Diabetes Medications for Type 2 Diabetes with Focus on HIV: Part 2

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Disclosures

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Objectives

• Understand how to safely prescribe and use “newer” diabetes medications

• Understand physiology and mechanism of action, efficacy, safety, tolerability, managing side effects, dosing and administration of individual drugs

• Understand how to use these medications in liver disease and CKD

• Assess the cardiac and renal benefits in these newer medications
Diabetes Medications

• Mechanism of action
• Efficacy (on average how much does it lower blood sugar)
• Does it cause hypoglycemia yes/no
• Common side-effects
• Serious side-effects
• Weight gain/Weight loss/Weight neutral
• Cardiovascular effects
• Use in Liver Disease
• Use in CKD and renal protective effect
Glucose-lowering medication in type 2 diabetes: overall approach.
Timing of CV safety trials with Drugs for Type 2 Diabetes

More than 200,000 people with T2D are currently participating in CVOTs.

THIAZOLIDINEDIONES: “TZDS”
### Thiazolidinediones: “TZDs”

<table>
<thead>
<tr>
<th>Class/Main Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>pioglitazone (Actos)</td>
<td>15 – 45 mg daily</td>
<td>Black Box Warning: TZDs may cause or worsen CHF. Monitor for edema and weight gain. Increased peripheral fracture risk. Actos may increase risk of bladder cancer. Lowers A1c 0.5% – 1.0%</td>
</tr>
<tr>
<td>“TZDs”</td>
<td>rosiglitazone (Avandia)</td>
<td>4 – 8 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

- Increases insulin sensitivity
TZD Adverse Effects

• Weight gain
• Increased risk of edema
• Contraindicated in Class III HF or higher and possible increase risk of HF
• Increased risk of long-bone fractures
• Possible increased risk macular edema
• Pioglitazone ?? Bladder cancer risk
Pioglitazone after CVA or TIA

Insulin Resistance Intervention After Stroke Trial (IRIS):

Cumulative Event-Free Survival Probability

24% RRR OF CVA

HR 0.76
95% CI, 0.62 to 0.93
P=0.007

*Inclusion Criteria: Insulin resistance (did not need a diagnosis of DM)

Fibrosis score: treatment difference, -0.5 [CI, -0.9 to 0.0]; P = 0.039

Resolution of NASH defined as absence of NASH after 18 mo of therapy with definite NASH at baseline

Summary: Thiazolidinediones (TZDs)

• Helps to target insulin resistance
• May improve dyslipidemia
• NASH (Non-Alcoholic liver disease)
• Established CVA may have some CV benefit
• Weight gain, edema, and fractures
• Risk for worsening HF - *do not use in CHF*
• Use in select population
• The available evidence does not support the use of thiazolidinediones lipoatrophy
GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RA)
Intensifying to injectable therapies

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSME to meet individualized treatment goals.

**If injectable therapy is needed to reduce A1C**

**Consider GLP-1 RA in most patients prior to Insulin**

**INITIATION**: Initiate appropriate starting dose for agent selected (varies within class)

**TITRATION**: Titration to maintenance dose (varies within class)

If already on GLP-1 RA or if GLP-1 RA not appropriate or Insulin preferred

If above A1C target

Add basal insulin

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

**Add basal analog or bedtime NPH insulin**

**INITIATION**: Start 10 IU a day OR 0.1-0.2 IU/kg a day

**TITRATION**:
- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate overbasalization and need to consider adjunctive therapies for basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-prandial differential, hypoglycemia (aware or unaware, high variability)

If above A1C target

Consider GLP-1 RA if not already in regimen

**For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors**

Add prandial insulin

Usual dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate.

**INITIATION**: 4 IU a day or 10% of basal insulin dose

If A1C <9% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

If on bedtime NPH, consider converting to twice-daily NPH regimen

Conversion based on individual needs and current glycemic control. The following is one possible approach:

**INITIATION**:
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:
- Titrate based on individualized needs

Stepwise additional injections of prandial insulin

(e.g., two, then three additional injections)

Proceed to full basal-bolus regimen (e.g., basal insulin and prandial insulin with each meal)

Consider self-mixed/spilt insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

**INITIATION**: Complete NPH dose = 80% of current NPH dose

- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

**TITRATION**: Titrate each component of this regimen based on individualized needs

Consider twice-daily premix insulin regimen

**INITIATION**: Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

**TITRATION**: Titrate based on individualized needs

1. Consider insulin as the first injectable if evidence of ongoing carbohydrate, symptoms of hypoglycemia are present, when A1C levels >10% (86 mmol/mol) or blood glucose levels >600 mg/dL (33.3 mmol/L) are very high, or a diagnosis of type 1 diabetes is possible.

2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If OAD, consider GLP-1 RA with proven OAD benefit. Oral or injectable GLP-1 RA are appropriate.

3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-dose combination product (Exenatide or Liraglutide).

4. Consider switching from evening NPH to a basal analog if the patient experiences hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.

5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.
### Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA)

<table>
<thead>
<tr>
<th>Class/Main Action</th>
<th>Name</th>
<th>Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Receptor Agonist (GLP-1 RA)</td>
<td>exenatide (Byetta)</td>
<td>5 and 10 mcg BID</td>
<td>Side effects for all: Nausea, vomiting, weight loss, injection site reaction. Report signs of acute pancreatitis (severe abdominal pain, vomiting), stop med. Renally excreted.</td>
</tr>
<tr>
<td>“Incretin Mimetic”</td>
<td>exenatide XR (Bydureon)</td>
<td>2 mg 1x a week Pen injector - Bydureon BCise</td>
<td>Black box warning: Thyroid C-cell tumor warning for exenatide XR, liraglutide, dulaglutide, and semaglutide (avoid if family history of medullary thyroid tumor).</td>
</tr>
<tr>
<td></td>
<td>liraglutide (Victoza)*</td>
<td>0.6, 1.2 and 1.8 mg daily Approved for pediatrics 10 yrs +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dulaglutide (Trulicity)*</td>
<td>0.75, 1.5, 3.0 and 4.5 mg 1x a week pen injector</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lixisenatide (Adlyxin)</td>
<td>10 mcg 1x a day for 14 days 20 mcg 1x day starting day 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>semaglutide (Ozempic)**+ (Rybelsus) Oral tablet</td>
<td>0.5 and 1.0 mg 1x a week pen injector 3, 7, and 14 mg daily in a.m. Take on empty stomach w/H2O sip</td>
<td>Black box warning: Thyroid C-cell tumor warning for exenatide XR, liraglutide, dulaglutide, and semaglutide (avoid if family history of medullary thyroid tumor).</td>
</tr>
<tr>
<td>Amylin Mimetic</td>
<td>pramlintide (Symlin)</td>
<td>Type 1: 15 - 60 mcg; Type 2: 60 - 120 mcg immediately before major meals</td>
<td>For Type 1 or 2 insulin. Severe hypoglycemic risk, decrease insulin dose when starting. Side effects: nausea, weight loss. Lowers A1c 0.5 – 1%</td>
</tr>
</tbody>
</table>

For Type 1 or 2 insulin. Severe hypoglycemic risk, decrease insulin dose when starting. Side effects: nausea, weight loss. Lowers A1c 0.5 – 1%
GLP-1 RA: Side-Effects /Potential Patient Perceived Barriers

- Nausea/diarrhea/constipation
- Possible risk for Pancreatitis??
- Theoretical risk for medullary thyroid cancer??
  - Induces rodent thyroid C-cell tumors
- Injection

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Ann Pharmacother 2011;45:850-860
<table>
<thead>
<tr>
<th>GLP-1 receptor agonists</th>
<th>GLP-1 receptor agonist/ basal insulin fixed-dose combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pen devices for injection</strong></td>
<td><strong>Pen for single or multiple use?</strong></td>
</tr>
<tr>
<td><strong>Drug name:</strong></td>
<td><strong>Pen for pre-determined single dose/ variable dosing</strong></td>
</tr>
<tr>
<td><strong>Generic</strong></td>
<td><strong>Pen devices available (maximum dose)</strong></td>
</tr>
<tr>
<td><strong>Commercial</strong></td>
<td><strong>Resuspension before injection necessary?</strong></td>
</tr>
</tbody>
</table>

| Exenatide b.i.d Byetta® | multiple |
| Lixisenatide Lyxumia® | multiple |
| Liraglutide Victoza® (original) | multiple |
| Exenatide once weekly Bydureon® BCise (improved) | single |
| Dulaglutide Trulicity® | single |
| Albigrutide Eperzan® Tanzeum® | single |
| Semaglutide Ozempic® | single |
| IdeglLira Xultophy® | multiple |
| iGlari lixi Soliqua® | multiple |

Pen devices available (maximum dose): 5 or 10 µg, 10 or 20 µg. Resuspension before injection necessary: no, no, no, yes. Pen for single or multiple use: multiple, multiple, multiple, single. Pen for pre-determined single dose/ variable dosing: single, variable (0.6, 1.2, or 1.8 mg), single, single, single, single, variable, for titration, variable, for titration. Pen devices available (maximum dose): 2 mg, 2 mg, 2 mg, 0.75 or 1.5 mg, 30 or 50 mg, 0.25, 0.5 or 1.0 mg. Pen devices available (maximum dose): Up to 1.8 mg (plus insulin degludec up to 50 IU), Up to 20 µg (plus insulin glargine up to 60 IU).
0.6, 1.2 and 1.8 daily dosing

0.75 and 1.5mg weekly dosing

Recent approval of 3.0 and 4.5mg dosing

0.25, 0.5mg, and 1mg weekly dosing
How to use Exenatide (Bydureon)

English: https://www.youtube.com/watch?v=72w756RKawY
Spanish: https://www.youtube.com/watch?v=Wqn1iKBiQkk

https://www.molinahealthcare.com/-/media/Files/formulary.pdf
Oral Semaglutide

Take on an empty stomach

Take with a small amount of water (no more than 4oz)

Wait 30 minutes after taking it and then eat food

3, 7, and 14 mg dosing
GLP-1 RA in CKD

• In CKD stages 2 and 3: no dose adjustment is required for liraglutide and dulaglutide, semaglutide, extended release exenatide
  • Exenatide: reduce dose to 5mcg bid if 30–50 mL/min

• In CKD stages 4 and 5: GLP-1 RA limited data

• What about Stage 3 CKD  GFR < 45??
GLP-1 use in CKD: LIRA-RENA Study

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.8 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 140)</td>
<td>(n = 137)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (46.4)</td>
<td>72 (52.6)</td>
</tr>
<tr>
<td>Male</td>
<td>75 (53.6)</td>
<td>65 (47.4)</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>68.0 (8.3)</td>
<td>66.3 (8.0)</td>
</tr>
</tbody>
</table>

**Can use/initiate in GFR 30-45**

<table>
<thead>
<tr>
<th>GFR</th>
<th>Liraglutide 1.8 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt; 45</td>
<td>61 (43.6)</td>
<td>59 (43.1)</td>
</tr>
<tr>
<td>45–59</td>
<td>78 (55.7)</td>
<td>78 (56.9)</td>
</tr>
<tr>
<td>&gt; 59</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
**GLP-1 RAs and CV Risk Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug tested</td>
<td>Lisixenatide</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Dose</td>
<td>20 µg/d</td>
<td>1.8 mg/d</td>
<td>0.5 or 1</td>
<td>1.5 mg/wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mg/wk</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>9901</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>60</td>
<td>64</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Percent women</td>
<td>31</td>
<td>36</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>Percent prior CVD</td>
<td><strong>100</strong></td>
<td><strong>81</strong></td>
<td><strong>59</strong></td>
<td><strong>31</strong></td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>30</td>
<td>33</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Mean HbA1c, %</td>
<td>7.7</td>
<td>8.7</td>
<td>8.7</td>
<td><strong>7.3</strong></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>MACE(^a)</td>
<td>MACE(^a)</td>
<td>MACE(^a)</td>
<td>MACE(^a)</td>
</tr>
<tr>
<td></td>
<td>or unstable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>angina</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CV and Renal Benefits of GLP-1 RAs

<table>
<thead>
<tr>
<th>Administration:</th>
<th>subcutaneous</th>
<th>oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound:</td>
<td>Exenatide</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td>Frequency:</td>
<td>b.i.d.</td>
<td>q.w.</td>
</tr>
<tr>
<td>Effects:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c reduction:</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-prandial glucose</td>
<td>++(^a)</td>
<td>++(^a)</td>
</tr>
<tr>
<td>Body weight reduction:</td>
<td>++(+)</td>
<td>+</td>
</tr>
<tr>
<td>Injection device:</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Convenience/adherence:</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>CV benefit („MACE“):</td>
<td>not known</td>
<td>±</td>
</tr>
<tr>
<td>Mortality benefit:</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Renal benefit:</td>
<td>±</td>
<td>(+)</td>
</tr>
<tr>
<td>Nausea/vomiting:</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immunogenicity(^c):</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

\(^a\) Increases in intrabody fat mass.

\(^b\) Not commercially available in all countries.

\(^c\) Very rare, under 0.1%.

YES

GLP-1 RA and Liver Disease

GLP-1 receptor agonists

- Induces weight loss
- Low risk of hypoglycemia
- Restores peripheral and hepatic insulin sensitivity
- Improves amiontransferases, hepatic steatosis/fibrosis in NAFLD/NASH
- May inhibit alcohol consumption in experimental models
- Eliminated by proteolytic degradation
- Limited therapeutic experience in advanced cirrhosis

Initial data on NASH and GLP-1 RA encouraging

Fasting serum GLP-1 levels were decreased in patients with chronic HCV, but not those with HBV

Diabetes Care. 2012 May; 35(5): e34.
NASH and GLP-1 RA

NASH resolution/no worsening of fibrosis: 59% vs. 17% (P<0.001)

Improvement in fibrosis stage occurred in 43% and in 33% vs. (P=0.48).
Summary: GLP-1 RAs

- Expensive
- May cause weight loss (8-12 pounds)
- CV benefit and renal benefit
- > 1% HbA1c reduction
- Weekly dosing likely improves compliance
- Low risk for hypoglycemia
- Oral version now available
- Nausea main side-effect
- I would consider in compensated cirrhosis especially NASH
SODIUM-GLUCOSE CO-TRANSPORTER INHIBITORS (SGLT2I)
# Sodium-Glucose Co-Transporter Inhibitors (SGLT2I)

<table>
<thead>
<tr>
<th>Class/Main Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Canagliflozin* (Invokana)</td>
<td>100 - 300 mg 1x daily</td>
<td><strong>Side effects:</strong> hypotension, UTIs, increased urination, genital infections, ketoacidosis.</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin* (Farxiga)</td>
<td>5 - 10 mg 1x daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin* (Jardiance)</td>
<td>10 - 25 mg 1x daily</td>
<td><strong>Monitor GFR and other considerations:</strong> See package insert for dosing based on GFR.</td>
</tr>
<tr>
<td></td>
<td>Ertugliflozin (Steglatro)</td>
<td>5 – 15 mg 1x daily</td>
<td>*Empagliflozin, Dapagliflozin, &amp; Canagliflozin: Reduce risk of CV death, heart failure and preserve long-term kidney function.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Don’t start if GFR &lt;45.</td>
<td><strong>Benefits:</strong> no hypo or weight gain. Lower A1c 0.6%-1.5%. Lowers wt 1-3 lbs.</td>
</tr>
</tbody>
</table>

- Decreases glucose reabsorption in kidneys
# Sodium-Glucose Co-Transporter Inhibitors (SGLT2i)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean A1C Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin 300 mg</td>
<td>-0.86% (-0.96 to -0.76)</td>
</tr>
<tr>
<td>Canagliflozin 100 mg</td>
<td>-0.76% (-0.86 to -0.66)</td>
</tr>
<tr>
<td>Dapagliflozin 10 mg</td>
<td>-0.66% (-0.74 to -0.58)</td>
</tr>
<tr>
<td>Dapagliflozin 5 mg</td>
<td>-0.56% (-0.67 to -0.44)</td>
</tr>
<tr>
<td>Empagliflozin 25 mg</td>
<td>-0.66% (-0.76 to -0.56)</td>
</tr>
<tr>
<td>Empagliflozin 10 mg</td>
<td>-0.60% (-0.70 to -0.50)</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin.
SGLT2 Inhibitors:

Warnings and Precautions - Canagliflozin/Dapagliflozin/Empagliflozin

- Hypoglycemia: risk with secretagogues, insulin
- Genital mycotic infections
- UTI, urosepsis
- Volume depletion/orthostatic changes

- DKA
- Bladder cancer (Dapagliflozin only)  
  - removed recently
- Increased fracture risk
- Increased risk for amputation

Diabetes Care 2015;38:1638-1642
Diabetes Ther. 2020 Jan; 11(1): 7–1
Fralick M et al. BMJ 2020; 370 :m2812
Demonstration of the cascade of clinical events and metabolic changes that contribute sequentially to progressive clinical deterioration and development of full-blown episodes of euDKA.
Risk for DKA, Genital Infections, Amputation and Fractures

- DECLARE and EMPA-REG: less than 0.1% risk for DKA
- CANVAS: The estimated DKA incidence rates—0.5, 0.8, and 0.2 per 1,000 patient-years
- EMPA-REG OUTCOME: 22 vs 75 had genital infections
- Rare case reports of ARI and risk for orthostatic hypotension
- Fournier's gangrene
- CANVAS increased fracture risk (4% vs. 2.6%) but neutral in pooled non-CANVAS studies
- CANVAS Amputation (6.3% vs 3.4%) but neutral in recent large retrospective study

EMPA-REG N Engl J Med 2015; 373:2117-2128
Yu O et al.. Diabetes Care. 2020 Oct;43(10):2444-2452
CANVAS. Lancet Diabetes Endocrinol. 2018 Sep;6(9):691-704
SGLT2 inhibitor use in CKD - For Glycemic Management

- Invokana (canagliflozin) < 45mL/min - Do Not use
- Jardiance (empagliflozin) < 45ml/min Do Not use
- Farxiga (dapagliflozin) < 60ml/min - Do Not Use

- Example: patient on empagliflozin GFR < 60 mL/min decrease to 10 mg daily when < GFR 45 mL/min stop

- At stage 3b CKD or greater, all SGLT-2 inhibitors are contraindicated, mainly because efficacy may be worst at GFR < 60mL/min
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE)

ADA guidelines: SGLT2 inhibitors for the prevention of kidney failure, cardiovascular events or both in patients with an eGFR >30 mL/min/1.73 m²

**Especially with severely increased albuminuria**

Canagliflozin: SGLT2I: For Renal and CV Benefit

- GFR ≥60 mL/min/1.73 m²: No dosage adjustment necessary.
- eGFR 30 to <60 mL/min/1.73 m²: 100 mg qDay.
- eGFR <30 mL/min/1.73 m² with albuminuria >300 mg/day: 100 mg qDay to reduce risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure.
CV Outcomes Comparison

CV Benefits and All Cause Mortality Benefit for GLP-1 RA & SGLT-2 I

**Heart Failure Benefit only in SGLT-2 I

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction With and Without DM

Primary Composite Outcome

CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65, 0.85)
P = 0.00001
NNT = 21

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2373</td>
<td>2371</td>
</tr>
<tr>
<td>3</td>
<td>2305</td>
<td>2258</td>
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Adapted from McMurray JJV et al. As presented during ESC Congress 2019, Hot Line Session 1.
SGLT-2 Inhibitors and Liver Disease

- Induces weight loss
- Low risk of hypoglycemia
- Improves hepatic steatosis on imaging and hepatic fibrosis markers in NAFLD/NASH
- Increased risk of urinary and genital tract infections
- Limited therapeutic experience in advanced cirrhosis

? Attenuate HCC development
Benefit in NASH
Baseline and posttreatment changes in liver fat in the empagliflozin and control groups as assessed by MRI-PDFF.
Summary: SGLT2 inhibitors

- CV and renal benefit for patients with DM
- HF benefit for patients with and without DM
- Risk for DKA, UTI, genital infections, amputation, bone loss
- Some weight loss
- Overall can be well tolerated
- NASH benefit and promising potential in liver disease but not well studied
- HbA1c drop is usually < 1.0%
- More expensive: Consider using 150 canagliflozin or 12.5mg empagliflozin (cut tablet in ½)
Conclusions

• Some medications for the treatment of T2D have cardiovascular and reno-protective effects in those with CVD or are high-risk for CVD

• As well, certain medications help initiate weight loss and are less likely to cause hypoglycemia than other agents

• Cost must be a factor in use of these medications

• Evolving data on diabetes medications for NASH and in Hep C and other chronic liver disease and limited data in HIV
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