Glucose control for prevention of Cardiovascular disease: lesson from large clinical trials

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Conflict of interest disclosure

None

Committee of Scientific Affairs
Diabetes and Cardiovascular disease

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>26,505</td>
<td>2.00 (1.83–2.19)</td>
<td>64 (54–71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05–2.60)</td>
<td>41 (24–54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</td>
<td>37 (19–51)</td>
</tr>
<tr>
<td>Stroke subtypes*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95–2.65)</td>
<td>1 (0–20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19–2.05)</td>
<td>0 (0–26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59–2.13)</td>
<td>33 (12–48)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51–1.98)</td>
<td>0 (0–26)</td>
</tr>
</tbody>
</table>

Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline.
UKPDS: HbA1c and rates for MI and microvascular complications
Hyperglycemia and CVD risk

Causes cardiovascular disease

Hyperglycemia

Glucose normalization

Should prevent CVD

Chronic hyperglycemia cause CVD

Reversibility is possible?
Glucose lowering and vascular benefits

Older trials
Demonstrating a positive impact of tight glycemic control on macrovascular disease in later follow-up period.

- DCCT/EDIC
- UKPDS

More recent trials
Demonstrating neutral/negative effects of tight glycemic control in patients with T2DM

- ACCORD
- ADVANCE
- VADT
Comparison of major trials of intensive glucose control and CV outcomes

<table>
<thead>
<tr>
<th></th>
<th>UKPDS33</th>
<th>UKPDS34</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject No.</strong></td>
<td>3,867</td>
<td>753</td>
<td>10,252</td>
<td>11,140</td>
<td>1791</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>53</td>
<td>53</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td><strong>Duration of diabetes (y)</strong></td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>History of CV disease (%)</strong></td>
<td>NR</td>
<td>NR</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td><strong>HbA1c at baseline (%)</strong></td>
<td>7.08</td>
<td>7.0</td>
<td>8.1</td>
<td>7.2</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Duration of F/U (y)</strong></td>
<td>10</td>
<td>10.7</td>
<td>3.7</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Achieved HbA1c (%)</strong></td>
<td>7.0 vs 7.9</td>
<td>7.4 vs 8.0</td>
<td>6.4 vs 7.5</td>
<td>6.3 vs 7.0</td>
<td>6.9 vs 8.5</td>
</tr>
<tr>
<td><strong>HR for primary outcome</strong></td>
<td>MI : 0.84 (0.71–1.00) NS</td>
<td>MI : 0.61 (0.41–0.89) p=0.01 Stroke : 0.59 (0.29–1.18) NS</td>
<td>0.90 (0.78–1.04) NS</td>
<td>0.94 (0.84–1.06) NS</td>
<td>0.88 (0.74–1.05) NS</td>
</tr>
<tr>
<td><strong>HR for all-cause mortality</strong></td>
<td>0.94 (0.80–1.10) NS</td>
<td>0.66 (0.45–0.91) p=0.011</td>
<td>1.22 (1.01–1.46) p = 0.02</td>
<td>0.93 (0.83–1.06) NS</td>
<td>1.07 (0.81–1.42) NS</td>
</tr>
</tbody>
</table>

Modified table from Diabetes care 2012:34;202-34
Achieving early glycaemic control may generate a “good legacy effect” in UKPDS post-trial.

Median HbA1c (%)

- 0.6
- 0.7
- 0.8
- 0.9
- 1.0

UKPDS 1998
Conventional Therapy
Metformin
Holman et al 2008
1997
2007

Conventional Therapy
Conv. (SU) 387 450 513 573 636 678
Metformin 73 83 92 106 118 126

Decrease in MI by HbA1c -0.9% in T2DM

- 0.55
- 0.6
- 0.65
- 0.7
- 0.75
- 0.8
- 0.85
- 0.9
- 0.95

1997
1999
2001
2003
2005
2007

HR

Difference in HbA1c was lost after first year but patients in the initial intensive arm still had lower incidence of any complication:
- 24% reduction in microvascular complications
- 15% reduction in MI
- 13% reduction in all-cause mortality

More than 8,000 peoples were monitored for a median of 8.8 years from randomization. At the end of the ACCORDION follow-up, the gap of HbA1c levels were decreased to 7.8% in intensive and 8.0% in conventional group.
Over a median follow-up of 10 years, the intensive-therapy reduce the primary outcome by 17% significantly, but did not have reduced cardiovascular mortality and all-cause mortality.

Impact of intensive therapy in diabetes in major clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>HbA1c Baseline</th>
<th>HbA1c Study End</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Std</td>
<td>Intensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>UKPDS</td>
<td>9</td>
<td>7.9</td>
<td>7</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>8.3</td>
<td>7.5</td>
<td>6.4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.5</td>
<td>7.0</td>
<td>6.4</td>
<td>↓</td>
<td>↔️</td>
</tr>
<tr>
<td>VADT</td>
<td>9.4</td>
<td>8.5</td>
<td>6.9</td>
<td>↓</td>
<td>↔️</td>
</tr>
</tbody>
</table>

Am J Med. 2010;123:374e9-e18
Meta-analyses of the main trials

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Trial</th>
<th>No.</th>
<th>Absolute decreased in HbA1c</th>
<th>Effects of intensive glycemic control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td>Ray et al.</td>
<td>UKPDS(33+34 combined) PROactive ACCORD ADVANCE VADT</td>
<td>33,040</td>
<td>0.9%</td>
<td>OR 0.85 (0.77–0.93)</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>UKPDS33 UKPDS34 ACCORD ADVANCE VADT</td>
<td>27,802</td>
<td>0.8%</td>
<td>OR 0.89 (0.81–0.96)</td>
</tr>
<tr>
<td>Mannucci et al.</td>
<td>UKPDS(33+34 combined) PROactive ACCORD ADVANCE VADT</td>
<td>32,632</td>
<td>0.9%</td>
<td>OR 0.86 (0.78–0.93)</td>
</tr>
<tr>
<td>Turnbull et al.</td>
<td>UKPDS 33 ACCORD ADVANCE VADT</td>
<td>27,049</td>
<td>0.9%</td>
<td>HR 0.85 (0.76–0.94)</td>
</tr>
</tbody>
</table>
Persistent questions in diabetes related to CV events

• Although there are some data suggestive of a possible CV protective effect of intensive glycemic control after long-term follow-up, these data are not consistent.

• Different strategies and characteristics of population of each trials make it difficult to elicit a definite conclusion.

• And also, increased mortality of ACCORD trial could not explain appropriately despite several reasons have been suggesting.

• In addition, some anti-diabetic agents were suspected to worsen cardiovascular outcomes(eg, rosiglitazone, muraglitazar).
Regulatory obligations for all new diabetes medications: 2008

Clinical Perspectives on FDA Guidance for Industry:
Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat T2DM

1. An upper bound of the 95% CI for the risk ratio of important CV events of \( \leq 1.3 \) should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes.
2. Study patients must include those with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
3. A minimum of 2 years’ CV safety data must be provided.
4. All phase 2 and 3 studies should include a prospective, independent adjudication of CV events. Adjudicated events should include CV mortality, myocardial infarction (MI), and stroke and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.
5. For satisfaction of the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials or an additional single large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before New Drug Application/Biologic License Application submission.
Cardiovascular outcomes trials timeline

- **Sitagliptin**
  - TECOS (N = 14,000)
- **Alogliptin**
  - EXAMINE (N = 5,400)
- **Canagliflozin**
  - CANVAS (N = 4,330)
- **Exenatide**
  - EXSCEL (N = 9,500)
- **Lixisenatide**
  - ELIXA (N = 6,000)
- **Empagliflozin**
  - N = 7,000
- **Liraglutide**
  - LEADER (N = 9,340)
- **Linagliptin**
  - CAROLINA (N = 6,000)
- **Dulaglutide**
  - REWIND (N = 9,622)
- **TAK-875**
  - (N = 5,000)
- **Insulin glargine**
  - ORIGIN (N = 12,537)
- **Aleglitazar**
  - AleCardio (N = 19,000)
- **Saxagliptin**
  - SAVOR (N = 16,500)
- **Dapagliflozin**
  - DECLARE (N = 17,150)

**Year**

2005  | 2010  | 2015  | 2020

Source: Clinicaltrials.gov and Frost & Sullivan analysis
DPP-4 inhibitors Trials
: SAVOR-TIMI, EXAMINE, and TECOS

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infaction

Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care

Trial Evaluating Cardiovascular Outcomes with Sitagliptin
# SAVOR, EXAMINE, and TECOS
## Key results

<table>
<thead>
<tr>
<th></th>
<th>SAVOR-TIMI</th>
<th>EXAMINE</th>
<th>TECOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents</strong></td>
<td>Saxagliptin vs Placebo</td>
<td>Alogliptin vs placebo</td>
<td>Sitagliptin vs placebo</td>
</tr>
<tr>
<td><strong>Median F/U</strong></td>
<td>2.1 years</td>
<td>18months</td>
<td>3.0 years</td>
</tr>
<tr>
<td><strong>HbA1c change</strong></td>
<td>Saxa 7.7 ± 1.4% Placeb0 7.9 ± 1.5%</td>
<td>LS mean difference - 0.36%(95% CI: -0.43, -0.28; P &lt; .001)</td>
<td>LS mean difference - 0.29%(95% CI: -0.32, -0.27)</td>
</tr>
<tr>
<td><strong>CV outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary HR 1.00(0.89, 1.27); NS</td>
<td>HR 0.96(≤ 1.16);NS</td>
<td>HR 0.98(0.88, 1.09); NS</td>
<td></td>
</tr>
<tr>
<td>Secondary HR 1.02(0.94, 1.11); NS</td>
<td>HR 0.95(≤ 1.14);NS</td>
<td>HR 0.99(0.89, 1.11); NS</td>
<td></td>
</tr>
<tr>
<td><strong>HF hospitalization</strong></td>
<td>1.27(1.07-1.51)</td>
<td>1.19(0.9-1.58)</td>
<td>1.09(0.83-1.20)</td>
</tr>
<tr>
<td><strong>Other S/E</strong></td>
<td>No difference in incidence of acute and chronic pancreatitis; fewer cases of pancreatic cancer in Saxa group.</td>
<td>No difference in incidence of acute and chronic pancreatitis, cancer, renal impairment, angioedema, or sever hypoglycemia</td>
<td>No difference in incidence of infection, cancer, renal failure, hypoglycemia, or nonCV death</td>
</tr>
</tbody>
</table>
DPP-4 inhibitors and HF

Table 1—Data from randomized placebo-controlled trials of DPP-4 inhibitors and the risk of HF

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>DPP-4 inhibitor</th>
<th>Population</th>
<th>Sample size</th>
<th>Median follow-up (years)</th>
<th>Hospitalization for HF</th>
<th>Rate (no. per 100 PYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DPP-4 inhibitor</td>
</tr>
<tr>
<td>SAVOR-TIMI</td>
<td>2013,</td>
<td>Saxagliptin</td>
<td>CVD or multiple CVD risk factors</td>
<td>16,492</td>
<td>2.1</td>
<td></td>
<td>1.71*</td>
</tr>
<tr>
<td>53 (5,6)</td>
<td>2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXAMINE</td>
<td>2013,</td>
<td>Alogliptin</td>
<td>Post-ACS</td>
<td>5,380</td>
<td>1.5</td>
<td></td>
<td>2.69†</td>
</tr>
<tr>
<td>(7,8)</td>
<td>2015</td>
<td></td>
<td>With history of HF</td>
<td>1,533</td>
<td></td>
<td></td>
<td>5.60†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With no history of HF</td>
<td>3,847</td>
<td></td>
<td></td>
<td>1.53†</td>
</tr>
<tr>
<td>TECOS</td>
<td>2015</td>
<td>Sitagliptin</td>
<td>CVD</td>
<td>14,671</td>
<td>3.0</td>
<td></td>
<td>1.07</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; PYs, person-years. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial. ‡Adjusted for baseline history of HF.

ACS, acute coronary syndrome; PYs, person-years.
FDA drug safety communication
April 5, 2016

- FDA adds warnings about HF risk to labels of T2DM medicines containing saxagliptin and alogliptin.

- Health care professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control.
- If a patient’s blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.
- Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:
  - Unusual shortness of breath during daily activities
  - Trouble breathing when lying down
  - Tiredness, weakness, or fatigue
  - Weight gain with swelling in the ankles, feet, legs, or stomach
- Patients should not stop taking their medicine without first talking to their health care professionals.

www.fda.gov/Drugs/DrugSafety/ucm486096.htm
Ongoing DPP-4 inhibitor trials

<table>
<thead>
<tr>
<th>Study</th>
<th>CAROLINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 i</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>N</td>
<td>6000</td>
</tr>
<tr>
<td>Estimated completion date</td>
<td>Sep, 2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 i</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>8300</td>
</tr>
<tr>
<td>Estimated completion date</td>
<td>Jan, 2018</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov.
ELIXA trial
study design

- Adults with T2D who had an ACS events within 180 days
- Randomised and treated (n=6068)
  - Lixisenatide 10 mcg/d (n=3034)
  - Placebo (n=3034)

- Phase 3b randomized, double-blind, placebo-controlled, multicenter study
- Run-in = 7 days for training in self-administration drug
- Outcomes;
  Primary composite: MACE + hospitalization for unstable angina
  Secondary & Others
  - Primary + hospitalization for HF
  - Primary + hospitalization for HF + coronary revascularization
  - % change ACR to week 108
  - All-cause of death
- Median follow-up: 25 months
ELIXA trial
Results

Table 2. Incidence Rates and Hazard Ratios, with Adjustment for Geographic Region, for the Primary Composite End Point, Its Components, and Other Efficacy Outcomes.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=3034)</th>
<th>Lixisenatide (N=3034)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event</td>
<td>No. of Events/100 Patient-Yr</td>
<td>Patients with Event</td>
<td>No. of Events/100 Patient-Yr</td>
</tr>
<tr>
<td>Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable angina — no. (%)</td>
<td>399 (13.2)</td>
<td>6.3</td>
<td>406 (13.4)</td>
<td>6.4</td>
</tr>
<tr>
<td>Components of primary end point — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>93/399 (23.3)</td>
<td>—</td>
<td>88/406 (21.7)</td>
<td>—</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>247/399 (61.9)</td>
<td>—</td>
<td>255/406 (62.8)</td>
<td>—</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>49/399 (12.3)</td>
<td>—</td>
<td>54/406 (13.3)</td>
<td>—</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>10/399 (2.5)</td>
<td>—</td>
<td>9/406 (2.2)</td>
<td>—</td>
</tr>
<tr>
<td>Patients with each primary end-point event — no. (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>158 (5.2)</td>
<td>2.4</td>
<td>156 (5.1)</td>
<td>2.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>261 (8.6)</td>
<td>4.1</td>
<td>270 (8.9)</td>
<td>4.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>60 (2.0)</td>
<td>0.9</td>
<td>67 (2.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>10 (0.3)</td>
<td>0.1</td>
<td>11 (0.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Secondary end points — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end-point event or hospitalization for heart failure</td>
<td>469 (15.5)</td>
<td>7.6</td>
<td>456 (15.0)</td>
<td>7.3</td>
</tr>
<tr>
<td>Primary end-point event, hospitalization for heart failure, or revascularization</td>
<td>659 (21.7)</td>
<td>11.2</td>
<td>661 (21.8)</td>
<td>11.1</td>
</tr>
<tr>
<td>Additional end points — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>127 (4.2)</td>
<td>1.9</td>
<td>122 (4.0)</td>
<td>1.8</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>223 (7.4)</td>
<td>3.3</td>
<td>211 (7.0)</td>
<td>3.1</td>
</tr>
</tbody>
</table>
EMPA-REG outcome trial

Screening (n=11531) ➔ Randomised and treated (n=7020) ➔ Placebo (n=2333)

Empagliflozin 10 mg (n=2345)
Empagliflozin 25 mg (n=2342)

Primary outcome

**3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

Key secondary outcome

**4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina

Further pre-specified outcomes

- CV death, Non-fatal MI, Non-fatal stroke, Hospitalization for heart failure, All-cause mortality
LEADER trial

9340 subjects
- Double blinded
- 2-week placebo run-in

Placebo run-in

Liraglutide 0.6–1.8 mg OD + standard of care

Placebo + standard of care

Safety follow-up

Safety follow-up

2 weeks

Duration 3.5–5 years

30 days

Screening

Randomization (1:1)

End of treatment

Key inclusion criteria
- T2DM, HbA1c ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure or
- Age ≥60 years and risk factors for CV disease

Primary objective
To assess the effect of treatment with liraglutide compared with placebo on the incidence of CV events in adults with T2DM that are at high risk for CV events

Primary endpoint
- Time from randomization to first occurrence of a composite CV outcome (CV death, non-fatal MI, or non-fatal stroke)

Key secondary endpoints
- Time from randomization to first occurrence of an expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, revascularization, unstable angina or hosp. for heart failure)
- Time from randomization to all cause death
- Time from randomization to each individual component of the expanded composite CV outcome

SUSTAIN-6 trial

- Phase 3a randomized, double-blind, placebo-controlled, parallel-group study
- Patients were randomized in a 1:1:1:1 ratio (826:822:824:825)
- Outcomes:
  - Primary composite: 3 points MACE
  - Secondary & Others
    - Primary + hospitalization for unstable angina or HF or
      + coronary revascularization
    - retinopathy complications
    - New or worsening nephropathy
## Comparisons of three benefit trials

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject No.</td>
<td>7,028</td>
<td>9,340</td>
<td>3,297</td>
</tr>
<tr>
<td>Mean duration of diabetes</td>
<td>&gt; 10 years (57 %)</td>
<td>12.8</td>
<td>14.0</td>
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<tr>
<td>Baseline HbA1c(%)</td>
<td>8.07</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>HbA1c change in investigating drug</td>
<td>-0.24 % in 10 mg</td>
<td>-0.4 %</td>
<td>-1.1 % in 0.5 mg</td>
</tr>
<tr>
<td></td>
<td>-0.36 % in 25 mg</td>
<td></td>
<td>-1.4 % in 1.0 mg</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>30.6</td>
<td>32.5</td>
<td>32.8</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>-1.8 kg in 10 mg</td>
<td>-2.3 kg</td>
<td>-3.6 kg in 0.5 mg</td>
</tr>
<tr>
<td></td>
<td>-2.7 kg in 25 mg</td>
<td></td>
<td>-4.9 kg in 1.0 mg</td>
</tr>
<tr>
<td>Median duration of study</td>
<td>2.6</td>
<td>3.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>14% ↓</td>
<td>13% ↓</td>
<td>26% ↓</td>
</tr>
<tr>
<td>CV death</td>
<td>38% ↓</td>
<td>22% ↓</td>
<td>2% ↓</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>13% ↓ (excl. silent MI)</td>
<td>12% ↓</td>
<td>26% ↓ (incl. silent MI)</td>
</tr>
<tr>
<td></td>
<td>28% ↑ silent MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14% ↓ (incl. all MI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>24% ↑</td>
<td>11% ↓</td>
<td>39% ↓</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>32% ↓</td>
<td>15% ↓</td>
<td>5% ↑</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>35% ↓</td>
<td>13% ↓</td>
<td>11% ↑</td>
</tr>
<tr>
<td>Time to benefit</td>
<td>within 3 months</td>
<td>12-18 months</td>
<td>12-18 months</td>
</tr>
</tbody>
</table>
Recent three benefit trials

EMPA-REG

LEADER

SUSTAIN-6

Beyond glucose lowering effect
- Weight reduction?
- BP lowering?
- Relatively low hypoglycemia?
- Hemodynamic factor?
- Anti-atherogenic effect?
- Pleiotropic effect?
CVOT according to the duration of diabetes, baseline CV risk, and duration of intervention

Modified figure from World J Diabetes 2015; 6(9): 1092-1096
Potential limitations of CV outcome trial for New drug

Traditional CV outcome trials:
- Demonstrate CV benefit (lower CV risk vs placebo or active comparator)

New drugs CV safety trials:
- Demonstrate CV safety (no increased CV risk vs placebo as part of standard care)

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**Traditional CV outcome trials**
- Initiation of blinded treatment or placebo
- Difference in HbA1c between treatment and placebo
- Long-term treatment
- CV benefit of treatment demonstrated by significant reduction in CV outcomes

**New drugs CV safety trials**
- Initiation of blinded treatment or placebo
- Small or no difference in HbA1c between treatment and placebo
- Short-term treatment
- No increased CV risk (CV safety) of treatment demonstrated by non-inferiority

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Trial include “Limited Population”
Metabolic Component of Diabetes
ADA treatment recommendations

- Reductions improve microvascular complications
- Reductions improve macrovascular complications

Blood pressure < 140/90 mmHg
HbA1c < 7%
Lower LDL cholesterol with statin

Prevention & Detection
Biomarker development
Education & Support
Weight control

Biomarker development

HbA1c < 7%
Blood pressure < 140/90 mmHg
Lower LDL cholesterol with statin

Smoking, 3%
SBP, 11%
HbA1c, 13%
Other, 73%
HDL-C, 25%

Reduction

ADA. Diabetes Care. 2016;39 Suppl 1:S1-S112
What can we learn from these large clinical trials of glycemic control for the cardiovascular disease?
Today’s summary
Lesson from large clinical trials

• Traditional CV outcome trials showed that cardiovascular protective effect by intensive glycemic control can be achieved after long-term follow-up.

• It takes long time to show the benefits of intensive glycemic control for the reduction of cardiovascular disease in diabetic patients.

• It has become clear that recent CV outcome studies can rule out harm but have been too short to evaluate for a beneficial effect of strict glycemic control.

• EMPA-REG, LEADER, and SUSTAIN-6 trials demonstrated the beneficial effects for CVD, however, It is unlikely that benefits are solely from glucose-lowering effect.

• And also, these CV benefits can’t be generalized to all diabetic patients and we need to observe how to translate into the real clinical practice.

• The pathophysiology of CVD in diabetic patients is very complex and multifactorial, we need to make a more exact risk stratification and appropriate strategies according to the individual characteristics.
Thanks for your attention!!

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