Emerging Challenges in Primary Care

Integrating Data on Macrovascular and Microvascular Outcomes into Diabetes Management: Evolving Treatment Strategies
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Disclosures

- **Richard S. Beaser, MD** has no financial relationships to disclose.

- **Robert S. Busch, MD, FACE** serves as a speaker for Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Shire. Dr. Busch also serves as a researcher for Astra Zeneca, Novo Nordisk, Janssen, and Amgen.

- **Mark Stolar, MD** serves as a speaker/advisory board member for Astra Zeneca.

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- **Jeff Unger, MD, ABFM, FACE** serves on the advisory board for Abbott, Novo Nordisk, Janssen, and Intarcia.
Learning Objectives

- Describe the role of the kidney in glucose metabolism in health and disease
- Review the physiologic effects and clinical efficacy of SGLT-2 therapy in various patient populations
- Review emerging data on possible renal and macrovascular effects of evidence-based diabetes treatment options
- Integrate the impact of treatment decisions on postprandial hyperglycemia and risk of hypoglycemia
Under normal conditions, the SGLT-2 and GLUT-2 transporters mediate reabsorption of about what proportion of glucose filtered by the kidney?

1. 10%
2. 35%
3. 70%
4. 90%
In the EMPA-REG trial, the use of empagliflozin in patients with high cardiovascular risk was associated with what significantly different outcome compared to placebo?

1. Reduced incidence of MI
2. Increased incidence of nephropathy
3. Reduce incidence of cardiovascular death
4. Increased risk for exacerbation of heart failure
Pre-test ARS Question 3

A 53-year-old obese woman with a history of hypertension and type 2 diabetes presents for a checkup. Her A1C is 7.9%. She reports recent weight gain (10 lbs) and occasional hypoglycemia (FPG <70 mg/dL). Current medications include metformin 1000 mg bid, glyburide 8 mg qd, basal insulin 40 U qam, and hydrochlorothiazide 25 mg qd. What might be an appropriate action at this time?

1. Add thiazolidinedione
2. Add DPP-4 inhibitor and reduce dose of basal insulin
3. Increase dose of basal insulin and administer at night
4. Discontinue glyburide and add SGLT-2 inhibitor or GLP-1 RA
A 57-year-old obese man with a history of type 2 diabetes, hypertension, reduced renal function (eGFR 55 mL/min/1.73m²), and prior NSTEMI presents for a checkup. His A1C today is 8.1% and average FPG over last two weeks, ~130 mg/dL.

Current medications include metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

**Discontinue sulfonylurea and add canagliflozin or empagliflozin:**

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 5

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

If canagliflozin started, limit dose to 100 mg qd:

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 6

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

Avoid all SGLT-2 inhibitors based on eGFR <60 mL/min/1.73m²:

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 7

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

Add prandial insulin tid and maintain current antidiabetic regimen:

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 8

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as **consistent** with or **not consistent** with best clinical practice:

**Increase dose of basal insulin and add DPP-4 inhibitor:**

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 9

How often do you modify antidiabetic therapy based on risk for hypoglycemia:

1. Never
2. Rarely
3. Sometimes
4. Very often
5. Always
Pre-test ARS Question 10

Please rate your confidence in your ability to select patients appropriate for treatment with SGLT-2 inhibitors:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Normal Glucose Homeostasis Reflects a Balance of Glucose Production, Absorption, and Excretion

- A delicate balance between several regulatory processes maintains glucose within a narrow range of ~80-120 mg/dL throughout the day

- Hormonal regulation
  - Insulin: glucose utilization and production
  - Glucagon: hepatic glucose production (together with insulin)

- Organs
  - Liver: glucose production (via gluconeogenesis and glycogenolysis)
  - Gastrointestinal tract: glucose absorption
  - Kidney: glucose production (via gluconeogenesis), glucose reabsorption, and glucose excretion

The Kidney Plays Key Roles in Maintaining Glucose Homeostasis: Production and Reabsorption of Glucose

- **Gluconeogenesis (Production)**
  - Estimated to be responsible for up to 20% of total glucose release

- **Glucose filtration**
  - Filters up to 180 g/day of glucose through the renal glomerulus

- **Glucose reabsorption**
  - Expedites reabsorption of filtered glucose into plasma and excretion of excess glucose in urine
  - At plasma glucose concentrations up to 180 to 200 mg/dL, essentially all glucose is reabsorbed
  - At levels ~200 to 250 mg/dL or when the filtered glucose load exceeds 375 mg/min, excess glucose is excreted in urine: “transport maximum (Tmax)”
  - Renal absorption from the kidneys is via SGLT-1 and SGLT-2 sodium co-transporters

Normal Glucose Homeostasis

Net balance ~0 g/day

Glucose input ~250 g/day:
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake ~250 g/day:
- Brain ~125 g/day
- Rest of the body ~125 g/day

The kidney filters circulating glucose
- Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose
- Glucose reabsorbed ~180 g/day

Renal Cortex: Releases Glucose
Renal Medulla: Reabsorbs Glucose

- **Renal Cortex**
  - In fasting state in healthy subjects, kidneys contribute 20% to 25% of the glucose released into the circulation via gluconeogenesis (15 to 55 g/d). Gluconeogenesis occurs in proximal tubule cells of renal cortex
  - Insulin directly REDUCES renal gluconeogenesis. In T2DM gluconeogenesis is increased 3 times
  - Insulin REDUCES the substrates of gluconeogenesis, thus controlling renal glucose production
  - Renal gluconeogenesis INCREASES 2 times in postabsorptive state in order to replenish hepatic glycogen stores. PP glucose renal release in T2DM is 100 g vs 70 g in euglycemic subjects

How is Glucose Reabsorbed in the Kidney (Renal Medulla)?

- Glucose reabsorption is mediated in the proximal tubules of the kidney
  - Actively through sodium-coupled glucose cotransporters (SGLT)
  - Passively through glucose transporters (GLUT)
- ~90% of glucose is reabsorbed by SGLT-2 and GLUT-2 in the S1 and S2 segments
- ~10% of glucose is reabsorbed by SGLT-1 and GLUT-1 in the S3 segment

Increased Glucose Transporter Activity in T2DM

SGLT-2 and GLUT-2 Protein Expression in Healthy Controls and Patients with T2DM

Is Pharmacologic Blockade of SGLT2 Safe?

Familial Renal Glycosuria (FRG)

- An inherited renal tubular disorder characterized by persistent isolated glucosuria in the absence of hyperglycemia

- Patients excrete >100 grams of glucose/day (normal glucose excretion = 0 g/d)

- Caused by mutations in the SGLT2 coding gene, SLC5A2

- Patients have normal renal function, are not overweight, and do not develop diabetes

- Asymptomatic

- Family members of FRG may show glycosuria when given a 50 grams of glucose tolerance test after 2 and 4 hours

SGLT-2 Inhibitors: Mechanism of Action (cont)

Juxtaglomerular Complex

Proximal Convoluted Tubules

Loop of Henle

Free Filtration of Solute

Active Reabsorption

Glucose

SGLT-2

SGLT-1

Type 2 Diabetes

Glucose
SGLT2 Inhibition Lowers $T_{\text{max}}$, Allowing Elimination of Excess Glucose

- Overexpression of SGLT2 shifts $T_{\text{max}}$ to the right, allowing excess glucose to be reabsorbed
- SGLT2 inhibition shifts $T_{\text{max}}$ to the left, eliminating excess glucose

Ominous Octet

The Benefits of SGLT2 Inhibitors Unique Mechanism of Action

Inhibition of SGLT2 results in:

Daily urinary excretion of excess glucose ~70 g, providing:\(^1\)
- Significant HbA\(_{1c}\) reductions (-0.34% to -1.03%)\(^2,3\)
- Additional benefits of weight reduction (-2.0 to -3.4 kg) and a reduction in blood pressure (cardioprotective)\(^2\)
- Reduction of fasting and PPG levels

SGLT2 Inhibitors act independently of insulin mechanisms\(^2\)

- Works regardless of β-cell function
- Complements insulin-dependent mechanisms
- Low propensity for hypoglycemia

Patient Case: Edward

**History**
- 54-year-old obese African American man
- Works as a tool and die machinist for 10 hour shifts
- 10-year history of T2DM
- Strong family history of T2DM
  - Maternal and paternal sides and 2 siblings

**Challenges**
- Gaining weight, despite lifestyle counseling
  - +15 lbs this year
- Poor compliance
  - Fears hypoglycemia while working on machinery
- Often eats “on the go”
- Episodes of hypoglycemia
  - Most recent was 58 mg/dL
Patient Case: Edward (cont’d)

**Findings**

- **Labs:**
  - A1C 8.2%
  - FPG 165 mg/dL
  - eGFR 45 mL/min/1.73m²
  - ACR 60 mcg/mg

- **CVD risk factors:**
  - BP 140/95 mmHg
  - Dyslipidemia
  - BMI 36 kg/m²

- **Physical exam:**
  - Acanthosis nigricans on neck
  - R-carotid bruit
  - Reduced vibratory sense in feet

**Medications**

- Metformin 1000 mg BID
- Glimepiride 8 mg QD
- Basal insulin glargine 60 u bid
- Enalapril/HCTZ 10 mg/25 mg QD
- Rosuvastatin 20 mg QD
# Change in HbA1C with Canagliflozin in Subjects with T2DM and Stage 3 Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline eGFR, mL/min/1.73m²</th>
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<tbody>
<tr>
<td></td>
<td>≥ 30 and &lt; 60†</td>
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<tr>
<td>HbA1C</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>-0.14 (0.06)</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>-0.52 (0.06)</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-0.38 (-0.50, -0.26)†</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>-0.62 (0.06)</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-0.47 (-0.60, -0.35)¥</td>
</tr>
</tbody>
</table>

Pooled analysis in pts with T2DM from placebo-controlled studies with eGFR ≥ 30 and < 60 mL/min/1.73m² (N = 1,085) and in subgroups with eGFR ≥ 45 and < 60 (n = 721) or ≥ 30 and < 45 (n = 364). Data presented as least squares mean (SE) change from baseline using ANCOVA and placebo-subtracted least squares mean (95% CI) values.

† Mean baseline age 67 yrs; HbA1C, 8.1%; eGFR, 48.2; B wt, 91 kg
‡ Mean baseline age 66 yrs; HbA1C, 8.1%; eGFR, 53.3; B wt, 90 kg
§ Mean baseline age 66 yrs; HbA1C, 8.1%; eGFR, 38.2; B wt, 92 kg
¥ P < 0.001 vs. placebo; P values reported for pre-specified comparisons only

ARS Question

Which of the following is/are contraindicated in patients with eGFR < 60 mL/min/1.73m²?

1. Canagliflozin
2. Dapagliflozin
3. Empagliflozin
4. All of the above
5. None of the above
Safety and Tolerability

- Common adverse events include slight increase versus placebo in rate of:
  - Urinary tract infections (~5% to 10%)\(^1\)-\(^8\)
  - Genital tract infections (~8% to 10%)\(^1\)-\(^8\)
  - Generally not serious but recurrence should assess for alternate therapy

- Renal dosing considerations\(^9\),\(^10\),\(^11\)
  - Dapagliflozin contraindicated for patients with eGFR <60 mL/min/1.73 m\(^2\)
  - Canagliflozin: Limit dose to 100 mg in patients with eGFR 45 to <60 mL/min/1.73 m\(^2\) contraindicated at eGFR <45 mL/min/1.73 m\(^2\). Potential for hypovolemic events, particularly in elderly patients or patients with renal impairment
  - Empagliflozin should be discontinued in patients with a persistent eGFR less than 45 mL/min/1.73 m\(^2\)
    - The risk of AKI (acute kidney injury) is rare but can occur especially in volume depleted patients

- Should not be used for patients with active bladder cancer\(^9\)

- Safe/well-tolerated when added to existing therapy for patients aged >55 years\(^12\)

Safety Issues to Watch for When Using SGLT-2 Inhibitors

- Orthostatic hypotension
- Transient decrease in GFR (common)
- Acute Kidney Injury (rare)
- Polyuria/ urinary frequency (discontinuation rate = placebo but occurs)
- Hyperkalemia (rare but routine metabolic panel at first follow up useful)
- Euglycemic DKA
? Amputation Risk With SGLT2s

- **CANVAS-R 4.5 year interim analysis:**
  - Risk of amputations were 7.5/1000 patient years in patients taking canagliflozin vs. 3/1000 pt years for those taking PBO

- European Medical Association concludes that the risk of amputations should be included in labels for ALL SGLT2 inhibitors

1) [https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm](https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm)
Conclusions Regarding Amputation Risk

- High risk patients and those with longer duration diabetes (CV and peripheral vascular disease) have a slightly higher risk of amputations.

- Mechanism may be volume depletion.

- Higher risk of amputations has also been noted with diuretic use.

- Consider DC drugs in pts who develop foot infections or ulcers.

- Stop meds if patients have known PVD.
## Patient Case: Felicia

### History
- 56 y/o African American woman
- 5-year history of T2DM
- Hypertension
- Systolic heart failure (HFrEF)
- Fracture of left femur 2012
- Idiopathic microhematuria
- Pancreatitis 1998, considered due to cholelithiasis

### Medications
- Metformin 1000mg BID
- Insulin detemir 70 units QAM
- Metoprolol tartrate 100mg BID
- Losartan 100mg QAM
- Furosemide 40mg BID
- Amlodipine 5mg QD
- Atorvastatin 20mg QD
Felicia: The Challenging Patient

- PE: Height 5ft 6 in, wt 210lb BMI 33.9
- BP 126/86 P 72
- Physical exam is normal except for an S4 and trace peripheral edema.
- Labs: HGB A1c 7.7% Creatinine 1.45 eGFR48
  Albumin 68mcg/mg creatinine (nml < 30)
Which of the following statements are false?

1. SGLT-2 inhibitors should not be used in a patient with history of fractures
2. Incretin-based therapy would be a good option for postprandial control in this patient
3. Pioglitazone would be an effective add-on therapy in this patient
4. All of the above
Which of the following complications of SGLT-2 therapy is the patient most at risk for?

1. Recurrent fracture
2. Ketoacidosis
3. Bladder Cancer
4. Orthostatic Hypotension
5. AKI (Acute kidney injury)
# SGLT2 Label Comparisons

<table>
<thead>
<tr>
<th>Topic</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose and timing</strong></td>
<td>100 mg/300 mg prior to 1&lt;sup&gt;st&lt;/sup&gt; meal of the day</td>
<td>5 mg/10 mg independent of meals</td>
<td>10/25 mg in AM independent of meals</td>
</tr>
<tr>
<td><strong>Dosing regarding GFR</strong></td>
<td>• 100 mg/d if GFR &gt;60 mL/min; titrate to 300 mg/d</td>
<td>• 5 mg if GFR ≥60 mL/min with titration to 10 mg</td>
<td>• Assess renal function 1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• 100 mg/day if GFR 45 to 60 mL/min</td>
<td>• Do NOT use if GFR &lt;60 mL/min</td>
<td>• Do NOT initiate if eGFR is &lt;45 mL/min</td>
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<tr>
<td></td>
<td></td>
<td>• Do NOT use if GFR &lt;60 mL/min</td>
<td>• Initial dose is 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do NOT use if GFR &lt;60 mL/min</td>
<td>• Can increase to 25 mg if tolerated</td>
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<tr>
<td><strong>Warnings/precautions</strong></td>
<td>• Hypotension with ACE and ARBS</td>
<td>• Hypotension</td>
<td>• Hypotension</td>
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<tr>
<td></td>
<td>• Hypo with SUs and insulin</td>
<td>• Hypoglycemia with SUs and insulin</td>
<td>• Risk of impaired renal function is higher in elderly</td>
</tr>
<tr>
<td></td>
<td>• Hyperkalemia</td>
<td>• Bladder cancer</td>
<td>• Hypo with SUs and insulin</td>
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<td></td>
<td>• Increased LDL-C</td>
<td>• Category C pregnancy rating</td>
<td>• Increased LDL-C</td>
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<tr>
<td></td>
<td>• DKA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased risk of bone fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduced bone density</td>
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SGLT 2 Inhibitors and DKA Concerns & ? Mechanisms

Concerns

- 20 cases of DKA in T2DM reported to the FDA Adverse Events Reporting System 3/13-6/14 + 13 published case of euDKA in patients with T1DM and T2DM
- Most were women
- 9 cases in T1DM, 4 in T2DM
- Most cases linked to reduced insulin doses
- Possible link to increased activity, recent illness, alcohol use, decreased food intake
- Some patients had no identifying cause
- All patients responded to IV rehydration and insulin
- All patients with T1DM should be counseled regarding off label use of SGLT2s

SGLT 2 Inhibitors and DKA Concerns & ? Mechanisms

Potential Mechanisms

SGLT2 Inhibition

- Increases glucose renal clearance
- Decreases renal clearance of ketone bodies
- Endogenous/exogenous insulin levels reduced
  - + dehydration or increased activity level
    - Increased in alpha cell secretion of glucagon (mediated by SGLT2)
- Increase in lipolysis
- “EuDiabetic Ketoacidosis”

ARS Question

Are SGLT-2 inhibitors indicated for both T1DM and T2DM?

1. Yes
2. No
3. Some agents have both indications
Patient Case: David

History

- 26-year-old Asian American man
- T1DM diagnosed 8 months ago
  - A1C at diagnosis 9.2%
- Placed on CSII;
  - A1C dropped to 7.2%
- Placed on canagliflozin 100 mg QD to reduce PPG spikes
- Patient warned about off-label use of canagliflozin

ER Presentation

- Developed severe muscle cramps and vomiting while helping brother move
- Labs in ER:
  - Random BG 212 mg/dL
  - A1C 6.6%
  - Creatinine 1.8 mg/dL
  - Serum ketones +
- Hydrated overnight and discharged
- Canagliflozin discontinued
Clinical Attributes of SGLT2 Inhibitors: Metabolic Effects

- Blood pressure: ↓ both SBP and DBP\textsuperscript{1-3}

- Lipids
  - Small, generally non clinically relevant ↑ LDL-C\textsuperscript{4,5}
  - Small ↓ TRG\textsuperscript{3}
  - Small ↑ HDL\textsuperscript{3,5}

- Renal
  - Small transient (1-4 weeks) ↓ eGFR returns to baseline.

Alogliptin (6.25, 12.5 or 25 mg/day*) + standard of care

Saxagliptin (2.5 or 5 mg/day**) + standard of care

Lixisenatide (10 or 20 µg/day†) + standard of care

Sitagliptin (100 or 50 mg/day***) + standard of care

**Hazard ratio (95% CI) 0.98; (0.88, 1.09)

p<0.001 for noninferiority

**Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)

**Hazard ratio (95% CI) 0.98; (0.88, 1.09)

p<0.001 for noninferiority

**Hazard ratio (95% CI) 0.96; (0.88, 1.09)

p<0.001 for noninferiority
## Selected CVOTs: Assessing CV benefit with antiglycemic agents

<table>
<thead>
<tr>
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<th>EMPA-REG&lt;sup&gt;1&lt;/sup&gt;</th>
<th>LEADER&lt;sup&gt;4&lt;/sup&gt;</th>
<th>SUSTAIN-6&lt;sup&gt;5&lt;/sup&gt;</th>
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<tr>
<td>Population</td>
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<td>T2D + high CV risk</td>
<td>T2D</td>
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<td>Drug (Class)</td>
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<td>Liraglutide (GLP-1RA)</td>
<td>Semaglutide (GLP-1RA)</td>
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<tr>
<td>Objective</td>
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<td>Endpoint</td>
<td>3-point MACE</td>
<td>3-point MACE</td>
<td>3-point MACE</td>
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<tr>
<td>Results</td>
<td>HR 0.86</td>
<td>HR 0.87</td>
<td>HR 0.74</td>
</tr>
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</table>

**3-point MACE:** first occurrence of CV death, nonfatal MI or nonfatal stroke; **MACE+**:
CV death, nonfatal MI, nonfatal stroke and hospitalisation for UA procedure ACS, acute coronary syndrome; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UA, unstable angina

ARS Question

The EMPA-REG trial reported which of the following significant outcomes with empagliflozin compared to placebo?

1. Reduced incidence of CV death
2. Reduced incidence of MI and stroke
3. Increased rate of chronic kidney disease
4. Reduced incidence of HF hospitalizations
5. All of the above
6. 1 and 4
Clinical Attributes of SGLT2 Inhibition: Cardiovascular Outcome Trial With Empagliflozin

**EMPA-REG OUTCOME Trial**

**Study Design**
- Multicenter, randomized, double blind, placebo controlled trial comparing the effect of CV outcomes between empagliflozin 10 & 25 mg with placebo
- Background therapy was continued, but pts were randomized following a 2 week placebo run-in phase
- Drug naive pts had A1C > 7.0 to < 9.0 at screening
- Subjects on background meds had A1C ≥ 7.0 to ≤ 10.0 at screening
- Pts had to be high risk for CV events
- Primary endpoint was first occurrence of CV death, non-fatal MI, or non-fatal stroke

**High Risk Definitions**
- Hx of MI > 2 mos prior
- Hx of multi-vessel CAD
- Presence of significant stenosis ≥ 50 % during angiography
- Hx of stent placement > 2 mos prior
- + ETT suggestive of ischemia
- Hospital admission for unstable angina within 12 mos
- Hx of stroke
- Hx of PAD or lower extremity amputation
- ABI < 0.9 in both legs

EMPA-REG Trial—Demonstrates Rapid Improvement in 3-Point MACE

Empa 10, 25 mg or standard of care

Cumulative Incidence of the Primary Outcome

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

14% risk reduction

Cumulative Incidence of Death From CV Causes

- **P<0.001**
- Hazard ratio, 0.62 (95% CI, 0.49–0.77)

38% risk reduction

Hospitalization for Heart Failure

- **P=0.002**
- Hazard ratio, 0.65 (95% CI, 0.50–0.85)

35% risk reduction

N=7020 patients with T2DM at high risk of cardiovascular events.
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
NEJM June 12, 2017 DOI: 10.1056/NEJMoa1611925
Double-blind, placebo controlled randomized trial evaluating the safety and efficacy of liraglutide vs. placebo (1:1) in pts with T2DM and prior CVD or >age 60 with risk

- A1C > 7 %

Inclusion criteria: > Age 50 with prior cvd or >60 with risk, at least 1 CV precondition (PVD, CKD stage 3 or greater, NYHA class II-III, microalbuminururia, LVH, ABI < 0.9, no prior usage of a GLP-1 RA.

- 9340 randomized patients. Retention rate over 5 years was 99 %. 80% had prior CVD

- Primary outcome was time to 1st occurrence of death from CV causes, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina, new onset macroalbuminuria

Marso SP, et al. NEJM. 6/13/16. DOI 10.1056NEJMoa1603827
Primary outcomes in LEADER and EMPA-REG
Timing of separation of treatment arms suggest different cardioprotective MoAs

3 Point MACE improvement not driven by glycemic efficacy!

**LEADER**

- **HR: 0.87** (95% CI: 0.78;0.97)
  - p=0.01 (superiority)

**EMPA-REG**

- **HR: 0.86** (95% CI: 0.74;0.99)
  - p=0.04 (superiority)

**3-point MACE**: first occurrence of CV death, nonfatal MI or nonfatal stroke

CI, confidence interval; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular event; MoA, mode of action

GLP-1RA and SGLT-2i
Proposed cardioprotective MoA

**Liraglutide**

- Proposed cardioprotective MoA$^{1,2}$
  - Anti-atherosclerotic
  - Reduced platelet aggregation
  - Anti-inflammatory effects
  - Established effects
    - Hyperglycaemia
    - Weight
    - Visceral adiposity
    - BP

**Empagliflozin**

- Proposed cardioprotective MoA$^3$
  - Fluid reduction
  - Hemodynamic effects
  - Heart metabolism
  - Established effects
    - Hyperglycaemia
    - Weight
    - Visceral adiposity
    - BP

*Increased urinary glucose excretion*

**Proposed cardioprotective MoA**

- Increased glucose uptake and glucagon synthesis (adipose, muscle, liver)

- Decreased appetite and food intake (brain)

- Increased insulin secretion, decreased glucagon secretion (pancreas)

BP, blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; MoA, mode of action; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

Empa-Reg Renal Data

Incidence of nephropathy by 39%
Symptomatic Severe Hypoglycemia: Tip of the Iceberg?

- Asymptomatic Severe
- Symptomatic Non-severe
- Asymptomatic Non-severe
- Asymptomatic severe

Symptomatic Severe
ACCORD and ADVANCE
Hypoglycemia vs Mortality

ACCORD\textsuperscript{1}

\begin{itemize}
\item Intensive
\item Standard
\end{itemize}

\begin{itemize}
\item No Hypo
\item 1+ Hypo
\end{itemize}

ADVANCE\textsuperscript{2}

\begin{itemize}
\item Intensive
\item Standard
\end{itemize}

\begin{itemize}
\item No Hypo
\item 1+ Hypo
\end{itemize}

ARS Question

Studies using continuous glucose monitoring suggest that about what proportion of hypoglycemic episodes in patients with T2DM are unrecognized?

1. 10%
2. 30%
3. 45%
4. 70%
Unreported Asymptomatic Episodes of Hypoglycemia

- >45% of patients with T2DM had asymptomatic (unrecognized) hypoglycemia, identified via continuous glucose monitoring
- Similar findings in other studies

 Patients With ≥1 Unrecognized Hypoglycemic Events, %

<table>
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<th>All Patients With Diabetes</th>
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<th>Type 2 Diabetes</th>
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Severe Hypoglycemia in Diabetes Patients May Prolong the Q-T Interval

13 patients with type 2 diabetes were studied during hypoglycemia; 8 patients were euglycemic controls. They were all treated with combined insulin and glibenclamide. The hypoglycemic clamp experiment was designed to achieve stable hypoglycemia between 45 mg/dL and 54 mg/dL during the last 60 minutes.

The hypoglycemic clamp experiment led to significantly prolonged Q-T intervals, which are associated with an increased risk of arrhythmias.
Prior hypoglycemia blunts subsequent counter-regulatory response (non-diabetic adults)

Hyperinsulinemic hypoglycemic clamps on 2 consecutive mornings, with interval afternoon clamped hypoglycemia in adults without diabetes.
Summary: SGLT2 Inhibitors

- **Benefits**
  - Glucose control (FPG, PPG, and A1c)
  - Weight reduction - excretion of 70 grams of glucose in urine each day = 280 kcal
  - BP reduction

- **Adverse effects**: predominantly mild and transient
  - Thirst, increase in urination frequency, UTI, mycotic infections
  - Hypoglycemia risk heightened when used with SUFs or insulin
  - Seniors: be vigilant for volume depletion and subsequent orthostasis
  - Monitor Renal Function (no toxicity with CKD, but lack of efficacy)

- Fracture risk increased with canagliflozin, off-label use in T1DM
POST-TEST QUESTIONS
Post-test ARS Question 1

Under normal conditions, the SGLT-2 and GLUT-2 transporters mediate reabsorption of about what proportion of glucose filtered by the kidney?

1. 10%
2. 35%
3. 70%
4. 90%
Post-test ARS Question 2

In the EMPA-REG trial, the use of empagliflozin in patients with high cardiovascular risk was associated with what significantly different outcome compared to placebo?

1. Reduced incidence of MI
2. Increased incidence of nephropathy
3. Reduce incidence of cardiovascular death
4. Increased risk for exacerbation of heart failure
A 53-year-old obese woman with a history of hypertension (BP 138/86) and type 2 diabetes presents for a checkup. Her A1C is 7.9%. She reports recent weight gain (10 lbs) and occasional hypoglycemia (FPG <70 mg/dL). Current medications include metformin 1000 mg bid, glyburide 8 mg qd, basal insulin 40 U qam, and hydrochlorothiazide 25 mg qd. What might be an appropriate action at this time?

1. Add thiazolidinedione
2. Add DPP-4 inhibitor and reduce dose of basal insulin
3. Increase dose of basal insulin and administer at night
4. Discontinue glyburide and add SGLT-2 inhibitor or GLP-1 RA
A 57-year-old obese man with a history of type 2 diabetes, hypertension, reduced renal function (eGFR 55 mL/min/1.73m²), and prior NSTEMI presents for a checkup. His A1C today is 8.1% and average FPG over last two weeks, ~130 mg/dL.

Current medications include metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

Discontinue sulfonylurea and add canagliflozin or empagliflozin:

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 5

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as **consistent** with or **not consistent** with best clinical practice:

**If canagliflozin started, limit dose to 100 mg qd:**

1. Yes, it is consistent
2. No, it is not consistent
57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

**Avoid all SGLT-2 inhibitors based on eGFR <60 mL/min/1.73m²:**

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 7

57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

Add prandial insulin tid and maintain current antidiabetic regimen:

1. Yes, it is consistent
2. No, it is not consistent
57 y/o obese – T2DM, HTN, CKD3 (eGFR 55 mL/min/1.73m²), and prior NSTEMI

A1C - 8.1%, average FPG over last two weeks, ~130 mg/dL.

Meds: metformin 1000 mg bid, glipizide 10 mg qd, basal insulin 60 U qam, lisinopril 20 mg qd, atorvastatin 80 mg qd, metoprolol 100 mg bid, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice:

Increase dose of basal insulin and add DPP-4 inhibitor:

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 9

How often will you now modify antidiabetic therapy, as a result of this conference, based on risk for hypoglycemia:

1. Never
2. Rarely
3. Sometimes
4. Very often
5. Always
Post-test ARS Question 10

Please rate your confidence in your ability to select patients appropriate for treatment with SGLT-2 inhibitors:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident