NEW PRODUCTS FOR DIABETES: AN UPDATE ON DIABETES MANAGEMENT
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OBJECTIVES
1. Identify the components, dosing, storage, and warnings of the newly approved diabetic medications.
2. Explain the place in therapy of the newer diabetes agents.
3. Evaluate key study results comparing A1C reductions.

DISCLOSURE
• Emily Knezevich, Pharm.D., BCPS, CDE
  • No conflicts of interest to disclose
  • Some off-label discussion
  • Will be noted as such

THE MANY PHYSIOLOGIC DEFECTS OF DIABETES

RECENT DIABETES DRUG APPROVALS

Canagliflozin
Glargine U-300
Degludec U-100, 200
Degludec U-100 (Bascoman)

2017 ADA GLYCEMIC CONTROL ALGORITHM

• See 2017 ADA Standards of Medical Care in Diabetes for Image


**Take Home Points from 2017 ADA Standards**

- Approaches to Glycemic Treatment Section (Pharmacologic treatment)
  - Consider use of Agents proven to reduce risk of CV related mortality – empagliflozin & liraglutide
  - Consider Use of GLP-1 added to Basal Insulin before Prandial
    - Less Weight Gain & Hypoglycemia
    - Similar Efficacy
  - High cost of antidiabetic agents acknowledged and should be considered when determining therapy

**Cardiovascular & Renal Benefits**

WHERE WE HAVE BEEN...

- Many studies have demonstrated lack of CV mortality benefit with improved glycemic control
  - UGlyA, ADVANCE, VADT
- ACCORD demonstrated worse mortality outcome with very tight glycemic control
  - All newly approved antidiabetic agents since 2006 have been required to demonstrate CV safety pre- and post-marketing
  - Failing to demonstrate safety was a basis for the FDA mandate

WHERE WE ARE TODAY: A GROWING BODY OF EVIDENCE

- GLP-1 Receptor Agonists
  - LEADER: RCT of Over 9,000 patients
    - *Primary outcome:* Liraglutide demonstrated 13% reduction in 3-point MACE (p=0.01)
    - Key secondary outcomes: 22% reduction in CV death (HR 0.78 – 0.94), 30% reduction in all-cause mortality (HR 0.70 – 0.89)
  - SUSTAIN-6: RCT of 3300 patients
    - **Primary outcome:** Semaglutide demonstrated 26% reduction in 3-point MACE (p=0.02)
    - Study did not meet US FDA requirements, fewer events, smaller enrollment
    - Key secondary outcomes: 39% reduction in non-fatal stroke (HR 0.61 – 0.99)
  - Lixisenatide and Exenatide have demonstrated CV safety, but not superiority. Albiglutide's study ongoing.
  - CV benefit of GLP-1 RA's has not yet been approved for labeling change
  - Semaglutide not approved in US

CV OUTCOMES TRIALS – SGLT-2 INHIBITORS

- EMPA-REG OUTCOME
  - RCT of nearly 7,000 patients receiving empagliflozin or PBO, 99% had established CVD
    - *Primary outcome:* demonstrated superior risk reduction in 3-point MACE (p=0.04)
    - Key secondary outcomes where significance met:
      - 38% reduction in CV death (CI 0.49–0.77), 35% reduction in hospitalization for HF, 32% reduction in All-cause mortality
- CVD-REAL
  - Retrospective review of >300,000 patients on any SGLT-2 inhibitor, 87% without known CVD
  - *Primary outcome:* demonstrated 39% reduction in hospitalization for HF (p < 0.001)
  - Key secondary outcome:
    - 51% reduction in all-cause death (p < 0.001)
- CANVAS
  - RCT of over 10,000 patients receiving canagliflozin or PBO, 65% had established CVD
  - *Primary outcome:* demonstrated 14% reduction in 3-point MACE (p=0.02)
  - Key secondary outcomes:
    - 22% reduction in hospitalization for HF (CI 0.52 – 0.87)

RENAL BENEFITS OF SGLT-2 INHIBITORS

- EMPA-REG OUTCOME – Renal

EXSCEL press release. AstraZeneca, May 2017
RENAL BENEFIT OF SGLT-2 INHIBITORS

CANVAS AND CANVAS-R

• See Neal et al. NEJM June 2017 for Image

LINGERING QUESTIONS

• Is CV/Renal benefit a class effect?
• Should we be using the agents with demonstrated benefit over others in the class?
• Is the CV mortality benefit evident in patients without established CVD?
• Do the benefits for use outweigh the risks?

SAFETY CONCERNS

SGLT-2 INHIBITORS AND SAFETY

• Well described increase in risk for GU infections
• Case reports and new findings from post-marketing studies have identified the following:
  • Bone fracture
  • Lower Limb Amputations
  • Acute Kidney Injury
  • Euglycemic Diabetic Ketoacidosis

A NEW TAKE ON AN OLD MED: METFORMIN DOSING GUIDELINES

• Updated dosing guidelines in 2016 recommend use of eGFR over Serum Creatinine for dosing metformin.
  • Previous confusion with limiting use if SCr < 1.4/1.5 mg/dL vs. Cr CL < 60 mL/min
  • New recommendations:
    • eGFR ≥ 45 mL/min/1.73 m² – no restrictions on dosing
    • eGFR 30-44 mL/min/1.73 m² – weight risks/benefits, consider decreasing to ½ normal dosing, do not start if metformin-naive
    • eGFR < 30 mL/min/1.73 m² – avoid use

SGLT-2 INHIBITORS

• Post-marketing reports of Bone Fracture, Amputations, Acute Kidney Injury and Euglycemic DKA

<table>
<thead>
<tr>
<th>Fracture**</th>
<th>Amputations</th>
<th>Acute Kidney Injury</th>
<th>Euglycemic DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin1</td>
<td>Significant increase (HR 1.97 vs. PBO)</td>
<td>No significant increase (HR 1.26 vs. PBO)</td>
<td>Significant increase (HR 1.26 vs. PBO)</td>
</tr>
<tr>
<td>Dapagliflozin2,3</td>
<td>No significant difference identified</td>
<td>No significant difference identified</td>
<td>Case reports only (15 cases in normal creatinine vs. &lt;60 mL/min)</td>
</tr>
<tr>
<td>Empagliflozin4,5</td>
<td>No increase in risk</td>
<td>Lower risk vs. PBO (HR 0.6% vs. 0.06%, p=0.05)</td>
<td>No significant increase (4 cases on metformin vs. 1 on placebo)</td>
</tr>
</tbody>
</table>

1. Neal et al. NEJM June 2017
2. Tang et al. 2016. Diabetes, Obesity and Metabolism

*Warning listed in all product labeling
**Only listed in canagliflozin labeling
TAKE HOME - SAFETY CONCERNS

- SGLT-2's
  - Bone fracture: caution in renal impairment with OP Risk
  - Euglycemic DKA: warn patients to avoid use in times of severe illness resulting in starvation/dehydration, encourage hydration and advice of signs of hypokalemia
  - Amputations – avoid use of canagliflozin and possibly all SGLT-2 axis in severe PAD or hx of amputation
- Metformin can be used in patients with moderate renal dysfunction – should monitor eGFR regularly

A FLURRY OF BASAL INSULINS

THE NEED FOR A BETTER BASAL

- Prior to 2015: detemir, glargine U-100, NPH
  - Large doses requiring multiple injections, hypoglycemia
  - Inter-day variability, need for BID dosing

- Ideal new insulin:
  - Glargine U-300 and Degludec U-100/U-200 approved in 2015
  - Concentrated insulins all delivered via pen device that adjusts volume for units to be universal when dosing

  Less variability in Effect
  Lower rates of hypoglycemia
  Dosing Flexibility
  Large dose per injection

INSULIN GLARGINE U-300

- Compared to Glargine U-100, demonstrates less peak/rough and has extended duration of action
- Half-life 24 hours vs. 12 hour of Glargine U-100

See Diabetes Care 2015;38:637–643 for image

- Solostar pen still only allows for 80 units to be delivered at one time, delivers 1/3 the volume of U-100 pen
  - 450 units per pen, 3 pens/box

WHY SHOULD WE CHANGE – LESS HYPOGLYCEMIA

- Glargine U300 and Degludec have demonstrated reduction in hypoglycemia compared to glargine U100
  - Kinetic data demonstrates less of a peak in concentration

  - DEVOTE Trial:
    - Degludec vs. Glargine U-100 – primary outcome looking at CV Safety
      - Secondary outcome demonstrated 40% reduction in severe hypoglycemia (p < 0.001) and 8% reduction in nocturnal hypoglycemia (p < 0.001)

  - EDITION 1 Trial
    - Glargine U-100 vs. Glargine U-100 – demonstrated non-inferiority in glucose lowering
      - Secondary outcome demonstrated 22% lower RR of severe nocturnal hypoglycemia (p < 0.001)

See T. et al, 2017;38:637-643 for image
WHY SHOULD WE CHANGE – MORE FLEXIBILITY IN DOSING

- Degludec FLEX Study
  - Compared 3 groups:
    - Degludec U-100 given at a prespecified dosing schedule — 8-40 hours separating injections
    - Degludec U-100 given at a set daily time
    - Glargine U-100 given at a set daily time
  - Results: Flexible dosing method was non-inferior to set daily dosing of either product in regard to A1c lowering
  - Secondary outcome: no significant differences in overall or nocturnal hypoglycemia
- May be beneficial for patients who have unreliable dosing frequency

REGULAR INSULIN U-500

- Older insulin product, now available in Kwikpen® delivery – can deliver up to 300 units in one injection
  - Beneficial to avoid confusion with converting dose when drawing up in syringe
  - 500 units/mL – pens come in 3 mL ~ 1500 units/pen, 2 pens/box
  - Can only dose in 5 unit increments
- Used for very insulin resistant patients needing >200 units/day
  - Replaces basal and bolus due to extended duration of action
  - Typically dose 60-90 minutes before a meal (onset remains 30 minutes)
  - If insurance does not cover pens, U-500 syringe now available as well
  - Can dose up to 250 units in one injection

CONCENTRATED BASAL INSULIN CONVERSIONS

<table>
<thead>
<tr>
<th>Glargin U-300</th>
<th>Degludec U-200</th>
<th>Humulin R U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>True basal insulin</td>
<td>True basal insulin</td>
<td>Penuline basal insulin</td>
</tr>
<tr>
<td>1 daily injection</td>
<td>1 to 1</td>
<td>1 to 1</td>
</tr>
<tr>
<td>2 daily injections</td>
<td>80% of total daily basal dose</td>
<td>Maximum single-dose injection</td>
</tr>
<tr>
<td>Maximum single-dose injection</td>
<td>80% of total daily basal dose</td>
<td>Maximum single-dose injection</td>
</tr>
<tr>
<td>240 units of insulin per pen</td>
<td>600 units of insulin per pen</td>
<td>1500 units of insulin per pen</td>
</tr>
<tr>
<td>Expects daily dose of Glargin U-300 to maintain glycemic control</td>
<td>Monitor for hypoglycemia</td>
<td></td>
</tr>
</tbody>
</table>

PRODUCT STORAGE AND EXPIRATION COMPARISON

ADA STANDARDS LANGUAGE

See 2017 ADA Standards of Medical Care in Diabetes for Image

COMBINATION INJECTABLE THERAPY
GLP-1 RA VS. MEALTIME INSULIN

- Goal with using either is to avoid “over-basalizing”
  - Recommend limiting basal dose to 0.5u/kg/day before considering addition of alternate injectable
  - Studies have demonstrated basal + GLP-1 RA is non-inferior to basal + 1 mealtime injection in regard to A1c lowering
  - Less hypoglycemia and weight gain
  - May be less well tolerated and more costly

- Bydureon is only GLP-1 RA not labeled for use with basal insulin

- Combination products Now available: lixisenatide + glargine U-100 & liraglutide + degludec U-100

DEGLUDEC 100U/ML & LIRAGLUTIDE 3.6MG/ML

- Degludec/liraglutide available in 3mL, fixed dose, Flextouch pen
  - Demonstrated up to 1.9% A1c lowering when combined with MTF
  - Starting dose: 16 units + Degludec 16 units + Liraglutide 0.58 mg
    - Titrate by 2 units every 3-4 days based on FBS to goal
    - Max dose 50 units
  - Nausea most common ADR - Lower GI ADRs vs. liraglutide alone due to slower titration

- Dual VII Results announced at ADA in June
  - Compared degludec/liraglutide with glargine U-100 + aspart at all main meals
    - Significantly lower insulin requirement (60.1 units vs. 64.6 units) (p<0.0001)
    - Degludec/liraglutide resulted in 0.8kg weight loss vs. 2.6kg gain for basal/bolus regimen (p<0.0001)
    - 83% lower rate of hypoglycemia (p<0.0001)

GLARGINE 100 UNITS/ML + LIXISENATIDE 33MCG/ML

- Glargine/Lixisenatide Available in fixed dose, 3mL, Solostar pen
  - Demonstrated additional 0.5% A1c reduction compared to glargine U-100
  - Starting dose:
    - For patients previously treated with < 30 units basal: 15 units = Glargine U-100 – 15 units + Lixisenatide – 3mg
    - For patients previously treated with > 30 units basal: 30 units = Glargine U-100 – 30 units + Lixisenatide – 10mg
  - Titrate up by 2 units every 3-4 days based on FBS to goal
    - Max dose 60 units
  - Nausea most common ADR (10%), dose dependent
  - Aroda et al compared to glargine +/- OADs
    - Significant reduction in HbA1c, larger proportion of patients meeting A1c target (p<0.0001)
    - Similar rates of hypoglycemia
    - Weight reduction of 0.7 kg with glargine/lixisenatide vs. glargine alone (p<0.0001)

1. Which of the following has been recently described as a potential adverse effect of canagliflozin?
   a. Myocardial Infarction
   b. Lower limb amputation
   c. Headache
   d. Nausea

2. Which of the following GLP-1 Receptor Agonists has shown superiority in reducing risk of death due to cardiovascular causes?
   a. Exenatide
   b. Lixisenatide
   c. Liraglutide
   d. Albiglutide

3. How many units of Insulin Degludec U-200 can be given in one injection?
   a. 60
   b. 80
   c. 160
   d. 300

4. Which of the following insulin products has demonstrated a reduction in rate of hypoglycemia compared to Glargine U-100?
   a. Insulin Glargine U-300
   b. Insulin Aspart
   c. NPH Insulin
   d. Regular U-500 Insulin

5. Which of the following products contains both a GLP-1 Receptor Agonist and basal insulin?
   a. 70/30 NPH/Regular Mix
   b. Degludec/Aspart
   c. Degludec/Liraglutide
   d. Empagliflozin/Linagliptin

6. Which of the following SGLT-2 Inhibitors has demonstrated benefit in reducing nephropathy?
   a. Albiglutide
   b. Liraglutide
   c. Dapagliflozin
   d. Empagliflozin

7. No dosing restrictions are recommended for patients whose eGFR is over what value?
   a. Dosing restrictions are not determined by renal function
   b. 45mL/min/1.73m²
   c. 30mL/min/1.73m²
   d. 15mL/min/1.73m²