Newer Therapies for Type 2 Diabetes

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Disclosures

• Nothing to disclose
Objectives

• Discuss recent data surrounding SGLT2 inhibitors

• Review GLP-1 agonists: some old and new

• Clarify types and roles of concentrated insulins

• Discuss use of inhaled insulin

• Identify clinical utility of professional-use CGM
Healthy eating, weight control, increased physical activity, and diabetes education

**Monotherapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

**Dual therapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

**Triple therapy**

**Combination injectable therapy**

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**Metformin**
- High
- Low risk
- Neutral / loss
- GI / lactic acidosis
- Low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin + Sulfonylurea: high, moderate risk, gain, hypoglycemia, low
- Metformin + Thiazolidinedione: high, low risk, gain, edema, HF, fsx, low
- Metformin + DPP-4 inhibitor: intermediate, low risk, rare, high
- Metformin + SGLT2 inhibitor: intermediate, low risk, loss, GU, dehydration, variable
- Metformin + GLP-1 receptor agonist: high, highest, high risk, gain, hypoglycemia, variable
- Metformin + Insulin (basal): high

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + SU
- Metformin + DPP-4 inhibitor + TZD
- Metformin + SGLT2 inhibitor + GLP-1-RA
- Metformin + GLP-1 receptor agonist + Insulin
- Metformin + Insulin (basal) + DPP-4-I

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtim insulin. In refractory patients consider adding TZD or SGLT2-I.

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**Basal insulin + Mealtim insulin or GLP-1-RA**

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Start with Monotherapy unless:

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

### Monotherapy

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
<td></td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>neutral/loss</td>
<td></td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>GI/lactic acidosis</td>
<td></td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Dual Therapy

<table>
<thead>
<tr>
<th></th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td>high</td>
<td>moderate risk</td>
</tr>
<tr>
<td><strong>Thiazolidinedione</strong></td>
<td>high</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitor</strong></td>
<td>intermediate</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitor</strong></td>
<td>intermediate</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonist</strong></td>
<td>high</td>
<td>high risk</td>
</tr>
<tr>
<td><strong>Insulin (basal)</strong></td>
<td>highest</td>
<td>high risk</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Triple Therapy

<table>
<thead>
<tr>
<th></th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea +</strong></td>
<td>TZD</td>
<td>SU</td>
</tr>
<tr>
<td>or <strong>DPP-4-i</strong></td>
<td>or DPP-4-i</td>
<td>SU</td>
</tr>
<tr>
<td>or <strong>SGLT2-i</strong></td>
<td>or SGLT2-i</td>
<td>SU</td>
</tr>
<tr>
<td>or <strong>GLP-1-RA</strong></td>
<td>or GLP-1-RA</td>
<td>SU</td>
</tr>
<tr>
<td>or <strong>Insulin$^+$</strong></td>
<td>or Insulin$^+$</td>
<td>SU</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
Start with Monotherapy unless:
A1C is greater than or equal to 9%, consider Dual Therapy.
A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

### Monotherapy

#### Metformin

| Efficacy* | High |
| HYPO RISK | Low risk |
| WEIGHT | Neutral/loss |
| SIDE EFFECTS | GI/lactic acidosis |
| COSTS* | Low |

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Dual Therapy

#### Metformin +

<table>
<thead>
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<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
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<th>SGLT2 inhibitor</th>
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</thead>
<tbody>
<tr>
<td>Efficacy*</td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Highest</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Loss</td>
<td>Gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>Hypoglycemia</td>
<td>Edema, HF, fxS</td>
<td>Rare</td>
<td>GU, dehydration, fxS</td>
<td>GI, Hypoglycemia</td>
</tr>
<tr>
<td>COSTS*</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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<th>SGLT2 inhibitor +</th>
<th>GLP-1 receptor agonist +</th>
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</thead>
<tbody>
<tr>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or TZD</td>
<td>or DPP-4-i</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or GLP-1-RA</td>
<td>or Insulin§</td>
<td>or Insulin§</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or Insulin§</td>
<td>or GLP-1-RA</td>
<td>or Insulin§</td>
<td>or GLP-1-RA</td>
</tr>
</tbody>
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If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

**Combination Injectable Therapy** (See Figure 8.2) ADA Standards of Medical Care in Diabetes Diabetes Care 2017; 40 S1-S135.
SGLT2 Inhibitors

• Canagliflozin
  – Invokana ®

• Empagliflozin
  – Jardiance ®

• Dapagliflozin
  – Farxiga ®

SGLT2-I and CV Outcomes

**EMPA-REG 2015**
- **Patients**
  - 7000+
  - T2DM with established CV disease
  - On statins, ACE-I/ARB, ASA
- **Primary Outcome**
  - Composite of death from CV cause, nonfatal MI, nonfatal CVA

**CANVAS/CANVAS-R 2017**
- **Patients**
  - 10,000+
  - Established CV disease or increased risk factors for CV disease
- **Primary Outcome**
  - Composite of death from CV cause, nonfatal MI, nonfatal CVA

Empa-Reg

A Primary Outcome: Composite outcome death from CV cause, non-fatal MI, or non-fatal CVA

No. at Risk
Empagliflozin  4687  4580  4455  4328  3851  2821  2359  1534  370
Placebo        2333  2256  2194  2112  1875  1380  1161  741  166

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)  
P=0.04 for superiority

A  Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

No. at Risk
Placebo  4347  4239  4153  4061  2942  1626  1240  1217  1187  1156  1120  1095  789  216
Canagliflozin  5795  5672  5566  5447  4343  2984  2555  2513  2460  2419  2363  2311  1661  448

Hazard ratio, 0.86 (95% CI, 0.75–0.97)
P<0.001 for noninferiority
P=0.02 for superiority

Placebo
Canagliflozin
### Table 2. Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>104.3</td>
<td>120.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>35.5</td>
<td>32.8</td>
<td>0.07</td>
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<tr>
<td>Serious and nonserious adverse events of interest recorded in the CANVAS Program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis (adjudicated)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell</td>
<td>0.6</td>
<td>0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.0</td>
<td>1.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Breast</td>
<td>3.1</td>
<td>2.6</td>
<td>0.65</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1.0</td>
<td>0.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (adjudicated)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.3</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fracture (adjudicated)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15.4</td>
<td>11.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Low-trauma</td>
<td>11.6</td>
<td>9.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Practice Considerations – SGLT2i

• Patient with T2DM and history of CV disease
  – Consider use of empagliflozin or canagliflozin

• Patient with T2DM at high risk for CV disease
  – Consider use of canagliflozin

• eGFR <30?
  – Do not use SGLT2i

• History of PVD or bone disease/fracture
  – Would not use canagliflozin
    • Of note, empagliflozin did not report on amputation

GLP-1 Agonists

OLD

• Exenatide
  – Byetta ®
  – Twice a day sc injection

• Liraglutide
  – Victoza ®
  – Once a day sc injection
LEADER Trial: Liraglutide

- Liraglutide effects on CV
  - Composite of death from CV cause, nonfatal MI, nonfatal CVA

- 9000+ T2DM patients
  - One CV condition or CV RF

LEADER Trial: Liraglutide

Adverse Events
• Pancreatitis
  – 18 pts liraglutide group
  – 23 patients placebo

• Pancreatic Cancer
  – 13 patients liraglutide
  – 5 placebo

Compare to Empa-Reg
• Pattern of CV benefits differ

• Time to benefit emerged earlier in Empa-Reg

• LEADER: modified progression of atherosclerotic disease

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>sulfonylurea</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>16,500</td>
<td>5,400</td>
<td>14,000</td>
<td>6,000</td>
<td>8,300</td>
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<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2017</td>
<td>2017</td>
</tr>
</tbody>
</table>

**Results**

- **SAVOR**: NEUTRAL
- **EXAMINE**: NEUTRAL
- **TECOS**: NEUTRAL

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
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<tr>
<td>Comparator</td>
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<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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</tr>
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<td>N</td>
<td>16,500</td>
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<td>6,000</td>
<td>5,400</td>
<td>8,300</td>
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<tr>
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<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

**Results**

- **LEADER**: NEUTRAL
- **ELIXA**: NEUTRAL
- **SUSTAIN 6**: NEUTRAL

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>NCT01986881</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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<tr>
<td>N</td>
<td>7300</td>
<td>4300</td>
<td>22,200</td>
<td>3900</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>

**Results**

- **SAVOR**: NEUTRAL
- **EXAMINE**: NEUTRAL
- **TECOS**: NEUTRAL

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Borrowed from Dr. Mahmud’s 11.2017 Updates in Endocrinology Talk.
GLP-1 Agonists

OLD
- Exenatide
  - Byetta ®
  - Twice a day sc injection
- Liraglutide
  - Victoza ®
  - Once a day sc injection

NEW
- Exenatide Extended-Release
  - Bydureon ®
  - 2mg sc once a week
- Dulaglutide
  - Trulicity ®
  - 0.75 or 1.5mg sc once a week
- Albiglutide
  - Tanzeum ®
  - 30 or 50mg sc once a week
Dulaglutide – Trulicity ®

- Once-weekly dosing
- No need to dial a dose
- No reconstitution required
- A pre-attached hidden needle
- Press and hold button for automatic needle insertion and retraction

Combination Insulin + GLP-1 Agonist

Glargine U100 + Lixisenatide
• Soliqua 100/33®

• Start at 15 units
  – Up to 60 units

Degludec U100 + Liraglutide
• Xultophy 100/3.6 ®

• Starts at 16 units
  – Up to 50 units

Practice Considerations – GLP1 Agonists

• Patient with T2DM and history of CV disease or high risk CV disease
  – Consider use of liraglutide therapy

• Not amenable to daily injections?
  – Consider XR GLP-1 agonist therapy

• If patient on DDP-IV inhibitor and considering addition of GLP-1 agonist, d/c DPP-IV inhibitor

NEWER INSULIN THERAPIES
Concentrated Insulins

- Humulin U500
- Glargine U300
- Degludec U100 and U200
U500 R contains 500 units of insulin in each mL (5 times more concentrated than U100).

U500 R allows a patient to inject one-fifth the insulin volume compared with injecting the same dose of a U100 insulin.

100 units of U100 insulin in a U100 insulin syringe (100 unit markings)

100 units of U500 insulin in a U100 insulin syringe (20 unit markings)

100 units of U500 insulin in a volumetric syringe (0.2 mL)

This shows the same dose (actual units).

Humulin® R U500 PI. 2016.
Humulin U500 ®

- Consider in patients on TDD >200 u/day
- Smaller volume injected
- TID or BID doses have been studied

Glargine U300 – Toujeo®
Practice Considerations – Glargine U300

- Lower glucose lowering effect than Glargine U100

- Increase dose by 20% when switching to U300
  - i.e. 30 units daily becomes 36 units daily

- Dose titrations no sooner than q3-4 days
Degludec U100/U200 – Tresiba

Injection of Tresiba®
(0.4 units/kg)

≈ 25 hour half-life
42+ hours duration of action

Time after injection (hours)

Degludec U200

SAME DOSE HALF THE VOLUME

50-unit injection with Tresiba® U-200 FlexTouch®

50-unit injection with insulin glargine U-100

Practice Considerations - Degludec

**What is different between the 2 pens?**

<table>
<thead>
<tr>
<th>Tresiba® U-200</th>
<th>Tresiba® U-100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>160</strong> unit max dose</td>
<td><strong>80</strong> unit max dose</td>
</tr>
<tr>
<td><strong>600</strong> total units</td>
<td><strong>300</strong> total units</td>
</tr>
<tr>
<td><strong>2</strong> unit increments</td>
<td><strong>1</strong> unit increments</td>
</tr>
<tr>
<td><strong>200</strong> units per milliliter</td>
<td><strong>100</strong> units per milliliter</td>
</tr>
</tbody>
</table>
Recombinant Insulin Human Inhalation Powder – Afrezza®

AFREZZA reaches maximum level, or peak, in 12 to 15 minutes

By 3 hours blood sugar levels return to baseline


Insulin human inhalation powder

Dosing

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA Dose</th>
<th># of cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td>4 unit (blue)</td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td>8 unit (green)</td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>12 unit (yellow)</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td></td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td></td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td></td>
</tr>
</tbody>
</table>

Caution

- Cough is most common side effect

Practice Consideration – Afrezza 

### Table 7: Key Points Regarding Afrezza Inhalation Powder

- Afrezza is an inhaled rapid-acting insulin.
- Perform thorough medical history, physical examination, and spirometry testing to rule out potential chronic lung diseases before initiating therapy.
- Assess pulmonary function (e.g., forced expiratory volume in one second) after six months of therapy and annually thereafter.
- May be used in adult patients with type-1 or type-2 diabetes mellitus.
- Must be used in combination with a long-acting insulin in type-1 diabetes mellitus patients.
- Not recommended for patients who smoke or for management of diabetic ketoacidosis.
- Contraindicated in patients with chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease).
- Most common adverse events include hypoglycemia and cough.
- A dose-conversion table is available for patients transitioning from subcutaneous prandial or premixed insulin (see Table 4).
- Screen patients for potential drug–drug interactions (see Table 5).
- Insulin cartridges are available in three strengths: 4 units, 8 units, and 12 units.

CONTINUOUS GLUCOSE MONITOR
Libre Pro Flash CGM
Daily Patterns (with Ambulatory Glucose Profile)
September 7, 2015 – September 20, 2015 (14 days)

Estimated A1c 7.8%, or 62 mmol/mol
Practice Consideration – Flash CGM

Patient Case

- 43yo man with T2DM
- Glimepiride 4mg BID and sitagliptin 100mg QD
- BG checks 2s/day
  - Am: 150-180
  - Pre-dinner: 100-130
- A1C 7/2017: 8.3%
  - No better than last check 3/2017

14 day CGM Trial

[Graph and data from LibreView showing glucose levels and time spent within target ranges.]
Changes Made

1) Stop sitagliptin

2) Start canagliflozin 100mg daily

3) Start dulaglutide 0.75mg injection weekly

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<tr>
<td>HEMOGLOBIN A1C</td>
<td>0 - 5.6 %</td>
<td>6.2 (H)</td>
<td>8.3 (H)</td>
<td>8.3 (H)</td>
<td>6.7 (H)</td>
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FDA Approves First Glucose Monitor Without Finger Stick

The U.S. Food and Drug Administration today approved the FreeStyle Libre Flash Glucose Monitoring System, the first continuous glucose monitoring system that does not require painful finger pricks for glucose measurements.
But wait, on the horizon...

• Ertugliflozin
  – SGLT2i

• Semaglutide
  – GLP-1 agonist sc once weekly or daily oral

• Faster-acting insulin aspart
  – Fiasp
Objectives

• Discuss recent data surrounding SGLT2 inhibitors

• Review GLP-1 agonists: some old and new

• Clarify types and roles of concentrated insulins

• Discuss use of inhaled insulin

• Identify clinical utility of professional-use CGM
Thank You
Determine the type of diabetes

**Type 1**

- Is the patient receiving once-daily or twice-daily basal insulin?
  - Once-daily
    - Is the patient's HbA₁₀ < 8.0% (<64 mmol/mol)?
      - Yes
        - Unit-to-unit adjustment
      - No
        - Dose determined on an individual basis
          - A 20% dose reduction may be considered when switching from a twice-daily basal insulin schedule. A dose reduction can also be considered if transitioning from a once-daily schedule, if the patient has a low HbA₁₀ value

**Type 2**

- What type of insulin regimen is the patient switching from?
  - Basal insulin
  - Basal–bolus
  - Premix
  - Self-mix

Fig. 3 – Dose adjustment algorithm providing guidance when switching to insulin degludec (IDeg) from other insulin-based products. *With further guidance from the patient's physician. †Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid- or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted. ‡Based on individual glycaemic response and guidance from the patient's physician.
Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo,
↓ dose by 4 units or 10–20%

If A1C not controlled, consider combination injectable therapy

Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C < 8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2–4 units or 10–20%

If A1C not controlled, advance to basal-bolus

Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)

Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C < 8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2–4 units or 10–20%

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into ⅔ AM, ⅓ PM or ⅔ AM, ⅓ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2–4 units or 10–20%

If A1C not controlled, consider changing to alternative insulin regimen

Add GLP-1 RA

If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, consider changing to alternative insulin regimen

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2–4 units or 10–20%

If A1C not controlled, advance to 3rd injection