SGLT-2 and GLP-1
Sodium Glucose Transporter
Type Two Inhibitors and
Glucagon-Like Protein Type One
Receptor Agonists

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Disclosures

• No financial interests in any drug manufacturers or other members of industry.
Objectives

• Provide brief pharmacologic review of SGLT-2 and GLP-1 drugs
• Highlight the effects of the drugs beyond glycemic control
• Provide practical guidance for patient selection and successful utilization of SGLT-2 and GLP-1 drugs
Sodium-Glucose Cotransporter Type 2 Inhibitors or SGLT-2

• Empagliflozin was added to IHS National Core Formulary (NCF) in November 2019 and is available to all eligible for care at IHS
• Canagliflozin
• Dapagliflozin
• Ertugliflozin
Glucagon-like Peptide Type 1 Receptor Agonists or GLP-1

• Dulaglutide-on NCF
• Exenatide
• Liraglutide-on NCF
• Lixisenatide
• Semaglutide-on NCF
IHS Diabetes Treatment Guidelines:
Glucose Management Algorithm

- First step is to decide on an A1C target
- Start metformin
- Start two agents if A1C is over 9 or there is catabolism evident
Glucose Management Algorithm: Step 2

Step 2: Initiate Medication Therapy
If significant weight loss or ketonuria, use insulin (hospitalize if acidotic).
Otherwise:
- Start metformin if A1C above patient's target but <9%.
- Start metformin and a second medication if A1C ≥9% (see Step 3).

Step 3: Increase Dosage(s) and/or Add Another Medication
Select additional medication(s) based on formulary options, side effects, cost, comorbidities (e.g., CVD), medication regimen complexity, and patient preference.
Glucose Management Algorithm: Step 3

**Step 3: Increase Dosage(s) and/or Add Another Medication**
Select additional medication(s) based on formulary options, side effects, cost, comorbidities (e.g., CVD), medication regimen complexity, and patient preference.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight</th>
<th>A1C</th>
<th>Risk of Hypoglycemia</th>
<th>Cost</th>
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<tr>
<td>Metformin</td>
<td>- to ↓</td>
<td>↓↓</td>
<td>-</td>
<td>$</td>
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<td>-</td>
<td>$$</td>
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<tr>
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<td>$$ to $$ $$</td>
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<td>↑</td>
<td>$</td>
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<tr>
<td>Thiazolidinedione</td>
<td>↑</td>
<td>↓↓</td>
<td>-</td>
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</table>

Do not use GLP-1 Receptor Agonists and DPP-4 inhibitors together as no A1C benefit
COST? $?

• The IHS National Core Formulary makes diabetes medications from each of the different classes available to all those people eligible for care with a valid prescription.
SGLT-2 Clinical Benefits

• A1C reduction is modest at 0.5-0.8%
• Reduction of death from CHF and improvement in CHF is a class effect
• Reduction in CKD progression is a class effect
• SGLT-2 is recommended as a second line rx for those with CVD/CKD or at increased risk by IHS, ADA, AHA care and treatment guidelines when metformin alone no longer provides glycemic control
• Empagliflozin is only SGLT-2 with all-cause mortality reduction
• Glucosuria promotes weight loss and natriuresis which has modest BP lowering impact as well
• ASCVD, CHF, CKD impact was demonstrated with empagliflozin at 10 mg dose level. Empagliflozin is titrated to 25 mg for glycemic control
SGLT-2 Clinical Cautions

• All agents are contraindicated in CKD once eGFR is < 30 ml/min
• Genital Mycotic Infections, UTI, and Fournier’s gangrene are listed as ADRs
• Canagliflozin carries LE amputation black-box warning
• BP tends to lower with use and care must be taken when adding SGLT-2 rx to patients already on diuretic rx.
• DKA risk increases and prior DKA is relative contraindication
• DKA may be more likely in perioperative period and FDA recommends SGLT-2 be stopped in pre-op period
• DKA can happen without hyperglycemia-”euglycemic DKA”-RARE
SGLT-2 Mechanism

• Glucose resorption is halted in proximal tubule, glucose is then excreted in urine-approx. 180 gm per day are filtered and reabsorbed in proximal tubule

• Does not require insulin to have an effect-can be helpful for those later in their diabetes disease progression (and more likely to have CVD or CKD)

• Has a BP lowering impact through promotion of natriuresis

• Weight loss is common with the class
SGLT-2 Summary

- SGLT-2 drugs have CVD and CKD preventing effects
- SGLT-2 is a strong consideration in any person with T2DM and reduced EF CHF
- SGLT-2 is effective down to GFR of 30 ml/min
- Caution if prior DKA and warn people of mycotic genital yeast infection
GLP-1 Clinical Benefits

• A1C reduction of 1.0-1.5%
• Weight loss is common with the class 2.2-4.4 kg
• Low risk for hypoglycemia
• Reduction in CVD risk
• Some reduction in CKD risk
• Consider addition of GLP-1 before adding insulin in people not controlled on metformin alone
• Consider addition of GLP-1 after basal insulin instead of mealtime insulin
GLP-1 Clinical Use - Cautions

- GI side effects are most common including nausea, vomiting, and diarrhea—adjust dose slowly or reduce if ADR accompanies increase
  - Use carefully when co-morbid GERD
  - Use carefully when co-morbid diabetes gastropathy

- Thyroid medullary carcinoma and MEN-2 are contraindications

- Pancreatitis was initially associated with the class—if pancreatitis occurs—stop GLP-1 and resume with caution or not at all

- Semaglutide is associated with worsening of existing retinopathy—use with caution and only after discussion with patient

- Absorption of oral semaglutide is inconsistent
GLP-1 Mechanism

• Stimulates insulin production when carbs are eaten (Incretin effect)
• Causes satiety thereby reducing food intake
• Suppresses hepatic gluconeogenesis
GLP-1 Summary

- GLP-1 add on therapy to metformin and/or basal insulin
- GLP-1 have good A1C lowering ability
- GLP-1 is excellent for weight loss
- GLP-1 is best early in disease and keeps people from gaining weight and developing macrovascular complications
- Caution if previous pancreatitis, and active retinopathy (semaglutide)
Utilization of SGLT-2 and GLP-1

• IHS
• National
Contemporary National Patterns of Eligibility and Utilization of Cardioprotective Anti-hyperglycemic Agents in Type 2 Diabetes

• T2DM Prevalence for NHANES-10.6% 2017-2018

• 1/2 of all people in the US with T2DM have an indication for SGLT-2 including ASCVD, Heart Failure, or CKD3/elevated UACR

• 1/3 of all people with T2DM in the US have indication for GLP-1 including ASCVD or at high risk for ASCVD
Utilization of each drug class across components of eligibility among patients with diabetes

<table>
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<tr>
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<th>SGLT-2 Inhibitors</th>
<th>GLP-1RAs</th>
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<tr>
<td>Weighted %</td>
<td>Weighted % [95% CI]</td>
<td>Weighted % [95% CI]</td>
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<tr>
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</tr>
<tr>
<td>CKD Stage III/A2-3</td>
<td>6.0 [2.1-15.8]</td>
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J Am Heart Assoc. 2021;10:e021084. DOI: 10.1161/JAHA.121.021084
# IHS Audit Data

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<td>CVD</td>
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Patient-Al T. Common - Story

• 57 yo male with recent MI, stent placed. During hospitalization he was found to have A1C of 9.5%. Seeing you in clinic to establish care
• Last doctor was about 10 years ago when they took out gallbladder
• Family Hx for MI and dialysis
• Crazy about his grandchildren, works a desk job
• Enjoys Hulu, Amazon Prime Video, and just bought HBO
• Meds Lisinopril 40 mg, Metoprolol 50 mg BID, Atorvastatin 40 mg, ASA 81 and Clopidogrel, Metformin 1 gm BID, Furosemide 40 mg BID
Al T. Common-data

• BP 145/95
• HR 66
• RR 16
• 70 inches
• 275 lbs
• Creat 1.5 eGFR 45
• A1C 9.5
• UaCR 250
• TG’s 250
• Cholesterol 180, HDL 25

• WBC 5.5
• Hgb 18
• PLT 105
• AST 88
• ALT 78
• Albumin 2.5
• T bili 1.3
• K 3.2
• CO2 20
• BUN 24
• TSH 2.0
Al T. Common-ROS

• Feels tired, winded with 5 stairs
• Weight loss of 20 lbs in last couple months without trying
• Has nausea and “poor digestion”
• Has daily heartburn and takes Prilosec OTC frequently
• Alcohol-Zero drinks for last 2 years
• Does not sleep well since stopped alcohol
• 3 times nocturia-more in last month
• Feet swell at times and never feel right, especially at night
Al T. Common

• Assessment
  • Uncontrolled T2DM with microvascular complications of CKD 3 and peripheral neuropathy, macrovascular complication of ASCVD with recent MI-EF was 40% on recent hospital discharge note
  • Metabolism-associated fatty liver disease with cirrhosis-compensated
  • Hypertension
  • Obstructive Sleep Apnea-likely

• Plan-Goal A1C<8 & hypoglycemia is Highly undesirable
  • Start insulin-long acting 25 units/day (0.2 U/kg)
  • Start empagliflozin 10 mg daily
  • SMBG QAM, before lunch, dinner and 2 hours after evening meal
  • Follow up in one week, labs before visit
Al T. Common-1 week follow up

• SMBG-Tested a couple days in the morning but bleeds too much so did not do any other testing. AM Glucose was about 250 on the 3 days tested. Only thing he noticed is that he is urinating less frequently

• BP 132/88, 272 lbs

• Creat 1.6, BUN 35, CO2 24, AST/ALT same, Hgb 18

• Assessment- Metabolism is improved but still with hyperglycemia and now hypovolemia

• Plan
  • Increase insulin 5 units at HS to 30 units. Increase 2 units every 2 days until fasting AM sugar is less than 150
  • Advise regular fluids and hold off on raising empagloflozin until hyperglycemia improved further/volume status improved
Waytoo Common

• 35 yo female whose dad just had an MI. Mother died of liver disease was on dialysis, wants to be checked for diabetes
  • G4P4 with GDM 3rd and 4th pregnancies, BTL after 4th child
  • Plays softball, volleyball, and sports with kids
  • No smoke, alcohol after games only
  • Does not sleep well
  • On metformin for DM prevention with A1C of 6.4 2 years ago-last fill on metformin was 8 months ago “Almost out of diabetes pills”
Waytoo Common-data

- 122/72
- 195 lbs
- 67 inches
- A1C-7.2
- Hgb 14
- Plt 200
- AST 48
- ALT 60
- Albumin 4
- UACR 32
Waytoo Common (con’t)

• Assessment
  • T2DM, uncontrolled on metformin
  • Obesity
  • Metabolism-associated liver disease
  • Microalbuminuria

• Plan
  • A1C goal of “as far below 7 as possible without hypoglycemia”
  • Weight loss goal of 45 lbs (BMI under 25)
  • Start semaglutide 0.25 mg subQ weekly for 4 weeks then increase to 0.5 mg weekly
  • Increase metformin to 2 gm daily
  • Stop all alcohol
In Summary

• GLP-1 add on therapy to metformin and/or basal insulin
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