Diabetes Update 2017:
New Basal Insulins, GLP-1/Basal Insulin Combinations, and CVOTs, Oh My!

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Director of Clinical Research
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Objectives

• Review recent advances in injectable anti-diabetic therapy

• Review the potential advantages of new basal insulins

• Review the results from recent cardiovascular outcome trials evaluating the safety of newer anti-diabetic therapies
Disclosures

• Speaker Bureau
  – AstraZeneca, Merck, Sanofi, Novo Nordisk

• Consultant
  – Novo Nordisk and Merck

• Research Support
  – Novo Nordisk, Merck
Injectable Therapies

• Basal insulin
  – Multiple new long-acting insulin products have recently become available
    • Tresiba®-insulin degludec U-100 and U-200
    • Toujeo® -insulin glargine U-300
    • Basaglar®-Biosimilar insulin glargine U-100

• GLP-1
  – Multiple new formulations
  – Twice daily>>>Once daily>>>Once weekly
  – Oral GLP-1 (future)

• Combination products with long-acting insulin and GLP-1 combined in same pen
  – iDegLira [insulin degludec + Liraglutide (GLP-1)] Xultophy®
  – iGlarLixi [insulin glargine + Lixisenatide (GLP-1)] Soliqua®
Basal Insulins
Glargine U300

- Flatter and more prolonged time action profile in T1D\(^\text{a,b}\)

- Similar HbA\(_1c\) reduction between glargine U300 and U100\(^\text{c}\) in T2D

Less nocturnal hypoglycemia\(^\text{c}\)
Smaller doses with same efficacy\(^\text{c}\)

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Hypoglycemia

Gla-300 controls HbA1c as well as Gla-100 for people with DM-2 treated with basal and mealtime insulin but with consistently **less risk of nocturnal hypoglycemia**

Insulin Degludec Versus Insulin Glargine in Insulin-Naive Patients With Type 2 Diabetes

A 1-year, randomized, treat-to-target trial (BEGIN Once Long)

OBJECTIVE — To compare ultra-long-acting insulin degludec with glargine for efficacy and safety in insulin-naive patients with type 2 diabetes inadequately controlled with oral antidiabetic drugs (OADs).

RESEARCH DESIGN AND METHODS — In this 1-year, parallel-group, randomized, open-label, treat-to-target trial, adults with type 2 diabetes with A1C of 7%–10%, taking OADs were randomized 3:1 to receive once daily degludec or glargine, both with metformin. Insulin was titrated to achieve prebreakfast plasma glucose (PG) of 3.9–4.9 mmol/L. The primary end point was confirmation of noninferiority of degludec to glargine in A1C reduction after 52 weeks in an intent-to-treat analysis.

RESULTS — In all, 1,030 participants (mean age 59 years; baseline A1C 8.2%) were randomized (degludec: 773, glargine: 257). Reduction in A1C with degludec was similar (noninferior) to that with glargine (1.06 vs. 1.19%), with an estimated treatment difference of degludec to glargine of 0.09% (95% CI −0.04 to 0.22). Overall rates of confirmed hypoglycemia (PG <3.1 mmol/L or severe episodes requiring assistance) were similar, with degludec and glargine at 1.52 versus 1.85 episodes/patient-year of exposure (PYE). There were few episodes of nocturnal confirmed hypoglycemia in the overall population, and these occurred at a lower rate with degludec versus glargine (0.25 vs. 0.30 episodes/PYE; P = 0.038). Similar percentages of patients in both groups achieved A1C levels <7% without hypoglycemia. End-of-trial mean daily insulin doses were 0.59 and 0.60 units/kg for degludec and glargine, respectively. Adverse event rates were similar.

CONCLUSIONS — Insulins degludec and glargine administered once daily in combination with OADs provided similar long-term glycemic control in insulin-naive patients with type 2 diabetes, with lower rates of nocturnal hypoglycemia with degludec.
Initiating insulin degludec in type 2 diabetes

A

$A_1c$ (%)

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Time (weeks)

B

FPG (mmol/L)

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<td>3.5</td>
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Time (weeks)
Overall Confirmed Hypoglycemic Episodes

Nocturnal confirmed hypoglycemic episodes

CONCLUSIONS
Insulins degludec and glargine administered once daily in combination with OADs provided similar long-term glycemic control in insulin-naive patients with DM2, with lower rates of nocturnal hypoglycemia with degludec

Tresiba® shows lower rate of hypoglycaemia than insulin glargine U100 in SWITCH 1 trial

**SWITCH 1 trial design**

- **Tresiba® once daily + 2-4 x IAsp**
  - 501 people with type 1 diabetes
  - Randomised 1:1 Double-blinded
  - 16 week titration\(^1\)
  - 16 week HbA\(_{1c}\) stable

- **IGlar once daily + 2-4 x IAsp**
  - 16 week titration\(^1\)
  - 16 week HbA\(_{1c}\) stable

**Headline results**

<table>
<thead>
<tr>
<th>Event rate per 100 patient years exposed in maintenance period</th>
<th>Tresiba®</th>
<th>IGlar</th>
<th>Tresiba® reduction vs IGlar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or BG confirmed symptomatic hypoglycaemia</td>
<td>2,201</td>
<td>2,463</td>
<td>11%*</td>
</tr>
<tr>
<td>Severe or BG confirmed symptomatic nocturnal hypoglycaemia</td>
<td>277</td>
<td>429</td>
<td>36%*</td>
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<tr>
<td>Severe hypoglycaemia</td>
<td>69</td>
<td>92</td>
<td>35%*</td>
</tr>
<tr>
<td>Proportions of subjects with severe hypoglycaemia</td>
<td>10%</td>
<td>17%</td>
<td>Significant reduction</td>
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</table>

\(^1\) 20% insulin dose reduction when initiating titration

Note: Daily injections of both Tresiba® and insulin glargine evenly split between morning and evening
IGlar: insulin glargine U100; IAsp: insulin aspart

\(* p < 0.001; BG: blood glucose;\)
Tresiba® shows lower rate of hypoglycaemia than insulin glargine U100 in SWITCH 2 trial

**SWITCH 2 trial design**

721 people with type 2 diabetes

- Randomised 1:1 Double-blinded

  - Tresiba® once daily ± OAD
  - IGLar once daily ± OAD

  - 16 week titration
  - 16 week HbA1c stable

**Headline results**

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<th>Event rate per 100 patient years exposed in maintenance period</th>
<th>Tresiba®</th>
<th>IGLar</th>
<th>Tresiba® reduction vs IGLar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or BG confirmed symptomatic hypoglycaemia</td>
<td>186</td>
<td>265</td>
<td>30%*</td>
</tr>
<tr>
<td>Severe or BG confirmed symptomatic nocturnal hypoglycaemia</td>
<td>55</td>
<td>94</td>
<td>42%*</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>5</td>
<td>9</td>
<td>46%</td>
</tr>
<tr>
<td>Severe hypoglycaemia (Full treatment period)</td>
<td>4</td>
<td>9</td>
<td>51%*</td>
</tr>
</tbody>
</table>

* p < 0.001; BG: Blood glucose;
Note: The confirmatory secondary endpoint of proportions of subjects experiencing severe hypoglycaemia during the maintenance period did not reach statistical significance.
DEVOTE, CVOT
Insulin Degludec

• A global study including 7,637 participants in 20 countries around the world

• Insulin degludec demonstrated superiority on the secondary confirmatory endpoint of severe hypoglycemia:
  – 27% fewer patients in the insulin degludec treated group experienced an episode of severe hypoglycemia, vs. insulin glargine
  – 40% overall reduction of total episodes of adjudicated severe hypoglycemia

• Patients in insulin degludec treated group experienced a 54% relative reduction in the rate of nocturnal severe hypoglycemia

• Insulin degludec CV safety established
Both LY IGlar and IGlar, when used in combination with oral antihyperglycemic medications, provided effective and similar glucose control with similar safety profiles in patients with DM2

Both LY IGlar and IGlar, when used in combination with mealtime insulin lispro, provided effective and similar glucose control and similar safety profiles in patients with DM1

Blevins TC et al. Diabetes Obes Metab. 2015;17(8):726-33.
Summary: New Basal Insulins

• Insulin degludec (Tresiba®) and insulin glargine U-300 (Toujeo®) vs. insulin glargine U-100 (Lantus®)
  – Flatter and more prolonged time-action profile
  – Less nocturnal hypoglycemia (Toujeo®)
  – Less nocturnal and severe hypoglycemia (Tresiba®)
  – Similar efficacy in terms of A1C lowering, when titrated accordingly
  – Currently no head-to-head studies comparing Tresiba® vs. Toujeo®

• Biosimilar insulin Glargine (Basaglar®)
  – Similar glucose control with similar safety vs. insulin glargine (Lantus®)

GLP-1 Receptor Agonists
Available Agents
Exenatide BID vs. Long-acting GLP-1 agonists

• Trials comparing exenatide BID with exenatide QW, liraglutide once daily, or dulaglutide once weekly, noted A1C reduction with daily or weekly GLP-1 agonists was significantly greater—Treatment difference -0.3 to -0.7%

• Generally speaking, the long-acting GLP-1 agonists have similar or better tolerability

GLP-1 Therapies
Which one to choose?

• Among the long-acting agents, patient preference and payer coverage are important considerations.

• Among the longer-acting GLP-1 agonists, small differences in glucose control favor once-daily liraglutide to exenatide once weekly and albiglutide.

• Glycemic control appears to be similar with liraglutide and dulaglutide.

Long-acting GLP-1
Other Considerations

• Tolerability

• Means of injection
  – Differences in device

• GFR
  – Exenatide not recommended in patients with CrCl <30 mL/minute or end-stage renal disease (ESRD)
Semaglutide Oral Formulation

Novo's oral version of semaglutide impresses in Phase II

DAILY NEWS | FEBRUARY 22, 2015
KEVIN OROGAN

Shares in Novo Nordisk have risen after the Danish company presented positive mid-stage results on OG217SC, an oral formulation of its long-acting GLP-1 analogue semaglutide.

A Phase II trial compared once-daily OG217SC with oral placebo or once-weekly subcutaneously-administered semaglutide in around 560 people with type 2 diabetes treated for 26 weeks.

People treated with oral semaglutide in five different doses ranging from 2.5 mg to 40 mg achieved dose-dependent improvements in HbA1c of 0.7% to 1.9% after 26 weeks. Those on a dose of 1 mg subcutaneous semaglutide or placebo achieved improvements of 1.9% and 0.3% respectively.

Weight loss

Novo also noted that from a mean baseline weight of 92kg, people treated with subcutaneous semaglutide experienced a weight loss of around 6.5kg, which was comparable to the weight loss experienced by the people treated with the highest doses of oral semaglutide. Those on placebo had a weight loss of just over 1kg.

Gastrointestinal adverse events appeared to be dose-dependent and were more prevalent for the highest doses of oral semaglutide compared to the subcutaneous version of the drug.

Mads Krogsgaard Thomsen, Novo's chief science officer, said the results confirm the potential of semaglutide both as a once-weekly subcutaneous injection (which is in Phase III) and as a once-daily tablet. He added that “this clinical proof of concept marks an important milestone for oral peptide therapy” and the firm will talk to regulatory authorities about whether it will progress OG217SC into Phase III as well.
New Therapies
Basal Insulin + GLP-1 Combination
Scientific Logic of Combining Basal Insulin With a GLP-1 Agonist

Basal insulin analogues
- Simple to initiate
- Control nocturnal and FPG
- Lower hypoglycaemia risk vs NPH
- Modest weight increase (1 to 3 kg)
- Achieve HbA$_{1c}$ targets in ~50-60%

Complementary actions

GLP-1 RAs
- Simple to initiate
- Pronounced PPG control
- No increase in hypoglycaemia
- Weight lowering/neutral effects
- Achieve HbA$_{1c}$ targets in ~40–60%

Additive effects

Courtesy of Julio Rosenstock, MD.
Xultophy: iDegLira

Soliqua: iGlarLixi
DUAL-1
IDegLira

Main phase - 26 weeks
- Open label randomisation (2:1:1) to receive either IDegLira, insulin degludec or liraglutide once daily
- IDegLira + met\textsuperscript{t} ± pio\textsuperscript{t} (n=834)
- Insulin degludec + met\textsuperscript{t} ± pio\textsuperscript{t} (n=414)
- Liraglutide 1.8 mg + met\textsuperscript{t} ± pio\textsuperscript{t} (n=415)

Extension phase - 26 weeks
- Extension Phase examined sustainability of endpoints (n=1311)
- IDegLira + met\textsuperscript{t} ± pio\textsuperscript{t} (n=665)
- Insulin degludec + met\textsuperscript{t} ± pio\textsuperscript{t} (n=333)
- Liraglutide 1.8 mg + met\textsuperscript{t} ± pio\textsuperscript{t} (n=313)

0 weeks
26 weeks
52 weeks

Continued allotted treatment

People with type 2 diabetes uncontrolled on oral antidiabetic therapy (OADs)* (n=1663)

\textsuperscript{t} met=metformin, \textsuperscript{pio}=pioglitazone
* OADs = metformin±pioglitazone
DUAL-1: IDegLira,* A Fixed-Ratio Combination in Patients with T2D

- **Study:** fixed ratio combination of insulin degludec (IDeg) and liraglutide (Lira)
- **Objective:** evaluate safety and efficacy of IDegLira compared with degludec or liraglutide alone

<table>
<thead>
<tr>
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<th>IDegLira*</th>
<th>Degludec</th>
<th>Liraglutide</th>
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<tr>
<td>(n=834)</td>
<td>(n=414)</td>
<td>(n=415)</td>
<td></td>
</tr>
<tr>
<td>Δ HbA₁c</td>
<td>-1.9%</td>
<td>-1.4%</td>
<td>-1.3%</td>
</tr>
<tr>
<td>Proportion achieving HbA₁c &lt;7.0%</td>
<td>81%</td>
<td>65%</td>
<td>60%</td>
</tr>
<tr>
<td>FPG</td>
<td>100 mg/dL</td>
<td>104 mg/dL</td>
<td>131 mg/dL</td>
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<tr>
<td>Δ body weight</td>
<td>-0.5 kg</td>
<td>+1.5 kg</td>
<td>-2.9 kg</td>
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</table>

- **Conclusion:** IDegLira improves glycemic control with a low risk of hypoglycemia, weight gain, or GI complaints

IDegLira*: Combination Insulin Degludec* and Liraglutide

- HbA$_{1c}$ decreased by 1.9% from 8.4% to 6.4% with IDegLira

DUAL™ I phase 3 trial confirms IDegLira efficacy and safety in people with type 2 diabetes

**Conclusion**

- Once daily IDegLira achieved a statistically significantly greater reduction in HbA$_{1c}$ (-1.9%) than insulin degludec (-1.4%) or liraglutide (-1.3%).
- Statistically significantly more people on once daily IDegLira achieved an HbA$_{1c}$ of <7% (81%) compared to insulin degludec (65%) or liraglutide (60%).
- IDegLira resulted in a statistically significantly 32% lower rate of hypoglycaemia than insulin degludec.
- IDegLira resulted in a statistically significantly greater weight loss vs. insulin degludec (-2.22 kg).
- GI side effects with IDegLira were less than with liraglutide (nausea: 8.8% vs. 19.7%; vomiting: 3.9% vs. 8.5%). No other significant differences were seen between arms in standard safety parameters.
**LixiLan-O: Study Design**

**Design**
- Randomized, open label, active controlled, 3-arm parallel-group trial
- 7.0% ≥ A1C ≤10.0%
  - FPG ≤250 mg/dL
  - Met ≥1500 mg/day

- Metformin alone or combined with a 2nd OAD
- A1C: 7.0–9.0% (if on 2 OADs)
- A1C: 7.5–10.0% (if on metformin alone)

**Objectives / Endpoints**

**Primary:**
- For A1C change at week 30:
  - Superiority of iGlarLixi over Lixisenatide and
  - Non-inferiority of iGlarLixi over Gla-100 (0.3% non-inferiority margin)
  
  - superiority tested if non-inferiority shown

**Secondary:**
- Compare treatments on:
  - Body weight
  - Postprandial glucose
  - % of patients with A1C <7.0% and no weight gain and/or documented hypoglycemia
  - 7-point SMPG profiles
  - Gla-100 dose
  - FPG

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OAD, oral antidiabetes drug; SMPG, self monitored plasma glucose; FPG, fasting plasma glucose; Sanofi, data on file.
LixiLan-O: Key results

**A1C Reduction**
- LS mean change (%)
  - iGlarLixi: -1.6
  - Gla-100: -1.3
  - Lixisenatide: -0.9
- P < 0.0001
- P < 0.0001

**PPG Reduction**
- 2-hour PPG (mmol/L)
  - LS mean change (mmol/L)
    - iGlarLixi: -5.7
    - Gla-100: -3.3
    - Lixisenatide: -1.1
    - 95% CI: -2.3, -2.0
    - 95% CI: -1.4, -0.6
- Excursion PPG (mmol/L)
  - LS mean change (mmol/L)
    - iGlarLixi: -2.4
    - Gla-100: -2.3
    - Lixisenatide: -2.1
    - 95% CI: -2.3, -1.8
    - 95% CI: 0.9, 1.4

**Patients at target A1C**
- Proportion of patients (%)
  - A1C < 7.0%
    - iGlarLixi: 40.6%
    - Gla-100: 36.4%
    - Lixisenatide: 25.6%
  - A1C ≤ 6.5%
    - iGlarLixi: 74%
    - Gla-100: 59%
    - Lixisenatide: 56%

**Weight change**
- Baseline
  - 89.4
  - 89.8
  - 90.8
- LS mean change (kg)
  - iGlarLixi: -0.3
  - Gla-100: 1.1
  - Lixisenatide: -2.3
  - 95% CI: -1.4, -0.9
  - 95% CI: 1.4, 2.6

**Hypoglycemia††**
- Patients with events (%)
  - Baseline
    - iGlarLixi: 25.6
    - Gla-100: 23.6
    - Lixisenatide: 6.4
- No. of events per patient year
  - iGlarLixi: 1.4
  - Gla-100: 1.2
  - Lixisenatide: 0.3

*P < 0.0001; †Mean body weight (kg) at baseline; ††Documented symptomatic hypoglycemia, defined as plasma glucose ≤ 70 mg/dL.
*One event of severe hypoglycemia was reported during the study and occurred in the Gla-100 group.

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Adult patients with T2DM uncontrolled on Lantus®

Mean baseline A1C: 8.1%
Range: 7.0% to 10%

SOLIQUA 100/33 (n=365)
Lantus® (n=365)

-1.1%
-0.6%
P<0.01

The mean difference (95% CI) in A1C reduction between SOLIQUA 100/33 and Lantus® was -0.5 [-0.6, -0.4] and statistically significant (P<0.01).

SOLIQUA 100/33 provided statistically significant reduction in mean A1C vs Lantus®

Please see full Important Safety Information for SOLIQUA 100/33 on slides 8-12.
Please see full Prescribing Information available at this event.
SOLIQUA 100/33 Prescribing Information. November 2016.
Cardiovascular Outcome Trials: CVOT

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

“We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs’ cardiovascular risks during the product’s development stage,” said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. “FDA’s guidance outlines the agency’s recommendations for doing such an assessment.”

More than 23 million people in the United States have been diagnosed with type 2 diabetes or diabetes mellitus, a chronic metabolic disorder characterized by abnormally high blood sugar levels known as hyperglycemia.

Patients with diabetes have a two- to four-times greater risk of heart disease than their non-diabetic counterparts, and none of the currently approved antidiabetic therapies has been convincingly proven to reduce that risk. Because diabetes often requires lifelong treatment, prescribers and patients need to know more about whether their antidiabetic therapies put patients at increased risk of heart attack. This is the purpose of today’s guidance, which has benefited from the July 2008 recommendation from FDA’s Endocrinologic and Metabolic Drugs Advisory Committee.

The guidance, which is effective immediately, defines more robust and adequate design and data collection approaches for Phase 2 and Phase 3 clinical trials than were previously required. Specifically, the guidance recommends that these studies demonstrate that new antidiabetic therapies do not increase cardiovascular risk in comparison with existing therapies — especially when the drugs are used by patients of advanced age or by those with advanced diabetes or renal impairment.

The FDA also recommends that manufacturers have any cardiovascular events in their clinical trials analyzed by committees of outside cardiologists who are unaware of which patients received the tested products and which were on placebo. Based on these evaluations, the FDA can better ensure that product labeling includes comprehensive information on safety and effectiveness. This will enable prescribers and patients to make better-informed decisions on the management of type 2 diabetes.

The FDA remains confident that currently marketed antidiabetic therapies are safe and effective when used according to approved labeling and advises patients to work with their healthcare professionals to select the most appropriate therapy to achieve adequate blood glucose control. The FDA is continuing to evaluate how today’s recommendations will be applied to already approved antidiabetic drugs and expects to release further guidance on this issue in the future.

“The FDA’s guidance and its ongoing evaluation of this issue supports our approach to drug regulation throughout the product life-cycle, by evaluating a drug’s safety before and after its approval,” said Janet Woodcock, M.D., director, CDER, FDA.

“Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” is posted on FDA’s website at http://www.fda.gov/cder/guidance/8570fr.pdf. It will be published in the Federal Register on December 19, 2008. In addition, the FDA has provided written notice of the recommendations from this guidance to more than 100 manufacturers who have submitted investigational new drug applications for type 2 diabetes treatment.
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

FDA NEWS RELEASE

For Immediate Release: Nov. 25, 2013
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FDA requires removal of certain restrictions on the diabetes drug Avandia

The U.S. Food and Drug Administration today announced it is requiring the removal of certain restrictions on prescribing and use of the diabetes drug Avandia (rosiglitazone) to reflect new information regarding the cardiovascular risk of the medicine. Today's actions are consistent with the recommendations of expert advisory committees.

Results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabestes (RECORD) clinical trial showed no elevated risk of heart attack or death in patients being treated with Avandia when compared to standard-of-care diabetes drugs. These data do not confirm the signal of increased risk of heart attacks that was found in a meta-analysis of clinical trials first reported in 2007.

# CVOT, DPP-4 Inhibitors

## Table 1: Main clinical features and outcomes of SAVOR TIMI 53, EXAMINE and TECOS trials

<table>
<thead>
<tr>
<th></th>
<th>SAVOR-TIMI 53 (26)</th>
<th>EXAMINE (27)</th>
<th>TECOS (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>16,402</td>
<td>5,380</td>
<td>14,671</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>T2D patients with CVD or high CV risk</td>
<td>T2D with an acute MI or UA requiring hospitalization within the previous 15-90 days</td>
<td>T2D patients with CVD or high CV risk</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Saxagliptin vs. placebo</td>
<td>Alogliptin vs. placebo</td>
<td>Sitagliptin vs. placebo</td>
</tr>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>65</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td><strong>Diabetes duration (years)</strong></td>
<td>10</td>
<td>7</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Established CVD (%)</strong></td>
<td>78</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td><strong>Mean HbA1c (%)</strong></td>
<td>8±1.4</td>
<td>8±1.1</td>
<td>7.2±0.5</td>
</tr>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td>31</td>
<td>28.7</td>
<td>30.2</td>
</tr>
<tr>
<td><strong>Prior HF</strong></td>
<td>12.8</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td><strong>Median follow-up (years)</strong></td>
<td>2.1</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>15.3</td>
<td>6.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.4</td>
<td>6.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Definition of primary outcome**

- CV death, non-fatal MI, non-fatal ischemic stroke
- CV death, non-fatal MI, non-fatal stroke
- CV death, non-fatal MI, non-fatal stroke, or UA hospitalization

**HR for primary outcome**

- 1.00 (0.89-1.12)
- 0.96 (0.81-1.16)
- 0.98 (0.89-1.06)

**Definition of secondary outcome**

- CV death, MI, stroke, hospitalization for UA, HF, or coronary revascularization due to UA within 24 hours after hospital admission
- CV death, nonfatal MI, or nonfatal stroke

**HR for secondary outcome**

- 1.02 (0.94-1.11)
- 0.95 (0.81-1.14)
- 0.99 (0.89-1.10)

**Hospitalization for HF**

- 1.27 (1.07-1.51)
- 1.19 (0.89-1.59)
- 1.00 (0.84-1.20)
CVOT: SGLT-2 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.,
Michela Matteus, 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

CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

Primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

There were no significant between-group differences in the rates of myocardial infarction or stroke

CVOT: GLP-1 Receptor Agonists

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D.,
Kenneth Dickstein, M.D., Ph.D., Hertzel C. Gerstein, M.D., Lars V. Kober, M.D.,
Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D.,
Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D.,
John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D.,
Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D.,
for the ELIXA Investigators*

CONCLUSIONS

In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events. (Funded by Sanofi; ELIXA ClinicalTrials.gov number, NCT01147250.)

CVOT: GLP-1 Receptor Agonists

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

Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24, June 13 2016, New Orleans, LA, USA.
The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13, 2016, New Orleans, LA, USA.
Time to non-fatal myocardial infarction

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Time to non-fatal stroke

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

A Primary Outcome

Hazard ratio, 0.74 (95% CI, 0.58–0.95)
P<0.001 for noninferiority
P=0.02 for superiority

No. at Risk
Placebo 1649 1616 1586 1567 1534 1508 1479
Semaglutide 1648 1619 1601 1584 1568 1543 1524

B Nonfatal Myocardial Infarction

Hazard ratio, 0.74 (95% CI, 0.51–1.08)
P=0.12

No. at Risk
Placebo 1649 1624 1598 1587 1562 1542 1516
Semaglutide 1648 1623 1609 1595 1582 1560 1543

C Nonfatal Stroke

Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04

No. at Risk
Placebo 1649 1629 1611 1597 1571 1548 1528
Semaglutide 1648 1630 1619 1606 1593 1572 1558

D Death from Cardiovascular Causes

Hazard ratio, 0.98 (95% CI, 0.65–1.48)
P=0.92

No. at Risk
Placebo 1649 1637 1623 1617 1600 1584 1566
Semaglutide 1648 1634 1627 1617 1607 1589 1579
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Dosage</th>
<th>Plasma half-life</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (approved 2005; USFDA)</td>
<td>Eli Lilly/Amylin 5 mcg bid to 10 mcg bid s/c</td>
<td>2.4 hr</td>
<td>Renal</td>
</tr>
<tr>
<td>Liraglutide (approved 2010; USFDA)</td>
<td>Novo Nordisk 0.6 mg to 1.8 mg s/c once a day</td>
<td>13 hrs</td>
<td>Metabolized by DPP4 and endopeptidase (not renally excreted) Renal</td>
</tr>
<tr>
<td>Exenatide LAR (approved EU, 2011)</td>
<td>Eli Lilly/Amylin 2 mg/week s/c</td>
<td>95.4 hr (4 days)</td>
<td>Renal</td>
</tr>
<tr>
<td>Taspoglutide (halted)</td>
<td>Roche</td>
<td></td>
<td>Halted by Roche because of gastrointestinal and hypersensitivity reactions</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Sanofi Aventis Uncertain (probably 20 mcg/day)</td>
<td>2-3 hrs</td>
<td>Renal (30% reduced clearance with GFR &lt; 30 ml/mt)</td>
</tr>
<tr>
<td>Albigrutide</td>
<td>Glaxo-Smith-Kline Uncertain (probably 30 mg/week)</td>
<td>6-8 days</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Eli Lilly Uncertain (once a week)</td>
<td>90 hrs</td>
<td></td>
</tr>
</tbody>
</table>
CV Risk Reduction

Number Needed to Treat (NNT)

• NNT with Empagliflozin for 3 years to prevent one CV death was 39

• NNT with Liraglutide for 3 years to prevent one CV death was 104

• Context: By comparison the NNT with Simvastatin or Ramipril for 5 years were 30 and 59, respectively

QUESTION 1

• Newer basal insulin analogues have the following characteristics and properties:
  A) Lower risk of nocturnal or severe hypoglycemia
  B) Longer duration of action
  C) Flatter action profile
  D) All of the above
Question 2

- Which of the below medications has not been demonstrated to reduce cardiovascular risk in high-risk patients:
  A) Liraglutide
  B) Semaglutide
  C) Lixisenatide
  D) Empagliflozin
Question 3

- Longer acting GLP-1 receptor agonists, vs. short acting GLP-1 receptor agonists, are associated with the following advantages:
  
  A) Better or similar tolerability
  B) Greater A1C reduction
  C) Less frequent administration
  D) All of the above
Thank You