New Treatments for Type 2 Diabetes: Implications of Cardiovascular Outcome Trials

Richard Pratley, M.D.

Samuel Crockett Chair in Diabetes Research
Director, Florida Hospital Diabetes Institute
Senior Investigator, Translational Research Institute
Adjunct Professor, Sanford Burnham Prebys Medical Discovery Institute
Orlando, Florida

Disclosures

- Advisory Board / Consultant: Boehringer-Ingelheim, GSK, Lilly, Merck, Novo Nordisk, Pfizer, Takeda
- Research Support: Lexicon, Lilly, Merck, Novo Nordisk, Pfizer, Sanofi, Takeda

All honoraria directed toward a non-profit which supports education and research
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
Multiple Metabolic Defects Contribute to Hyperglycemia in T2DM

- Islet β-cell: Impaired Insulin Secretion
- Islet α-cell: Increased Glucagon Secretion
- Increased Glucagon Secretion
- Increased HGP
- Decreased Incretin Effect
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

From DeFronzo, Diabetes: 2009
Type 2 Diabetes: A Progressive Disease

Normal $\leftrightarrow$ IGT $\leftrightarrow$ Type 2 Diabetes $\rightarrow$ Complications $\rightarrow$ Disability Death

Prediabetes state

Primary Prevention

Clinical disease

Secondary Prevention

Complications

Tertiary Prevention

Disability

Death

86 million

29 million

IGT = impaired glucose tolerance

Microvascular Complications of T2DM

- In 2005-2008, of adults ≥40 years of age with diabetes, 4.2 million (28.5%) had diabetic retinopathy.
  - 655,000 (4.4%) had advanced diabetic retinopathy
- In 2010, about 73,000 non-traumatic lower-limb amputations were performed in adults ≥20 years of age with diabetes.
- About 60% of non-traumatic lower-limb amputations among adults ≥20 years of age are in people with diabetes.
- Diabetes was listed as the primary cause of kidney failure in 44% of all new cases in 2011.

Diabetes Doubles the Risk for Vascular Outcomes

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05–2.60)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</td>
</tr>
<tr>
<td>Stroke subtypes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95–2.56)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19–2.05)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59–2.13)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51–1.98)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

# 12 Classes of Antihyperglycemic Agents for T2DM

<table>
<thead>
<tr>
<th>Class</th>
<th>$A_1c$ Reduction</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing (times/day)</th>
<th>Other Safety Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>GI, lactic acidosis, B12 deficiency</td>
</tr>
<tr>
<td>Basal insulin analog</td>
<td>1.5–2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1, injected</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Rapid-acting insulin</td>
<td>1.5–2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-4, injected</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1</td>
<td>Allergies, secondary failure</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5–1.4</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>Edema, CHF, bone fractures</td>
</tr>
<tr>
<td>Short-acting GLP-1 RAs</td>
<td>0.5–1.0</td>
<td>No</td>
<td>Loss</td>
<td>2, injected</td>
<td>GI, ? pancreatitis, ARF</td>
</tr>
<tr>
<td>Long-acting GLP-1 RAs</td>
<td>~1.5</td>
<td>No</td>
<td>Loss</td>
<td>1, injected</td>
<td>GI, ? pancreatitis, ?MTC, ?ARF</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1–1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>0.5–0.8</td>
<td>Rare</td>
<td>Gain</td>
<td>3</td>
<td>GI</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>0.5–0.8</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>GI</td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>0.5–1.0</td>
<td>No</td>
<td>Loss</td>
<td>3, injected</td>
<td>GI</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.6–0.8</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>0.5</td>
<td>No</td>
<td>Neutral</td>
<td>1 or 2</td>
<td>GI</td>
</tr>
<tr>
<td>Bromocriptine quick release</td>
<td>0.7</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>GI</td>
</tr>
<tr>
<td>SGLT2s</td>
<td>0.8–1.0</td>
<td>No</td>
<td>Loss</td>
<td>1</td>
<td>Genital mycotic infections</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; RA = receptor agonist; CHF = congestive heart failure; ARF = acute renal failure; MTC = medullary thyroid carcinoma; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-dependent glucose cotransporter.

Complementary Mechanisms of Action of Current Diabetes Medications

- **Insulin Sulfonylureas Meglitinides**
  - Impaired Insulin Secretion
  - Increased Glucagon Secretion

- **GLP-1 RA DPP-4 inhibitors**
  - Decreased Incretin Effect
  - Increased Lipolysis

- **SGLT-2 inhibitors**
  - Increased Glucose Reabsorption
  - Decreased Glucose Uptake

- **Metformin**
  - Increased HGP

- **Bromocryptine**
  - Neurotransmitter Dysfunction

- **TZDs**

From DeFronzo, Diabetes: 2009
# Properties of Established Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| **Biguanides** (Metformin) | • Activates AMP-kinase  
• ↓ Hepatic glucose production | • Extensive experience  
• No hypoglycemia  
• Weight neutral  
• ? ↓ CVD events | • Gastrointestinal  
• Lactic acidosis  
• B-12 deficiency  
• Contraindications | Low |
| **SUs / Meglitinides** | • Closes KATP channels  
• ↑ Insulin secretion | • Extensive experience  
• ↓ Microvascular risk | • Hypoglycemia  
• Weight gain  
• Low durability  
• ? ↓ Ischemic preconditioning | Low |
| **TZDs** | • Activates PPAR-γ  
• ↑ Insulin sensitivity | • No hypoglycemia  
• Durability  
• ↓ TGs, ↑ HDL-C  
• ? ↓ CVD events (pio) | • Weight gain  
• Edema / heart failure  
• Bone fractures  
• ? ↑ MI (rosi)  
• ? Bladder ca (pio) | Low |

The Incretin Defect in T2DM

- Substantial impairment – 40% of normal response
- Not due to impaired secretion of GLP-1 or GIP
- Absent insulinotropic response to GIP
  - Beta-cell GIP receptor down-regulation
- Decreased response to GLP-1
  - Can be overcome by achieving higher than physiologic GLP-1 levels
- GLP-1 infusions that achieve higher levels effective at enhancing insulin secretion and suppressing glucagon in a glucose-dependent manner

Incretin Therapies to Treat T2DM

Incretin effect is impaired in T2DM
Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:
**Injectables**

- Exendin-4 Based:
  - Exenatide
  - Exenatide QW

- Human GLP-1:
  - Liraglutide
  - Albiglutide
  - Dulaglutide

Block DPP-4, the enzyme that degrades GLP-1:
**Oral agents**

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

## Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Alogliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Phase 3 Dose</strong></td>
<td>25, 50, 100 mg QD</td>
<td>6.25, 12.5 25 mg QD</td>
<td>2.5, 5 mg QD</td>
<td>5 mg QD</td>
</tr>
<tr>
<td><strong>Half Life (t1/2)</strong></td>
<td>12.4h</td>
<td>12.5 to 21.1h (25mg)</td>
<td>2.2 to 3.8h</td>
<td>40 h</td>
</tr>
<tr>
<td><strong>DPP-4 inhibition at 24h</strong></td>
<td>~80% at 24h</td>
<td>~78% at 24h (25 mg)</td>
<td>5 mg: ~55% at 24h</td>
<td>75% at 24 h</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Kidney (mostly unchanged)</td>
<td>Kidney (mostly unchanged)</td>
<td>Liver and kidney Active metabolite</td>
<td>Bile (mostly unchanged)</td>
</tr>
<tr>
<td><strong>Renal Dose Adjustments Required</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Selectivity for DPP-4</strong></td>
<td>&gt;2600 fold vs DPP-8 &gt;10,000 fold vs DPP-9</td>
<td>&gt;10,000 fold vs DPP-8/9</td>
<td>&gt;400 fold vs DPP-8 &gt;100 vs DPP-9</td>
<td>&gt;10,000 fold vs DPP-8/9</td>
</tr>
<tr>
<td><strong>Potential for DDI</strong></td>
<td>Low</td>
<td>Low</td>
<td>Strong CYP3A4/5 inhibitors&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Strong CYP3A4/5 inhibitors&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Efficacy of DPP-4 Inhibitor Therapy Added to Metformin

DPP-4 Inhibitors vs Sulfonylureas Added to Metformin – 2-Year Results

**Table:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Δ Weight, kg</th>
<th>Hypoglycemia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPP-4i</td>
<td>SU</td>
</tr>
<tr>
<td>ALO&lt;sup&gt;1,a&lt;/sup&gt;</td>
<td>−0.9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>+1.0</td>
</tr>
<tr>
<td>LINA&lt;sup&gt;2,b&lt;/sup&gt;</td>
<td>−1.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>+1.3</td>
</tr>
<tr>
<td>SAXA&lt;sup&gt;3,c&lt;/sup&gt;</td>
<td>−1.5</td>
<td>+1.3</td>
</tr>
<tr>
<td>SITA&lt;sup&gt;4,d&lt;/sup&gt;</td>
<td>−1.6</td>
<td>+0.7</td>
</tr>
</tbody>
</table>

**Notes:**
GLP-1 Receptor Agonists

GLP-1 RA

- Exendin-4 analogues
  - Lixisenatide
  - Exenatide BID
  - Exenatide QW
- Human GLP-1 Analogues[^4]
  - Liraglutide
  - Albiglutide
  - Dulaglutide
  - Semaglutide*

*Not approved

Structural modifications confer albumin (liraglutide, albiglutide) or IgG Fc fraction (dulaglutide) binding

---

GLP-1 RA Administration and Devices

1. BYETTA Prescribing Information.
2. Victoza Summary of Product Characteristics.
5. BYDUREON Prescribing Information.

- **Dulaglutide**
  - Automatic Injection
  - Hidden needle
  - *Not FDA approved

- **Exenatide BID**
  - 2 pre-filled pens (5 µg and 10 µg)
  - Needle (29-31 gauge) needs attaching prior to use

- **Albiglutide**
  - 2 pre-filled pens; 30 mg (gold pen) or 50 mg (purple pen)
  - Needs reconstitution
  - Needle needs attaching prior to use

- **Liraglutide**
  - 1 pre-filled pen; each delivers 0.6, 1.2, and 1.8 mg
  - ≥32-gauge needle needs attaching prior to use

- **Lixisenatide**
  - 2 pre-filled pens; each dose contains 10 µg (green pen) or 20 µg (purple pen)
  - Needle (29-32 gauge) needs attaching prior to use

- **Exenatide QW**
  - Powder and syringe; needs reconstitution
  - 23-gauge needle needs attaching prior to use

*Not FDA approved

1. BYETTA Prescribing Information.
2. Victoza Summary of Product Characteristics.
5. BYDUREON Prescribing Information.
## Short-Acting vs. Long-acting GLP-1 RAs: Pharmacokinetic Differences

<table>
<thead>
<tr>
<th>Category</th>
<th>Agent</th>
<th>Half-life</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting GLP-1 RAs</td>
<td>Exenatide BID(^1)</td>
<td>2.4 h</td>
<td>2 h</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide(^2)</td>
<td>2.7–4.3 h</td>
<td>1.25–2.25 h</td>
</tr>
<tr>
<td>Long-acting GLP-1 RAs</td>
<td>Liraglutide(^3)</td>
<td>13 h</td>
<td>8–12 h</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide(^4)</td>
<td>90 h</td>
<td>24–48 h</td>
</tr>
<tr>
<td></td>
<td>Albiglutide(^5)</td>
<td>5 days</td>
<td>3–5 days</td>
</tr>
<tr>
<td></td>
<td>Semaglutide(^6)</td>
<td>~7 days</td>
<td>1–1.5 days</td>
</tr>
<tr>
<td></td>
<td>Exenatide OW(^7)</td>
<td>7–14 days</td>
<td>6–7 weeks</td>
</tr>
</tbody>
</table>

OD, once daily; $T_{\text{max}}$, time to reach maximum concentration

GLP-1RA Duration Influences FPG, PPG and A1c

Short-acting

FPG
PPG

Long-acting

FPG
PPG

FPG, fasting plasma glucose; PPG, postprandial plasma glucose
Head-to-Head Trials Comparing Efficacy of GLP-1 RAs

a \( P < .05 \) between groups.
b Noninferiority vs LIRA not met.
c DULA noninferior to LIRA, \( P < .0001 \).

GLP-1 RAs vs DPP-4 Inhibitors
Added to Metformin

<table>
<thead>
<tr>
<th>Agent</th>
<th>Δ Weight, kg</th>
<th>Hypoglycemia, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GLP-1 RA</td>
<td>DPP-4i</td>
</tr>
<tr>
<td>EXEN BID&lt;sup&gt;1,d&lt;/sup&gt;</td>
<td>−2.8</td>
<td>NA</td>
</tr>
<tr>
<td>EXEN QW&lt;sup&gt;2,e&lt;/sup&gt;</td>
<td>−2.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.8</td>
</tr>
<tr>
<td>LIRA&lt;sup&gt;3,f&lt;/sup&gt;</td>
<td>−3.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−1.0</td>
</tr>
<tr>
<td>DULA&lt;sup&gt;4,g&lt;/sup&gt;</td>
<td>−3.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−1.5</td>
</tr>
<tr>
<td>ALBI&lt;sup&gt;5,h&lt;/sup&gt;</td>
<td>−0.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−0.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>P<0.0001 vs DPP-4 inhibitor; <sup>b</sup>P<0.001 vs DPP-4 inhibitor; <sup>c</sup>P<0.05 vs DPP-4 inhibitor; <sup>d</sup>No statistical analysis performed; <sup>e</sup>EXEN BID: 30-week study of exenatide twice daily; baseline A1C, 8.2%; <sup>f</sup>EXEN QW: 26-week trial of exenatide once weekly; baseline A1c, 8.4%; <sup>g</sup>LIRA: 26-week trial with liraglutide; baseline A1c, 8.5%; <sup>h</sup>DULA: 52-week trial; baseline A1c, 8.1%; <sup>i</sup>ALBI: 26-week trial of albiglutide; baseline A1c, 8.2%; <sup>j</sup>Almost all patients experiencing hypoglycemia were also taking a sulfonylurea.

SGLT-2 Inhibition

**Insulin-Independent Reversal of Glucotoxicity**

## FDA-approved SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>• Oral, once daily&lt;br&gt;• Taken before the first meal of the day</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>• Oral, once daily</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>• Taken in the morning with or without food</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitors vs Sulfonylureas
Added to Metformin

- **CANA**1,a: \(-4.0^a\) vs \(+0.7\) SU.
- **DAPA**2,b: \(-3.2^a\) vs \(+1.4\) SU.
- **EMPA**3,c: \(-3.2^a\) vs \(+1.6\) SU.

**Δ Weight, kg**

<table>
<thead>
<tr>
<th>Agent</th>
<th>SGLT-2 Inhibitor</th>
<th>SU</th>
<th>SGLT-2 Inhibitor</th>
<th>SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANA1,a</td>
<td>(-4.0^a)</td>
<td>+0.7</td>
<td>5^a</td>
<td>34</td>
</tr>
<tr>
<td>DAPA2,b</td>
<td>(-3.2^a)</td>
<td>+1.4</td>
<td>3^a</td>
<td>41</td>
</tr>
<tr>
<td>EMPA3,c</td>
<td>(-3.2^a)</td>
<td>+1.6</td>
<td>2^a</td>
<td>24</td>
</tr>
</tbody>
</table>

\(^aP < 0.0001\) vs SU.

\(^b\) CANA: 52-week trial of canagliflozin; baseline A1c, 7.8%;
\(^c\) DAPA: 52-week trial of dapagliflozin; baseline A1c, 7.7%;
\(^d\) EMPA: 104-week trial of empagliflozin; baseline A1c, 7.9%.

Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
Diabetes and Cardiovascular Disease: The Perfect Storm

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.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

For completed studies prior to NDA:

- Integrated meta-analysis of phase 2/3 trials to compare CV events in patients randomized to investigational drug vs. control

- Demonstrate new therapy will not result in an unacceptable CV risk
  - Evaluated by Major Adverse Cardiovascular Events (MACE)
  - Estimated risk ratio for upper bound of the 2-sided CI for the investigational drug should be <1.8
  - If upper CI = 1.3 - 1.8, post-marketing CV surveillance trial may be required
# Traditional CV Outcome Trials vs Diabetes CV Safety Trials

<table>
<thead>
<tr>
<th>Traditional (eg, LDL-C) CV Outcome Trials</th>
<th>Diabetes CV Safety Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Designed to Demonstrate CV Benefit</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td><strong>Primarily Designed to Demonstrate CV Safety</strong>&lt;sup&gt;3–5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lower CV risk vs Placebo or Active comparator</td>
<td>No increased CV risk vs Placebo as part of standard care</td>
</tr>
<tr>
<td>Initiation of blinded treatment or placebo or active comparator</td>
<td>Initiation of blinded treatment or placebo</td>
</tr>
<tr>
<td>No adjustment to maintain LDL-C levels the same in both groups</td>
<td>Adjustment to maintain HbA&lt;sub&gt;1c&lt;/sub&gt; levels the same in both groups</td>
</tr>
<tr>
<td>Difference in LDL-C between treatment and placebo or active comparator</td>
<td>Small or no difference in HbA&lt;sub&gt;1c&lt;/sub&gt; between treatment and placebo</td>
</tr>
<tr>
<td>CV benefit of treatment demonstrated by significant reduction in CV outcomes</td>
<td>No increased CV risk (CV safety) of treatment demonstrated by noninferiority</td>
</tr>
</tbody>
</table>

**CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; LDL-C = low density lipoprotein cholesterol.**

Cardiovascular Outcomes Trials in Diabetes

Boxes with broken lines are for completed CVOTs
CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; QW, once weekly; SGLT-2i, sodium glucose co-transporter 2 inhibitor; SU, sulphonylurea

Source: clinicaltrials.gov (October 2016)
T2DM Patients in CV Outcomes Trials

- 25 Trials Ongoing/Completed
- 8 classes of medications
- >200,000 planned participants

Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
PROactive: Significant Reduction in Secondary Outcome

All-cause mortality, nonfatal MI*, stroke

- Pioglitazone: 301 events
- Placebo: 358 events

16% RRR
HR 0.84 (0.72–0.98)
P = 0.027

*Excluding silent MI

## PROactive: HF Hospitalization and Mortality

- **HF leading to hospital admission***
  - **Pioglitazone**: 149 (5.7%)
  - **Placebo**: 108 (4.1%)
  - **P**: 0.007

- **Fatal HF**
  - **Pioglitazone**: 25 (0.96%)
  - **Placebo**: 22 (0.84%)
  - **P**: NS

---

*N = 5238

---

*Non-adjudicated

---

Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip D Home, Stuart J Pocock, Henning Beck-Nielsen, Paula S Curtis, Ramon Gomis, Markolf Hanefeld, Nigel P Jones, Michel Komajda, John J V McMurray, for the RECORD Study Team*


- 5½-year study
- 338 centers
- 23 countries in Europe, Australia, and New Zealand

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>2220</td>
</tr>
<tr>
<td></td>
<td>2086</td>
</tr>
<tr>
<td></td>
<td>1981</td>
</tr>
<tr>
<td></td>
<td>1883</td>
</tr>
<tr>
<td></td>
<td>1795</td>
</tr>
<tr>
<td></td>
<td>1720</td>
</tr>
<tr>
<td></td>
<td>918</td>
</tr>
<tr>
<td>Active control</td>
<td>2227</td>
</tr>
<tr>
<td></td>
<td>2101</td>
</tr>
<tr>
<td></td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>1895</td>
</tr>
<tr>
<td></td>
<td>1798</td>
</tr>
<tr>
<td></td>
<td>1697</td>
</tr>
<tr>
<td></td>
<td>908</td>
</tr>
</tbody>
</table>
Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip D Home, Stuart J Pocock, Henning Beck-Nielsen, Paula S Curtis, Ramon Gomis, Markolf Hanefeld, Nigel P Jones, Michel Komajda, John J V McMurray, for the RECORD Study Team*

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosiglitazone (N=2220)</th>
<th>Active control (N=2227)</th>
<th>HR</th>
<th>Rate difference per 1000 person-years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or CV hospitalisation</td>
<td>321</td>
<td>323</td>
<td>0.99 (0.85 to 1.16)</td>
<td>-0.2 (-4.5 to 4.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>All-cause death</td>
<td>136</td>
<td>157</td>
<td>0.86 (0.68 to 1.08)</td>
<td>-1.7 (-4.3 to 0.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>CV death</td>
<td>60</td>
<td>71</td>
<td>0.84 (0.59 to 1.18)</td>
<td>-0.9 (-2.7 to 0.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>64</td>
<td>56</td>
<td>1.14 (0.80 to 1.63)</td>
<td>0.6 (-1.1 to 2.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke*</td>
<td>46</td>
<td>63</td>
<td>0.72 (0.49 to 1.06)</td>
<td>-1.4 (-3.1 to 0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>154</td>
<td>165</td>
<td>0.93 (0.74 to 1.15)</td>
<td>-1.0 (-3.9 to 1.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>61</td>
<td>29</td>
<td>2.10 (1.35 to 3.27)</td>
<td>2.6 (1.1 to 4.1)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Data are numbers, HR (95% CI), or rate differences (95% CI). CV=cardiovascular. MI=myocardial infarction. *Fatal and non-fatal.

Table 4: Deaths and hospitalisations from cardiovascular causes

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

**Eligibility:**
- Recent TIA or Ischemic Stroke
- Non-Diabetic
- Insulin Resistant (HOMA > 3.0)
- No CHF

**IRIS: Trial Design**

- Placebo
  - Fatal/non-fatal MI
  - Fatal/non-fatal stroke
- Pioglitazone
  - 15mg → 45 mg
  - 5 years

*R  N=3895*

*90% power to detect a 20% RRR from 27% in the placebo group to 22% in the pioglitazone group at an alpha level of 0.05*

Viscoli CM et al. Am Heart J 2014;168:823

ClinicalTrials.gov Identifier: NCT00091949
IRIS: Primary Outcome

Cumulative Event-Free Survival Probability

HR 0.76
95% CI, 0.62 to 0.93
P=0.007

Summary: Thiazolidinedione Cardiovascular Outcomes Trials

- No apparent increased risk of MI or MACE
  - Some benefit apparent with pioglitazone
  - Cannot assume that this is a class effect
- Increased risk for heart failure
  - No increased risk for heart failure deaths
- Increased risk for fractures
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
Saxagliptin in Patients with Acute Coronary Syndrome: Effects on Subclinical Atherosclerosis

Eugene B. Braunwald, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., Boaz Hirsh, M.D., Matthias Pfisterer, M.D., Nihar R. Desai, M.D., Kausik K. Ray, M.D., Matthew Vranic, M.D., Jennifer B. Miller, M.D., John B. Ettinger, M.D., Robert M. Califf, M.D., Scott Korn, M.D., Michael J. McKinney, M.D., and Boaz Hirsh, M.D.

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE
**Cardiovascular Outcomes Trials for DPP-4 Inhibitors**

**SAVOR-TIMI 53**

- **Primary Endpoint**: CV death, nonfatal MI, or nonfatal stroke
- **Hazard Ratio**: 1.00 (95% CI 0.89, 1.12)  
  p=0.99

**EXAMINE**

- **Primary Endpoint**: CV death, nonfatal MI, or nonfatal stroke
- **Hazard Ratio**: 0.96 (upper boundary of 1-sided repeated CI 1.16)  
  p=0.315

**TECOS**

- **Primary Endpoint**: CV death, nonfatal MI, or nonfatal stroke, or UA requiring hospitalization
- **Hazard Ratio**: 0.98 (95% CI 0.88, 1.09)  
  p=0.645 (superiority)
- **Hazard Ratio**: 0.99 (95% CI 0.89, 1.10)  
  p=0.84 (superiority)

---

**Randomization** | **Year 1** | **Year 2** | **Year 3**
--- | --- | --- | ---
**Median Duration of Follow-up**

---

Cardiovascular Outcomes Trials for DPP-4 Inhibitors

Saxagliptin (SAVOR-TIMI 53 Trial\(^1\))

- \(N=16,492\)
- Composite of CV death, MI, or ischemic stroke
- Hazard ratio: 1.00 (95% CI: 0.89–1.12)
- \(P < 0.001\) (noninferiority)

0 12 24 36 48 60 72 84

Alogliptin (EXAMINE Trial\(^2\))

- \(N=5380\)
- Composite of CV death, nonfatal MI, or nonfatal stroke
- Hazard ratio: 0.96 (upper boundary of one-sided repeated 95% CI: 1.16)

0 6 12 18 24 30

Sitagliptin (TECOS Trial\(^3\))

- \(N=14,671\)
- Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
- Hazard ratio: 0.98 (95% CI: 0.89, 1.08)
- \(P = 0.65\)

SAVOR-TIMI 53, EXAMINE, and TECOS: MACE Outcomes

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>n/N (%)</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (saxagliptin vs placebo)</td>
<td>613/8280 (7.4%)</td>
<td>609/8212 (7.4%)</td>
<td>1.00</td>
<td>0.89, 1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>EXAMINE (alogliptin vs placebo)</td>
<td>305/2701 (11.3%)</td>
<td>316/2679 (11.8%)</td>
<td>0.96</td>
<td>NA, 1.16</td>
<td>0.315</td>
</tr>
<tr>
<td>TECOS (sitagliptin vs placebo)</td>
<td>745/7332 (10.2%)</td>
<td>746/7339 (10.2%)</td>
<td>0.99</td>
<td>0.89, 1.10</td>
<td>0.844</td>
</tr>
<tr>
<td>SAVOR + EXAMINE + TECOS</td>
<td>1663/18313 (9.1%)</td>
<td>1671/18230 (9.2%)</td>
<td>0.99</td>
<td>0.92, 1.06</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity for 3 trials: $p=0.877$, $I^2=0\%$

*Lower Confidence Limit not given for EXAMINE trial; MACE = major adverse cardiac events.

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Study Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR-TIMI</strong>&lt;br&gt;(saxagliptin vs placebo)</td>
<td>289/8280 (3.5%)</td>
<td>228/8212 (2.8%)</td>
<td>1.27</td>
<td>1.07, 1.51</td>
<td>0.009*</td>
</tr>
<tr>
<td><strong>EXAMINE</strong>&lt;br&gt;(alogliptin vs placebo)</td>
<td>106/2701 (3.9%)</td>
<td>89/2679 (3.3%)</td>
<td>1.19</td>
<td>0.89, 1.58</td>
<td>0.238</td>
</tr>
<tr>
<td><strong>TECOS</strong>&lt;br&gt;(sitagliptin vs placebo)</td>
<td>228/7332 (3.1%)</td>
<td>229/7339 (3.1%)</td>
<td>1.00</td>
<td>0.83, 1.20</td>
<td>0.983</td>
</tr>
</tbody>
</table>

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.

Summary: DPP-4 Inhibitor Cardiovascular Outcomes Trials

- All trials met the primary goal of demonstrating that there is no increased risk of CVD
  - No benefit is apparent
  - Cannot assume that this is a class effect
  - There may be heterogeneity with respect to heart failure

- These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  - Decreased rates of albuminuria

- More precise estimates of the risk of other rare events
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
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
EMPA-REG Outcomes Trial: Design

Screening (n=11531) → Randomised and treated (n=7020)

- Placebo (n=2333)
- Empagliflozin 10 mg (n=2345)
- Empagliflozin 25 mg (n=2342)

Key inclusion criteria:
- Adults with type 2 diabetes
- BMI < 45 kg/m²
- HbA1c 7-10%
- Established cardiovascular disease

Key exclusion criteria:
- eGFR < 30 mg/min/1.73 m² (MDRD)

Median treatment duration = 2.6 years

EMPA-REG Outcomes Trial: Main Results

**Cumulative Incidence of the Primary Outcome**

- **Empagliflozin**: Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
- **Placebo**: Hazard ratio, 1.00
- *P*=0.04 for superiority

**Cumulative Incidence of Death From CV Causes**

- **Empagliflozin**: Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- **Placebo**: Hazard ratio, 1.00
- *P*<0.001

**Hospitalization for Heart Failure**

- **Empagliflozin**: Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- **Placebo**: Hazard ratio, 1.00
- *P*=0.002

---

*Cumulative incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
N=7020 patients with T2DM at high risk of cardiovascular events.*

### EMPA-REG Outcomes Trial: CV Death, MI and Stroke

<table>
<thead>
<tr>
<th>Patients with event/analysed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.92, 1.67)</td>
<td>0.1638</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 Outcomes Trial: Renal Outcomes

- Lower rates of acute renal failure and kidney injury (5.2% vs 6.6% and 1.0% vs 1.6%, respectively; \( P < .05 \) vs placebo)\(^1\)
- A1C reduction of \(-0.52\% \) to \(-0.68\% \) vs placebo in CKD stage 2-3 (eGFR \( \geq 30 \) to \(< 90 \) mL/min/1.73m\(^2\)), \( P < .0001 \)\(^2\)
- Equivalent adverse event rates as placebo in patients in CKD stage 2-3\(^2\)

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*
# Baseline Demographics and Disease History

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female, %</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Mean duration of diabetes, y</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Heart failure (NYHA I-III), %</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>65</td>
<td>67</td>
</tr>
</tbody>
</table>
CANVAS: Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)  
p < 0.0001 for noninferiority  
p = 0.0158 for superiority

No. of patients
Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661

CANVAS: Renal Outcomes

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

Hazard ratio 0.60 (95% CI, 0.47-0.77)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
<td></td>
<td>21</td>
</tr>
</tbody>
</table>

Patients with an event (%)

No. of patients

Placebo  4347
Canagliflozin  5795

Years since randomization

## CANVAS: Amputation Risk

### Highest Level of Amputation

<table>
<thead>
<tr>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canagliflozin</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>All amputations (n = 187)</td>
<td>6.3</td>
</tr>
<tr>
<td>Minor amputation (71%)</td>
<td>4.5</td>
</tr>
<tr>
<td>Toe</td>
<td>3.4</td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.0</td>
</tr>
<tr>
<td>Major amputation (29%)</td>
<td>1.8</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
</tr>
<tr>
<td>Below-knee</td>
<td>1.2</td>
</tr>
<tr>
<td>Above-knee</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Summary: SGLT-2 Inhibitor Cardiovascular Outcomes Trials

- Both trials met the primary goal of demonstrating that there is no increased risk of CVD
  - MACE benefit with both empagliflozin and canagliflozin
  - Heart failure benefit for both empagliflozin and canagliflozin
  - Mortality benefit with empagliflozin but not canagliflozin

- These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  - Decreased rates of albuminuria

- More precise estimates of the risk of other rare events
  - Amputation and fracture risk with canagliflozin
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
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. Køber, 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*
ELIXA Study: Lixisenatide vs. Placebo

6,068 subjects with T2DM and recent ACS event randomized to lixisenatide vs placebo

**Run-in period**
- Patients were trained in self-administration of daily subcutaneous volume-matched placebo

**Titration**
- Lixisenatide or matching placebo (1:1)
  - Initial dose 10 μg/day
  - Down- or up-titration permitted to maximum of 20 μg/day

**Trial information**
- Multi-centre
- Double-blind
- Parallel-group
- Event-driven
- Randomised

- Glucose control was managed by site investigators’ judgement

Bentley-Lewis R et al. *AHJ* 2015; 169:631-638.e7; Results of ELIXA, oral presentation 3-CT-SY28. Presented at the American Diabetes Association 75th annual scientific sessions, Boston, 8 June 2015
ELIXA Study: Primary Composite Endpoint

Time to first occurrence of the primary CV event: CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina\(^1\)

Patients with event (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>36</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

HR = 1.02 (0.89, 1.17)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3034</td>
<td>3034</td>
</tr>
<tr>
<td>12</td>
<td>2759</td>
<td>2785</td>
</tr>
<tr>
<td>24</td>
<td>1566</td>
<td>1558</td>
</tr>
<tr>
<td>36</td>
<td>476</td>
<td>484</td>
</tr>
</tbody>
</table>

CV, cardiovascular; MI, myocardial infarction


Results of ELIXA, oral presentation 3-CT-SY28. Presented at the American Diabetes Association 75th annual scientific sessions, Boston, 8 June 2015
## ELIXA Study: Lixisenatide vs Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lixisenatide n=3034</th>
<th>Placebo n=3034</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA)</td>
<td>13.4%</td>
<td>13.2%</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>Primary outcome plus hospitalization for HF</td>
<td>15%</td>
<td>15.5%</td>
<td>0.97 (0.85–1.10)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>4.0%</td>
<td>4.2%</td>
<td>0.96 (0.75–1.23)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>–</td>
<td>–</td>
<td>0.94 (0.78–1.13)</td>
</tr>
</tbody>
</table>

ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; ACS = acute coronary syndrome; UA = unstable angina; HF = heart failure.

Trial data presented by Pfeffer, MA et al, ADA Scientific Sessions, June 8 2015, Boston  
*Patients followed for a mean of 2.1 years*
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*
**LEADER: Liraglutide vs. Placebo Cardiovascular Outcomes Trial**

**Key inclusion criteria**

Adult T2D patients:
- $\text{HbA}_1c \geq 7.0\%$
- Antidiabetic drug naïve; or
- Treated with one or more OADs; or
- Treated with basal or premix insulin (alone or in combination with OADs)
- High-risk CV profile

**Placebo** run-in period of ≥2 weeks

Patients demonstrating ≥50% adherence to regimen and willingness to continue with injection protocol for duration of trial proceeded to randomisation

\[ N=9340 \]

Randomisation (1:1)

- Standard of care + liraglutide (0.6–1.8 mg once daily)
- Standard of care + placebo*

3.5–5 year follow-up

---

*Daily single-blind subcutaneous injection of placebo
CV, cardiovascular; OAD, oral antidiabetic drug; T2D, type 2 diabetes

LEADER: Primary and Secondary Outcomes with Liraglutide

**Primary Outcome**
- Hazard ratio, 0.87 (95% CI, 0.78–0.97)
- \(P<0.001\) for noninferiority
- \(P=0.01\) for superiority

**Cardiovascular-Related Death**
- Hazard ratio, 0.78 (95% CI, 0.66–0.93)
- \(P=0.007\)

**Death From Any Cause**
- Hazard ratio, 0.85 (95% CI, 0.74–0.97)
- \(P=0.02\)

---

\(^{a}\)Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

N=9340 patients with T2DM and high cardiovascular risk.

LEADER: Time to First Renal Event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

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; ESRD: end-stage renal disease; HR: hazard ratio.

HR: 0.78
95% CI (0.67–0.92)
p=0.003

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

SUSTAIN 6: Primary and Secondary Outcomes With Semaglutide

A. Primary Outcome

B. Nonfatal Myocardial Infarction

C. Nonfatal Stroke

D. Death from Cardiovascular Causes

Marso et al. NEJM, Oct 2016
Intarcia Announces Successful Cardiovascular Safety Results in Phase 3 FREEDOM-CVO Trial for ITCA 650, an Investigational Therapy for Type 2 Diabetes

Company also Reports New $75 Million Financing for Manufacturing Scale-Up and Inventory Build for Anticipated Global Launch of ITCA 650

- FREEDOM-CVO Phase 3 safety trial in more than 4,000 patients meets its primary and secondary endpoints by demonstrating FDA required non-inferiority for pre-approval cardiovascular (CV) safety. Final data to be published and presented at major future medical meeting.

- Comprehensive Phase 3 data and manufacturing data packages will be in hand during 3Q; Regulatory filing targeted for the end of 3Q 2016 in the U.S.

Boston, MA – May 6, 2016 – Intarcia Therapeutics, Inc. today announced top-line results from its more than 4,000 patient Cardiovascular Safety Study (FREEDOM-CVO trial), clearing the last major clinical hurdle in the global FREEDOM Phase 3 Clinical Trial Program that started in early 2013. Regulatory filing in the U.S. is targeted for end of 3Q, 2016. The Company also announced a $75 million round of debt financing timed to facilitate ongoing scale-up of manufacturing and the production of inventory for the anticipated global launch of ITCA 650 in type 2 diabetes. The new credit facility is with MidCap Financial and Silicon Valley Bank.
Summary: GLP-1 Receptor Agonist Cardiovascular Outcomes Trials

- All trials met the primary goal of demonstrating that there is no increased risk of CVD

- LEADER (liraglutide) and SUSTAIN 6 (semaglutide) demonstrated a benefit on MACE and mortality (liraglutide)

- ELIXA (lixisenatide), EXSCEL (exenatide) and FREEDOM (exenatide) did not demonstrate a CV benefit

- These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  - Decreased rates of albuminuria
  - More precise estimates of the risk of other rare events
    - No increased rate of pancreatitis
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

**DEVOTE: Trial Design**

- **Randomization:** 7637 patients randomized
- **Insulin degludec once daily (blinded vial) + Standard of care**
- **IGlar U100 once daily (blinded vial) + Standard of care**
- **Follow-up period**
- **Interim analysis (150 MACE accrued)**
- **End of treatment (633 MACE accrued)**
- **30 days**

**Primary endpoint**
Time from randomization to first occurrence of a 3-point MACE: cardiovascular death*, non-fatal myocardial infarction* or non-fatal stroke*

**Secondary endpoints**
- Rate of severe hypoglycemic episodes**‡
- Incidence of severe hypoglycemic episodes**‡

Marso S. et al. NEJM, June 14, 2017
## Study Drugs

<table>
<thead>
<tr>
<th></th>
<th>Insulin degludec</th>
<th>IGlar U100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of insulin</strong></td>
<td>New generation long-acting basal insulin analog</td>
<td>First generation basal insulin analog</td>
</tr>
<tr>
<td><strong>Mode of protraction</strong></td>
<td>Forms soluble multihexamers</td>
<td>Precipitates as microcrystals</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>~25 hours</td>
<td>~12 hours</td>
</tr>
<tr>
<td><strong>Day-to-day variability (AUC\text{GIR,0–24h})</strong></td>
<td>Coefficient of variation 20%</td>
<td>Coefficient of variation 80%</td>
</tr>
</tbody>
</table>

AUC\text{GIR}, area under the curve for glucose infusion rate; IGlar U100, insulin glargine U100
DEVOTE: Time to First 3-point MACE

Full analysis set; Cox regression analysis accounting for treatment. Analysis includes events between randomization date and follow-up date. Patients without an event are censored at the time of last contact (phone or visit).

EAC, Event Adjudication Committee; N, number of patients at risk; PYO, patient-years of observation

Marso S. et al. NEJM, June 14, 2017
DEVOTE: Glycemic Control and Severe Hypoglycemia

- Glycemic control (insulin degludec vs. IGlar U100):
  - End of treatment mean HbA$_{1c}$ values 7.55% vs. 7.50%
  - Change in FPG levels -39.9 mg/dL vs. -34.9 mg/dL
- 27% fewer patients experienced severe hypoglycemia with insulin degludec
- 40% rate reduction of severe hypoglycemia
- 53% rate reduction of nocturnal severe hypoglycemia
Outline

- Overview of new classes of diabetes drugs
- Rationale for CVOTs in diabetes
- Cardiovascular safety of new diabetes drugs: evidence to date
  - Thiazolidinediones
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
  - GLP-1 Receptor Agonists
  - Insulin
- Implications of CVOTs for clinical practice
Putting the Mortality Rates From EMPA-REG and LEADER into Perspective

ACE, acetylcholinesterase; ARB, Angiotensin II Receptor Blocker; HF, heart failure; MRA, Mineralocorticoid receptor antagonist

- SOLVD Treatment; CHARM Alternative; COPERNICUS and MERIT-HF; RALES and EMPHASIS-HF; PARADigm, EMPA-REG OUTCOME, LEADER

Considerations for Selecting Therapies

- Current HbA1c and magnitude of reduction needed to reach goal
- Potential effects on body weight and BMI
- Potential for hypoglycemia – age, lack of awareness of hypoglycemia, disordered eating habits
- Effects on CVD risk factors – blood pressure and blood lipids
- Comorbidities – CAD, heart failure, CKD, liver dysfunction
- Patient factors – adherence to medications and lifestyle changes, preference for oral vs injected therapy, economic considerations

# How Do Comorbidities Affect Anti-Hyperglycemic Therapy in T2DM?

<table>
<thead>
<tr>
<th>Coronary Disease</th>
<th>Heart Failure</th>
<th>Renal Disease</th>
<th>Liver Dysfunction</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin: CVD benefit (UKPDS)</td>
<td>Metformin: May use unless condition is unstable or severe</td>
<td>↑ risk of hypoglycemia</td>
<td>Most drugs not tested in advanced liver disease</td>
<td>Emerging concerns regarding association with increased morbidity / mortality</td>
</tr>
<tr>
<td>Avoid hypoglycemia</td>
<td>Avoid TZDs</td>
<td>Metformin &amp; lactic acidosis</td>
<td>Pioglitazone may help steatosis</td>
<td>Proper drug selection is key in hypoglycemia prone</td>
</tr>
<tr>
<td>? SUs &amp; ischemic preconditioning</td>
<td>Avoid saxagliptin</td>
<td>Caution with SUs</td>
<td>Insulin best option if disease severe</td>
<td>DPP-4i, GLP-1 RA, SGLT-2i</td>
</tr>
<tr>
<td>? Pioglitazone &amp; ↓ CVD events</td>
<td>Empagliflozin, Canagliflozin</td>
<td>DPP4-Is – dose adjust for most</td>
<td></td>
<td>Degludec</td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin, Canagliflozin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADA Glycemic Treatment Recommendations for T2DM

Healthy eating, weight control, increased physical activity, diabetes education

Monotherapy
- Not at target HbA1c after ~3 months
- Metformin
  - SU
  - TZD
  - DPP-4i
  - SGLT2i
  - GLP-1 RA
  - Insulin (basal)

Dual therapy
- Metformin +
  - SU +
  - TZD +
  - DPP-4i +
  - SGLT2i +
  - GLP-1 RA +
  - Insulin (basal) +

Triple therapy
- Not at target HbA1c after ~3 months
  - Metformin +
    - SU +
    - TZD +
    - DPP-4i +
    - SGLT2i +
    - GLP-1 RA +
    - Insulin (basal) +

Combination injectable therapy
- Metformin + basal insulin + mealtime insulin or GLP-1 RA

DPP-4i, dipeptidyl peptidase-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GU, genitourinary; HbA1c, glycosylated hemoglobin; HF, heart failure; SU, sulfonylurea; SGLT2-i, sodium-glucose co-transporter 2 inhibitor; TZD, thiazolidinedione.

A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.
Completed long-term CV safety trials have demonstrated no increased risk of CV events associated with newer antihyperglycemic agents

- DPP-4 inhibitors not associated with an increased overall risk
- Investigation continues to identify mechanisms and/or factors that may explain the potential for increased HF risk with some DPP-4 inhibitors

The LEADER trial (liraglutide) and SUSTAIN-6 trial (semaglutide) demonstrated some CV benefit, whereas ELIXA (lixisenatide) EXSCEL and FREEDOM (exenatide) did not

The EMPA-REG Outcomes Trial (empagliflozin) and CANVAS (canagliflozin) demonstrated a CV benefit, decreased mortality (empagliflozin) and less heart failure hospitalizations

- Label recently updated to reflect this

Guidelines are evolving rapidly to reflect the new evidence