Making Sense of New DM Therapies and Technologies

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Updates in Internal Medicine
10/20/2017
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
### Multitherapy Algorithm

#### Monotherapy
- **Efficacy**
  - Metformin: high, low, neutral/loss
  - Sulfonylurea: high, moderate risk
  - Thiazolidinedione: high risk, intermediate
  - DPP-4 inhibitor: intermediate
  - SGLT2 inhibitor: intermediate
  - GLP-1 receptor agonist: high

- **Hypo risk**
  - Low
  - Low risk
  - Intermediate
  - Intermediate
  - Intermediate
  - High

- **Weight**
  - Gain
  - Loss
  - Gain
  - Loss
  - Gain

- **Side effects**
  - Hypoglycemia
  - Edema, HF, fx
  - Low
  - Low
  - Low

- **Costs**
  - High
  - High
  - High
  - Variable

#### Dual Therapy
- **Efficacy**
  - Metformin + Sulfonylurea: high
  - Metformin + Thiazolidinedione: high risk
  - Metformin + DPP-4 inhibitor: intermediate
  - Metformin + SGLT2 inhibitor: intermediate
  - Metformin + GLP-1 receptor agonist: high
  - Metformin + Insulin (basal): highest

- **Hypo risk**
  - Gain
  - Loss
  - Gain
  - Loss
  - Gain

- **Weight**
  - Hypoglycemia
  - Edema, HF, fx
  - Low
  - Low
  - Low

- **Side effects**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

- **Costs**
  - Hypoglycemia
  - Edema, HF, fx
  - Low
  - Low
  - Low

#### Triple Therapy
- **Efficacy**
  - Metformin + Sulfonylurea: high
  - Metformin + Thiazolidinedione: high risk
  - Metformin + DPP-4 inhibitor: intermediate
  - Metformin + SGLT2 inhibitor: intermediate
  - Metformin + GLP-1 receptor agonist: high
  - Metformin + Insulin (basal): highest

- **Hypo risk**
  - Gain
  - Loss
  - Gain
  - Loss
  - Gain

- **Weight**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

- **Side effects**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

- **Costs**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

#### Combination Injectable Therapy
- **Efficacy**
  - Metformin + Basal insulin + Mealtime insulin or GLP-1-RA

- **Hypo risk**
  - Gain
  - Loss
  - Gain
  - Loss
  - Gain

- **Weight**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

- **Side effects**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

- **Costs**
  - Hypoglycemia
  - Edema, HF, fx
  - Rare
  - Rare
  - Rare

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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

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

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

No. at Risk

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4687</td>
<td>2333</td>
</tr>
<tr>
<td>4580</td>
<td>2256</td>
</tr>
<tr>
<td>4455</td>
<td>2194</td>
</tr>
<tr>
<td>4328</td>
<td>2112</td>
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<tr>
<td>3851</td>
<td>1875</td>
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<tr>
<td>2821</td>
<td>1380</td>
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<tr>
<td>2359</td>
<td>1161</td>
</tr>
<tr>
<td>1534</td>
<td>741</td>
</tr>
<tr>
<td>370</td>
<td>166</td>
</tr>
</tbody>
</table>
A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

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

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
### 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>
</tr>
<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>

*event rate per 1000 patient-yr*
Practice Considerations – SGLT2i

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

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
Exenetide XR – Bydureon®
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 + 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

- U500 kwikpen
- Glargine U300
- Degludec U100 and U200
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

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Tresiba® U-200</th>
<th>Tresiba® U-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max dose</td>
<td>160 units max dose</td>
<td>80 units max dose</td>
</tr>
<tr>
<td>Units per pen</td>
<td>600 total units</td>
<td>300 total units</td>
</tr>
<tr>
<td>Select dose in</td>
<td>2 unit increments</td>
<td>1 unit increments</td>
</tr>
<tr>
<td>Concentration</td>
<td>200 units per milliliter</td>
<td>100 units per milliliter</td>
</tr>
</tbody>
</table>

What is different between the 2 pens?
Recombinant Insulin Human Inhalation Powder – Afrezza ®

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></td>
<td>4 unit (blue)</td>
<td>8 unit (green)</td>
</tr>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td></td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>+</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
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

LibreView

Daily Glucose Summary
July 12, 2017 - July 26, 2017 (14 Days)

- Average Glucose: [chart data]
- Time in Target: x%
- Time Below Target: x%
- Time Above Target: x%
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 not requiring a finger stick to obtain blood glucose readings.
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
## CV outcome trials: different CV event rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>SGLT-2 inhibitors</th>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMPA-REG</td>
<td>CANVAS</td>
<td>SAVOR</td>
</tr>
<tr>
<td>3pt MACE</td>
<td>0.86*</td>
<td>0.86*</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>0.74, 0.99</td>
<td>0.73, 0.97</td>
<td>0.89, 1.17</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>0.72, 1.06</td>
<td>0.78, 1.32</td>
<td>0.83, 1.22</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.85</td>
<td>1.03</td>
<td>1.95</td>
</tr>
<tr>
<td></td>
<td>0.70, 1.09</td>
<td>0.87, 1.22</td>
<td>0.88, 1.12</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24</td>
<td>1.12*</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>0.92, 1.67</td>
<td>0.87, 1.22</td>
<td>0.88, 1.39</td>
</tr>
<tr>
<td>Hospitalized HF</td>
<td>0.67</td>
<td>0.95</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>0.80, 0.85</td>
<td>0.75, 1.23</td>
<td>1.07, 1.51</td>
</tr>
<tr>
<td>All cause death</td>
<td>0.68*</td>
<td>0.87</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>0.57, 0.82</td>
<td>0.78, 1.13</td>
<td>0.88, 1.16</td>
</tr>
</tbody>
</table>

- *statistically significant
- *RECIPIENT endpoint was a 3pt MACE of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina.
- **Focal and non-fatal MI and stroke CVs, cerebrovascular disease.

References: