Incretins and SGLT-2 Inhibitors in the Treatment of Diabetes.

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In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure:

Steven B. Magill, MD, PhD

Has disclosed no conflict of interest
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular and renal outcomes.
- Case.
- History lesson.
Case 1

- A 58 year old man comes to the clinic for a diabetes visit.
- He was diagnosed with type 2 diabetes in 2007.
- The antiglycemic regimen:
  - Metformin, 1000 mg bid
  - Glimepiride, 4 mg/day
- The HbA1c in clinic is 9.3%.
Case

- He has hypertension.
  - 20 mg of lisinopril/day
  - 25 mg of hydrochlorothiazide/day

- Dyslipidemia
  - 40 mg of atorvastatin/day

- Exam
  - Ht 70 inches (1.78 m), weight 247 pounds (112.3 kg), BMI 35.4, BP 140/84 mm Hg, p 78 bpm
  - He has central weight distribution without acanthosis nigricans
Steps in the Treatment of the Diabetes

- What is the goal HbA1c?
  - This needs to be discussed with each patient.
- Nutrition counseling.
- Exercise.
- Weight loss.
- He needs to be started on a third antiglycemic agent.
  - There are multiple medication classes available.
**Hyperglycemia in Type 2 Diabetes**

- **Glucose**
  - Adipocytes (Fat)
  - Pancreas
  - Muscle

- **Carbohydrate**
  - Neurotransmitter dysfunction ?
  - Brain
  - Liver
  - Gut
  - Brain
  - Liver

- **Glu**
  - FFA
  - Increased hepatic glucose output
  - Increased glucose reabsorption
  - Beta cells-impairment ↓ insulin secretion due to lipo- and gluco-toxicity
  - Alpha cells- Increased glucagon

- **Hyperglycemia**
  - Increased glucose reabsorption
  - Increased glucagon
  - Decreased glucose uptake
  - Increased hepatic glucose output

- **Adipocytes (Fat)**
  - Decreased incretin effect
  - Increased lipolysis and reduced glucose uptake

- **Kidney**
  - Increased glucose reabsorption

- **Muscle**
  - Decreased glucose uptake
Pathophysiology of Type 2 Diabetes

Neurotransmitter dysfunction
- GLP-1 receptor agonists
- Amylin
- Bromocriptine

Increased lipolysis and reduced glucose uptake
- Thiazolidinediones

Impaired insulin secretion
- Sulfonylurea
- Meglitinide
- GLP-1 receptor agonists
- DPP-4 inhibitors

Increased glucagon secretion
- GLP-1 receptor agonists
- DPP-4 inhibitors
- Amylin

Increased hepatic glucose production
- Metformin
- Insulin
- Thiazolidinediones

Decreased incretin effect
- Metformin
- α-Glucosidase inhibitors
- Colesevelam

Decreased glucose uptake
- Metformin
- Insulin
- Thiazolidinediones

DeFronzo RA. [20]
Tahrani AA. et al. [25]
Traditional ADA Targets for Diabetes Treatment

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>ADA(^1) Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Preprandial glucose†</td>
<td>90-130 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial glucose†</td>
<td>&lt;180 mg/dL</td>
</tr>
</tbody>
</table>

\(^1\) American Diabetes Association (ADA)

*The 2007 American Diabetes Association (ADA) guidelines suggest that the A1c goal for the individual patient is an A1c as close to normal (< 6%) as possible without significant hypoglycemia.

† Based on measurements of plasma glucose
ANTI-HYPERGLYCEMIC THERAPY in Type 2 Diabetes

Therapeutic options:

**Oral agents & non-insulin injectables**

- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 receptor agonists
- SGLT-2 inhibitors
- Meglitinides
- α-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- Amylin mimetics

PK Profile of Available Insulins in the US

Inhaled insulin
- Aspart, Lispro, Glulisine
- Regular
- Intermediate (NPH insulin)
- Long (Insulin detemir)
- Long (Insulin glargine) (Toujeo)
- Ultralong (U-300 glargine)
- degludec (Tresiba)

PK: pharmacokinetics.  NPH: Neutral protamine Hagedorn

Step-Care Approach to Treatment with Insulin in Type 2 Diabetes

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- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.
Incretins

- Gut peptides stimulated by nutrient ingestion.
- Favorable effects on glucose metabolism.
- Major human incretins\textsuperscript{1,2}
  - Glucagon-like peptide-1 (GLP-1) \(\checkmark\)
  - Glucose-dependent insulinotropic polypeptide (GIP)

\textsuperscript{1}\textsuperscript{Drucker DJ. Diabetes Educator. 32 (Suppl 2):65S-71S, 2006.}
\textsuperscript{2}\textsuperscript{Vilsbøll T, Holst JJ. Diabetologia. 47:357-366, 2004.}
Incretin Effect - Difference in the Insulin Response to Oral vs IV Glucose

Postprandial GLP-1 Levels are Decreased in Subjects With IGT and Type 2 Diabetes

GLP-1 Acts Directly on the Endocrine Pancreas, Stomach, Brain and Possibly the Heart.
GLP-1 Agonists

- Augment insulin secretion.
- Decrease hepatic glucose output via inhibition of glucagon.
- Increase satiety.
- Weight loss of 5-7% in most patients.
- Delay stomach emptying.
GLP-1 also indirectly affects target organs via stimulation of the vagus nerve in the portal vein.

GLP-1 glucagon like peptide 1; DPP-4: dipeptidyl peptidase-4
GLP-1R: glucagon like peptide 1 receptor.

Exenatide

- Exenatide is the synthetic recombinant version of exendin-4.
- Exendin-4 was derived from the saliva of the Gila monster.
Effect of Exenatide on Postprandial Glucose and Glucagon in Type 2 Diabetes

Plasma Glucagon (pg/mL)

Plasma Glucose (mmol/L)

Exenatide or Placebo

Standardized Breakfast

Time (min)

Extended Release Exenatide

Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study

Daniel J Drucker, John B Buse, Kristin Taylor, David M Kendall, Michael Trautmann, Dongliang Zhuang, Lisa Porter, for the DURATION-1 Study Group

Summary
Background Exenatide is an incretin mimetic that shares glucoregulatory properties with glucagon-like peptide 1 (GLP-1), and improves glycaemic control, with progressive bodyweight reductions, when administered twice a day in patients with type 2 diabetes. We compared the efficacy of a once-weekly formulation of exenatide to that of a twice daily dose.

Methods A 30-week, randomised, non-inferiority study compared a long-acting release formulation of exenatide 2 mg administered once weekly to 10 μg exenatide administered twice a day, in 295 patients with type 2 diabetes (haemoglobin A₁c [HbA₁c] 8·3% [SD 1·0], mean fasting plasma glucose 9·4 [SD 2·4] mmol/L, weight 102 [SD 20] kg, diabetes duration 6·7 [SD 5·0] years). The patients were naive to drug therapy, or on one or more oral antidiabetic agents. The primary endpoint was the change in HbA₁c at 30 weeks. This study is registered with ClinicalTrials.gov, number NCT00308139.

Findings At 30 weeks, the patients given exenatide once a week had significantly greater changes in HbA₁c than those given exenatide twice a day (−1·9 [SE 0·1%] vs −1·5 [0·1%], 95% CI −0·54% to −0·12%; p=0·0023). A significantly greater proportion of patients receiving treatment once a week versus twice a day achieved target HbA₁c levels of 7·0% or less (77% vs 61% of evaluable patients; p=0·0039).

Interpretation Exenatide once weekly resulted in significantly greater improvements in glycaemic control than exenatide given twice a day, with no increased risk of hypoglycaemia and similar reductions in bodyweight.

Funding Amylin Pharmaceuticals Inc and Eli Lilly and Company.

Change in HbA1c (B) and Body Weight (C) over 30 Weeks in Patients with Type 2 Diabetes Treated with Exenatide ER (2 mg) vs Exenatide (10 mcg bid).

Least square mean ±SE, intention-to-treat, n=295.
GLP-1 Analogs Available in the US

GLP-1 receptor agonists on the market

Human GLP-1 based

Daily
- Liraglutide (Victoza®) 2010

Weekly
- Albiglutide (Tanzeum®) 2014
- Dulaglutide (Trulicity®) 2014

Exendin-4 based

Daily
- Exenatide (Byetta®) 2005
- Lixisenatide (Lyxumia®) 2013 (EMA)

Weekly
- Exenatide LAR (Bydureon®) 2012
Liraglutide

- Liraglutide is a recombinant analog of human GLP-1.
- Close homology with native GLP-1.
- Has plasma half life of 13 hours.
- Administered sc once daily.
- Does not have to be timed before a meal.
Change in HbA1c With Liraglutide vs Exenatide LAR.

- Open-label randomized, parallel 26 week trial in patients with T2DM treated with oral anti-glycemic agents.

- 1.8 mg of liraglutide Qd vs 2 mg of exenatide LAR given once weekly.

- Liraglutide was more potent than exenatide LAR.


*p<0.0001. † p=0.0005. ‡ p=0.0012. § p=0.0018.
Proportion of Patients who Develop Nausea

![Graph showing the proportion of patients who develop nausea over time for Liraglutide 1.8 mg once a day and Exenatide 10 µg twice a day. The graph indicates a significant difference (p<0.0001) between the two treatments.](www.thelancet.com Vol 374 July 4, 2009)
Change in HbA1c in Patients With T2DM Randomized to Liraglutide vs Sitagliptin.

All patients were also treated with ≥1500 mg/day of metformin.

Liraglutide (Victoza)

- Available as a single pen for all doses.
- Start with 0.6 mg sc dose given once daily for the first week.
  - To reduce any GI side effects.
- After one week increase to the 1.2 mg per day dose.
- If the 1.2 mg dose is not effective:
  - The dose can be increased to 1.8 mg per day after several months.
GLP-1 Regulates Central Feeding Behavior

Appetite Suppression Requires Increased GLP-1 Levels in Rats

2-Hour Food Intake (g)

Intracerebroventricular GLP-1 (μg)

- 0
- 0.3
- 1.0
- 3.0
- 10
- 30

*P* < .05

High-Density GLP-1 Binding Sites

Change in Body Weight with Liraglutide

Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward. These data were used in part for FDA approval for Saxenda for obesity.

## GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Generic Trade name</th>
<th>Exenatide (Byetta)</th>
<th>Liraglutide (Victoza)</th>
<th>Exenatide ER (Bydureon)</th>
<th>Dulaglutide (Trulicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Half-life</td>
<td>2-4 hr bid</td>
<td>12-14 hr Qd</td>
<td>&gt; 1 wk Once weekly</td>
<td>&gt;1 week Once weekly</td>
</tr>
<tr>
<td>2. Administered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Fasting blood glucose</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>↓ Postprandial plasma glucose</td>
<td>↓↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>↓ HbA1c (%)</td>
<td>~0.7 -0.9</td>
<td>~1.1-1.6</td>
<td>~1.4 to 1.7</td>
<td>~1.2 to 1.6%</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>Decrease 1-5 % of body weight (in some patients -even more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>Nausea, other GI side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Glucose Control with GLP-1 Receptor Agonists

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb¹</td>
<td>Dul²</td>
<td>Exe³</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.1</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Placebo-adjusted Δ HbA1c

*Metformin with or without SU or TZD. †Metformin with or without SU. ‡Absolute change from baseline (active-controlled trial).

DPP-4 Inhibitors

- Prolong the action of native GLP-1 by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4).
- Oral agents.
- Less potent than GLP-1 analogs.
- Weight neutral.
Sitagliptin (100 mg/day): Effect on A1C When Added to Metformin or Pioglitazone

24-week change from baseline

Add-on to metformin study

Mean Baseline A1C: 8.0%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in A1C from Baseline, %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Placebo</td>
<td>-0.0%</td>
<td>224</td>
</tr>
<tr>
<td>Metformin + sitagliptin</td>
<td>-0.7%</td>
<td>453</td>
</tr>
</tbody>
</table>

Add-on to pioglitazone study

Mean Baseline A1C: 8.0%, 8.1%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in A1C from Baseline, %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone + Placebo</td>
<td>-0.2%</td>
<td>174</td>
</tr>
<tr>
<td>Pioglitazone + sitagliptin</td>
<td>-0.9%</td>
<td>163</td>
</tr>
</tbody>
</table>

*Compared with placebo.

**Glucose Control with DPP-4 Inhibitors**

**Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)**

<table>
<thead>
<tr>
<th>Baseline A1C (%)</th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alo&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Lin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Sax&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>7.9</td>
<td>-0.57</td>
<td>-0.69</td>
<td>0.65</td>
</tr>
<tr>
<td>8.0</td>
<td>-0.69</td>
<td>0.65</td>
<td>-0.67&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>8.0</td>
<td>0.65</td>
<td>-0.67&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>-0.67&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SU + metformin. †With or without metformin. ‡Absolute change from baseline (active-controlled trial).

<table>
<thead>
<tr>
<th>Generic Trade name</th>
<th>Sitagliptin Januvia</th>
<th>Saxagliptin Onglyza</th>
<th>Linagliptin Tradjenta</th>
<th>Alogliptin Nesina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>25, 50, 100 mg once daily</td>
<td>2.5, 5.0 mg once daily</td>
<td>5 mg once daily</td>
<td>6.25 to 25 mg day</td>
</tr>
<tr>
<td>24-h DPP-4 inhibition</td>
<td>≈ 80%</td>
<td>5 mg: ≈ 55%</td>
<td>&gt; 90%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney (mostly unchanged)</td>
<td>Liver and kidney active metabolite</td>
<td>Liver, &lt;5% renal</td>
<td>Liver and kidney</td>
</tr>
<tr>
<td>Dose adjustments for renal impairment</td>
<td>50 mg eGFR&lt;50 25 mg eGFR&lt;30</td>
<td>2.5 mg eGFR&lt;50</td>
<td>None</td>
<td>12.5 mg eGFR&lt;60 6.25 mg eGFR&lt;30</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>Low</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Low</td>
</tr>
</tbody>
</table>
## Safety Considerations with DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>GL adverse events</th>
<th>• Minimal</th>
</tr>
</thead>
</table>
| Pancreatitis      | • Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established  
• Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
• Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected |
| Pancreatic cancer | • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
• Further assessments required from long duration-controlled studies or epidemiological databases |
| Renal impairment  | • Kidney function monitoring and dose reduction required for alogliptin, saxagliptin, and sitagliptin when used in patients with moderate-to-severe renal impairment  
• Linagliptin does not require dose adjustment or periodic monitoring of drug-related kidney function |
| CHF               | • Potentially increased risk of congestive heart failure hospitalization with alogliptin and saxagliptin |

Pancreatitis and Incretins: Is There a Link?

- Pancreatitis first reported by the FDA in 2006 in patients treated with exenatide.
- The first FDA report of pancreatitis associated with sitagliptin was announced in 2009.
- Subsequent studies:
  - Exenatide:
    - No relationship found between use of exenatide and the risk of pancreatitis.
  - Sitagliptin:
    - No increased risk of pancreatitis in patients treated with sitagliptin.

Disclosure: These three studies were sponsored by industry.
The Risk of Acute Pancreatitis in Patients With Type 2 Diabetes Treated with Incretins

<table>
<thead>
<tr>
<th>Site</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>1.49 (0.72-3.08)</td>
</tr>
<tr>
<td>UK CPRD</td>
<td>1.13 (0.67-1.91)</td>
</tr>
<tr>
<td>Manitoba</td>
<td>2.17 (0.92-5.14)</td>
</tr>
<tr>
<td>US MarketScan</td>
<td>0.93 (0.79-1.09)</td>
</tr>
<tr>
<td>Ontario</td>
<td>0.83 (0.49-1.42)</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>4.32 (0.23-79.92)</td>
</tr>
<tr>
<td>Quebec</td>
<td>1.09 (0.79-1.51)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.03 (0.87-1.22)</td>
</tr>
</tbody>
</table>

Large International nested case control study of 1,532,513 patients with type 2 diabetes treated with incretins between 1/1/2007 and 6/30/2013.

Incretins and Pancreatitis

- Association does not equal causation.

- However, use caution in prescribing incretins in the following situations:
  - Prior history of pancreatitis.
    - Especially if possibly induced by an incretin.
  - Active cholelithiasis.
  - Alcohol dependency.
  - Triglycerides >1000 mg/dl.
Pharmacy

“Don’t take these if you are nursing, pregnant, or about to become pregnant.”
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.
Sodium Glucose Transporter-2 Inhibitors (SGLT-2)

- Inhibit the action of sodium-glucose transporter 2 (SGLT-2) in the proximal convoluted tubule of the kidney.
- No direct effect on the beta cell, adipocytes or liver.
- Oral agents.
Glucose Handling in the Proximal Tubule of the Kidney

162 g glucose filtered each day

90% of glucose reabsorbed by SGLT-2

10% of glucose reabsorbed by SGLT-1

No glucose excreted

SGLT-2 Inhibitors

- Canagliflozin (Invokana)
  - 100 and 300 mg tablets
- Dapagliflozin (Farxiga)
  - 5 and 10 mg tablets
- Empagliflozin (Jardiance)
  - 10 and 25 mg tablets
## Glucose Control with SGLT2 Inhibitors

### Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to Insulin +/- OAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline A1C (%)</strong></td>
<td>8.1</td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Placebo-Adjusted Δ HbA1c</strong></td>
<td>-0.2</td>
<td>-0.4</td>
<td>-0.4</td>
</tr>
<tr>
<td>Can¹</td>
<td>Dap²</td>
<td>Emp³</td>
<td>Can⁴</td>
</tr>
<tr>
<td>8.1</td>
<td>7.8</td>
<td>7.9</td>
<td>8.1</td>
</tr>
<tr>
<td>0</td>
<td>-0.2</td>
<td>-0.86</td>
<td>0</td>
</tr>
</tbody>
</table>

*Absolute change from baseline (active-controlled trial).

SGLT-2 Inhibitors - Precautions

- Patients with CKD.
  - Reduce the dose if the eGFR is between 40 and 50.
  - Contraindicated if the eGFR <30.

- May reduce intravascular volume (diuresis effect).
  - ↑ risk for hypotension.
  - Especially common in the first few weeks of treatment.
  - Use cautiously in elderly patients.

- The SGLT-2 inhibitors can increase fracture risk.
  - Pooled analysis from 8 phase III studies with canagliflozin demonstrated a 30% increased risk of fracture. Kwon H. FDA Drug Advisory Committee Meeting, 2013. UCM336234.pdf.
Infections in Women Treated with Dapagliflozin

Statistical significance not reported.
SGLT-2 Inhibitors and Euglycemic Ketoacidosis

- 13 episodes of “Euglycemic” DKA.
  - Nine patients with T1DM
  - Two patients with T2DM
  - Glucose levels generally in the 100-200 mg/dl range.

- Possible precipitants:
  - Reduced insulin doses
  - Reduced caloric intake
  - Surgery
  - EtoH

- Ketoacidosis went unrecognised by the patients and providers.
SGLT-2 Inhibitors and Euglycemic Ketoacidosis

- I would not use the SGLT-2 inhibitors in patients with type 1 diabetes until we have more information.

- Use caution in patients with latent autoimmune diabetes in adults (LADA) treated as T1DM.

- These agents may need to stopped several days before surgery.

- It may be prudent to provide patients with ketostix for urine ketone testing.
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Validity?
- Cardiovascular outcomes.
- Case.
- History lesson.
Liraglutide and T1DM

- 72 overweight or obese patients with T1DM randomized to 1.2 or 1.8 mg of liraglutide vs placebo and followed for 12 weeks.
- 63 patients completed the study.

<table>
<thead>
<tr>
<th></th>
<th>1.2 mg Liraglu</th>
<th>1.8 mg Liraglu</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.78% *</td>
<td>-0.42% (ns)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>↓5 kg **</td>
<td>↓5 kg **</td>
</tr>
<tr>
<td>Total insulin dose</td>
<td>↓12.1 units*</td>
<td>↓10 units*</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

*p<0.05,  **P<0.01,  ns: not significant.

Liraglutide in T1DM

- Double blind, treat-to-target trial of 1398 patients with type 1 diabetes randomized 3:1 to liraglutide (0.6, 1.2 or 1.8 mg/day) vs placebo added to insulin for 52 weeks.

<table>
<thead>
<tr>
<th></th>
<th>1.2 mg Liraglu</th>
<th>1.8 mg Liraglu</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>↓0.15%</td>
<td>↓0.20%</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>↓5%</td>
<td>↓8%</td>
</tr>
<tr>
<td>(total dose/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weight loss</td>
<td>↓3.6 kg</td>
<td>↓4.9 kg</td>
</tr>
<tr>
<td>Symptomatic hypo</td>
<td>↑1.27 RR</td>
<td>↑1.31 RR</td>
</tr>
<tr>
<td>Hyperglycemia with</td>
<td>-</td>
<td>↑2.22 RR (1.13 to 4.34)</td>
</tr>
<tr>
<td>ketosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Canagliflozin and T1DM

- Double blind phase II study of 351 patients with T1DM, randomized to 100 or 300 mg of canagliflozin and followed for 18 weeks.

<table>
<thead>
<tr>
<th></th>
<th>100 mg Cana</th>
<th>300 mg Cana</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.29%</td>
<td>-0.24%</td>
</tr>
<tr>
<td>Δ Weight</td>
<td>↓3.4%</td>
<td>↓5.3%</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>↓4.1 units</td>
<td>↓7.6 units</td>
</tr>
<tr>
<td>Severe hypoglyc</td>
<td>2.6%*</td>
<td>6.8%*</td>
</tr>
<tr>
<td>Ketone AE</td>
<td>5.1%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

*Placebo incidence 0%

30 patients with T1DM were randomized in a 2:1 ratio to receive 10 mg of dapagliflozin vs placebo in addition to liraglutide for 12 weeks.

**Dapagliflozin (vs placebo)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>↓0.66%*</td>
</tr>
<tr>
<td>Δ Weight</td>
<td>↓1.9 kg**</td>
</tr>
<tr>
<td>Hypoglycemia rate</td>
<td>Unchanged.</td>
</tr>
<tr>
<td>Acetoacetate level</td>
<td>↑67%**</td>
</tr>
<tr>
<td>Hydroxybutyrate</td>
<td>↑254%**</td>
</tr>
</tbody>
</table>

Two patients in the Dapagl group developed DKA (10%). *P<0.01, ** P<0.05

GLP-1 Analogs or SGLT-2 Inhibitors in T1DM?

- The jury is still out.

- The benefit ratio for GLP-1 analogs or SGLT-2 inhibitors in the treatment of T1DM is slim.

- There are potential risks.
  - SGLT-2 inhibitors may lead to euglycemic ketoacidosis or frank DKA in a subset of patients with T1DM.
  - Added cost.
  - Increased complexity of the antidiabetic regimen.
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.
Lower A1C: Decreased Risk of Myocardial Infarction

United Kingdom Prospective Diabetes Study

Hazard ratio (HR) for Myocardial infarction

14% Decrease in the HR for every 1% reduction in A1c

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

DCCT
T1DM, 5-6 years duration (N=1441)

42% risk reduction
$P=0.02$

UKPDS
T2D, newly diagnosed (N=4209)

15% risk reduction
$P=0.01$

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

**Intensive Glycemic Control Does Not Reduce Macrovascular Risk in Older Patients With Longer Duration of Disease**

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D duration (years)</td>
<td>10</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>A1C reduction (%)*</td>
<td>0.9</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Macrovascular risk (%)*</td>
<td>10</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>( P = 0.16 )</td>
<td></td>
<td>( P = 0.32 )</td>
<td>( P = 0.14 )</td>
</tr>
</tbody>
</table>

*Intensive vs standard glucose control.

# CAD Outcomes and Newer Antiglycemic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Population</th>
<th>HbA1c Change</th>
<th>Duration (mos)</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>16,492</td>
<td>80% +CAD</td>
<td>-0.2-0.3</td>
<td>24</td>
<td>Non-inferiority for CAD events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Slight but significant ↑CHF events</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>5,380</td>
<td>MI or angina</td>
<td>-0.36</td>
<td>18</td>
<td>Non-inferiority for CAD events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Trend toward more CHF events</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>14,671</td>
<td>+CAD</td>
<td>-0.3</td>
<td>36</td>
<td>Non-inferiority for CAD events</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>6,068</td>
<td>MI or angina</td>
<td>-0.27</td>
<td>25</td>
<td>Non-inferiority for CAD events</td>
</tr>
</tbody>
</table>
Empagliflozin and CAD Events

- 7028 patients with T2DM randomized to 10 or 25 mg of empagliflozin vs placebo as add-on to antiglycemic treatment.
- 99% had established CAD.
- Median duration of treatment 2.6 yrs.
- Primary outcome was a composite of CAD mortality, non-fatal MI and non-fatal stroke.
- Industry supported study.

## EMPA-REG

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 2333)</th>
<th>Empagliflozin 10 mg (N = 2345)</th>
<th>Empagliflozin 25 mg (N = 2342)</th>
<th>Pooled empagliflozin (N = 4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>63.2 ± 8.8</td>
<td>63.0 ± 8.6</td>
<td>63.2 ± 8.6</td>
<td>63.1 ± 8.6</td>
</tr>
<tr>
<td>Male – no. (%)</td>
<td>1680 (72.0)</td>
<td>1653 (70.5)</td>
<td>1683 (71.9)</td>
<td>3336 (71.2)</td>
</tr>
<tr>
<td>Race – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1678 (71.9)</td>
<td>1707 (72.8)</td>
<td>1696 (72.4)</td>
<td>3403 (72.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>511 (21.9)</td>
<td>505 (21.5)</td>
<td>501 (21.4)</td>
<td>1006 (21.5)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>120 (5.1)</td>
<td>119 (5.1)</td>
<td>118 (5.0)</td>
<td>237 (5.1)</td>
</tr>
<tr>
<td>Other/missing</td>
<td>24 (1.0)</td>
<td>14 (0.6)</td>
<td>27 (1.2)</td>
<td>41 (0.9)</td>
</tr>
<tr>
<td>Ethnicity – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>1912 (82.0)</td>
<td>1909 (81.4)</td>
<td>1926 (82.2)</td>
<td>3835 (81.8)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>418 (17.9)</td>
<td>432 (18.4)</td>
<td>415 (17.7)</td>
<td>847 (18.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Region – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>959 (41.1)</td>
<td>966 (41.2)</td>
<td>960 (41.0)</td>
<td>1926 (41.1)</td>
</tr>
<tr>
<td>North America (plus Australia and New Zealand)</td>
<td>462 (19.8)</td>
<td>466 (19.9)</td>
<td>466 (19.9)</td>
<td>932 (19.9)</td>
</tr>
<tr>
<td>Asia</td>
<td>450 (19.3)</td>
<td>447 (19.1)</td>
<td>450 (19.2)</td>
<td>897 (19.1)</td>
</tr>
<tr>
<td>Latin America</td>
<td>360 (15.4)</td>
<td>359 (15.3)</td>
<td>362 (15.5)</td>
<td>721 (15.4)</td>
</tr>
<tr>
<td>Africa</td>
<td>102 (4.4)</td>
<td>107 (4.6)</td>
<td>104 (4.4)</td>
<td>211 (4.5)</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>86.6 ± 19.1</td>
<td>85.9 ± 18.8</td>
<td>86.5 ± 19.0</td>
<td>86.2 ± 18.9</td>
</tr>
<tr>
<td>Body mass index – kg/m²</td>
<td>30.7 ± 5.2</td>
<td>30.6 ± 5.2</td>
<td>30.6 ± 5.3</td>
<td>30.6 ± 5.3</td>
</tr>
<tr>
<td>CV risk factor – no. (%)</td>
<td>2307 (98.9)</td>
<td>2333 (99.5)</td>
<td>2324 (99.2)</td>
<td>4657 (99.4)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1763 (75.6)</td>
<td>1782 (76.0)</td>
<td>1763 (75.3)</td>
<td>3545 (75.6)</td>
</tr>
<tr>
<td>Multi-vessel coronary artery disease</td>
<td>1100 (47.1)</td>
<td>1078 (46.0)</td>
<td>1101 (47.0)</td>
<td>2179 (46.5)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1083 (46.4)</td>
<td>1079 (46.4)</td>
<td>1083 (46.3)</td>
<td>2190 (46.7)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>563 (24.1)</td>
<td>594 (25.3)</td>
<td>581 (24.8)</td>
<td>1175 (25.1)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>553 (23.7)</td>
<td>535 (22.8)</td>
<td>549 (23.4)</td>
<td>1084 (23.1)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>479 (20.5)</td>
<td>465 (19.8)</td>
<td>517 (22.1)</td>
<td>982 (21.0)</td>
</tr>
<tr>
<td>Single vessel coronary artery disease*</td>
<td>238 (10.2)</td>
<td>258 (11.0)</td>
<td>240 (10.2)</td>
<td>498 (10.6)</td>
</tr>
<tr>
<td>Cardiac failure*</td>
<td>244 (10.5)</td>
<td>240 (10.2)</td>
<td>222 (9.5)</td>
<td>462 (9.9)</td>
</tr>
<tr>
<td>Glycated hemoglobin – %</td>
<td>8.08 ± 0.84</td>
<td>8.07 ± 0.86</td>
<td>8.06 ± 0.84</td>
<td>8.07 ± 0.85</td>
</tr>
<tr>
<td>Time since diagnosis of type 2 diabetes – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>≤1 years</th>
<th>&gt;1 to 5 years</th>
<th>&gt;5 to 10 years</th>
<th>&gt;10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose-lowering therapy – no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication taken alone or in combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
<td>3459 (73.8)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
<td>2252 (48.0)</td>
</tr>
<tr>
<td>Median daily dose – IU¹</td>
<td>52.0</td>
<td>52.5</td>
<td>54.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>992 (42.5)</td>
<td>985 (42.0)</td>
<td>1029 (43.9)</td>
<td>2014 (43.0)</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitor</td>
<td>267 (11.4)</td>
<td>282 (12.0)</td>
<td>247 (10.5)</td>
<td>529 (11.3)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>101 (4.3)</td>
<td>96 (4.1)</td>
<td>102 (4.4)</td>
<td>198 (4.2)</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 agonist</td>
<td>70 (3.0)</td>
<td>68 (2.9)</td>
<td>58 (2.5)</td>
<td>126 (2.7)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>691 (29.6)</td>
<td>704 (30.0)</td>
<td>676 (28.9)</td>
<td>1380 (29.4)</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>1148 (49.2)</td>
<td>1110 (47.3)</td>
<td>1149 (49.1)</td>
<td>2259 (48.2)</td>
</tr>
<tr>
<td>Anti-hypertensive therapy – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers</td>
<td>1868 (80.1)</td>
<td>1896 (80.9)</td>
<td>1902 (81.2)</td>
<td>3798 (81.0)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1498 (64.2)</td>
<td>1530 (65.2)</td>
<td>1526 (65.2)</td>
<td>3056 (65.2)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>968 (42.3)</td>
<td>1036 (44.2)</td>
<td>1011 (43.2)</td>
<td>2047 (43.7)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>788 (33.8)</td>
<td>781 (33.3)</td>
<td>748 (31.9)</td>
<td>1529 (32.6)</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>136 (5.8)</td>
<td>157 (6.7)</td>
<td>148 (6.3)</td>
<td>305 (6.5)</td>
</tr>
<tr>
<td>Renin inhibitors</td>
<td>19 (0.8)</td>
<td>16 (0.7)</td>
<td>11 (0.5)</td>
<td>27 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>191 (8.2)</td>
<td>193 (8.2)</td>
<td>190 (8.1)</td>
<td>383 (8.2)</td>
</tr>
<tr>
<td>Lipid-lowering therapy – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>1864 (79.9)</td>
<td>1926 (82.1)</td>
<td>1894 (80.9)</td>
<td>3820 (81.5)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1773 (76.0)</td>
<td>1827 (77.9)</td>
<td>1803 (77.0)</td>
<td>3630 (77.4)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>199 (8.5)</td>
<td>214 (9.1)</td>
<td>217 (9.3)</td>
<td>431 (9.2)</td>
</tr>
<tr>
<td>Niacin</td>
<td>81 (3.5)</td>
<td>95 (4.1)</td>
<td>94 (4.0)</td>
<td>189 (4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (1.5)</td>
<td>56 (2.4)</td>
<td>35 (1.5)</td>
<td>91 (1.9)</td>
</tr>
<tr>
<td>Anti-coagulants – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1927 (82.8)</td>
<td>1939 (82.7)</td>
<td>1937 (82.7)</td>
<td>3876 (82.7)</td>
</tr>
</tbody>
</table>
Glycemic Control with Empagliflozin

Cardiovascular Outcomes and All Cause Mortality in EMPA-REG

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

Hazard ratio (95% CI)  P value

- Primary composite endpoint* 0.86 (0.74-0.99)  0.04
- Secondary composite endpoint† 0.89 (0.78-1.01)  0.08
- Death from any cause 0.68 (0.57-0.82)  <0.001
- CV death 0.62 (0.49-0.77)  <0.001
- Fatal or nonfatal MI 0.87 (0.70-1.09)  0.23
- Hospitalization for HF 0.65 (0.50-0.85)  0.002
- Hospitalization for HF or CV death 0.66 (0.55-0.79)  <0.001

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.


Favors empagliflozin
Liraglutide and CAD Outcomes

- Double-blind randomized, controlled trial of 9340 patients with T2DM treated with 1.8 mg of liraglutide vs placebo.
- Age >50 with CAD or >60 with one or more CV risk factors.
- Median followup 3.8 yrs.
- Primary outcome- a composite of CAD mortality, non-fatal MI or stroke.

Cardiovascular Outcomes in the LEADER Trial

Kaplan-Meier Curves. The primary composite outcome.

Pub online 6/13/2016.
Cardiovascular Outcomes in the LEADER Trial

Kaplan-Meier Curves.

Pub online 6/13/2016.
### Clinical Outcomes with Liraglutide

**LEADER**

(N=9340)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Empagliflozin and Kidney Disease

- Randomized, double-blind study of 6185 patients with T2DM who were assigned 10 or 25 mg of empagliflozin vs placebo.
- Renal outcomes: incident or worsening nephropathy (progress to macroalbuminuria, doubling of creatinine, initiation of renal replacement or death from renal disease) or incident albuminuria.
- 99% had established CHD.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

ABSTRACT

BACKGROUND
Diabetes confers an increased risk of adverse cardiovascular and renal events. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. We wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.

METHODS
We randomly assigned patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m² of body-surface area to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.
Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients (%)</th>
<th>Relative Risk Reduction</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy</td>
<td>18.8</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-hoc composite outcome</td>
<td>9.7</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>16.2</td>
<td>38%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Arrows = relative risk reduction.

*Doubling of SCR + eGFR ≤45 mL/min/1.73 m², initiation of renal replacement therapy, or death from renal disease.

CI, confidence interval; eGFR, estimated glomerular filtration rate; SCR, serum creatinine.

### Renal Outcomes with Empagliflozin Over 3.2 Years

#### EMPA-REG RENAL (N=7020)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or CV death</td>
<td>0.61 (0.55-0.69)</td>
<td>&lt;0.001</td>
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<td>Incident or worsening nephropathy</td>
<td>0.61 (0.53-0.70)</td>
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</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>0.62 (0.54-0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45</td>
<td>0.56 (0.39-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.45 (0.21-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death</td>
<td>0.54 (0.40-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria*</td>
<td>0.95 (0.87-1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*In patients with normal albuminuria at baseline.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine.

SGLT-2 Inhibition and Heart Failure

T2DM Anti-hyperglycemic Therapy: General Recommendations

### ADA Treatment Algorithm

**Healthy eating, weight control, increased physical activity**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination
(order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Sulfonylurea†</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (usually basal)</th>
</tr>
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<tr>
<td>high</td>
<td>moderate risk</td>
<td>high</td>
<td>low</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>gain</td>
<td>hypoglycemia‡</td>
<td>edema, HF, fx‡</td>
<td>loss</td>
<td>gain</td>
<td>high</td>
</tr>
<tr>
<td>low</td>
<td></td>
<td>high</td>
<td>neutral</td>
<td></td>
<td>hypoglycemia§ variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination
(order not meant to denote any specific preference):

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<tbody>
<tr>
<td>TZD</td>
<td>SU†</td>
<td>DPP-4-i</td>
<td>SU†</td>
<td>SU†</td>
<td>TZD</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or DPP-4-i</td>
<td>or GLP-1-RA</td>
<td>or TZD</td>
<td>or Insulin§</td>
<td>or GLP-1-RA</td>
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If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-5 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

**Insulin**

(multiple daily doses)
Points to Consider when Choosing a Diabetes Agent

- **Efficacy**
  - HbA1c
  - Fasting glucose
- **Mechanism of action**
- **Side effects**
  - Hypoglycemia
  - Other side effects
- **Effect on weight**
- **Patient considerations**
  - Oral vs injectable
  - Convenience
  - Complexity of regimen
  - Cost
- **Outcomes**
  - Microvascular
  - Macrovascular
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.
Case 1

■ A 58 year old man comes to the clinic for a diabetes visit.

■ He was diagnosed with type 2 diabetes in 2007.

■ The antiglycemic regimen:
  - Metformin, 1000 mg bid
  - Glimepiride, 4 mg/day

■ BMI 35.4

■ The HbA1c in clinic is 9.3%.
Case 1a
Traditional approach

Plan:
1. Start basal or intermediate insulin in the evening.
2. Or use 70/30 insulin before dinner.

- Start with 0.1 to 0.15 units/kg
  ~ 11-17 units
- He should continue to take the two oral agents.
- The sulfonylurea should be stopped once the patient is on ≥ 2 injections of insulin per day.
Case 1b
The patient refuses to consider any injectable medication

Plan:
1. Start empagliflozin at 10 mg/d and increase to 25 mg/d if needed.
   - Or use one of the other SGLT-2 inhibitors.
2. Adding a DPP-IV inhibitor would not be a good option as the goal HbA1c of 7 to 7.5% would not be achieved.
4. Continue the metformin and glimepiride.
Case 1c
The patient’s chief concern is obesity and weight gain

Plan:

1. Start one of the GLP-1 analogs.
   - Liraglutide (Victoza), 1.2 to 1.8 mg sc/day.
   - Extended release exenatide (Bydureon), 2 mg sc/week.
   - Dulaglutide (Trulicity), 1.5 mg sc/week.

2. Continue the metformin and glimepiride.
Case 1d

- If he is treated with a non-insulin approach, eventually basal insulin will need to be started.
- If he fails to lose weight, bariatric surgery may be considered as a treatment option.
Key Points in the Management of Hyperglycemia in Diabetes

- Glucose targets and glucose lowering therapies need to be individualized.
  - Focus on the patients’ needs and preferences.
- Diet, exercise and education remain the foundation.
- Unless contraindicated, metformin in the optimal 1st line drug in the treatment of type 2 diabetes.
- Combination therapy with 2 -3 oral antiglycemic medications is reasonable. Weigh the pros and cons of each agent for the individual.
- Ultimately many patients will require insulin, initially in combination with oral agents.
- Cardiovascular risk reduction is still a goal.
Overview

- Case.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History of Diabetes and the ADA.
1921-Insulin is Shown to Control Diabetes in Pancreatectomized Dogs.

- **1921.** Frederick Banting, MD, and his medical student assistant, Charles Best, extract a crude form of insulin from dog pancreata.

- They used laboratory space at the University of Toronto provided by Professor J. J. R. Macleod.

- They injected the insulin extract into dogs whose pancreases had been removed, and the animals’ blood sugar levels decreased.
Banting and Macleod were Awarded the Nobel Prize in Medicine for the discovery of insulin in 1923.

First Human Patient

On Jan. 11, 1922, 14-year-old Leonard Thompson was the first human patient to receive insulin made by Banting and Best.

The initial test failed, causing only slight reductions in blood glucose levels.

A second series of “purified” insulin injections, produced by J.B. Collip, achieved the desired results.

Leonard’s blood glucose dropped to normal, and he began to gain weight.
DEAR DR. BANTING
I AM A LITTLE QUITE IN TEXAS WHO IS TAKING
I LET IN IT IS MAKING ME FEEL BETTER AND I AM SO HAPPY I WANT TO THANK YOU MERRY XMAS BETSY A. LANCE 2911 AVE O GALVESTON TEXAS
1923-Commercial Production of Insulin Began

1923-Eli Lilly and Company and Nordisk Insulin Laboratorium began commercial production of insulin in North America and Europe, respectively.

Labelling boxes of insulin at Eli Lilly, ca. 1924. Photo Credit: Smithsonian Institution, The National Museum of American History
1940 - The American Diabetes Association is Founded.

The American Diabetes Association is founded to address:
- The increasing incidence of diabetes
- The complications that develop from the disease.

Professional Membership: $2 per year.
1947- The First Diabetes Camp for Children is Established.

In 1947, an American Diabetes Association Affiliate sponsored Camp Seale Harris in Montgomery, Alabama.

In 2014, the Association hosted more than 5,400 children with diabetes at more than 50 sessions of camps in 24 states.

The average A1c of campers dropped from 7.63% before camp to 7.05% following camp.

Photo from Camp Seale Harris, ca. 1988
Camp Lakota – Session I

When: June 18 to June 23, 2017
Ages: 9 to 16 years
Where: Wisconsin Lions Camp
3834 County Road A
Rosholt, Wisconsin 54473

- See more at: http://www.diabetes.org/in-my-community/diabetes-camp/camps/Lakota-1.html#sthash.1LYKylIGs.dpuf

Camp Lakota-Session II
Camp Needlepoint, Hudson, WI

Camp Needlepoint - Session 1
When: August 14 to August 20, 2016
Ages: 8 to 16 years
Where: YMCA Camp St. Croix 532 County Road F
Hudson, Wisconsin 54016
Related Sessions: Camp Needlepoint - Session 2 –
The First Insulin Pump Prototype was Developed in 1963.

- Dr. Arnold Kadish of Los Angeles developed the first “portable” insulin pump in 1963.

- The pump was the size of a marine backpack.
Boston researchers developed a test to measure glycosylated hemoglobin (A1C). A1C testing became the gold standard for measuring long-term diabetes control.
1980-Intensive Insulin Therapy Used Twice-Daily Split-Mixed Regimen

Step Out: Walk to Stop Diabetes is the signature fundraising walk of the American Diabetes Association. Formerly Step Out: Walk to Fight Diabetes and America’s Walk for Diabetes, the event has raised more than $200 million to Stop Diabetes.

In 2014, more than 100,000 walkers participated in 105 Step Out events across the country to raise nearly $24 million.
ADA Tour de Cure

2017 Milwaukee Tour de Cure July 22nd, 2017 @ Hoyt Park

2017 Madison Tour de Cure 9/16/2017
@ American Family Corporate Headquarters

- The first Tour de Cure events were held at five pilot sites, including Buffalo, NY; New Jersey; New Hampshire; Napa, CA; and St. Louis, MO in 1991.

- The Tour de Cure is a series of fundraising cycling events held in 44 states.

- In 2014, 89 Tour de Cure events attracted more than 61,000 cyclists who raised more than $26 million to support the mission of the American Diabetes Association.
1993-Tight Glucose Control Shown to Reduce Complications in Type 1 Diabetes

The Diabetes Control and Complications Trial (DCCT) showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve complications caused by diabetes. In fact, it demonstrated that any sustained lowering of blood glucose helps, even if the person has a history of poor control. This landmark study, along with the later UKPDS study showing similar outcomes for tight blood glucose control in type 2 diabetes, and continuing long term followup reports have effectively ended the debate on the link between tight control of blood glucose and improved health outcomes for people with diabetes.
1997-New Diabetes Terminology and Diagnostic Levels Adopted

- The terms “insulin-dependent diabetes” (IDDM) and “non-insulin-dependent diabetes” (NIDDM) were no longer to be used.

- The terms type 1 diabetes and type 2 diabetes were adopted to define diabetes by cause rather than by treatment.

- In addition, the fasting glucose level for diagnosing diabetes was lowered from 140 mg/dl to 126 mg/dl to better reflect the point at which diabetes complications begin to develop.
The United Kingdom Prospective Diabetes Study (UKPDS) showed that people with type 2 diabetes who practice tight control of blood sugar levels and blood pressure levels reduce their risk of complications, similar to the results of the DCCT in people with type 1 diabetes. The UKPDS trials demonstrated the importance of the management of hypertension, dyslipidemia as well as hyperglycemia.
The California Supreme Court ruled in a landmark case that non-medical school staff can administer insulin to students in the state's public schools. The ADA led the fight, which helped prevent students from being denied access to insulin at school.