Off the Beaten Path: Non-Insulin Medications to Manage Type 1 Diabetes

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Cleveland Clinic Diabetes Center
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Learning Objectives

• Explain the rationale for non-insulin therapies in the management of type 1 diabetes.

• Describe the clinical evidence of non-insulin agents in the management of type 1 diabetes.

• Outline treatment plans for metformin, GLP-1 agonists, and SGLT-2 inhibitors in type 1 diabetes.

Disclosure to Participants

• Notice of Requirements For Successful Completion
  – Please refer to learning goals and objectives
  – Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

• Conflict of Interest (COI) and Financial Relationship Disclosures:
  – Presenter: Jennifer N. Clemens, PharmD, FCCP, BCPS, CDE, BCACP – No COI/Financial Relationship to disclose
  – Presenter: Diana Isaacs, PharmD, BCPS, BC-ADM, CDE – Advisory Board-Sanofi

• Non-Endorsement of Products:
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• Off-Label Use:
  – Participants will be notified by speakers to any product used for a purpose other than for which it was approved by the Food and Drug Administration.

Epidemiology

Patients with type 1 diabetes (T1DM) often have difficulty achieving hemoglobin A1C (HbA1C) goals due to hypoglycemia risk.

Overweight and obesity is an increasing problem in T1DM, with an estimated prevalence of 50%.

Patients with T1DM are 8x more likely to develop cardiovascular (CV) disease than the general population.
Importance of Glycemic Control

Diabetes Control and Complications Trial
- Retinopathy ↓ 76%
- Nephropathy ↓ 50%
- Neuropathy ↓ 60%
  [Average weight gain = 4.75 kg]

T1DM and Weight Trends

Pittsburgh Epidemiology of Diabetes Complications Study

<table>
<thead>
<tr>
<th>Baseline:</th>
<th>18 years later:</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.6% overweight</td>
<td>47% overweight</td>
</tr>
<tr>
<td>3.4% obese</td>
<td>23.8% obese</td>
</tr>
</tbody>
</table>

Other Considerations

Weight Gain

CV disease (CVD)  Heart failure  Death from CVD  Death
Limitations with Basal-Bolus Insulin

- Hypoglycemia
- Weight gain
- Adherence with regimen
- Untreated glucagon dysfunction
- Stress/Mental burden

Priorities for Patients with T1DM

1. Simplified, predictable management
2. HbA1C within target
3. Time within range
4. Lower mental burden

“The majority (93%) of patients had a preference for the adjunct therapy (either dose [sotagliflozin 200 or 400 mg]) over placebo.”

TIMELINE OF APPROVALS: DIABETES MELLITUS

- 1920: Insulin isolated
- 1950s: Biguanides
- 1990s: Insulin analogs
- 2005: DPP-IVi
- 2009: GLP-1RA
- 2011: DPP-IVi
- 2011: GLP-1RA
- 2013: SGLT-2 inhibitors
- 2014: Insulin oral inhalation
- 2015-2017: Concentrated insulins; GLP-1+insulin
Defects

Pathophysiology

Medications

Gluconeogenesis

- insulin secretion

- glucagon

α cells

β cells

Metformin (primary action)

TZD (secondary action)

β cells: Sulfonylureas, glinides,

DPP-IV inhibitors, GLP-1 agonists

Alpha-cells: DPP-IV inhibitors, GLP-1 agonists,

amylin derivative

Insulin resistance

- free fatty acids - triglycerides

TZD (primary action)

Metformin (secondary action)

Images available in public domain through Google.

Carbohydrate intake

- incretin effect

- glucose reabsorption

α-glucosidase inhibitor

GLP-1 agonists

GLP-1 agonists, amylin derivative

SGLT-2 inhibitors

Images available in public domain through Google.

Metformin
**Metformin**

*Activation of AMP-activated protein kinase*

- Reduces hepatic gluconeogenesis
- Decreases intestinal glucose absorption
- Promotes glucose uptake in periphery

**Benefits of Metformin**

<table>
<thead>
<tr>
<th>HbA1C reduction</th>
<th>Microvascular benefit</th>
<th>Macrovascular benefit</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Weight loss</td>
<td>Generic / low cost</td>
<td></td>
</tr>
</tbody>
</table>

**Metformin in Adults with T1DM**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Inclusion Criteria</th>
<th>Baseline Characteristics</th>
<th>Mean Reduction in HbA1C (%)</th>
<th>Mean Reduction in Insulin Doses (units)</th>
<th>Mean Reduction in Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td>Randomized trials, at least 1 week in length with metformin vs placebo</td>
<td>10 to 92 patients (per trial) with metformin 1000 to 2550 mg per day over 7 days to 12 months</td>
<td>0.6 to 0.9</td>
<td>5.7 to 10</td>
<td>1.7 to 6</td>
</tr>
</tbody>
</table>
Metformin in Adults with T1DM

Meta-analysis of 8 trials (n=300)

Mean difference of weight: -2.41 kg

Mean difference of daily insulin dose: -1.36 units


Reducing with Metformin Vascular Adverse Lesions (REMOVAL) Trial

Randomized 428 patients (≥40 years of age with diabetes for at least 5 years) and at least 3 CV risk factors

Metformin 1000 mg twice daily (n=219)

Placebo (n=209)


• REMOVAL Study (cont)
  – ↓ HbA1C by 0.13%
    • P-value = 0.0060
  – ↓ insulin dose by 0.023 units per kg
    • P-value = 0.5450
  – ↑ gastrointestinal adverse events
    • 27% vs 12% with placebo; P-value = 0.0002
  – ↑ vitamin B12 deficiency
    • 12% vs 5% with placebo; P-value = 0.0094

Gastrointestinal Side Effects

Start with low doses and titrate slowly (i.e., weekly) to maximum effective dose of 2000 mg per day.

Take with food, preferably after meals.

Effects will lessen over several weeks. If not, change from immediate to extended release formulation.

Lactic Acidosis

Use caution or temporarily discontinue in situations that could lead to increased metformin concentrations.

Be aware and monitor for tissue hypoperfusion (↑ lactic acid production) or impaired hepatic function (↓ lactic acid removal).

Renal Impairment

<table>
<thead>
<tr>
<th>eGFR (mL/min per 1.73 m²)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>No adjustment with metformin. Monitor renal function every year.</td>
</tr>
<tr>
<td>&lt; 60 and ≥ 45</td>
<td>Prescribe metformin with caution. Monitor renal function every 3 to 6 months.</td>
</tr>
<tr>
<td>&lt; 45 and ≥ 30</td>
<td>Reduce metformin by 50% or half-maximal dose. Monitor renal function every 3 months.</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Discontinue metformin.</td>
</tr>
</tbody>
</table>

Meet Mark
• ... who is a 35 yo male with T1DM (for 20 years).
  – Currently, he is injecting Lantus 50 units at bedtime and Novolog 15 units with meals.
  – He also has gastroparesis.
  – HbA1c = 8.1% (no change in 6 months despite lifestyle modifications).

What Else Would You Most Like to Know about Mark?
A. Vitamin B12 level?
B. Renal function?
C. Weight?
D. Cardiovascular risk factors?

Is Mark a Candidate for metformin?
A. Yes
B. No

Why or why not?
If starting metformin, what would be the best recommendation for the insulin regimen?

A. Continue basal and bolus.
B. Decrease by 10% basal and bolus.
C. Decrease by 10% bolus only.
D. Increase by 10% bolus only.

Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA)

The Mechanism of GLP-1 RA

### Benefits of GLP-1 RA

- **HbA1C reduction**
- **Macrovascular benefits**
- **Renal outcomes**
- **Weight loss**
- **Low risk of hypoglycemia (monotherapy)**

### Review of GLP-1 RA

<table>
<thead>
<tr>
<th></th>
<th>Short-acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Twice-daily or once-daily (exenatide)</td>
<td>Once-daily (fragylide) or once-weekly</td>
</tr>
<tr>
<td><strong>Effect on HbA1c</strong></td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Effect on FBG</strong></td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Effect on PPBG</strong></td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Nausea, vomiting, weight loss</td>
<td>Nausea, vomiting, weight loss, injection site nodules</td>
</tr>
</tbody>
</table>

### GLP-1 RA in T1DM

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study Duration (weeks)</th>
<th>Number of Patients</th>
<th>Duration of T1DM (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>4</td>
<td>39</td>
<td>3.7 to 23.1</td>
</tr>
<tr>
<td>2015</td>
<td>12</td>
<td>40</td>
<td>18.3 to 19.5</td>
</tr>
<tr>
<td>2016</td>
<td>12</td>
<td>72</td>
<td>20 to 30</td>
</tr>
<tr>
<td>2016</td>
<td>24</td>
<td>100</td>
<td>20 to 26</td>
</tr>
<tr>
<td>2016</td>
<td>52</td>
<td>1398</td>
<td>20.9 to 21.6</td>
</tr>
<tr>
<td>2016</td>
<td>26</td>
<td>835</td>
<td>20.7 to 21.4</td>
</tr>
</tbody>
</table>
GLP-1 RA in T1DM

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Most Effective Treatment Arm</th>
<th>Reduction in HbA1C (%)</th>
<th>Change in insulin dose</th>
<th>Reduction in body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>C-peptide negative with Liraglutide 1.2 mg SC QD</td>
<td>0.47 ↓ 0.13 units per kg</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Liraglutide 1.2 mg SC QD</td>
<td>0.6 NR</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Liraglutide 1.2 mg SC QD</td>
<td>0.78 ↓ 12.1 units</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Liraglutide 1.8 mg SC QD</td>
<td>0.5 ↑ 4.1 units</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Liraglutide 1.8 mg SC QD</td>
<td>0.54 ↓ 5%</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Liraglutide 1.8 SC QD</td>
<td>0.35 NR</td>
<td>5.1</td>
<td></td>
</tr>
</tbody>
</table>

NR = not reported


Gastrointestinal Side Effects

Counsel on the frequency, depending on the products.
Encourage smaller portions.
Inform about tolerance after 2 to 6 weeks, depending on product.
Do not use with history of pancreatitis or severe gastrointestinal disease.

Other Safety Concerns

• Symptomatic Hypoglycemia
Other Safety Concerns

- Hyperglycemia with Ketosis
  - ADJUNCT Trials
    - Liraglutide 1.8 mg SC QD: RR 2.22 to 3.96
      - Lower risk among C-peptide positive patients
  - ADJUNCT ONE
    - Risk factors and C-peptide status
  - ADJUNCT TWO
    - Initial two months and insulin dose titrations

Meet Vince

- ... who is 28 yo male (BMI=33kg/m²).
  - Medical history includes: T1DM x 11 years, celiac disease, Hashimoto’s thyroiditis
  - He currently uses Tandem Basal IQ with CGM.
  - Weight has steadily increased since high school.
  - HbA1C = 7.2% (improved from 8% with insulin pump, but recently gained 10-lbs) and TG = 250 mg/dL.

What Else Would You Most Like to Know about Vince?

A. Insulin antibodies?
B. C-peptide level?
C. Frequency of missed insulin doses?
D. Frequency of alcohol intake?
Is Vince a Candidate for a GLP-1 RA?

A. Yes
B. No

Why or why not?

If starting liraglutide, what would be the best recommendation for the insulin regimen?

A. Decrease by 20% basal and bolus.
B. Decrease by 20% bolus only.
C. Decrease by 10% basal and bolus.
D. Decrease by 10% bolus only.

Sodium Glucose Cotransporter Inhibitors (SGLT Inhibitors)
SGLT and the Kidney

SGLT-2 Inhibitors: Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Renal Threshold for Initiation</th>
<th>Outcomes</th>
<th>CV Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100-300 mg QAM</td>
<td>eGFR &gt;65 mL/min</td>
<td>CANVAS, CREDENCE</td>
<td>Reduce risk of heart attack, stroke or CV death in T2DM</td>
</tr>
<tr>
<td>(Invokana)</td>
<td>max 100 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5-10 mg QAM</td>
<td>eGFR &gt;65 mL/min</td>
<td>DECLARE-TIMI 58, Dapagliflozin</td>
<td>No</td>
</tr>
<tr>
<td>(Farxiga)</td>
<td>max 10 mg daily</td>
<td></td>
<td>OAD, Dapa-HF</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10-25 mg QAM</td>
<td>eGFR &gt;65 mL/min</td>
<td>EMPA-REG OUTCOME, EMPEROR-Preserved, EMPEROR-Reduced</td>
<td>Reduce risk of CV death in T2DM</td>
</tr>
<tr>
<td>(Jardiance)</td>
<td>max 15 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>5-15 mg QAM</td>
<td>eGFR &gt;60 mL/min</td>
<td>VERTIS CV</td>
<td>No</td>
</tr>
<tr>
<td>(Steglatro)</td>
<td>max 10 mg daily</td>
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</tr>
</tbody>
</table>

Sotagliflozin (Zynquista)

- Dual SGLT1/SGLT2 inhibitor:
  - SGLT1: small intestine
  - SGLT2: nephron (proximal convoluted tubules)
- Hypothesis:
  - SGLT2 inhibition leads to SGLT1 upregulation
  - Decrease postprandial glucose
  - Suppress glucagon

Renal Benefits

- Patients with T1DM are more likely to develop end stage renal disease (ESRD) – approximately 30%.
- EMPA-REG OUTCOME trial
  - Slower progression of kidney disease
  - Lower rates of doubling of serum creatinine level and initiation of renal-replacement therapy


Renal Benefits: The Credence Trial

Double-blind randomized controlled trial to evaluate a primary outcome: composite ESRD (dialysis, transplant, eGFR<15), doubling serum creatinine or death from renal/CV causes

4401 patients T2DM, median follow-up: 2.62 years, stopped early

RRR 34% (HR=0.66, P<0.001)


Benefits of SGLT-2 Inhibitors

- HbA1C reduction
- Weight loss
- Cardiovascular benefits
- Renal outcomes
- Reduction in insulin doses
- Blood pressure reduction
Side Effects of SGLT-2 Inhibitors

- Genitourinary infections
- Urinary tract infections
- Increased urination
- Hypotension
- Hyperkalemia
- Amputation
- Decreased bone mineral density
- Bladder cancer

# Diabetic ketoacidosis (DKA)

Sotagliflozin Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Population</th>
<th>Treatment Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>inTandem 1</td>
<td>793</td>
<td>T1DM</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Randomized, double-blind, placebo-controlled</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 52 weeks</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HbA1c change from baseline of 7.57% vs. placebo (Primary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin 200 mg: -0.36%, Sotagliflozin 400 mg: -0.41%, P&lt;0.001 for comparisons</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DKA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin 200 mg: 3.4%, Sotagliflozin 400 mg: 4.2%, Placebo: 0.4%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin 200 mg: 6.5%, Sotagliflozin 400 mg: 6.5%, Placebo: 9.7%</td>
</tr>
<tr>
<td>inTandem 2</td>
<td>782</td>
<td>T1DM</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Randomized, double-blind, placebo-controlled</td>
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<td></td>
<td>Follow-up: 52 weeks</td>
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<td></td>
<td></td>
<td>DKA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin 200 mg: 2.3%, Sotagliflozin 400 mg: 3.4%, Placebo: 0%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin 200 mg: 5.0%, Sotagliflozin 400 mg: 2.3%, Placebo: 5.0%</td>
</tr>
<tr>
<td>inTandem 3</td>
<td>1402</td>
<td>T1DM</td>
<td></td>
</tr>
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<td></td>
<td>Randomized, double-blind, placebo-controlled</td>
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<td></td>
<td>Follow-up: 24 weeks</td>
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<td></td>
<td>Patients achieving HbA1c lower than 7.0% without DKA (Primary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sotagliflozin: 200 of 699 patients (28.6%), Placebo: 107 of 703 (15.2%), P&lt;0.001</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Adverse effects</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Genital mycotic infections more common in sotagliflozin group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe hypoglycemia occurred in 3% of the sotagliflozin group and 2.4% in placebo group</td>
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<td></td>
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<td></td>
<td>DKA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.0% sotagliflozin vs 0.6% placebo</td>
</tr>
</tbody>
</table>


Dapagliflozin Clinical Trials

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<th>Trial</th>
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<td>T1DM</td>
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<td></td>
<td></td>
<td>Follow-up: 24 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary: Change in A1C vs. placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dapagliflozin 5 mg: −0.42% [95% CI −0.56 to −0.28; p&lt;0.0001]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dapagliflozin 10 mg: −0.45% [−0.58 to −0.31; p&lt;0.0001]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time in range increased 43.2% vs placebo</td>
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<td></td>
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<td></td>
<td>DKA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dapagliflozin 5 mg: 1%, Dapagliflozin 10 mg: 2%, Placebo: 1%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Other adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Similar rates of hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More UTIs with dapagliflozin 5 mg (7%), dapagliflozin 10 mg (4%) vs placebo (5%)</td>
</tr>
<tr>
<td>DEPICT 2</td>
<td>1465</td>
<td>T1DM</td>
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<tr>
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<td></td>
<td>Dapagliflozin 5 mg: -0.37% vs placebo</td>
</tr>
<tr>
<td></td>
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<td>Total insulin dose: -10.78%, body weight: -3.21% (P&lt;0.001 for all comparisons above)</td>
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<td></td>
<td>DKA</td>
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<td></td>
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<td>Dapagliflozin 10 mg: 13 events, Dapagliflozin 5 mg: 5 events, none with placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemia similar between groups</td>
</tr>
</tbody>
</table>

Empagliflozin Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Population</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASE 1</td>
<td>75</td>
<td>T1DM</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>- Average age: 40 yrs</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>- Race: 96% white</td>
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<tr>
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<td></td>
<td>- Average A1C: 8.53%</td>
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<td></td>
<td></td>
<td>- Average BMI: 28 kg/m²</td>
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<td></td>
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<td>- Insulin pump: 37%</td>
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<td></td>
<td></td>
<td>- DM Duration: 20 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 4 weeks</td>
<td>- Primary: Change in A1C vs. placebo</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>- Mean body weight was reduced by empagliflozin vs placebo (1.5-1.9kg, p&lt;0.001) and A1C was reduced (0.35-0.49%, p&lt;0.05).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- No cases of DKA</td>
</tr>
</tbody>
</table>

| EASE 2 | 730 | T1DM       | Randomized, double-blind, placebo-controlled | - Average age: 42 yrs |
|        |     |            |           | - Race: 80% white |
|        |     |            |           | - Average A1C: 8.1% |
|        |     |            |           | - Average BMI: 27 kg/m² |
|        |     |            |           | - Insulin pump: 34% |
|        |     |            |           | - DM Duration: 20 yrs |
|        |     |            | Follow-up: 26-52 weeks | - Primary: Change in A1C vs. placebo |
|        |     |            |           | - A1C was reduced with all study doses compared to placebo: -0.28%, -0.54%, and -0.53%, respectively (p<0.0001 for all). |
|        |     |            |           | - Weight reduction: 5 mg - 1.8kg, 10 mg - 3kg, 25 mg - 3.4kg respectively after 26 weeks (p<0.001 for all). |
|        |     |            |           | - CGM demonstrated a 2-hour/day increase in time in range with empagliflozin: 10 mg - 2.9 hours/day, 25 mg - 3.1 hours/day (p<0.0001 for both doses). |
|        |     |            |           | - DKA occurred more in the 10 mg (4.3%) and 25 mg group (3.3%), compared to the 2.5 mg group (1.2%) and placebo (0.8%). |

EASE 3 977 Randomized, double-blind, placebo-controlled | Follow-up: 26 weeks

Ease 2 and Ease 3 Published concurrently in 1 manuscript

CGM Changes

EASE 2/3

DEPICT-2

The Link to DKA

InTandem-1

DEPICT-1
SGLT Clinical Trials in T1DM Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>HbA1c</th>
<th>Hypoglycemia</th>
<th>DKA</th>
<th>Insulin doses</th>
<th>Weight</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASE-1</td>
<td>Empagliflozin</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>EASE-2 and EASE-3</td>
<td>Empagliflozin</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>DEPCT-1</td>
<td>Dapagliflozin</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>DEPCT-2</td>
<td>Dapagliflozin</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>InTANDEM1</td>
<td>Sotagliflozin</td>
<td>Yes</td>
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<tr>
<td>InTANDEM2</td>
<td>Sotagliflozin</td>
<td>Yes</td>
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<tr>
<td>InTANDEM3</td>
<td>Sotagliflozin</td>
<td>Yes</td>
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<tr>
<td>Henry et al.</td>
<td>Caragliflozin</td>
<td>Yes</td>
<td></td>
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</tr>
</tbody>
</table>

FDA Submissions

- Dapagliflozin submitted to EU and FDA
  - EMA recommended approval for T1DM who meet certain criteria
  - BMI >27kg/m² not at glycemic targets despite high insulin doses
  - Insulin doses need to be continuously optimized by a diabetes specialist
  - Waiting on decision from FDA

- Sotagliflozin submitted to EU and FDA
  - FDA advisory committee voted 8-8 if benefits outweigh risks
  - FDA rejected
  - EU approved with same criteria as dapagliflozin

- Ipragliflozin approved for T1DM in Japan

Why DKA?

- Several mechanisms
  - Reduction of total daily insulin dose may cause failure to suppress lipolysis and ketogenesis
  - Association with increase in glucagon
  - Reduction in renal clearance of ketone bodies
Risk of DKA

- **High**: Reduced basal by more than 10-20%; insulin pump or infusion site failure; reduced or consistent carbohydrate intake; excessive alcohol, illicit drugs, dehydration, acute illness, vomiting.

- **Moderate**: Vigorous or prolonged exercise; reduced prandial insulin by more than 10-20%; travel with disruption in usual schedule or insulin regimen; insulin pump use.

- **Low**: BMI <25kg/m²; inconsistent calorie intake; moderate alcohol use; female.

Insulin Dose Adjustments

- **HbA1C <7.5%**
  - 10-20% insulin reduction
  - SGLT-2 inhibitors: More basal or equal basal/bolus reductions
  - Start with lowest dose possible: even consider ½ tablets

- **HbA1C ≥7.5%**
  - Only slight or no insulin reduction
  - SGLT-1/2 inhibitors: More bolus reductions, less impact on basal

Monitoring

- Blood ketones: beta-hydroxybutyrate
  - Urinary ketones are second best (cheaper) but only measures acetoacetate.
- Frequency: individualize
- DKA symptoms
  - Malaise, fatigue, nausea, vomiting, changes in diet/activity, insulin, infection, dehydration, surgery, injury, pump occlusion, stress

Holding Therapy

- Nausea, vomiting, abdominal discomfort
- Hospitalization
- Acutely ill
- Not eating normally
- Prior to medical procedure (3 days)

If Ketones are Present...

S
Stop SGLT inhibitor
T
I
Inject bolus Insulin
C
Consume 30 g Carbohydrates
H
Hydrate (drink water)

Meet Anna

... who is 42 yo female.
- Medical history: T1DM x 25 years; retinopathy; mild peripheral neuropathy
- She is injecting insulin degludec 34 units Sc QD, insulin aspart 1 units/10 grams of carb, 1:25 sensitivity for BG>120.
- Other information include BMI = 29kg/m² and HbA1C = 8.2%. 
What Else Would You Like to Know?
A. Alcohol use?
B. Frequency of DKA (i.e., last episode)?
C. Meal schedule; calorie intake; carbs/day?
D. Missed insulin doses?
E. Knowledge of/access to ketone testing?
F. Level of engagement?

Is Anna a Candidate for a SGLT Inhibitor?
A. No, because she’s not on an insulin pump.
B. No, because she has already development diabetes complications.
C. Yes, because she’s over 40 years of age.
D. Yes, because she has no major risk factors for DKA.

If starting a SGLT-2 inhibitor, what would be the best recommendation for the insulin regimen?
A. Decrease by 20%
   – Insulin degludec: 27 units daily
   – Insulin aspart: 1 unit for 12 grams of carbs, sensitivity: 30
B. Decrease by 10%
   – Insulin degludec: 31 units daily
   – Insulin aspart: 1 unit for 11 grams of carbs, sensitivity: 28
C. Decrease by 10% basal only
   – Insulin degludec: 31 units daily
   – Insulin aspart: 1 unit for 10 grams of carbs, sensitivity: 25
D. Decrease by 5%
   – Insulin degludec: 32 units daily
   – Insulin aspart: 1 unit for 10.5 grams of carbs, sensitivity: 26