0.92, 1.67)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>60/2333</td>
<td></td>
</tr>
<tr>
<td><strong>4-point MACE</strong></td>
<td>Empagliflozin</td>
<td>599/4687</td>
<td>0.89 (0.78, 1.01)*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>333/2333</td>
<td></td>
</tr>
</tbody>
</table>

*Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI
EMPA-REG OUTCOME:
Empagliflozin and CV Outcomes

Death from any cause

- Empagliflozin: HR=0.68 (95% CI: 0.57, 0.82)
- Placebo: HR=1.00
- P<0.001

Hospitalization for heart failure

- Empagliflozin: HR=0.65 (95% CI: 0.50, 0.85)
- Placebo: HR=1.00
- P=0.002

No. at risk

<table>
<thead>
<tr>
<th>Month</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4687</td>
<td>2333</td>
<td>4687</td>
<td>2333</td>
</tr>
<tr>
<td>6</td>
<td>4651</td>
<td>2303</td>
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<td>2271</td>
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<td>2280</td>
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<td>2226</td>
</tr>
<tr>
<td>18</td>
<td>4128</td>
<td>2243</td>
<td>4427</td>
<td>2173</td>
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<tr>
<td>24</td>
<td>3079</td>
<td>2012</td>
<td>3988</td>
<td>1932</td>
</tr>
<tr>
<td>30</td>
<td>2617</td>
<td>1503</td>
<td>2950</td>
<td>1424</td>
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<td>36</td>
<td>1722</td>
<td>1281</td>
<td>2487</td>
<td>1202</td>
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<tr>
<td>42</td>
<td>414</td>
<td>825</td>
<td>1634</td>
<td>775</td>
</tr>
<tr>
<td>48</td>
<td>177</td>
<td>117</td>
<td>395</td>
<td>168</td>
</tr>
</tbody>
</table>
Cardioprotective Results From EMPA-REG are Likely to be Unrelated to Glycemic Control

No significant difference in HbA1c by study end

How Applicable Might the EMPA-REG Results Be To The General Population of Patients with T2DM?

17.9% of patients with T2DM had a first CV presentation.
SGLT2 inhibitors modulate a range of factors related to CV risk

Based on clinical and mechanistic studies

Super-fuel Hypothesis: Shift in Fuel Metabolism with SGLT2i

Improvements in...

- Myocardial energy substrate metabolism
- Myocardial contractility
- Cardiac efficiency

... by shifting to a more energy-efficient fuel: ketone bodies instead of fatty acids / glucose

The lesson of the cardiovascular outcome trials

• All trials on DPP4 inhibitors (SAVOR, EXAMINE, TECOS) have achieved the primary endpoint of safety. In the SAVOR study was observed an increase in hospitalizations for heart failure in patients treated with saxagliptin, despite not being observed an increase in death from CV causes. This has led to further analysis in observational studies and meta-analyses that have finally concluded the effect neutrality of DPP4 inhibitors in risk of HF.

• The ELIXA study with lixisenatide showed neutrality on CV outcomes, no increase in the risk of hospitalizations for heart failure.

• The LEADER study with liraglutide showed superiority on CV outcomes, no increase in the risk of hospitalizations for heart failure.

• The EMPA-REG and LEADER trials support the use of empagliflozin or liraglutide in patients who have previous CV or MACE diseases

• So far between the two GLP1 RA evaluated in CV outcomes trial, only liraglutide and not lixisenatide showed a cardioprotective effect but before concluding that it is a specific drug effect is to assess differences in the population of patients between the two studies and design of these, waiting to have the results of ongoing trials of other GLP1 RA.

• Patients with renal impairment are those who have benefited most of the treatments with empagliflozin and liraglutide.

Conclusions

• FDA guidance from 2008 requests CV outcome trials (CVOTs) to demonstrate CV safety of all new glucose-lowering compounds

• CVOTs designed to assess impact of drugs on CV outcomes (MACE) vs placebo on top of usual care for glucose and CV risk factor management

  – Not designed to assess impact of differences between treatment arms in, for example, HbA$_{\scalebox{0.7}{1c}}$ on CV outcomes

• Completed CVOTs in DPP4 inhibitor and GLP1 class report neutral or superior effects on CV outcomes confirming CV safety as defined by FDA

• Ongoing CVOTs will provide further clarity on the CV safety of individual glucose-lowering agents

Comorbidities-driven treatment

<table>
<thead>
<tr>
<th>Stage I-II CKD</th>
<th>Normal or subclinical ENDOTHELIAL DYSFUNCTION</th>
<th>ESTABLISHED ATHEROSCLEROSIS</th>
<th>ACUTE CORONARY SYNDROME</th>
<th>HEART FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 90-60 ml/min/1.73 m²</td>
<td>Metformin&lt;sup&gt;a&lt;/sup&gt;, Pioglitazone&lt;sup&gt;b&lt;/sup&gt;, DPP4-I&lt;sup&gt;c,e&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, SGLT2-I&lt;sup&gt;g&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;, SU&lt;sup&gt;1&lt;/sup&gt;, GLP-1RA&lt;sup&gt;i&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;, Gliclazide&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Metformin, SGLT2-I&lt;sup&gt;g&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, Pioglitazone&lt;sup&gt;b&lt;/sup&gt;, DPP4-I&lt;sup&gt;c,e&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;, Gliclazide&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Insulin&lt;sup&gt;m&lt;/sup&gt;, DPP4-I&lt;sup&gt;e&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;</td>
<td>SLGT2-I&lt;sup&gt;g&lt;/sup&gt;, DPP4-I&lt;sup&gt;e&lt;/sup&gt;, GLP-1RA&lt;sup&gt;i&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage III CKD</td>
<td>Metformin&lt;sup&gt;2&lt;/sup&gt;, Pioglitazone&lt;sup&gt;3b&lt;/sup&gt;, SGLT2-I&lt;sup&gt;4g&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, DPP4-I&lt;sup&gt;2c,e&lt;/sup&gt;, Gliclazide&lt;sup&gt;k&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Metformin&lt;sup&gt;2&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, SGLT2-I&lt;sup&gt;4g&lt;/sup&gt;, Pioglitazone&lt;sup&gt;3b&lt;/sup&gt;, DPP4-I&lt;sup&gt;2c,e&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;, Gliclazide&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Insulin&lt;sup&gt;m&lt;/sup&gt;, DPP4-I&lt;sup&gt;e&lt;/sup&gt;, GLP-1 RA&lt;sup&gt;i&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;</td>
<td>SLGT2-I&lt;sup&gt;g&lt;/sup&gt;, DPP4-I&lt;sup&gt;e&lt;/sup&gt;, GLP-1RA&lt;sup&gt;i&lt;/sup&gt;, Insulin&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage IV CKD</td>
<td>Pioglitazone&lt;sup&gt;3&lt;/sup&gt;, DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Pioglitazone&lt;sup&gt;3&lt;/sup&gt;, DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage V CKD</td>
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<td>Pioglitazone&lt;sup&gt;3&lt;/sup&gt;, DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DPP4-I&lt;sup&gt;2&lt;/sup&gt;, Insulin&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Evidence of efficacy**

**Evidence of safety**

**Author consensus**

Fig. 1 A treatment algorithm based on cardiac and renal co-morbidities and CVOTs. <sup>1</sup>To be used with caution because of the risk of hypoglycemia; <sup>2</sup>consider dose reduction (except for linagliptin) and monitor eGFR frequently; <sup>3</sup>preferred in the presence of marked insulin resistance; <sup>4</sup>initiation of therapy currently not recommended. <sup>a</sup>UKPDS; <sup>b</sup>PROACTIVE trial; <sup>c</sup>SAVOR; <sup>d</sup>TECOS, <sup>e</sup>EXAMINE; <sup>f</sup>LEADER trial; <sup>g</sup>EMPA-REG Outcome trial; <sup>h</sup>ORIGIN trial; <sup>i</sup>ADVANCE; <sup>j</sup>ELIXA; <sup>k</sup>DIGAMI 1
Grazie per l’attenzione!