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

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Presenter Disclosure Information

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.
Glucose Adipocytes (Fat) Pancreas Muscle

Hyperglycemia in Type 2 Diabetes

Brain Liver Gut Adipocytes (Fat) Muscle

Neurotransmitter dysfunction
Increased hepatic glucose output
Increased lipolysis and reduced glucose uptake
Decreased glucose uptake
Decreased incretin effect
Increased glucagon
Decreased glucose uptake
Increased lipolysis and reduced glucose uptake
Decreased glucose uptake
Increased glucose reabsorption

Hyperglycemia in Type 2 Diabetes

Glu
FFA
TNF

Pathophysiology of Type 2 Diabetes

Impaired insulin secretion
- Sulfonylureas
- Meglitinides
- GLP-1 receptor agonists
- DPP-4 inhibitors
Increased glucagon secretion
- GLP-1 receptor agonists
- Amino
- Bromonortone
Increased hepatic glucose production
- Metformin
- Insulin
- Thiazolidinediones
Decreased incretin effect
- Metformin
- DPP-4 inhibitors
- GLP-1 receptor agonists

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(^6)</td>
<td>90-130 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial glucose(^6)</td>
<td>&lt;180 mg/dL</td>
</tr>
</tbody>
</table>

\(^1\) American Diabetes Association (ADA)
\(^6\) 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**

- Insulin degludec (Tresiba) - PK: pharmacokinetics, NPH: Neutral protamine Hagedorn
- Aspart, Lispro, Glulisine
- Regular
- Intermediate (NPH insulin)
- Long (Insulin detemir)
- Long (Insulin glargine)
- Ultralong (U-300 glargine) (Toujeo)
- Degludec (Tresiba)
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- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
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Incretins

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

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.

Secretion and Metabolism of Glucagon-like Peptide-1 (GLP-1)

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)

Effect of Exenatide on Postprandial Glucose and Glucagon in Type 2 Diabetes

- Exenatide or Placebo
- Standardized Breakfast

- Time (min): 0 60 120 180 240 300


Extended Release Exenatide

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

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).

- B: Exenatide once a week, n=148), baseline 8.3%
- Exenatide once a day, n=148), baseline 8.3%

- C: Exenatide once a week, n=148), baseline 102 kg
- Exenatide twice a day, n=142), baseline 102 kg

www.thelancet.com; Vol 272; October 6, 2008

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

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<0.001, † p<0.0005, ‡ p=0.0012, § p=0.0018.
Proportion of Patients who Develop Nausea

Change in HbA1c in Patients With T2DM Randomized to Liraglutide vs Sitagliptin.

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.

All patients were also treated with ≥1500 mg/day of metformin.
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>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>111</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;0.7 -0.3</td>
<td>&lt;1.1 -1.6</td>
<td>&lt;1.4 to 1.7</td>
<td>&lt;1.2 to 1.9</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></th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1C (%)</td>
<td>8.0%</td>
<td>7.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0%</td>
<td>-1.0</td>
<td>-1.3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Add-on to metformin study1</th>
<th>Add-on to pioglitazone study2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline A1C</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Metformin</td>
<td>placebo</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>-0.0%</td>
<td>P&lt;0.01</td>
<td>-0.2%</td>
</tr>
<tr>
<td>-0.7%</td>
<td>placebo-subtracted result</td>
<td>-0.9%</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>7.8</td>
<td>-0.2</td>
<td>-0.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>8.0</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.4</td>
</tr>
<tr>
<td>8.5</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>8.8</td>
<td>-0.8</td>
<td>-0.8</td>
<td>-0.8</td>
</tr>
<tr>
<td>9.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>9.5</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>10.0</td>
<td>-1.4</td>
<td>-1.4</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

Comparison of DPP-4 Inhibitors

<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>5.35 to 25 mg daily</td>
</tr>
<tr>
<td>24-h DPP-4 inhibition</td>
<td>&gt; 80%</td>
<td>5-10%</td>
<td>&gt; 95%</td>
<td>&gt;90%</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;60</td>
<td>25 mg eGFR&lt;60</td>
<td>None</td>
<td>12.5 mg eGFR&lt;60</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>Low</td>
<td>Strong CYP3A45 inhibitors</td>
<td>Strong CYP3A45 inhibitors</td>
<td>Low</td>
</tr>
</tbody>
</table>

Safety Considerations with DPP-4 Inhibitors

- **GI adverse events**
  - Minimal
- **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 >40,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents
  - Labeled for all incretins states these agents should be immediately discontinued if pancreatitis is suspected
- **Pancreatic cancer**
  - Extensive review by FDA of studies involving >40,000 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
- **CVD**
  - 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

- 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.
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)

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


Monotherapy Add-on to Metformin Add-on to Insulin +/- OAs

Can1 Dap2 Emp3 Can4 Dap5 Emp6 Can7 Dap8 Emp9

Baseline A1C (%)
8.1 7.8 7.9 8.1 8.2 7.9 8.2 8.6 8.3

Placebo-Adjusted ∆HbA1c

0.6 0.5 0.2 0.4 0.3 0.2 0.1 0.4 0.3

-0.3 -0.2 -0.3 -0.2 -0.2 -0.2 -0.3 -0.4 -0.4
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 39% increased risk of fracture. Kwon H. FDA Drug Advisory Committee Meeting, 2013. UCM336234.pdf.

Infections in Women Treated with Dapagliflozin

Statistical significance not reported.

Short- and Long-Term Trials Combined

% of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DAPA 10 mg</th>
<th>Placebo</th>
<th>DAPA 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Infections</td>
<td>1.9</td>
<td>11.5</td>
<td>10.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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- 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 ketosis</td>
<td>-</td>
<td>↑2.22 RR (1.13 to 4.34)</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%


Dapagliflozin Added to Liraglutide in T1DM (!!!)
- 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.

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (vs placebo)</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.

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Lower A1C: Decreased Risk of Myocardial Infarction

United Kingdom Prospective Diabetes Study

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

**UKPDS**
- T2D, newly diagnosed (N=4209)
- 15% risk reduction

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>T2D duration (years)</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VAADT</th>
</tr>
</thead>
<tbody>
<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>0</td>
<td>17</td>
</tr>
</tbody>
</table>

Mortality increased in intensively treated patients (P=0.04)

CAD Outcomes and Newer Antiglycemic Agents

<table>
<thead>
<tr>
<th>Antiglycemic Agent</th>
<th>N</th>
<th>Population</th>
<th>HbA1c Duration</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>16,482</td>
<td>80% +CAD</td>
<td>-0.2-0.3</td>
<td>24 mos</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>5,380</td>
<td>MI or angina</td>
<td>-0.36</td>
<td>18 mos</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>14,671</td>
<td>+CAD</td>
<td>-0.3</td>
<td>36 mos</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>6,068</td>
<td>MI or angina</td>
<td>-0.27</td>
<td>25 mos</td>
</tr>
</tbody>
</table>

*Intensive vs standard glucose control.

Slight but significant ↑CHF events

Trend toward more CHF events

Non-inferiority for CAD events

Non-inferiority for CAD events

Non-inferiority for 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.
Glycemic Control with Empagliflozin

![Graph showing glycemic control with Empagliflozin](Zinman, B, et al. N Engl J Med. Published online Sept. 17, 2015)

Cardiovascular Outcomes and All Cause Mortality in EMPA-REG


Clinical Outcomes with Empagliflozin

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.8 (0.67-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.82 (0.70-0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.85 (0.70-1.00)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>0.75 (0.60-0.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


- Primary composite endpoint includes CV death, nonfatal MI (excluding silent MI), or nonfatal stroke.
- Secondary composite endpoint includes CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.
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.

Clinical Outcomes with Liraglutide

LEADER
(N=9340)

<table>
<thead>
<tr>
<th>Outcome</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.

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL
(N=7020)

Incident or worsening nephropathy

9.7%

Post-hoc composite outcome*

11.2%
### 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>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>0.61 (0.53-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to microalbuminuria</td>
<td>0.62 (0.54-0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤ 45</td>
<td>0.68 (0.59-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.43 (0.21-0.90)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤ 45, renal replacement therapy, or renal death</td>
<td>0.54 (0.40-0.73)</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.


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### SGLT-2 Inhibition and Heart Failure


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### ADA Treatment Algorithm

TZDM Anti-hyperglycemic Therapy: General Recommendations
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.

Student assistant Charles H. Best (left) with Dr. Frederick Banting

First Human Patient

On Jan. 11, 1922, Leonard Thompson was the first human patient to receive insulin made by Banting and Best. The patient initially failed, causing only slight reductions in blood glucose levels. A second series of “specific” insulin injections, produced by J.B. Collip, achieved the desired results. Leonard’s blood glucose dropped to normal, and he began to gain weight.

Banting and Macleod were Awarded the Nobel Prize in Medicine for the discovery of insulin in 1923.

Insulin—the Game-Changer
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 5,600 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.1LYyklGs.dpuf

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.
1977 - HbA1c Test Developed

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


1991 - First Step Out Walk Held

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, 86 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.
1998-Tight Control of Blood Glucose Shown to Reduce Complications in Type 2 Diabetes

UKPDS

- 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.

2013- Safe at School
Landmark Ruling Issued

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.

Thank You