Diabetes Management Update- Non-insulin therapies

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Conflicts of Interest

• No actual or potential conflicts of interest to disclose in relation to this presentation

Pharmacist Objectives

• Assess new and emerging non-insulin treatment options for hyperglycemia to determine appropriate place in therapy

• Analyze recent literature assessing the cardiovascular (CV) benefits of non-insulin pharmacologic therapies

Technician Objectives

• List the non-insulin treatment options for hyperglycemia

• Identify the newest Food and Drug Administration (FDA) indication for empagliflozin

Patient case

BG is a 60 y.o. Caucasian male

• HPI: Patient presenting to clinic for follow up on T2DM, diagnosed ~ 5 months ago. A1C at diagnosis 8.4%
• PMH: MI ~5 months ago
• Social and Family History: Does not consume alcohol, former smoker, married, semi-retired, father died MI at 68 y.o.
• Meds: ASA 81mg, Prasugrel 10mg, Atorvastatin 80mg, Lisinopril 20mg, Metoprolol XL 50mg, Amlodipine 5mg, Metformin 1000mg BID

Vitals: BP 146/82 HR 85 Weight-121kg (5 lbs from hospitalization) BMI-52

Labs: CMP- WNL except BG 110mg/dL; HgbA1C 7.6%
HDL 38mg/dL, LDL 68mg/dL; TG 200mg/dL; Microalbumin:Cr 45
Fasting BG averages- 113mg/dL

Patient asks you for advice on another medication he can take to improve his diabetes and decrease his risks
Review of the guidelines

American College of Physicians 2017 Update – Oral Medications T2DM

- Recommendation 1:
  - Prescribe metformin to pts with T2DM if therapy needed to improve glucose

- Recommendation 2:
  - Consider adding either sulfonylurea, thiazolidinedione (TZD), SGLT-2 inhibitor, or DPP-4 inhibitor to metformin when second therapy needed and after discussing benefits, adverse effects, and costs

American Diabetes Association (ADA) Standards of Care 2017

- Metformin- preferred monotherapy
- A1C ≥9%- consider dual therapy
- A1C ≥10%, BG >300mg/dL, or symptomatic- consider combination injectable therapy
- Drug choice based on patient preferences, disease, and minimize side effects

Other benefits:

- Clinical Outcomes
  - Metformin ↓ CV mortality vs. sulfonylurea (SU)
  - A1C lowering
  - Most drugs reduce to similar levels
  - DPP-4 inhibitors less than metformin and SU
  - Combination with metformin > metformin alone
- Weight loss
  - Metformin > TZD, SU, or DPP-4
  - Combination metformin and SGLT-2 > metformin alone
  - TZD and SU alone and in combination, worst
- Systolic blood pressure
  - SGLT-2, with or without metformin > metformin alone

AACE/ACE 2017 Algorithm

Summary

- No clear favored 2nd or 3rd line therapy
- Patient-centered approach preferred
- Medications with CV benefit desired
Metformin updates

- Updated labeling for use in mild-moderate CKD from FDA April 2016
  - Obtain eGFR prior to metformin initiation
  - Use appropriate if eGFR > 45mL/min/1.73 m²
  - Discontinue if eGFR < 30mL/min/1.73 m²
  - Initiation not recommended if eGFR 30-45mL/min/1.73 m²
  - Additional updates regarding use prior to contrast
- Recommendation of periodic B12 monitoring in ADA Standards of Care 2017
- Monotherapy associated with CV ↓ mortality
- Off label use in T1DM

Lixisenatide (Adlyxin)

- Approved July 2016, initial NDA pulled by Sanofi in 2013
- Dosage: 10 mcg daily 1 hour before first meal X 14 days then 20mcg daily
- A1C reduction 0.5-1%, weight loss ~2kg
- ELIXA study: Rate of pancreatitis and serious ADEs lower in lixisenatide

Available GLP-1 agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>A1C reduction</th>
<th>Weight loss</th>
<th>Price per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>5mg weekly up to 1mg weekly</td>
<td>~1%</td>
<td>~1kg</td>
<td>~$480</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.6mg BID then 1mg BID daily</td>
<td>~1.5%</td>
<td>~2.5kg</td>
<td>~$625</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5mg weekly</td>
<td>~1%</td>
<td>~2kg</td>
<td>~$610</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6mg daily X 7 days then 2mg daily</td>
<td>~1.5%</td>
<td>~2.5kg</td>
<td>~$600-$750</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10mg daily X 14 days then 20mcg daily</td>
<td>0.5-1%</td>
<td>~2kg</td>
<td>~$600 (20mcg dose)</td>
</tr>
</tbody>
</table>

Duration differences in GLP-1s

<table>
<thead>
<tr>
<th>Short-Acting GLP-1 RAs</th>
<th>Long-Acting GLP-1 RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose levels</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Postprandial hypoglycemia</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Fasting insulin secretion</td>
<td>Modest stimulation</td>
</tr>
<tr>
<td>Postprandial insulin secretion</td>
<td>Reduction</td>
</tr>
</tbody>
</table>

Sodium-glucose co-transporter 2 (SGLT-2) Inhibitors

- Estimated A1C reduction 0.5-1%
- Cost relatively equivalent (~$340/month)
- Common ADE: genital mycotic infections, UTIs, ↑ urination, hypotension, ↑ LDL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>eGFR cutoff</th>
<th>Additional warnings</th>
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</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100mg daily</td>
<td>&lt;45 mL/min/1.73 m²</td>
<td>Bone fracture, ↑ BMD, AKI</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5mg daily</td>
<td>&lt;40 mL/min/1.73 m²</td>
<td>Bladder cancer, AKI</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10mg daily</td>
<td>&lt;45 mL/min/1.73 m²</td>
<td></td>
</tr>
</tbody>
</table>
Acute Kidney Injury
- Risk factors: ACE-I, diuretic, NSAIDs, pre-existing CKD, history of AKI

Euglycemic DKA
- Risk factors: Reduced appetite, pancreatic insulin deficiency, alcohol abuse, insulin reduction

Amputations
- CANVAS trial: 2x more leg and foot vs. placebo
- CANVAS-R trial: no increase vs. placebo at 9 mo

Ertugliflozin
- CV outcome study: VERTIS CV to be completed in October 2019

Sotagliflozin- dual SGLT1/2 inhibitor

Cardiovascular outcomes of DM medications

EMPA-REG OUTCOME: Game changer?
- Published December 2015
- 7020 T2DM pts with established CVD

<table>
<thead>
<tr>
<th>Empagliflozin 10mg</th>
<th>Empagliflozin 25mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Follow up mean 3.1 years</td>
<td></td>
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<tr>
<td>Primary outcome: Time to first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (MACE)</td>
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<tr>
<td>FDA indication update December 2016: Reduce risk of CV death in adults with established CV disease</td>
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EMPA-REG results
- Primary outcome
- Death from CV causes

EMPA-REG: Focus on kidney disease
Is Liraglutide the new LEADER in GLP-1s?

- Published July 2016
- 9340 T2DM pts with increased risk of CVD
- Followed for mean 3.8 years
- Primary outcome: MACE

Study Name | Major Inclusion Criteria | Primary Outcome | Major Results and Conclusions
---|---|---|---
ELIXA (lixisenatide) | Acute coronary event within previous 180 days | 4-point MACE | No difference in primary outcome
SAVOR-TIMI 53* (saxagliptin) | Established CV disease or multiple risk factors for vascular disease | MACE | No difference in primary outcome
EXAMINE* (alogliptin) | Acute coronary event within previous 15-90 days | MACE | No difference in primary outcome

Overview of CV studies on new DM medications

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>Anticipated completion date</th>
<th>Major inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXSCEL</td>
<td>Exenatide (once weekly)</td>
<td>April 2018</td>
<td>Patients ≥ 18 y.o. with and without CVD included</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>February 2017</td>
<td>Patients ≥ 50 y.o. with CVD</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>Dapagliflozin</td>
<td>April 2019</td>
<td>Patients ≥ 40 y.o. with high risk of CVD</td>
</tr>
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</table>
“We urge that the time is right to convene a committee of diabetes community leaders and researchers to reevaluate the current outmoded DM classification system.”

BG is a 60 y.o. Caucasian male presenting to clinic for follow up on T2DM. A1C at diagnosis 8.4% 5 mo ago, now 7.6%. PMH for MI 5 mo ago. BP 146/82 BMI-32 Meds: ASA 81mg, Prasugrel 10mg, Atorvastatin 80mg, Lisinopril 20mg, Metoprolol XL 50mg, Amlodipine 5mg, Metformin 1000mg BID

Patient asks you for advice, what would you recommend?
Conclusion

- Metformin continues to be 1st line agent and should be continued in combination therapy unless contraindicated
- Positive outcomes on CVD for various antihyperglycemic agents do not appear drug class related
- Treatment of hyperglycemia continues to be individualized to patient based on variety of factors