Newer Diabetes Medications and Technologies

Lindsay Collins, MD
Objectives

• Introduce GLP1- RA and SGLT2 inhibitors

• Discuss the Cardiac and Renal Benefits of these Agents

• Review Adverse Events and Side Effects

• Interpret Continuous Glucose Sensor data
Development of Glucose Lowering Agents

Year


Animal Insulin

Sulfonylureas

Metformin

Human Insulin

Alpha-glucosidase Inhibitors

Insulin Analogues

Thiazolidinediones

DPP-4 Inhibitors

GLP-1 Receptor Agonists

Pramlintide

Inhaled Insulin

SGLT2 Inhibitors

Bromocriptine

Colesevelam

Inhaled Insulin

Kahn SE et al: Lancet 2014; 383 (9922)
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity). If HbA1c above target proceed as below:

**Established ASCVD or CKD**

**ASCVD predominates**
- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit, if eGFR adequate

If HbA1c above target:
- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SU

**HF or CKD predominates**
- PREFERABLY
  - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
  - OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit

If HbA1c above target:
- Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CVD benefit
    - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
    - Basal insulin
    - SU
Effects of Incretins

- Decreased appetite
- Increased satiety
- Decreased food intake
- Delayed gastric emptying
- Increased insulin secretion
- Decreased glucagon secretion
- Increased glucose uptake

GLP-1, GIP
Incretin Pathway

Active GLP-1

GLP-1 receptor

DPP

Inactive GLP-1
Dipeptidylpeptidase-4 Inhibitors

Active GLP-1

GLP-1 receptor

Inactive GLP-1

Sitagliptin
Saxagliptin
Linagliptin
Glucagon Like Peptide -1 Receptor Agonists

Active GLP-1

DPP

Inactive GLP-1

GLP-1 receptor
Glucagon Like Peptide -1 Receptor Agonists

Active GLP-1

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Inactive GLP-1

Exenatide
dulaglutide
Liraglutide
Semaglutide

GLP-1 receptor
# Differences in Incretin Therapies

<table>
<thead>
<tr>
<th>Properties/Effect</th>
<th>GLP-1 Receptor Agonists</th>
<th>DPP-4 Inhibitors</th>
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<tbody>
<tr>
<td>↑ Insulin production</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>↑ First-phase insulin response</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>↓ Glucagon</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>↓ Hepatic glucose output</td>
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<tr>
<td>Gastric emptying</td>
<td>Delayed</td>
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<tr>
<td>Food intake</td>
<td>↓</td>
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</tr>
<tr>
<td>Body weight</td>
<td>↓</td>
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<tr>
<td>Hypoglycemia (as monotherapy)</td>
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<tr>
<td>Adverse effects</td>
<td>Nausea, vomiting</td>
<td>Minimal</td>
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<tr>
<td>↓A1c</td>
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Why are GLP-1 Agonists Preferred in Patients with ASCVD?
Leader Trial

A Primary Outcome

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

B Death from Cardiovascular Causes

- Hazard ratio, 0.78 (95% CI, 0.66–0.93)
- P=0.007

Meta-analysis of CV Trials of GLP-1 RA: Reduction in MACE

What Effects do GLP-1 agonists have on the Kidneys?
Leader-Renal Trial

**A** Composite Renal Outcome

Hazard ratio, 0.78 (95% CI, 0.67–0.92)
P = 0.003

**B** New Onset of Persistent Macroalbuminuria

Hazard ratio, 0.74 (95% CI, 0.60–0.91)
P = 0.004

**C** Persistent Doubling of Serum Creatinine Level

Hazard ratio, 0.89 (95% CI, 0.67–1.19)
P = 0.43

**D** Continuous Renal-Replacement Therapy

Hazard ratio, 0.87 (95% CI, 0.61–1.24)
P = 0.44

---

Renal Outcomes in GLP1 RA in T2 DM

GLP-1 Agonist Summary

Disadvantages:
- Cost
- GI SE
- MTC; Pancreatitis

Advantages:
- Weight loss
- Cardiovascular Benefits
- Rare Hypoglycemia
Oral Semaglutide

Average Hgb A1c is 1% lower

Average weight loss 4.2kg

Husain M, et al. NEJM 2019; 381:841-851
Oral Semaglutide vs Subq Liraglutide

• Semaglutide 14mg PO vs Liraglutide 1.8mg subq

• Change in Hemoglobin A1c
  – Semaglutide: -1.2%
  – Liraglutide: -1.1%

• Weight Loss after 26 weeks
  – Semaglutide: -4.4kg
  – Liraglutide: -3.1 kg

MACE Oral Semaglutide

**A. Composite Primary Outcome**
- Hazard ratio, 0.79 (95% CI, 0.57–1.11)
- Oral semaglutide, 61 events
- Placebo, 76 events
- P<0.001 for noninferiority
- P=0.17 for superiority

**B. Nonfatal Myocardial Infarction**
- Hazard ratio, 1.18 (95% CI, 0.73–1.90)
- Oral semaglutide, 37 events
- Placebo, 31 events

**C. Nonfatal Stroke**
- Hazard ratio, 0.74 (95% CI, 0.35–1.57)
- Oral semaglutide, 12 events
- Placebo, 16 events

**D. Death from Cardiovascular Causes**
- Hazard ratio, 0.49 (95% CI, 0.27–0.92)
- Oral semaglutide, 15 events
- Placebo, 30 events

Husain M, et al. NEJM 2019; 381:841-851
SEMAGLUTIDE (RYBELSUS)

FDA APPROVED
GLP-1 Agonist Summary

Disadvantages
- Cost
- Injectable
- GI SE
- MTC; Pancreatitis

Advantages
- Weight loss
- Cardiovascular Benefits
- Rare Hypoglycemia
SGLT2 Inhibitors

- Empagliflozin
- Canagliflozin
- Dapagliflozin
SGLT-2 Inhibitors

Glucose $\rightarrow$ SGLT-2 $\rightarrow$ Reabsorption 90% $\rightarrow$ SGLT-1

S1/S2 segments of proximal tubule
S3 segment of proximal tubule

Collecting duct

Glucosuria
Effect of Inhibiting SGLT2 on Renal Threshold for Glucose Excretion

Non-diabetes: ~ 180 mg/dl

Type 2 diabetes: ~ 250 mg/dl

SGLT2 inhibitor in type 2 diabetes: ~ 70-90 mg/dl
Glucose Reduction

SGLT2 Inhibitors Added to Metformin (Absolute Changes from Baseline; Not Head-to-Head Trials)

Baseline A1C (%)

Canagliflozin

7.8

Dapagliflozin

7.9

-0.52

Empagliflozin

7.9

-0.77

Δ A1C (%)
Why are SGLT2 inhibitors Preferred in Patients with ASCVD and HF?
Canvas Trial

A Primary Outcome

Hazard ratio, 0.86 (95% CI, 0.74–0.99)
P=0.04 for superiority

B Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001

D Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
Empa Reg Trial

A Primary Outcome

Hazard ratio, 0.86 (95% CI, 0.74–0.99)
P-value: 0.04 for superiority

B Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P-value < 0.001

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P-value < 0.001

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P-value: 0.002

No. at Risk

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SGLT-2 Inhibitors Improve CV Outcomes: Meta-analysis

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
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Fixed effects model for atherosclerotic cardiovascular disease (p=0.0002)

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<tr>
<th>Patients with multiple risk factors</th>
<th>Events</th>
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Fixed effects model for multiple risk factors (p=0.98)

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Renal Outcomes

SGLT-2 Inhibitors

- Once daily oral dosing
  - ↓ A1c ~0.5-0.9%
  - ↓ FPG, PPG
  - ↓ Weight
  - ↓ BP
  - ↓ CHF
  - ↓ CHF Hospitalizations
  - ↓ Risk of ASCVD events
  - ↓ Decrease Renal Progression

- Dehydration
- Hypotension
- Mycotic Genital infections
- ↑ Risk of Amputations
- Diabetic ketoacidosis
- Cost/Insurance
Effects on Hemoglobin A1c

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<tr>
<th>GLP1 Agonists</th>
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<td>Exenatide</td>
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ΔA1C (%)

Effects on Weight Loss

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</table>

Δ Weight (kg)

-5.8
-4
-2.6
-2.8
-2.0
-2.5
-4
-3.2

References:
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA1c above target proceed as below.

If HbA1c above target:

**ESTABLISHED ASCVD OR CKD**

**ASCVD PREDOMINATES**

- **Either/Or**
  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit, if eGFR adequate

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
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**HF OR CKD PREDOMINATES**

**PREFERABLY**

- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

**OR**

- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

If HbA1c above target:

- Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CVD benefit
    - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
    - Basal insulin
    - SU
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA1c above target proceed as below

**No**

**Established ASCVD or CKD**

**ASCVD Predominates**

**HF or CKD Predominates**

**Either/Or**

- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit

**Preferably**

- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- GLP-1 RA with proven CVD benefit

**If HbA1c above target**

**Without Established ASCVD or CKD**

**Compelling Need to Minimize Hypoglycemia**

**If HbA1c above target**

- SGLT2i
- GLP-1 RA
- DPP-4i

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- DPP-4i
Continuous Glucose Sensors
Libre vs Dexcom

Type 2
- Affordable
- 14 day sensor
- Only connects with Iphone > 8
- No Alarms
- Less accurate with low gluoses

Type 1
- Alarms for highs and lows
- Reduces severe hypoglycemia
- Connects with Android, iphone or Apple Watch
- More Accurate
- Higher Cost
Who should get a Libre Sensor?

• FDA approval for adults with diabetes

• Any patient with T2 DM
  – Increase engagement
  – No more fingersticks
  – Education on diet and exercise effects

• Improves data for MDs to titrate diabetic regimen
How to Use Sensor Data?

Glucose

Estimated A1c 8.3%, or 67 mmol/mol

Average Glucose: 191 mg/dL

% above target: 84%
% in target: 15%
% below target: 1%

Graph showing average glucose levels over the day.
How to Use Sensor Data?

- **Glucose**
  - **Thu 19 Sep**: Average Glucose 199 mg/dL
  - **Fri 20 Sep**: Average Glucose 185 mg/dL
  - **Sat 21 Sep**: Average Glucose 197 mg/dL
**Glucose**

**Estimated A1c 9.9%, or 85 mmol/mol**

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<th>237 mg/dL</th>
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<td>% above target</td>
<td>64 %</td>
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<tr>
<td>% in target</td>
<td>29 %</td>
</tr>
<tr>
<td>% below target</td>
<td>7 %</td>
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**LOW GLUCOSE EVENTS**

- **5**
- Average duration **99 Min**

---

**Sensor Usage**

- **SENSOR DATA CAPTURED 95 %**
- Daily scans **8**

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**Average Glucose**

- Median
- 10th to 90th Percentile

**Low Glucose Events**

- Graph showing glucose levels over time.
Conclusions

• Use SGLT2 Inhibitors or GLP1 agonists in patients with known ASCVD

• Consider SGLT2 inhibitors in patients with HF

• Try Freestyle Libre Sensor for patients with Type 2 diabetes