Second-Line Treatment for Diabetes: SGLT-2 Inhibitors vs. GLP-1 Receptor Agonists

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SECOND-LINE TREATMENT FOR DIABETES
SGLT-2 INHIBITORS VS. GLP-1 RECEPTOR AGONISTS

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NOVEMBER 1, 2019

Objectives

• Review second-line agents for diabetes recommended in the 2019 ADA Guidelines
• Discuss the advantages and disadvantages of SGLT-2 inhibitors and GLP-1 receptor agonists
• Evaluate literature comparing the use of SGLT-2 inhibitors and GLP-1 receptor agonists
• Provide evidence-based recommendations on appropriate selection of second-line treatment for diabetes

Patient Case

TJ is a 56 year old Hispanic female with a PMH of HTN, T2DM, hyperlipidemia, and stroke. She presented to the clinic for diabetes follow-up.

CC: “I want to have better control over my sugars.”

Current medications:
• Metformin ER 1000mg BID
• Losartan 50mg daily
• Amlodipine 10mg daily
• Apixaban 5mg BID
• Atorvastatin 40mg daily

Allergies: NKDA
FH: mother had T2DM
SH: no alcohol, tobacco products, or illicit drug use

Patient Case

Labs (from last office visit 1 month ago)

Vitals
BP: 124/77 mmHg
Pulse: 80 bpm
RR: 20
Weight: 75 kg
Height: 63 in
Temp: 98.3°F

HbA1c: 8.1%
BMI: 29.2
SCR: 1.6
10 year ASCVD risk: 6.1%

Lipid Panel:
• TC: 158 mg/dL
• HDL: 36 mg/dL
• TG: 156 mg/dL
• LDL: 91 mg/dL

Patient Case

The endocrinologist asks you for your recommendation on an appropriate second-line agent that can be added to TJ's current regimen. What would you recommend?

a. Empagliflozin 10mg – 1 tablet PO daily
b. Pioglitazone 15mg – 1 tablet PO daily
c. Liraglutide 1.8mg/3mL – inject 0.6mg SQ daily
d. Sitagliptin 100mg – 1 tablet PO daily
e. Glipizide XL 5 mg – 1 tablet PO daily 30 minutes before breakfast

Patient Case

Allergies: NKDA
FH: mother had T2DM
SH: no alcohol, tobacco products, or illicit drug use
A QUICK REVIEW

What is diabetes?

Diabetes is characterized by hyperglycemia due to decreased insulin secretion and/or decreased insulin sensitivity.

There are 2 types of diabetes:

- **Type 1**: insulin deficiency → autoimmune β-cell destruction
- **Type 2**: insulin resistance → progressive loss of β-cell insulin secretion and decreased insulin sensitivity

Glycemic Targets per the 2019 ADA Guidelines

<table>
<thead>
<tr>
<th>HbA1c Goal</th>
<th>Target Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6%</td>
<td>Pregnant women without significant risk for hypoglycemia*</td>
</tr>
<tr>
<td>&lt; 6.5%</td>
<td>Healthy patients with low risk of hypoglycemia, short duration of diabetes, long life expectancy, no significant CV disease</td>
</tr>
<tr>
<td>&lt; 7%</td>
<td>Most healthy non-pregnant adults</td>
</tr>
<tr>
<td>&lt; 7.5%</td>
<td>Healthy older adults</td>
</tr>
<tr>
<td>8 – 8.5%</td>
<td>Older adults with multiple comorbidities, cognitive impairment, or high risk for hypoglycemia</td>
</tr>
</tbody>
</table>

*Target can be increased to 7% if necessary to prevent hypoglycemia


Monitoring per the 2019 ADA Guidelines

- HbA1c should be tested at least 2 times a year in patients at goal
- HbA1c should be tested quarterly in patients not at goal

Controversy

What is the best second-line treatment option for diabetes?

5 drug classes available as 2nd line therapy:
- GLP-1 RA, SGLT-2i, DPP-4i, TZD, SU
### What is NOT preferred?

<table>
<thead>
<tr>
<th>SU</th>
<th>DPP-4i</th>
<th>TZDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c reduction</td>
<td>1-2%</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>Contraindications</td>
<td>T1DM, DKA</td>
<td>N/A</td>
</tr>
<tr>
<td>Advantages</td>
<td>Cheap</td>
<td>Minimal GI discomfort</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>• Higher risk of hypoglycemia</td>
<td>• Smaller reduction in HbA1c</td>
</tr>
<tr>
<td></td>
<td>• Weight gain</td>
<td>• Acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of HF with saxagliptin and alogliptin</td>
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</tbody>
</table>

### SU/Thiazolidinediones

**Contraindications**
- T1DM
- DKA

**Advantages**
- Cheap
- Minimal GI discomfort

**Disadvantages**
- Higher risk of hypoglycemia
- Weight gain
- Smaller reduction in HbA1c
- Acute pancreatitis
- Risk of HF with saxagliptin and alogliptin

### Glucagon-like Peptide 1 Receptor Agonists

**Mechanism of Action**
Inhibition of GLP-1 in the PCT prevents reabsorption of glucose and facilitates its excretion in urine.

**Stimulation of GLP-1 receptors increases glucose-dependent insulin release from pancreatic islets. It has also been shown to:**
- Slow gastric emptying
- Inhibit glucagon release
- Increase satiety
- Improve β-cell function

### Advantages of Each Class

**Sodium-glucose Cotransporter 2 Inhibitors**
- Empagliflozin
- Canagliflozin
- Dapagliflozin

**Glucagon-like Peptide 1 Receptor Agonists**
- Exenatide
- Liraglutide
- Lixisenatide
- Albiglutide
- Dulaglutide
- Semaglutide

### Disadvantages of Each Class

**Sodium-glucose Cotransporter 2 Inhibitors**
- Hypotension
- More UTIs and genital mycotic infections
- Increased frequency of urination
- More renal dosing adjustments

**Glucagon-like Peptide 1 Receptor Agonists**
- GI side effects: N/V/D
- Contraindicated with gastroparesis
- Pancreatitis

**Avoid or use caution in patients with history of proliferative retinopathy or medullary thyroid carcinomas**
**Second-Line Agents with CV Benefit**

**Sodium-glucose Cotransporter 2 Inhibitors**

**Empagliflozin**
- Significant reduction in:
  - All-cause mortality
  - CV death
  - CHF hospitalization

**Glucagon-like Peptide 1 Receptor Agonists**

**Liraglutide**
- Significant reduction in:
  - All-cause mortality
  - CV death
  - MI

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**Dosing Frequency**

- All SGLT-2 inhibitors are once daily dosing
- Dosing for GLP-1 RAs vary per product

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**Renal Dosing**

**SGLT-2 Inhibitors**

- **Canagliflozin***
  - eGFR < 45 mL/minute/1.73m²: not recommended
  - eGFR < 30 mL/minute/1.73m²: contraindicated

- **Empagliflozin**
  - eGFR < 50 mL/minute/1.73m²: not recommended

- **Dapagliflozin**
  - eGFR < 45 mL/minute/1.73m²: not recommended
  - eGFR < 30 mL/minute/1.73m²: contraindicated

**GLP-1 Receptor Agonists**

- **Exenatide**
  - CrCl < 30 mL/min: not recommended

- **Exenatide ER**
  - eGFR < 45 mL/minute/1.73m²: not recommended

- **Liraglutide**
  - eGFR < 30 mL/minute/1.73m²: not recommended

- **Lixisenatide**
  - eGFR < 45 mL/minute/1.73m²: not recommended

- **Albiglutide**
  - eGFR < 60 mL/minute/1.73m²: not recommended

- **Dulaglutide**
  - eGFR < 60 mL/minute/1.73m²: not recommended

- **Semaglutide (injectable)**
  - eGFR < 60 mL/minute/1.73m²: not recommended

- **Semaglutide (oral)**
  - eGFR < 60 mL/minute/1.73m²: not recommended

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**Overall HbA1c and Body Weight Reduction**

**SGLT-2 Inhibitors**

- **Empagliflozin**
  - Average Reduction (% in HbA1c): 0.65% - 0.89%
  - Average Body Weight Reduction (kg): 2.1 - 2.5

- **Canagliflozin**
  - Average Reduction (% in HbA1c): 0.5% - 1%
  - Average Body Weight Reduction (kg): 2.3 - 4

- **Dapagliflozin**
  - Average Reduction (% in HbA1c): 0.55% - 0.9%
  - Average Body Weight Reduction (kg): 2.65 - 3.2

**GLP-1 Receptor Agonists**

- **Exenatide**
  - Average Reduction (% in HbA1c): 0.74% - 1.39%
  - Average Body Weight Reduction (kg): 1.4 - 4

- **Exenatide ER**
  - Average Reduction (% in HbA1c): 1.3% - 1.9%
  - Average Body Weight Reduction (kg): 1.6 - 3.7

- **Liraglutide**
  - Average Reduction (% in HbA1c): 0.9% - 2.2%
  - Average Body Weight Reduction (kg): 2 - 6

- **Lixisenatide**
  - Average Reduction (% in HbA1c): 0.3% - 0.7%
  - Average Body Weight Reduction (kg): 1.3 - 3

- **Albiglutide**
  - Average Reduction (% in HbA1c): 0.5% - 0.8%
  - Average Body Weight Reduction (kg): 0.4 - 1.1

- **Dulaglutide**
  - Average Reduction (% in HbA1c): 0.7% - 1.6%
  - Average Body Weight Reduction (kg): 0.8 - 2.9

- **Semaglutide (injectable)**
  - Average Reduction (% in HbA1c): 1.4% - 1.6%
  - Average Body Weight Reduction (kg): 2.3 - 6.3

- **Semaglutide (oral)**
  - Average Reduction (% in HbA1c): 1.4%
  - Average Body Weight Reduction (kg): 4.2 - 4.7

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**WHAT DO WE CHOOSE FOR OUR PATIENT?**

Let’s look at what the literature recommends…

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**Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis.**
Zheng, et al. 2018

**Objective**
- To compare the clinical efficacy of SGLT-2i, GLP-1 RA, and DPP-4i for treatment of type 2 diabetes

**Design**
- Systematic review and meta analysis


**Endpoints**

**Primary Endpoint**
- All-cause mortality

**Secondary Endpoints**
- CV mortality
- HF events
- MI
- Unstable angina

**Safety Endpoints**
- # of adverse events
- Hypoglycemia


**Methods**

**Trial eligibility**
1. Randomized control trial
2. Patients with T2DM
3. Compared SGLT-2i, GLP-1 RA, and DPP-4i
4. Follow-up of at least 12 weeks

**Baseline characteristics**
- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials

Articles until November 11, 2017


**Results**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absolute RD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2i</td>
<td>-1.0%</td>
<td>[-1.5% to -0.6%]</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>-0.6%</td>
<td>[-1.0% to 0.3%]</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>No reduction</td>
<td></td>
</tr>
</tbody>
</table>


**Study Limitations and Critiques**

- Study did not include dapagliflozin, dulaglutide, or albiglutide
- Data was not stratified based on any baseline patient characteristics
- Evaluation by drug class assumes that all medications within that class are interchangeable and the same.
- Meta-analysis unable to determine superiority of one drug class over another


Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus
Zelniker, et al. 2019

Objective
- To compare the efficacy of SGLT-2 inhibitors and GLP-1 receptor agonists for prevention of major adverse cardiovascular and renal outcomes in patients with T2DM

Design
- Systematic review and meta-analysis

Primary Endpoint
- (1) Composite of myocardial infarction, stroke, and cardiovascular death (MACE), (2) hospitalization for HF, and (3) progression of kidney disease


Zelniker, et al. 2019: Methods

Meta-analysis performed using PRISMA-P

Data search of all randomized, placebo-controlled, cardiovascular outcomes trials of GLP-1 RA and SGLT2i

Databases: PubMed & EMBASE

Articles until November 11, 2018


- Data search and extraction performed by 2 independent reviewers
- Patients were stratified into 2 groups:
  - Established ASCVD
  - Multiple risk factors for ASCVD


Zelniker, et al. 2019: Results

<table>
<thead>
<tr>
<th></th>
<th>SGLT-2 Inhibitors (n=34,322)</th>
<th>GLP-1 Receptor Agonists (n=42,920)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE reduction MI</td>
<td>11%</td>
<td>12%</td>
<td>0.86</td>
</tr>
<tr>
<td>Stroke</td>
<td>11%</td>
<td>9%</td>
<td>0.87</td>
</tr>
<tr>
<td>CV Death</td>
<td>7% (nonsignificant)</td>
<td>14%</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>12%</td>
<td>0.51</td>
</tr>
<tr>
<td>MACE reduction in patients with ASCVD</td>
<td>14%</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td>MACE reduction in patients without ASCVD</td>
<td>No significant reduction</td>
<td>No significant reduction</td>
<td></td>
</tr>
<tr>
<td>Reduction in relative risk of hospitalization for HF</td>
<td>31%</td>
<td>7% (nonsignificant)</td>
<td>0.003</td>
</tr>
<tr>
<td>Reduction in broad composite kidney outcome</td>
<td>38%</td>
<td>18%</td>
<td>0.010</td>
</tr>
</tbody>
</table>


Study Limitation and Critiques

- Data was not stratified based on any baseline patient characteristics
- Evaluation by drug class assumes that all medications within that class are interchangeable and the same.
- Meta-analysis unable to determine superiority of one drug class over another


PIONEER 2 Trial

Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin


Objective
• To compare the efficacy and safety of oral semaglutide versus empagliflozin in patients with T2DM uncontrolled on metformin

Design
• Randomized, open-label, multinational, phase 3 trial

Inclusion Criteria
• 18+
• T2DM
• HbA1c 7.0-10.5%
• Receiving stable dose of metformin (≥ 1500mg or max tolerated dose) for ≥ 90 days prior to screening

Exclusion Criteria
• Any medication for diabetes or obesity within previous 90 days other than metformin
• eGFR < 60 mL/min/1.73m2
• Proliferative retinopathy or maculopathy requiring acute treatment
• History of pancreatitis

Rodbard, et al. 2016: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Oral semaglutide</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>49.9</td>
<td>49.0</td>
</tr>
<tr>
<td>Race (%) – White</td>
<td>86.5</td>
<td>86.1</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.2</td>
<td>7.8</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>32.9</td>
<td>32.8</td>
</tr>
<tr>
<td>Mean eGFR</td>
<td>96</td>
<td>95</td>
</tr>
</tbody>
</table>

Rodbard, et al. 2016: Endpoints

Primary Endpoint
• Changes in HbA1c from baseline to week 26

Secondary Endpoints
• Changes in HbA1c and body weight (kg) from baseline to week 52
• Changes in fasting plasma glucose from baseline to weeks 26 and 52
• BMI
• Fasting lipid profile

Safety Endpoints
• # of adverse events
• Incidence of severe or confirmed symptomatic hypoglycemic episodes (BG < 56 mg/dL)
• Changes from baseline in HR and BP

Rodbard, et al. 2016: Results

<table>
<thead>
<tr>
<th></th>
<th>Oral semaglutide</th>
<th>Empagliflozin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c reduction (%) at 26 weeks</td>
<td>1.3</td>
<td>0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c, reduction (%) at 52 weeks</td>
<td>1.9</td>
<td>-0.1</td>
<td>0.0719</td>
</tr>
<tr>
<td>Achieved predefined HbA1c target of ≤ 6.5% at 26 weeks</td>
<td>186 (47.4%)</td>
<td>68 (17.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Achieved predefined HbA1c target of ≤ 6.5% at 52 weeks</td>
<td>182 (47.4%)</td>
<td>60 (15.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean fasting plasma glucose at week 52 (mg/dL)</td>
<td>156.0</td>
<td>145.1</td>
<td>0.0719</td>
</tr>
<tr>
<td>Mean 7-point post-prandial BG (mg/dL) at 52 weeks</td>
<td>13</td>
<td>-5.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>Achieved body weight (kg) reduction ≥ 10% at week 26</td>
<td>45 (12.5%)</td>
<td>27 (7.8%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Achieved body weight (kg) reduction ≥ 10% at week 52</td>
<td>58 (15.0%)</td>
<td>30 (7.8%)</td>
<td>0.0028</td>
</tr>
</tbody>
</table>
### Rodbard, et al. 2016: Adverse Events

<table>
<thead>
<tr>
<th>Symptomatic hypoglycemia</th>
<th>Oral semaglutide (n=410)</th>
<th>Empagliflozin (n=409)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

| Nausea                   | 81 (39.8%)               | 10 (2.4%)             |
| Diarrhea                 | 38 (9.3%)                | 13 (3.2%)             |
| Vomiting                 | 30 (7.3%)                | 7 (1.7%)              |
| Decreased appetite       | 21 (5.1%)                | 2 (0.5%)              |
| Genital mycotic infections Female | 4 (2%)            | 17 (8.5%)             |
| Male                     | 8                        | 14 (6.9%)             |
| Increased urination      | 3 (0.7%)                 | 26 (6.4%)             |
| Adverse event resulting in trial discontinuation | 10.7% | 4.4% |

### Study Limitation and Critiques

- Open-label design
- Inclusion criteria excluded patients with HbA\(_1c\) higher than 10.5%
- Adherence was not measured

### Patient Case

The endocrinologist asks you for your recommendation on an appropriate second-line agent that can be added to TJ’s current regimen. What would you recommend?

a. Empagliflozin 10mg – 1 tablet PO daily
b. Pioglitazone 15mg – 1 tablet PO daily
c. Liraglutide 18mg/3mL – inject 0.6mg SQ daily
d. Sitagliptin 100mg – 1 tablet PO daily
e. Glipizide XL 5 mg – 1 tablet PO daily 30 minutes before breakfast

### Conclusions

- Selection of an appropriate second-line agent should depend on patient specific factors
- Consider a SGLT-2i or a GLP-1 RA before other second-line agents due to CV benefits
- SGLT-2i are preferred for HF and GLP-1 RA are preferred for stroke
- GLP-1 RA are associated with a higher reduction in HbA\(_1c\) and body weight
QUESTIONS?

References

- Ahren B, Atkin Sl, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. Diabetes Obes Metab. 2018;20:2210-2219
APPENDIX A: Abbreviations

ADA: American Diabetes Association
ASCVD: atherosclerotic cardiovascular disease
CHF: congestive heart failure
CrCl: creatinine clearance
CV: cardiovascular
DKA: diabetic ketoacidosis
DPP-4i: dipeptidyl peptidase 4 inhibitors
eGFR: estimated glomerular filtration rate
GLP-1 RA: glucagon-like peptide 1 receptor agonists
HbA1c: hemoglobin A1c
HDL: high-density lipoprotein
HF: heart failure
HTN: hypertension
LDL: low-density lipoprotein
MI: myocardial infarction
N/V/D: nausea, vomiting, diarrhea
PCT: proximal convoluted tubule
RCT: randomized control trial
SBP: systolic blood pressure
SGLT-2i: sodium glucose co-transporter 2 inhibitors
SU: sulfonylureas
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
TC: total cholesterol
TG: triglycerides
TZD: thiazolidinediones
UTI: urinary tract infection
APPENDIX C

Secondary endpoints included:

- Changes from baseline to week 52 in HbA1c and body weight (kg)
- Changes from baseline to weeks 26 and 52 in fasting plasma glucose
- Self-measured blood glucose profile (7-point profile and mean postprandial increment over all meals)
- Fasting C-peptide
- Fasting insulin
- Fasting pro-insulin
- Fasting glucagon
- HOMA-IR
- HOMAB
- C-reactive protein
- Body weight (%)
- BMI
- Waist circumference
- Fasting lipid profile
- Proportion of patients achieving: HbA1c < 7% (53 mmol/mol) or ≤ 6.5% (48 mmol/mol)
- Weight loss of ≥ 5% or ≥ 10%
- Composite endpoint of HbA1c < 7% (53 mmol/mol) without severe or symptomatic hypoglycemia (blood glucose < 56 mg/dL [≤ 3.1 mmol/l]) and no weight gain
- Composite endpoint of an absolute reduction in HbA1c of ≥ 1.0%-points (10.9 mmol/mol) and body weight loss of ≥ 3% (weeks 26 and 52)
- Changes from baseline to weeks 26 and 52 in the patient-reported outcomes, SF-36v2® Health Survey (acute version) (27) and Control of Eating Questionnaire (CoEQ) (28)