CSHP SEMINAR 2016
TRANSITIONS IN PHARMACY
DISNEYLAND® RESORT • OCTOBER 27th – 30th
New Treatment Guidelines & Emerging Issues in Diabetes

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Disclosure

Dr. Morello has no conflicts of interest to disclose.
Learning Objectives

1. Describe the newest American Diabetes Association treatment guidelines for helping patients achieve their glycemic goals.

2. Identify emerging safety precautions as well as cardiovascular effects of specific diabetes medications.

3. Using a case-based approach provide personalized care incorporating the latest treatment guidelines and therapeutic issues.
Diabetes Today: New Era

Diabetes
  ◦ Target pathophysiology by combining treatment options

Current treatment guidelines

Clearer picture of second line agents?
  ◦ SGLT2 inhibitor data & safety update
  ◦ GLP1-agonist data & safety update

Case
68 yo male, T2DM since 2000 presents to clinic.

**PMH:** T2DM, HTN, hyperlipidemia with CAD, morbid obesity, osteoporosis, GERD, microalbuminuria

**DM Meds:** metformin 1gm BID, glipizide 10mg daily

**Other Daily Meds:** fosinopril 40mg, aspirin 81mg, atorvastatin 80mg, omeprazole 20mg, alendronate 10 mg

**ROS:** Polyuria Q 20 min & nocturia 4-6x/nt; affecting productivity,

**Other:** No SMBG, afraid of needles, married, retired, no family history of cancer or heart disease

**Current Labs:**

<table>
<thead>
<tr>
<th>A1C</th>
<th>Wt</th>
<th>BMI</th>
<th>BP</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
<th>TC</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>280</td>
<td>36</td>
<td>134/78</td>
<td>65</td>
<td>140</td>
<td>35</td>
<td>165</td>
<td>88</td>
</tr>
</tbody>
</table>
FDA-Approved Diabetes Therapies

**Oral**
- **Sulfonylureas**
  - Glipizide, Glimepiride
- **Biguanide**
  - Metformin
- **Non-sulfonylurea insulin secretagogues**
  - Repaglinide, Nateglinide
- **Alpha-glucosidase inhibitors**
  - Acarbose, Miglitol
- **Thiazoladinediones**
  - Rosiglitazone, Pioglitazone
- **DPP4 Inhibitors**
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Linagliptin (Tradjenta)
  - Alogliptin (Nesina)

**SGLT-2 Inhibitors**
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

**Injectable**
- **Insulin**
  - Rapid acting
    - Insulin lispro, Insulin aspart, Insulin glulisine (Apidra)
  - Short acting
    - Regular insulin
  - Intermediate acting
    - NPH
  - Long acting
    - Insulin detemir (Levemir)
    - Insulin glargine (Lantus; U100 & U300)
    - Insulin degludec (Tresiba; U100 & U300)
- **Amylin analog**
  - Pramlintide (Symlin)
- **GLP-1 Receptor Agonist (incretin mimetic)**
  - Exenatide (Byetta), Liraglutide (Victoza)
- **GLP-1 Receptor Agonist ONCE WEEKLY**
  - Exenatide (Bydureon),
  - Albiglutide (Tanzeum)
  - Dulaglutide (Trulicity)

**Inhaled**
- **Insulin Powder**
  - Rapid acting (Afrezza)
How Diabetes Medications Target Pathophysiologic Defects of Diabetes: Combining Medications is Key!

**Brain:** GLP-1 RA, amylin analog (satiety)

**Mouth:** GLP-1 RA, amylin analog (reduced caloric intake)

**Muscles and tissues:** TZD, Metformin (insulin sensitivity), Insulin (peripheral glucose uptake)

**Stomach:** GLP-1 RA and amylin analog (slows gastric emptying)

**Liver:** Metformin, Insulin, GLP-1 RA, amylin analog, DPP-4 Inh (↓ Hepatic glucose output)

**Pancreas/Alpha cells:** GLP-1 RA, amylin analog, DPP-4 Inh (↓ postprandial glucagon secretion)

**Pancreas/Beta cells:** SFU, Glinides (insulin secretion) GLP-1 RA, DPP-4 Inh (glucose-dependent insulin secretion)

**Gut:** GLP-1 RA

**Kidneys:** SGLT-2 inh (increases glucose urinary output)

**Gut (other):** AGI /BAS (delays CHO breakdown/absorption)

# ADA 2016 Diabetes Diagnosis - new emphasis

## Diagnostic Criteria

<table>
<thead>
<tr>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG*</td>
<td>≥ 126 mg/dL</td>
</tr>
<tr>
<td>Casual Glucose</td>
<td>≥ 200 mg/dL**</td>
</tr>
<tr>
<td>A1C</td>
<td>≥ 6.5%</td>
</tr>
<tr>
<td>OGTT post 75 gm glucose load</td>
<td>≥ 200 mg/dl at 2 hrs</td>
</tr>
</tbody>
</table>

* in the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

* Fasting: no food for 8 hours

**accompanied by polyuria, polydipsia, or unexplained weight loss

[ADA Standards of Medical Care in Diabetes-2016. *Diabetes Care* 2016;39(supp 1).]
# Guidelines for Glycemic Control

<table>
<thead>
<tr>
<th>2016:</th>
<th>ADA/EASD Goals</th>
<th>AACE/ACE Goals</th>
</tr>
</thead>
</table>
| HbA1C | < 7.0% (individualization)* | ≤6.5 if NO concurrent serious illness & not at risk for hypoglycemia  
> 6.5 if concurrent serious illness and at risk for hypoglycemia |
| Preprandial glucose | 80-130 mg/dL | ≤110 |
| Postprandial glucose | < 180 mg/dL | ≤140 |

* ADA A1C goal Individualization is key:
  - **Tighter targets (6.0 - 6.5%)** for younger, healthier
  - **Looser targets (7.5 - 8.0%)** for older, comorbidities, hypoglycemia prone, etc.
  - **Avoidance of hypoglycemia**

ADA Standards of Medical Care in Diabetes-2016. *Diabetes Care* 2016;39(supp 1).
ADA: Selecting a Personalized A1C Goal

Consider A1C 6-6.5%

Consider A1C 7.5-8% or higher

PATIENT / DISEASE FEATURES
- Risks potentially associated with hypoglycemia and other drug adverse effects
- Disease duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude and expected treatment efforts
- Resources and support system

more stringent

A1C 7%

less stringent

Frail or high fall risk

ADA. 6. Glycemic Targets. Diabetes Care 2015;38(suppl 1):S37. Figure 6.1; adapted with permission from Inzucchi SE, et al. Diabetes Care, 2015;38:140-149
2012 T2DM Treatment General Recommendations & Algorithm

Healthy eating, weight control, increased physical activity

Metformin
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea
  - high
  - moderate risk
  - gain
  - hypoglycemia
  - low
- Metformin + Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, fx
  - high
- Metformin + DPP-4 Inhibitor
  - intermediate
  - low risk
  - neutral
  - rare
  - high
- Metformin + GLP-1 receptor agonist
  - high
  - high
  - high
  - high
  - variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + DPP-4 Inhibitor
- Metformin + DPP-4 Inhibitor + GLP-1 RA
- Metformin + GLP-1 receptor agonist + Insulin

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- Insulin (multiple daily doses)

From Figure 2 in Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
A Patient Centered Approach

ADA T2D 2015 Treatment:

- Figure 7.1; adapted with permission from Inzucchi SE, et al. Diabetes Care, 2015;38:140-149

Diabetes & Complications - U.S. Health Impact

Diabetes

7th leading cause of death

Life expectancy ↓ 5 to 10 yr

Cardiovascular disease 2-4 times

Renal Disease

Blindness

Amputations

Nerve Damage in 60% to 70% of patients

*Diabetes is the leading cause of renal failure, new cases of blindness, and nontraumatic amputations

Globally, 387 million people are living with diabetes\(^1\)

- At least 68% of people >65 years with diabetes die of heart disease\(^2\)

Mortality risk associated with diabetes (n=820,900)\(^3\)

\(^1\) IDF DIABETES ATLAS 6TH EDITION 2014 [http://www.idf.org/diabetesatlas]; \(^2\) CENTERS FOR DISEASE CONTROL AND PREVENTION 2011; \(^3\) SESHASAI ET AL. NEJM 2011;364:829-41
Diabetes is associated with significant loss of life years

On average, a 50-year-old PWD and no vascular disease history will die 6 years earlier compared to someone without diabetes
**Impact of Intensive Therapy in Type 2 Diabetes Summary of Major Clinical Trials:**

**BUT** Subset Evaluations Show Reduced CV Outcomes if shorter duration of DM, without significant pre-existing complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UGDP</strong></td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>UKPDS</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>DCCT/EDIC</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>ACCORD</strong></td>
<td>↓</td>
<td>↔</td>
<td>↑ (unadj.), ↔ (adj.)</td>
</tr>
<tr>
<td><strong>ADVANCE</strong></td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>VADT</strong></td>
<td>↔</td>
<td>↔</td>
<td>↑→hypoglycemia and weight gain</td>
</tr>
</tbody>
</table>


Obesity Lecture by Saanley Schwartz, MD.

*T2DM study.
T2D Landmark Studies: 2015 & 2016

FDA CV safety studies requirement:
- cardiovascular safety study for a diabetes drug to show cardiovascular benefit, rather than just lack of harm

EMPA-REG: Empagliflozin
LEADER: Liraglutide
SGLT-2 Inhibitors

Canagliflozin (Invokana)  
J&J

Dapagliflozin (Farxiga)  
Astra Zenica

Empagliflozin (Jardiance)  
Boehringer Ingelheim & Eli Lilly

FDA Approval
- March 2013
- January 2014
- August 2014
SGLT-2 Inhibitors

**MOA**
- inhibit the reabsorption of glucose into the blood
- urine glucose output

Blocks approximately 50-80 grams of glucose per day from being reabsorbed into the blood
Randomized, double-blind, placebo-controlled CV outcomes trial

Study medication was given in addition to standard of care.

Key inclusion criteria:
- Adults with type 2 diabetes and CV disease (heart attack, stroke, etc.)
- HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)

- 1° outcome = ‘3-point MACE’ (CV death, non-fatal MI, non-fatal stroke)
- Baseline characteristics all groups: mean age 63, male 71-72%, A1C 8%
**EMPA-REG OUTCOME:**

### 3-point MACE and 4-point MACE

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
<tr>
<td>4-point MACE</td>
<td>599/4687</td>
<td>333/2333</td>
<td>0.89</td>
<td>(0.78, 1.01)*</td>
<td>0.0795</td>
</tr>
</tbody>
</table>

*COX REGRESSION ANALYSIS: MACE, MAJOR ADVERSE CARDIOVASCULAR EVENT; HR, HAZARD RATIO; CV, CARDIOVASCULAR; MI, MYOCARDIAL INFARCTION

*95.02% CI, ZINMAN B ET AL. N ENGL J MED 2015 [EPUB AHEAD OF PRINT].
**EMPA-REG OUTCOME:** All-cause mortality, CV death and non-CV death

<table>
<thead>
<tr>
<th>Patients with event/analysed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>269/4687</td>
<td>194/2333</td>
<td>0.68</td>
<td>(0.57, 0.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>97/4687</td>
<td>57/2333</td>
<td>0.84</td>
<td>(0.60, 1.16)</td>
<td>0.2852</td>
</tr>
</tbody>
</table>

**COX REGRESSION ANALYSIS.** CV, CARDIOVASCULAR; HR, HAZARD RATIO, ZINMAN B ET AL. N ENGL J MED 2015 [EPUB AHEAD OF PRINT].

![Graph showing HR and 95% CI for each category with p-values.]
EMP A-REG OUTCOME: Cardiovascular death

HR 0.62
(95% CI 0.49, 0.77)
p=0.0001

\[ \text{N=7020} \]

\[ \downarrow \text{38%} \]
EMPA-REG OUTCOME: Hospitalization for heart failure

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017

N = 7020

EMPA-REG OUTCOME: Hospitalization for heart failure or CV death

HR 0.66
(95% CI 0.55, 0.79)
P<0.0001

EMPA-REG OUTCOME: Hospitalization or death from heart failure

HR 0.61
(95% CI 0.47, 0.79)
*p=0.0002

## EMPA-REG; Safety
### Adverse events: Genital Infection

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate</td>
<td>n (%)</td>
</tr>
<tr>
<td>Events consistent with genital infection</td>
<td>42 (1.8%)</td>
<td>0.73</td>
<td>153 (6.5%)</td>
</tr>
<tr>
<td>Serious events</td>
<td>3 (0.1%)</td>
<td>0.05</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Events leading to discontinuation</td>
<td>2 (0.1%)</td>
<td>0.03</td>
<td>19 (0.8%)</td>
</tr>
<tr>
<td>By sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (1.5%)</td>
<td>0.60</td>
<td>89 (5.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (2.6%)</td>
<td>1.09</td>
<td>64 (9.2%)</td>
</tr>
</tbody>
</table>

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug based on 88 MedDRA preferred terms
# EMPA-REG; Safety

Other Adverse Events Similar to Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate</td>
<td>n (%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis*</td>
<td>1 (&lt;0.1%)</td>
<td>0.02</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Acute kidney injury†</td>
<td>155 (6.6%)</td>
<td>2.77</td>
<td>121 (5.2%)</td>
</tr>
<tr>
<td>Events consistent with volume depletion§</td>
<td>115 (4.9%)</td>
<td>2.04</td>
<td>115 (4.9%)</td>
</tr>
<tr>
<td>Serious events</td>
<td>24 (1.0%)</td>
<td>0.42</td>
<td>19 (0.8%)</td>
</tr>
<tr>
<td>Events leading to discontinuation</td>
<td>7 (0.3%)</td>
<td>0.12</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td>Venous thrombotic events**</td>
<td>20 (0.9%)</td>
<td>0.35</td>
<td>9 (0.4%)</td>
</tr>
</tbody>
</table>

Rate = per100 patient-years

*BASED ON 4 MEDDRA PREFERRED TERMS. †BASED ON 1 STANDARDISED MEDDRA QUERY. §BASED ON 8 MEDDRA PREFERRED TERMS. **BASED ON 1 STANDARDISED MEDDRA QUERY.
EMPASET OUTCOME®: Summary Points

• Empagliflozin reduced

  • Hospitalization for Heart Failure by 35%
  • CV death by 38%
  • All-cause mortality by 32% (1 in 3 improved survival)

• Regardless of empagliflozin dose (10 mg and 25 mg), similar magnitude of reductions

• Metabolic benefits; reduction in weight and blood pressure
  • Low hypoglycemia, DKA, acute renal, and bone fracture risk; higher genital infections

CV, CARDIOVASCULAR, ZINMAN B ET AL. N ENGL J MED 2015 [E PUB AHEAD OF PRINT].
Empa CV outcomes: a Class Effect or Not?
Fuel Metabolism & Energetics:

Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

Possible mechanism for physiologic effects with SGLT2 inhibitors

Mudaliar S et al. Dia Care 2016;39:1115-1122
Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy

T2DM Heart
↑ Fat Oxidation
↓ Glucose Oxidation
↓ P/O Ratio
↓ Cardiac Work Efficiency

↓ Myocardial Contractility

↑ Incidence/Progression of Heart Failure

With SGLT2i Treatment

↓ Fat Oxidation
↑ Glucose Oxidation
↑ BHOB Ox
↑ P/O Ratio
↑ Cardiac Work Efficiency

↑ Myocardial Contractility

↓ Incidence/Progression of Heart Failure

©2016 by American Diabetes Association
From Fig 1 in Mudaliar S et al. Dia Care 2016;39:1115-1122.
Postulated changes in whole-body and organ fuel energetics in T2DM before and after SGLT2 inhibitor (SGLT2i) therapy.

Fuel Energetics in T2DM

Heart
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↓Fox, ↑Gox, ↑↑BHOB ox

Muscle
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↑↑Fox, ↓Gox, ↔BHOB ox

Kidney
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↓Fox, ↓Gox, ↑↑BHOB ox

Fox = fatty acid oxidation
Gox = glucose oxidation
BHOB ox = beta-hydroxybutyrate oxidation
↔ = no change

From Figure 2 in Mudaliar, S et al. Dia Care 2016;39:1115-1122.

©2016 by American Diabetes Association
Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy.

<table>
<thead>
<tr>
<th>T2DM Kidney</th>
<th>Preferred Substrate In</th>
<th>T2DM Kidney with SGLT2i Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate/FFA Glutamate</td>
<td>S1/S2 Segments</td>
<td>↓ Lactate/FFA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ Glutamate</td>
</tr>
<tr>
<td>Lactate/FFA Glutamate/Glucose</td>
<td>S3 Segment</td>
<td>↓ Lactate/FFA</td>
</tr>
<tr>
<td>BHOB</td>
<td></td>
<td>↓ Glutamate/Glucose</td>
</tr>
<tr>
<td>Lactate/FFA Glucose</td>
<td>Distal Collecting Tubules/Cortical Collecting Tubules</td>
<td>↑ BHOB</td>
</tr>
<tr>
<td>BHOB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased Energy Expenditure

Renal Hypoxia

Progressive Renal Dysfunction

With SGLT2i Treatment

Improved Renal Oxygenation

Improved Renal Outcomes
Bone fracture risk (Warnings/Precautions)
- fractures occur more frequently with canagliflozin than placebo.
- as early as 12 weeks canagliflozin start.
- In clinical trials, when trauma occurred prior to a fracture, it was usually minor, such as falling from no more than standing height.

Decreased bone mineral density (ADR)
- changes to BMD over two years in 714 elderly individuals and showed that canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo.
Osteoporosis- SGLT2 Inh Class Effect or Not?

Dapa evidence:

- Bone fractures were more common in patients receiving dapagliflozin (7.7%) than placebo (0%) in a long-term study carried out in patients with T2DM and moderate renal impairment

- No evidence that dapagliflozin induced bone demineralization or increased fracture rates in individuals with normal renal function or mild renal impairment.

- Unclear; possibly related to renal function

Empa evidence:

- Bone fractures was low and bone fracture was no more common with empagliflozin than with placebo.

- No bone mineral density loss was observed after up to 2 years of empagliflozin treatment.

- No strong evidence to date.

DKA- SGLT2 Inhibitor Class Effect or Not?

FDA Adverse Event Reporting System (FAERS): FDA Update Dec 2015

- (3/13-6/14) 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis
- All required ER or hospitalization treatment.
- Atypical T2D incidence
  - Only slightly increased BG

Common triggering factors: undergoing surgery, major illness or trauma, serious infection (30-50% of cases), reduced food/fluid intake, or reduced insulin dose.

Class effect- ?

AACE/ACE Position Statement On SGLT-2 Inhibitors and DKA Risk 5/14/16
“AACE/ACE position statement: DKA risk no greater with SGLT2 inhibitor” Endocrine Today 4/20/16

To minimize DKA risk associated with SGLT-2 inhibitors:

• Consider: stop SGLT-2 inhibitor at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon. Urinary glucose loss due to SGLT-2 inhibition may persist after the drug is stopped.

• Avoid stopping insulin or decreasing the dose excessively.

• For emergency surgery or any extreme stress event, stop drug immediately, and appropriate clinical care should be provided.

• Routine urine ketones measurement is not recommended during use of SGLT-2 inhibitors because this measurement can be misleading.

• Instead, measurement of blood ketones is preferred for diagnosis of DKA in symptomatic patients.

• Patients taking SGLT-2 inhibitors should avoid excess alcohol intake

• Patients taking SGLT-2 inhibitors should avoid very-low-carbohydrate/ketogenic diets.

Cana and Dapa: FDA PI Update (June 2016)
Acute Kidney Injury

FAERS post marking data (10/14-9/15):
- 101 reported cases involving canagliflozin (75) and dapagliflozin (26)
- 96 required hospitalization, 22 required ICU, 4 deaths during hospitalization
- Risk factors: Chronic Kidney Disease, ACEI + diuretic

Glucagon-like Protine-1 (GLP1) Receptor Agonist:

Liraglutide (Victoza®)

- Incretin Mimetic
- Compared to human GLP; longer t ½ resistant to DPP-4
- Small injectable protein:

- Efficacy: 1-1.7% A1C reduction
- Other effects: ~11.2 lb wt loss, Favorable CV profile (LDL – 6%, HDL + 24%), Moderate BP reduction
- Contraindications: hypersensitivity, personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- Thyroid cancer risk: **black box warning**
  - Dose- and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both sexes of *rats and mice*
LEADER Trial: Liraglutide & CV Outcomes in T2D

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

- Double-blind, randomized, placebo controlled study in type 2 diabetes with high CV risk; noninferiority study
- Primary outcome: 1st occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
- Major inclusion: T2D, A1C ≥ 7%, CV condition ≥1
- Major exclusion: T1D, GLP1/DPP4/Pramlintide/RAI use, medullary thyroid CA
- N= 9340, 32 countries, mean 3 years duration

Marso SP et al., NEJM 2016;311-322
LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016;311-322.
LEADER trial:
Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016
LEADER Trial: Key Findings

Liraglutide use in T2D patients for 3 years had a:
- 13% lower risk of having MI or stroke
- 22% lower risk of cardiovascular disease death
- 22% reduced risk of new evidence of advanced kidney disease, compared with those receiving a placebo.

A1C reduction at 3 years – 0.4%

Safety

Marso SP et al., NEJM 2016;311-322
Based on Landmark Studies Outcomes: New Era for T2D Treatment

**Empagliflozin**
- SGLT2 inhibitor
- EMPA-REG OUTCOME Trial
  - Significantly reduced the incidence of worsening nephropathy by 39% in high CV risk T2D patients
  - d/t sig dec in new onset macroalbuminura

**Liraglutide**
- GLP1 receptor agonist
- LEADER Outcomes Trial
  - Reduces CV events in T2D in patients with elevated CV risk

May soon see a change in T2D treatment guidelines, allowing for a clearer, 2\textsuperscript{nd} line choice after metformin. Patient specific evaluation is a must for safe use.
68 yo male, T2DM since 2000 presents to clinic.

PMH: T2DM, HTN, hyperlipidemia with CAD, morbid obesity, osteoporosis, GERD, microalbuminuria

DM Meds: metformin 1gm BID, glipizide 10mg daily

Other Daily Meds: fosinopril 40mg, aspirin 81mg, atorvastatin 80mg, omeprazole 20mg, alendronate 10 mg

ROS: Polyuria Q 20 min & nocturia 4-6x/nt; affecting productivity,

Other: No SMBG, afraid of needles, married, retired, no family history of cancer or heart disease

Current Labs:

<table>
<thead>
<tr>
<th>A1C</th>
<th>Wt</th>
<th>BMI</th>
<th>BP</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
<th>TC</th>
<th>GFR</th>
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<tr>
<td>9.8</td>
<td>280</td>
<td>36</td>
<td>134/78</td>
<td>65</td>
<td>140</td>
<td>35</td>
<td>165</td>
<td>88</td>
</tr>
</tbody>
</table>

What is this patient’s personalized A1C goal?

1. <6.5%
2. <7.0%
3. <8.0%
4. <9.0%
68 yo male, T2DM since 2000 presents to clinic.

**PMH:** T2DM, HTN, hyperlipidemia with CAD, obesity, osteoporosis, GERD, NPDR OS

**DM Meds:** metformin 1gm BID, glipizide 10mg daily

**Other Daily Meds:** fosinopril 40mg, aspirin 81mg, atorvastatin 80mg, omeprazole 20mg, alendronate 10 mg

**ROS:** nocturia 0-1 times (rare)

**Other:** No SMBG, afraid of needles, married, retired, no family history of cancer or heart disease

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Which of the following issues must be considered when selecting drug therapy?

1. Duration of diabetes
2. CV status: hyperlipidemia with CAD and HTN
3. Obesity
4. Non-Proliferative diabetic retinopathy
5. Osteoporosis
6. GERD
7. Concurrent drugs
8. Personal preferences
9. Adherence
10. All of the above
68 yo male, T2DM since 2000 presents to clinic.

**PMH:** T2DM, HTN, hyperlipidemia with CAD, obesity, osteoporosis, GERD, NPDR OS

**DM Meds:** metformin 1gm BID, glipizide 10mg daily

**Other Daily Meds:** fosinopril 40mg, aspirin 81mg, atorvastatin 80mg, omeprazole 20mg, alendronate 10 mg

**ROS:** nocturia 0-1 times (rare), occ lower extremity edema

**Other:** No SMBG, afraid of needles, married, retired, no family history of cancer or heart disease

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**Which of the following which would you RULE IN for potential use in this patient?**

1. Increase metformin to 850 mg orally TID
2. Empagliflozin 10 mg orally once daily
3. Linagliptin 5 mg orally once daily
4. Pioglitazone 15 mg orally daily
5. Liraglutide 0.6 mg subcutaneously once daily with titration
6. Basal insulin
Summary

Exciting times for diabetes patients and practitioners

- More treatment options & more data

Keep an eye out for changes in newest guidelines

Major emphasis- patient-specific
Session Code:

1. Write down the course code. Space has been provided in the daily program-at-a-glance sections of your program book.

2. To claim credit: Go to www.cshp.org/cpe before December 1, 2016.