Weighing Risks and Benefits: Finding the Sweet Spot for SGLT-2 Inhibitor Use in Treatment of Type 2 Diabetes

Sarah Rumbellow, PharmD
PGY1 Pharmacy Resident
South Texas Veterans Health Care System
The University of Texas at Austin College of Pharmacy
UT Health San Antonio

January 19, 2018

Objectives
I. Outline current guideline recommendations for the treatment of type 2 diabetes mellitus (T2DM) and the use of sodium-glucose cotransporter 2 inhibitors (SGLT-2i)
II. Analyze the results of recent research on SGLT-2i use with respect to potential cardiovascular benefits and safety concerns
III. Select patient populations most appropriate for treatment with SGLT-2i
I. Diabetes mellitus (DM)

a. Disease burden
   i. As of 2015, 9.4% of the United States (US) population had a diagnosis of DM
   ii. DM was the seventh leading cause of death in the US in 2015
   iii. Total direct and indirect cost of diagnosed DM was $245 billion in 2012 (including complications, see Table 1)

b. T2DM
   i. Accounts for 90-95% of all cases of diabetes
   ii. Characterized by relative insulin deficiency and peripheral insulin resistance
   iii. Insulin secretion is insufficient to compensate for the level of hyperglycemia

c. Risk factors for development of T2DM
   i. Advancing age
   ii. Physical inactivity
   iii. Prior gestational DM
   iv. Cardiovascular disease (CVD)
   v. Hypertension (HTN)
   vi. Dyslipidemia
   vii. African American, Hispanic/Latino, American Indian, or Asian American ethnicity
   viii. First degree relative with T2DM
   ix. Polycystic ovary syndrome (PCOS)
   x. Obesity

Table 1: Complications of Uncontrolled DM

<table>
<thead>
<tr>
<th>Macrovascular complications</th>
<th>Microvascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease (CHD)</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Peripheral arterial disease (PAD)</td>
<td>Peripheral &amp; autonomic neuropathy</td>
</tr>
</tbody>
</table>

*Risk for complications exist if long-standing hyperglycemia regardless of diagnosis

II. Treatment of T2DM (see Table 2)

Table 2: Guideline Recommendations for the Treatment of T2DM

<table>
<thead>
<tr>
<th>American Academy of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2017 Clinical Practice Guidelines</th>
<th>American Diabetes Association (ADA) 2018 Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lifestyle therapy</td>
<td>• Lifestyle therapy, medical evaluation, management of comorbidities, and management of obesity for all patients</td>
</tr>
<tr>
<td>• Medication management – first line agents</td>
<td>• Medication management</td>
</tr>
<tr>
<td>o Metformin</td>
<td>o First line - metformin first line if tolerated and not contraindicated</td>
</tr>
<tr>
<td>o Glucagon-like peptide-1 receptor agonists (GLP-1 RA)</td>
<td>o Second line or add-on: basal insulin or other oral agent</td>
</tr>
<tr>
<td>o SGLT-2i</td>
<td>o Patients with established atherosclerotic cardiovascular disease (ASCVD): prefer liraglutide or empagliflozin as add-on to reduce cardiovascular (CV) and all-cause mortality</td>
</tr>
<tr>
<td>o Dipeptidyl peptidase-4 inhibitors (DPP-4i)</td>
<td>• Manage CVD &amp; CVD risk</td>
</tr>
<tr>
<td>o Alpha-glucosidase inhibitor (AGI)</td>
<td>o Blood pressure (BP) management</td>
</tr>
<tr>
<td></td>
<td>o Lipid management</td>
</tr>
</tbody>
</table>

*See Appendix A for more details on treatment of T2DM
Management of common comorbidities (see Appendix B for more information)

a. Risk factors for complications of DM include HTN, dyslipidemia, uncontrolled hyperglycemia, overweight or obesity, and smoking\footnote{1}

b. CVD\footnote{1,5}
   i. Includes: cerebrovascular disease (stroke), coronary artery disease, and CHD
   ii. In 2014, 7.2 million hospital discharges included DM as a diagnosis with 1.5 million of those also including major CVD
   iii. CVD is the primary cause of death for most diabetic patients and at least 68% of those ≥ 65 years old with DM die from CVD
   iv. Adults with DM are two to four times more likely to have a stroke than their non-diabetic peers
   v. Antiplatelet therapy for CVD risk reduction (recommendations in Appendix B)
      1. Primary prevention - consider in patients with T2DM with high ASCVD risk
      2. Secondary prevention for patients with a history of clinical ASCVD

c. Heart failure (HF)\footnote{2,4,6}
   i. Develops in up to 50% of patients with T2DM
   ii. European Society of Cardiology (ESC) 2016 Heart Failure Guideline
      1. Recommends metformin first-line for patients with DM and stable HF (avoid use in unstable, hospitalized HF patients)
      2. Consider empagliflozin to prevent development of HF (Table 3)

d. HTN\footnote{4-5,7-9,10}
   i. Present in approximately 66% of patients with diagnosed T2DM
   ii. Associated with increased risk of CVD, microvascular and macrovascular damage
   iii. Reduction in blood pressure (BP) decreases risk of negative outcomes - reduction by 10 mmHg in systolic BP provides a 17% decrease in diabetes-related mortality, a 12% decrease in myocardial infarction (MI) and a 13% decrease in microvascular endpoints
   iv. Management of HTN in T2DM
      1. BP goal of < 130/80 mmHg is recommended
      2. Pharmacotherapy recommended immediately in diabetics with BP above goal
         a. First line agents: angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or thiazide
         b. Prefer ACEI or ARB if urine albumin-to-creatinine ratio ≥ 300 mg/g

e. Dyslipidemia\footnote{3-4,11,14-15}
   i. In The National Health and Nutrition Examination Survey (NHANES) 1999-2010 analysis, 79.22% of patients with T2DM had elevated cholesterol
   ii. T2DM can cause elevated triglycerides
   iii. Regular screening for dyslipidemia recommended
   iv. American College of Cardiology (ACC) and American Heart Association (AHA) 2013 guidelines recommend lipid-lowering therapy for certain diabetic patients (see Appendix B for details)

f. Obesity\footnote{3-4,12-13,15}
   i. According to NHANES 1999-2010, 26% of patients with T2DM were overweight, and an additional 58.81% were obese
   ii. Associated issues: increased CVD risk, increased insulin resistance, limited physical activity
   iii. AACE and ADA recommend all patients with T2DM be evaluated for obesity
   iv. Weight loss
      1. Can increase insulin secretion and insulin sensitivity
      2. Use of antihyperglycemic agents that promote weight loss can be beneficial (Table 3)
### IV. Antidiabetic agents & CVD effects (Tables 3 and 4)

**Table 3: Antidiabetic agents with proven CV benefits**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CVD Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>↓ risk of MI by 39%</td>
</tr>
<tr>
<td></td>
<td>↓ risk of other diabetes-related endpoints</td>
</tr>
<tr>
<td></td>
<td>↓ overall mortality by 36%</td>
</tr>
<tr>
<td></td>
<td>↓ risk of diabetes-related death by 42%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>↓ risk of MI and stroke</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>LEADER trial: ↓ rate of first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke when compared to placebo</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN-6 trial: ↓ incidence of CV death, nonfatal MI, or nonfatal stroke when compared to placebo in patients with high CVD risk</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>See information on EMPA-REG OUTCOME below</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>See information on CANVAS below</td>
</tr>
</tbody>
</table>

CV: cardiovascular; CVD: cardiovascular disease; MI: myocardial infarction; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; T2DM: type 2 diabetes mellitus; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes trial; FDA: Food and Drug Administration; EMPA-REG OUTCOME: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; CANVAS: Canagliflozin Cardiovascular Assessment Study

**Table 4: Antidiabetic agents with proven CV harms**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CVD harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>↑ CV risk</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Possible ↑ risk of HF</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>↑ hospitalizations for heart failure (HHF)</td>
</tr>
</tbody>
</table>

CV: cardiovascular; DPP-4i: dipeptidyl peptidase-4 inhibitor; HF: heart failure

**V. SGLT-2i**

**Table 5: FDA Approved SGLT-2i**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date approved</td>
<td>March 2013</td>
<td>January 2014</td>
<td>August 2014</td>
<td>December 2017</td>
</tr>
<tr>
<td>FDA indication(s)</td>
<td>T2DM in adults</td>
<td>T2DM in adults</td>
<td>CV disorder prophylaxis in T2DM, T2DM in adults</td>
<td>T2DM in adults</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg – 300 mg daily</td>
<td>5 mg – 10 mg daily</td>
<td>10 mg – 25 mg daily</td>
<td>5 mg – 15 mg daily</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; SGLT-2i: Sodium-glucose cotransporter 2 inhibitor; T2DM: type 2 diabetes mellitus; CV: cardiovascular

*see Appendix C for more detailed information on available SGLT-2i

**a. Mechanism of action (MOA) in T2DM**

i. Sodium-glucose cotransporter 2 (SGLT-2) receptors in the proximal tubule are responsible for reabsorption of about 90% of glucose in the kidney (Figure 1)

ii. Expression and activity of SGLT-2 increases in hyperglycemia, leading to maintenance of elevated blood glucose levels

iii. SGLT-2i block SGLT-2 → prevent glucose reabsorption → increase glucose excretion → net lowering of glucose in blood

1. Inhibition of SGLT-2 decreases renal glucose reabsorption by 30-50%

2. Effect: decreased fasting and post-prandial blood glucose levels

3. MOA is independent of beta cell function, therefore low hypoglycemia risk
b. Proposed MOA in HF & CVD
   
   i. Originally proposed osmotic diuretic mechanism, but cannot explain the HF-only benefit through blood glucose lowering or osmotic diuresis alone
   
   ii. SGLT-2i differ from diuretics
   
   1. Sustained decrease in body weight
   
   2. Decreased plasma volume without electrolyte imbalances
   
   3. Hemoconcentration
   
   4. Long term improvements in renal function
   
   iii. Novel mechanism proposed: interact with sodium-hydrogen exchanger (NHE, Figure 2)
   
   1. Kidney proximal tubule: NHE causes majority of tubular sodium reuptake, increases sodium retention → increases blood volume → cardiac stress
   
   2. Cardiac myocytes: increased NHE activity → increases intracellular calcium → cardiomyopathy
   
   3. NHE activity is increased in HF patients
   
   4. SGLT-2i block NHE
   
   a. Decreases sodium reuptake in kidney → decreases cardiac stress
   
   b. Decreases intracellular calcium in cardiac muscle → prevents cardiomyopathy
   
   c. Favorable effect on arterial stiffness and diastolic cardiac filling
   
   d. Could benefit both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)
c. Efficacy & benefits of use\textsuperscript{2-3,19,23}

\begin{itemize}
  \item Expected decrease in A1c ~0.6%
    \begin{enumerate}
      \item A1c effect blunted if eGFR < 60 mL/min/1.73 m\textsuperscript{2}
      \item CV benefits remain with eGFR > 30 mL/min/1.73 m\textsuperscript{2}
    \end{enumerate}
  \item Weight loss
    \begin{enumerate}
      \item Between 0.6 – 2.19 kg loss
      \item Generally due to decreased body fat
    \end{enumerate}
  \item Decrease in visceral adiposity when compared to glimepiride
  \item Decreased systolic and diastolic BP (SBP, DBP)
    \begin{enumerate}
      \item SBP decrease 1.4 – 5.4 mmHg
      \item DBP decrease 0.6 – 2.0 mmHg
      \item Theorized to be partly due to osmotic diuretic effect
    \end{enumerate}
\end{itemize}
v. Possible CV benefit
   1. Possible HF benefit with empagliflozin
   2. Decreased triglycerides
   3. Reduced arterial wall stiffness (not due to reduction in BP or renin-aldosterone-angiotensin system (RAAS) effects, possibly anti-inflammatory effect)
vi. Possible renal benefits: decreased albuminuria found in several studies
vii. Neutral hypoglycemia risk and gastrointestinal adverse effects

d. Safety concerns\(^{2-3,19,25}\)
   i. Fracture risk - increased with canagliflozin
      1. More common if lower baseline eGFR, diuretic use, older age
      2. Decrease in bone mineral density documented
   ii. Genitourinary infection
      1. Genital mycotic infections generally only with associated risk factor
      2. Rarely urinary tract infection (UTI), urosepsis, pyelonephritis
   iii. Diabetic ketoacidosis (DKA) – avoid SGLT-2i use if
      1. Critical illness, surgical procedures
      2. Ketones present
      3. Prolonged fasting
   iv. Polyuria, dehydration, volume depletion, hypotension
      1. Risk factors: elderly, use of diuretics or aldosterone antagonists, low baseline SBP, renal impairment
      2. Prevention: maintain hydration, effective counseling
   v. Increased low density lipoprotein cholesterol (LDL-C)
   vi. Transient increase in creatinine
   vii. Increased low density lipoprotein cholesterol (LDL-C)
   viii. Acute kidney injury (AKI)
      1. Studies show SGLT-2i are well tolerated in CKD up to stage 3
      2. Changes in eGFR occur early after starting SGLT-2i, are not sustained
      3. Recommendations: assess AKI risk before starting, discontinue SGLT-2i immediately if AKI occurs
      4. Monitoring: eGFr, SCr
   ix. Recent finding of increased risk of amputation with use of canagliflozin (see CANVAS analysis below)

e. Safety analyses
   i. Canagliflozin & fracture risk analysis by Watts, et al. published in 2016\(^{26}\)
      1. N=10,194
      2. Results: incidence of fracture similar for canagliflozin vs. comparator
         a. CANVAS alone: significant increase seen (4% vs. 2.6%)
         b. Overall pooled analysis: 2.7% vs. 1.9% (driven by CANVAS results)
      3. Conclusion: fracture risk higher with canagliflozin, mainly seen in older patients with history of or risk for CVD, lower baseline eGFR, higher incidence of diuretic use
   ii. Systematic review of 34 DKA case reports by Burke, et al. published in 2017\(^{27}\)
      1. Common precipitating factors: diagnosis of T2DM later found to have latent autoimmune diabetes of adults, recent major surgery, patients with recent decrease in or discontinuation of insulin use
      2. Conclusion: incidences of DKA all had a causative factor, none were fatal
iii. Meta-analysis by Monami, et al. investigating the effect of SGLT-2i on DKA or severe adverse drug reaction (ADR), published in 201728

1. Results: no increase in risk of DKA with use of individual SGLT-2i or as a class
2. Conclusion: when SGLT-2i are used correctly, DKA risk is negligible

VI. Recommended use of SGLT-2i

a. T2DM only, not yet studied in type 1 diabetes (T1DM)
b. Not studied in eGFR < 45 ml/min/1.73 m² (3)
c. Can combine with any oral agent or insulin19
d. From T2DM treatment guidelines2-3
   i. Not yet in pre-diabetes algorithm
   ii. ADA: second-line, empagliflozin or liraglutide preferred if ASCVD
   iii. AACE: first-line agent by AACE for any baseline A1c
e. ESC 2016 Heart Failure Guideline6
   i. “Empagliflozin should be considered in patients with T2DM in order to prevent or delay the onset of HF and prolong life.” (Class Iia recommendation, level B evidence)
   ii. Recent evidence for HF benefit, reduced hospitalizations for heart failure (HHF)
   iii. Uncertain if class-wide effect

VII. Clinical Question & Evidence Review

Table 6: EMPA-REG OUTCOME Summary & Analysis29


<table>
<thead>
<tr>
<th>Objective</th>
<th>Examine the effects of empagliflozin compared to placebo on CV morbidity and mortality in patients with T2DM at high risk for CV events who are receiving standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled trial at 590 sites in 42 countries</td>
</tr>
<tr>
<td>Patient Population</td>
<td></td>
</tr>
</tbody>
</table>
| Inclusion | Adults ≥ 18 years old with T2DM  
At high risk for CV event  
A1c 7-9% + no glucose-lowering agents for 12 weeks before randomization or A1c 7-10% + stable glucose-lowering agents for at least 12 weeks before randomization  
BMI ≤ 45 kg/m² |
| Exclusion (partial list) | Fasting blood glucose > 240 during placebo run-in at least twice  
Evidence of liver disease  
eGFR < 30 ml/min/1.73 m² at screening or during run-in  
ACS, TIA, or stroke in prior 2 months |
| Intervention | 2-week open-label, placebo run-in period with unchanged background T2DM therapy  
Randomized 1:1:1 to empagliflozin 10 mg daily, empagliflozin 25 mg daily, or placebo  
Stratified by A1c (< 8.5% or ≥ 8.5%), BMI (< 30 or ≥ 30 kg/m²), renal function (eGFR 30-59, 60-89, or ≥ 90 ml/min/1.73 m²) |
| Outcomes | Primary composite of death from CV causes, nonfatal MI (including silent), or nonfatal stroke |
| Secondary primary outcomes plus hospitalization for unstable angina |
| Methods | Adjustment of glucose-lowering therapy at discretion of provider after first 12 weeks to target glucose level per local guidelines |
Encouraged treatment of other CV risk factors (dyslipidemia, HTN)
Follow-up conducted throughout study and 30 days after end of treatment
Continued until primary outcome occurred in at least 691 patients
Safety: adverse events during study, days after last dose; reviewed by independent committee every 90 days
Analyzed change in: A1c, weight, waist circumference, BP, pulse, LDL, HDL, uric acid
Subgroup analyses: age, HbA1c, BMI, weight, geographical region, race, gender, ethnicity, time since diagnosis of T2DM, BP, eGFR, urine albumin:creatinine ratio, glucose-lowering medication, use of statins/ezetimibe, use of antihypertensives, use of aspirin, CV complications and cohort, hypoglycemia

Follow-up conducted throughout study and 30 days after end of treatment
Continued until primary outcome occurred in at least 691 patients
Safety: adverse events during study, days after last dose; reviewed by independent committee every 90 days
Analyzed change in: A1c, weight, waist circumference, BP, pulse, LDL, HDL, uric acid
Subgroup analyses: age, HbA1c, BMI, weight, geographical region, race, gender, ethnicity, time since diagnosis of T2DM, BP, eGFR, urine albumin:creatinine ratio, glucose-lowering medication, use of statins/ezetimibe, use of antihypertensives, use of aspirin, CV complications and cohort, hypoglycemia

Results

7020 patients treated from September 2010 to April 2013 for a median of 2.6 years
  97% completed study, 25.4% discontinued study drug early
  Final vital status available for 99.2% of patients enrolled
Baseline: well balanced, average age 63 years, mostly white and Asian males with DM for > 5 years
  Most taking metformin, aspirin, statin, 94% on antihypertensive medications
  Average A1c ~8%, 68% with A1c < 8.5%
  >99% with established CVD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95.02% CI) for empagliflozin</th>
<th>P value non-inferiority</th>
<th>P value superiority</th>
<th>NNT per 100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0.86 (0.74-0.99)</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>15</td>
</tr>
<tr>
<td>Key secondary</td>
<td>0.89 (0.78-1.01)</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95.02% CI) for empagliflozin</th>
<th>P value non-inferiority</th>
<th>NNT per 100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV causes</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
<td>13</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
<td>38 (25 mg), 41 (10 mg)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
<td>19</td>
</tr>
<tr>
<td>Fatal/non-fatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Fatal/non-fatal stroke</td>
<td>1.18 (0.89-1.56)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>HHF or death from CV cause excluding fatal stroke</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
<td>9</td>
</tr>
</tbody>
</table>

• 0.54% average A1c decrease with 10 mg, 0.6% with 25mg
• Consistent benefit for CV outcomes across all subgroups
• Observed more weight loss, ↓ waist circumference, ↓ SBP in empagliflozin groups
• More genital infection in empagliflozin groups, other safety outcomes non-significant
• Many patients did not reach glycemic targets (average A1c 7.81% - 8.1%)

Reviewer critique

Strengths
• Benefits observed started early in the trial and continued throughout
• Stratification before randomization to prevent some potential confounding
• Included appropriate adverse events in analysis (most common events for these agents)
• Continued background standard care
• More realistic patient cohort with higher A1c at end of trial (many not reaching goal)

Limitations
• Selected for patients with somewhat better DM control (max A1c 10%); however, may be appropriate given estimated 0.5% A1c reduction by empagliflozin
• Short treatment duration (3 years) analyzed compared to expected DM treatment duration
• Decreased effect of glucose control over time, longer-term effects uncertain
• Patients had well-treated CV disease, effect uncertain if other disease states untreated or poorly controlled
• Extrapolate only to patients with established CVD

Conclusions
• Empagliflozin use leads to significantly lower rates of composite death from CV causes, nonfatal MI, or nonfatal stroke in patients with T2DM and established CVD
• Difference driven by reduction in death from CV causes, no difference in MI or stroke
• Generally well tolerated with expected A1c lowering with empagliflozin is about 0.5%
• Other potential benefits include modest weight loss, BP reduction, reduced HHF

BMI: body mass index; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ACS: acute coronary syndromes; TIA: transient ischemic attack; MI: myocardial infarction; HTN: hypertension; LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c; T2DM: type 2 diabetes mellitus; BP: blood pressure; HR hazard ratio; CI: confidence interval; NNT: number needed to treat; HHF: hospitalization for heart failure; CVD: cardiovascular disease
a. EMPA-REG EXTEND MET\textsuperscript{30} – empagliflozin added to metformin
   i. Exploratory endpoint analysis: change in A1c from baseline, weight, BP at week 72
   ii. Results & conclusions: significant reductions in A1c and BP seen at week 24 were sustained at week 76; agent is well-tolerated over a longer-term treatment with increased genital infections

b. EMPA-REG\textsuperscript{31}
   i. Time-to-benefit post-hoc analysis of EMPA-REG OUTCOME with groups split by 5-year HF risk into low (< 10%), high (10-20%), or very high risk (≥ 20%)
   ii. Results: decreased risk of HF outcomes in all three risk groups for empagliflozin arm
   iii. Conclusions:
      1. Authors: most patients with T2DM and CVD have very high HF risk at baseline, and empagliflozin improves HF outcomes in all HF risk groups
      2. Presenter: use of empagliflozin in patients with T2DM and CVD but WITHOUT HF may reduce HF incidence/outcomes, need further studies to prove benefit

### Table 7: CANVAS Summary & Analysis\textsuperscript{25}

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Show CV safety of canagliflozin, evaluate the balance between potential benefits and risks, and assess effects on albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Two sister randomized, double-blind, placebo-controlled trials in 667 centers in 30 countries</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td></td>
</tr>
<tr>
<td>Inclusion (identical for both trials)</td>
<td>T2DM with A1c ≥ 7% and ≤ 10.5%</td>
</tr>
<tr>
<td></td>
<td>eGFR &gt; 30 mL/min/1.73 m\textsuperscript{2}</td>
</tr>
<tr>
<td></td>
<td>One of the following</td>
</tr>
<tr>
<td></td>
<td>≥ 30 years old with history of symptomatic ASCVD</td>
</tr>
<tr>
<td></td>
<td>≥ 50 years old with ≥ 2 risk factors for CVD</td>
</tr>
<tr>
<td>Exclusion (partial list)</td>
<td>History of DKA, T1DM</td>
</tr>
<tr>
<td></td>
<td>Changed hypoglycemics in past 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose &gt; 270 mg/dL at baseline</td>
</tr>
<tr>
<td></td>
<td>Glucose &lt; 110 mg/dL if on insulin or sulfonylurea or severe hypoglycemia in last 6 months</td>
</tr>
<tr>
<td></td>
<td>MI, unstable angina, CVA within last 3 months or planned coronary intervention</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>CANVAS: 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or placebo</td>
</tr>
<tr>
<td></td>
<td>CANVAS-R: 1:1 to canagliflozin 100 mg (optional increase to 300 mg after week 13) or placebo</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary composite of death from CV causes, nonfatal MI, nonfatal stroke</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>Death from any cause</td>
</tr>
<tr>
<td></td>
<td>Death from CV cause</td>
</tr>
<tr>
<td></td>
<td>Progression of albuminuria</td>
</tr>
<tr>
<td></td>
<td>Composite death from CV causes and HHF</td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td>Nonfatal MI</td>
</tr>
<tr>
<td></td>
<td>Nonfatal stroke</td>
</tr>
<tr>
<td></td>
<td>HHF</td>
</tr>
<tr>
<td></td>
<td>Regression of albuminuria</td>
</tr>
<tr>
<td></td>
<td>Total hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Renal composite: 40% decrease in eGFR sustained for at least 2 measures, need for RRT, or death from renal causes</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>2-week single-blind, placebo run-in period</td>
</tr>
<tr>
<td></td>
<td>Allowed other treatment for glycemic control and CV risk factors</td>
</tr>
<tr>
<td></td>
<td>Follow-up visits 3 times during first year, then at 6-month intervals</td>
</tr>
<tr>
<td></td>
<td>Complete when at least 688 CV events observed and all participants with 78 weeks of follow-up (ended Feb 2017)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Total 10,142 participants enrolled, 9734 (96%) completed the trial, ~29% discontinued drug early in both arms</td>
</tr>
<tr>
<td></td>
<td>Mean follow-up of 188 weeks (3.3 years)</td>
</tr>
<tr>
<td></td>
<td>Baseline characteristics well balanced &amp; similar for both CANVAS and CANVAS-R</td>
</tr>
<tr>
<td></td>
<td>Mean age 63 years old, mostly white, 35.8% female, average duration of DM 13.5 years, average baseline A1c 8.2%, about 65% with history of CVD</td>
</tr>
<tr>
<td></td>
<td>Most patients on appropriate CV-risk reduction therapy (statin, ACEI, beta-blocker)</td>
</tr>
<tr>
<td></td>
<td>Use of other hypoglycemic agents 9.3% lower in canagliflozin group</td>
</tr>
<tr>
<td></td>
<td>CV risk markers canagliflozin v. placebo (p&lt;0.001 for all):</td>
</tr>
<tr>
<td></td>
<td>Difference in A1c: -0.58% (95% CI -0.61 to -0.56)</td>
</tr>
<tr>
<td></td>
<td>Difference in body weight: -1.60 kg (95% CI -1.70 to -1.51)</td>
</tr>
</tbody>
</table>
c. Canagliflozin effect on CV biomarkers in older adults
   i. Use of canagliflozin delayed increase of NT-pro-BNP and troponin I for over 2 years in adults with T2DM aged 55-80 years old
   ii. Supports potential for CV benefit of canagliflozin in older adults with T2DM
Table 8: CVD-REAL Summary & Analysis


**Objective**
Compare risk of HHF, death, and combined endpoint of HHF & death in patients with T2DM who were new users of SGLT-2i compared to other glucose lowering drugs (oGLD) in real-world practice

**Design**
Retrospective analysis of de-identified health records from 6 countries

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age ≥ 18 years old on index date</td>
<td>- T1DM</td>
</tr>
<tr>
<td>- T2DM diagnosis code</td>
<td>- Gestational diabetes</td>
</tr>
<tr>
<td>- New start of SGLT-2i or oGLD between November 2012 and July 2013</td>
<td>-</td>
</tr>
<tr>
<td>- &gt; 1 year history of information in database</td>
<td>-</td>
</tr>
</tbody>
</table>

**Intervention**
Analyzed various health claims databases across the US, Germany, Sweden, Norway, Denmark, United Kingdom (UK) from index date to date of treatment end, leaving database, last date of data collection, outcome date, or censoring date

**Outcomes**

<table>
<thead>
<tr>
<th>Primary HHF – definitions by country:</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HF as primary discharge diagnosis in US, UK</td>
<td>- All cause death</td>
</tr>
<tr>
<td>- Documented in health record in Germany</td>
<td>- Composite HF and all-cause death (time-to-first-event)</td>
</tr>
<tr>
<td>- Hospital or outpatient visit with primary diagnosis of HF for Nordic countries</td>
<td></td>
</tr>
</tbody>
</table>

**Methods**
- Propensity score used for matching 1:1 SGLT-2i to oGLDs
- Included first incidence of HHF or death
- Analyzed primary outcomes by on-treatment approach (start of treatment to end of treatment plus grace period for days supply of medication)

**Results**
- Baseline before matching: patients on SGLT-2i younger, less CKD or CV complications, more microvascular disease, receiving more statins, antihypertensive drugs, fewer loop diuretics
- Baseline after matching: well matched
  - Mean age 57 years, 44% female, 79% on metformin
  - 13% established CVD
  - < 7% drug exposure time was with empagliflozin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients</th>
<th>Person-years of follow-up (mean duration)</th>
<th>Events</th>
<th>HR SGLT-2i vs. oGLD (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHF</td>
<td>309,056</td>
<td>190,164 (239 days)</td>
<td>961</td>
<td>0.61 (0.51 - 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>215,622</td>
<td>153,990 (251 days)</td>
<td>1334</td>
<td>0.49 (0.41 - 0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HHF &amp; death</td>
<td>215,622</td>
<td>143,342 (253 days)</td>
<td>1983</td>
<td>0.54 (0.48 - 0.60)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Sensitivity analyses - similar results for all adjustments

**Reviewer Analysis**

**Strengths**
- First large trial to look at real-world practice using SGLT-2i
- First to look for a class effect of SGLT-2i
- First to include a majority of patients without established CVD
- First to look at HHF and all-cause death

**Limitations**
- Observational study (possible confounding)
- Focused on HHF and all-cause death, not MI or stroke
- No analysis of safety outcomes
- Differences in definition of HHF across countries (however, results consistent)
- Distribution of use of specific SGLT2i variable

**Conclusions**
- Suggests results from EMPA-REG OUTCOME may be true in real-world setting
- CV benefit of SGLT-2i likely a class effect
- CV benefit of SGLT-2i use likely includes patients without diagnosed CVD
- Treatment with SGLT-2i associated with lower HHF, all-cause death in patients with T2DM with and without pre-existing CVD (mainly without)
- Should test in randomized trial with broader patient population to confirm results

Table 9: Summary of meta-analyses of SGLT-2i

<table>
<thead>
<tr>
<th>Authors (year published)</th>
<th>Included studies</th>
<th>Efficacy outcome(s)</th>
<th>Safety outcome(s)</th>
</tr>
</thead>
</table>
| Vasilakou, et al.34 (2013) | Randomized, comparing SGLT-2i to placebo or other T2DM treatment | • A1c ↓ 0.66%  
• ↓ weight with SGLT-2i  
• ↓ SBP with SGLT-2i  
• ↓ CV outcomes: OR 0.73 (dapagliflozin), OR 0.95 (canagliflozin)  
• No significant difference in all-cause mortality | • ↑ renal-related adverse events with SGLT-2i  
• ↑ UTI: OR 1.34  
• ↑ genital tract infection: OR 3.50 vs. placebo, OR 5.06 vs. active  
• ↑ hypotension with SGLT-2i: OR 2.68  
• Non-significant ↑ in fracture with canagliflozin |
| Wu, et al.35 (2016) | Prospective randomized controlled trials of SGLT-2i vs. control | • ↓MACE* with SGLT-2i: RR = 0.84, p=0.006  
• ↓MACE plus hospital admission for unstable angina: RR=0.85, p=0.008  
• ↓ CV death: RR 0.63, p<0.0001  
• ↓ HF: RR 0.65, p=0.002  
• ↓ all-cause death: RR 0.71, p<0.0001  
• No benefit: nonfatal MI, unstable angina  
• Benefits driven by empagliflozin | • ↑ nonfatal stroke with SGLT-2i: RR 1.3, p=0.049  
• ↑ UTI risk  
• ↑ genital infection  
• ↑ volume depletion  
• No difference in cancer, hypoglycemia, acidosis, bone fracture, kidney disease |
| Tang, et al36 (2016) | Randomized controlled trials of SGLT-2i use for at least 24 weeks | • ↓ risk of MACE, all-cause mortality, incidence of HF with empagliflozin  
• Non-significant difference in MACE, all-cause mortality, HF for dapagliflozin & canagliflozin  
• No difference in unstable angina, atrial fibrillation, TIA  
• Results driven by EMPA-REG OUTCOME | No prespecified safety outcomes, but no harm seen from any SGLT-2i noted |
| Monami, et al17 (2017) | Randomized trials | • ↓ in MI with SGLT-2i: MH-OR 0.77 [0.63–0.94], p < 0.01  
• No change in stroke risk  
• ↓ all-cause mortality: MH-OR 0.70 [0.59–0.83], p < 0.001  
• ↓ CV mortality: MH-OR 0.43 [0.36–0.53], p < 0.001 | No safety outcomes assessed |

*MACE: major adverse cardiovascular events (includes CV death, nonfatal MI, nonfatal stroke)  
SGLT-2i: sodium glucose cotransporter-2 inhibitor; SBP: systolic blood pressure; CV: cardiovascular; OR: odds ratio; UTI: urinary tract infection; RR: relative risk; MI: myocardial infarction; MH-OR: Mantel Haenszel odds ratio; TIA: transient ischemic attack

VIII. Summary

a. SGLT-2i currently recommended for treatment of T2DM by ADA (preferred second line in ASCVD) and AACE (first-line option)
b. ESC HF guidelines recommend use of empagliflozin in T2DM for prevention of HHF
Table 10: Summary of evidence reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Key Outcomes &amp; Takeaway</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>In patients with existing CVD, empagliflozin lowered risk for composite outcome (death from CV causes, nonfatal MI, or nonfatal stroke), lowered risk of HHF, lowered risk of death from CV causes and death from any cause</td>
</tr>
<tr>
<td>CANVAS</td>
<td>In patients with and without existing CVD, canagliflozin lowered risk of death from CV causes, nonfatal MI or nonfatal stroke, trended toward a decrease in HHF, and increased risk of amputation and fracture in certain patient groups</td>
</tr>
<tr>
<td>CVD-REAL</td>
<td>In patients mainly without existing CVD, SGLT-2i use was associated with lower HHF and all-cause death which appear to be class effects</td>
</tr>
<tr>
<td>Safety data</td>
<td>UTI, urosepsis risk very low; DKA, amputation, volume depletion risk possibly increased in specific populations; possible increase in fracture risk with use; increased risk of genital mycotic infections with SGLT-2i</td>
</tr>
</tbody>
</table>

IX. Ongoing Trials

a. DECLARE-TIMI 58
   i. Dapagliflozin effect on CV events
   ii. Estimated completion April 2019

b. VERTIS CV Study
   i. CV outcomes following ertugliflozin treatment in T2DM participants with vascular disease
   ii. Expected completion October 2019

X. Recommendations

c. Established ASCVD (see Appendix B) or high risk for HF: recommend use of empagliflozin or canagliflozin preferentially over other hypoglycemic agents to prevent negative CV outcomes
   i. In addition to metformin in patients who can tolerate metformin
   ii. Use first-line in patients with established ASCVD or high risk for HF if unable to tolerate metformin
   iii. Unlikely to decrease risk of MI or stroke
   iv. High risk of HF: 5-year risk of HF ≥ 10% using Health ABC Heart Failure Risk Score, CHD, elevated SBP, current smoker, left ventricular hypertrophy

d. T2DM regardless of pre-existing CVD or HF: consider use of empagliflozin or canagliflozin to prevent development of HF, HHF, all-cause death

e. CV benefit may be a class effect though only conclusive evidence with canagliflozin and empagliflozin so currently recommend these agents over dapagliflozin

f. Consider in patients who could benefit from modest weight loss and/or BP lowering

g. Expected average A1c lowering is 0.5%, recommend combination therapy if need larger effect

h. Avoid use of canagliflozin (likely all SGLT-2i) in patients with a history of PVD or amputation

i. Caution SGLT-2i use (not contraindication) for the following populations
   i. History of frequent genital mycotic infections or at high risk for UTI
   ii. Elderly patients on diuretics, with reduced eGFR, baseline high risk for falls or fracture
   iii. Possible not true T2DM (e.g. underlying latent autoimmune diabetes of adults)
   iv. Unable to maintain adequate hydration
XI. References


APPENDIX A: TREATMENT OF T2DM\textsuperscript{3-4}

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- **A1C is less than 9%**: consider Monotherapy.
- **A1C is greater than or equal to 9%**: consider Dual Therapy.
- **A1C is greater than or equal to 10%**: healthcare provider should consider a combination injectable therapy (See Figure 8.2).

### Monotherapy

**Lifestyle Management + Metformin**

- Initiate metformin therapy if no contraindications\textsuperscript{5}(See Table 8.1)

- **A1C at target after 3 months of monotherapy?**
  - Yes: Monitor A1C every 3-6 months
  - No: Assess medication-taking behavior
    - Consider Dual Therapy

### Dual Therapy

**Lifestyle Management + Metformin + Additional Agent**

- **ASCVD?**
  - Yes: Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations in Table 8.1)
  - No: Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

- **A1C at target after 3 months of dual therapy?**
  - Yes: Monitor A1C every 3-6 months
  - No: Assess medication-taking behavior
    - Consider Triple Therapy

### Triple Therapy

**Lifestyle Management + Metformin + Two Additional Agents**

- Add third agent based on drug-specific effects and patient factors\textsuperscript{5.6}(See Table 8.1)

- **A1C at target after 3 months of triple therapy?**
  - Yes: Monitor A1C every 3-6 months
  - No: Assess medication-taking behavior
    - Consider Combination Injectable Therapy (See Figure 8.2)

### Combination Injectable Therapy

(See Figure 8.2)

---

**APPENDIX B: TREATMENT OF COMORBIDITIES**

Table 1B: Management goals for CV risk factors\textsuperscript{10, 39-40}

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommended Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant therapy</td>
<td>Use aspirin for primary prevention and secondary prevention of CVD events</td>
</tr>
<tr>
<td>Weight</td>
<td>Reduce by 5-10%; avoid weight gain</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 200 mg/dL</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt; 100 mg/dL; &lt; 70 mg/dL for very high risk patients</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;140/90 mmHg</td>
</tr>
</tbody>
</table>

CV: cardiovascular; CVD: cardiovascular disease; LDL: low-density lipoprotein

1. Management of dyslipidemia in T2DM\textsuperscript{3-4, 14}
   a. Dietary and lifestyle changes, patient education\textsuperscript{14}
   b. Pharmacologic therapy if goals are not met with lifestyle changes alone
   c. Statins remain the drug of choice\textsuperscript{11, 14}
d. ACC/AHA 2013 guidelines and ADA 2018 guidelines recommend treatment for patients\textsuperscript{4,14}

i. With established ASCVD (defined as history of acute coronary syndromes including MI, stable or unstable angina, or arterial revascularization, history of stroke or TIA, history of coronary artery disease, PAD, CHD)\textsuperscript{11,25,29,41}

ii. With familial hyperlipidemias (LDL-C ≥ 190 mg/dL at baseline)

iii. With T2DM and age 40-75 years (see Table 2B for ASCVD risk factors)
   1. 10-year ASCVD risk < 7.5% $\rightarrow$ moderate-intensity statin
   2. 10-year ASCVD risk ≥ 7.5% $\rightarrow$ high-intensity statin
   3. ADA 2018 guideline recommends moderate intensity statin in all diabetic patients

iv. Less evidence for patients with T2DM < 40 or > 75 years old – consider moderate-intensity statin
   1. T2DM age < 40 years with ASCVD risk factors (see Table 2B)
   2. T2DM age > 75 years

Table 2B: Major ASCVD Risk Factors\textsuperscript{14}

<table>
<thead>
<tr>
<th>Major</th>
<th>Additional</th>
<th>Nontraditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Obesity or abdominal obesity</td>
<td>Elevated lipoprotein (a)</td>
</tr>
<tr>
<td>Elevated total serum cholesterol</td>
<td>Family history of dyslipidemia</td>
<td>Elevated clotting factors</td>
</tr>
<tr>
<td>Elevated non-HDL-C</td>
<td>Elevated small, dense LDL-C</td>
<td>Inflammation markers (hsCRP)</td>
</tr>
<tr>
<td>Elevated LDL-C</td>
<td>Increased Apo B</td>
<td>Elevated homocysteine</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>Increased LDL particle number</td>
<td>Apo E4 isoform</td>
</tr>
<tr>
<td>DM</td>
<td>Fasting/postprandial hypertriglyceridemia</td>
<td>Elevated uric acid</td>
</tr>
<tr>
<td>HTN</td>
<td>PCOS</td>
<td>Elevated TG-rich remnants</td>
</tr>
<tr>
<td>CKD stage 3 or 4</td>
<td>Dyslipidemic triad*</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of ASCVD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASCVD: atherosclerotic cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; DM: diabetes mellitus; HTN: hypertension; CKD: chronic kidney disease; Apo B: apoprotein B; PCOS: polycystic ovarian syndrome; hsCRP: high-sensitivity c-reactive protein; Apo E4: apoprotein E4; TG: triglyceride

*Hypertriglyceridemia; low high-density lipoprotein cholesterol; and small, dense low-density lipoprotein cholesterol.

e. Combination therapy or alternatives available if goals not met or contraindications to statin therapy
   i. Bile acid sequestrants
   ii. Ezetimibe in combination with statin
   iii. PCSK-9 inhibitors combined with statin in familial hypercholesterolemias or inadequate control with statin monotherapy

f. Fibrates or omega-3 fatty acids recommended for treatment of hypertriglyceridemia
   i. Goal triglycerides (TG) < 150 mg/dL for all patients, always treat if TG ≥ 500 mg/dL\textsuperscript{4,14}
   ii. Consider addition to lower ASCVD risk in patients with TG ≥ 200 mg/dL

2. Treatment of heart failure\textsuperscript{4,41}
   a. Use ACEI or ARB (if intolerant to ACEI) to decrease mortality in HFrEF; valsartan/sacubitril if New York Heart Association class II or III symptomatic HF and able to tolerate ACEI or ARB
   b. Beta blockers in patients with HFrEF or ivabradine if beta blocker does not achieve HR < 70 beats/min
   c. Diuretics for symptom management as needed
   d. Add on: aldosterone antagonist, BiDil, ICD, CRT, ivabradine
   e. HFrEF: can use aldosterone antagonist, ACEI, ARB, BB to manage atrial fibrillation and HTN
   f. Avoid TZD therapy in patients with symptomatic HF
3. **CVD – antiplatelet therapy**
   
a. **Primary prevention - consider in T2DM with high ASCVD risk**
   
i. Age ≥ 50 years with one additional risk factor
   
   ii. Risk factors: HTN, dyslipidemia, family history of premature ASCVD, smoking, albuminuria (Table 2B for additional risk factors)\(^4\)
   
   iii. Clinical judgment for patients < 50 years
   
   iv. Do not use for primary prevention in low risk patients
   
b. **Secondary prevention for patients with a history of clinical ASCVD**
   
c. **Choice of agent**
   
i. Aspirin 75-162 mg daily\(^4\)
   
   ii. Clopidogrel 75 mg daily if aspirin allergy/intolerance

---

**APPENDIX C: SGLT-2i DRUG INFORMATION\(^{4,20}\)**

**Table 1C: SGLT-2i Drug Information**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date approved</td>
<td>March 2013</td>
<td>January 2014</td>
<td>August 2014</td>
<td>December 2017</td>
</tr>
<tr>
<td>FDA indication(s)</td>
<td>T2DM in adults</td>
<td>T2DM in adults</td>
<td>CV disorder prophylaxis in T2DM, T2DM in adults</td>
<td>T2DM in adults</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg – 300 mg daily</td>
<td>5 mg – 10 mg daily</td>
<td>10 mg – 25 mg daily</td>
<td>5 mg – 15 mg daily</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Hypoglycemia, polyuria, UTI, genital mycotic infections, hypovolemia, pancreatitis, hypotension, hypersensitivity reaction, bone fracture, DKA, AKI, pyelonephritis, leg/foot limb loss, angioedema</td>
<td>Hypoglycemia, UTI, genital mycotic infections, hypotension, hypersensitivity reaction, bone fracture, bladder cancer, DKA, AKI, pyelonephritis, urosepsis</td>
<td>Hypoglycemia, UTI (higher in age ≥75 years), mycotic infections, DKA, AKI, pyelonephritis, urosepsis</td>
<td>UTI, hypovolemia, increased thirst, genital mycotic infections, hypoglycemia (if used with insulin)</td>
</tr>
<tr>
<td>PK/PD</td>
<td>All agents: highly protein bound, (V_d \approx 70-80)L, metabolized by liver, renal and fecal elimination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interactions</td>
<td>UGT inducers decrease canagliflozin concentration; can increase digoxin serum level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnings</td>
<td>Consider risk of amputation before initiation (history of amputation, PVD, neuropathy, foot ulcers), correct volume before initiation, risk of bone fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DKA risk possible with all agents, possible volume depletion, possible LDL increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same warnings for amputation and volume risk as canagliflozin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{T2DM: type 2 diabetes mellitus; CV: cardiovascular; UTI: urinary tract infection; DKA: diabetic ketoacidosis; AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; V_d: volume of distribution; t_{1/2}: half-life}\)