What Can SGLT-2 Inhibitors Do For the Cardiovascular Patient?

Alison L. Bailey MD, FACC
Erlanger Heart and Lung Institute/University of Tennessee COM Chattanooga
@a_l_bailey
Objectives

• Review the increased CV risk in patients with DM 2
• Describe the role of sodium–glucose cotransporter 2 (SGLT2) in health
• Discuss the clinical trial data for SGLT2 Inhibitors
Most Cardiovascular Patients Have Abnormal Glucose Metabolism

GAMI  
- Normoglycemia: 35%  
- Prediabetes: 31%  
- DM 2: 34%

EHS  
- Normoglycemia: 37%  
- Prediabetes: 18%  
- DM 2: 45%

CHS  
- Normoglycemia: 37%  
- Prediabetes: 36%  
- DM 2: 27%

Anselmino M, *Diabetes Vasc Dis Res* 2008
Increased Mortality in DM 2

Death from Any Cause

Death from CV Disease

Mortality after ACS Higher in Diabetics

HR 1.57; 1.23-2.00; p<0.001

DM

No DM

HR 2.04; 1.49-2.78; p<0.001

DM—Insulin

DM—No Insulin

No DM

Karayiannides S, J Am Coll Cardiol 2018
Prevalance of DM 2 in Saudi Arabia

Alotaibi A. J Epidemiol Glob Health 2017
Al Habib KF. Can J Cardiol 2009

>50% of ACS patients
Control of DM 2 in Saudi Arabia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glycaemic control</th>
<th>Poor (HbA1c ≥ 8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (HbA1c &lt; 7.0%)</td>
<td>Partial (HbA1c 7.0% - 7.9%)</td>
</tr>
<tr>
<td>n = 263</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>28.4 (109)</td>
<td>22.4 (86)</td>
</tr>
<tr>
<td>46–60 years</td>
<td>21.4 (123)</td>
<td>21.6 (124)</td>
</tr>
<tr>
<td>&lt; 46 years</td>
<td>23.1 (31)</td>
<td>20.2 (27)</td>
</tr>
</tbody>
</table>

Alramadan MJ. BMC Endocrine Disorders 2018
Primary Prevention of CV Events in DM 2

Newman JD. J Am Coll Cardiol 2017

*all-cause mortality; †revascularization or amputation; ‡hospitalization for angina.
Healthy Lifestyle Factors* and CVD in DM 2

*High-quality diet; nonsmoking; 150 min/week moderate- to vigorous-intensity physical activity; and drinking alcohol in moderation (5 -15 g/day ♀ and 5 to 30 g/day ♂)

Liu G. J Am Coll Cardiol 2018
Mechanisms of Hyperglycemia

Ferrannini E. Eur Heart J 2015
Sodium–glucose co-transporter 2 (SGLT2)

- Located in the proximal tubule
- Patients with DM2 express a significantly higher number of SGLT2s in the proximal tubule

Zelniker TA. J Am Coll Cardiol 2018
Sodium–glucose co-transporter 2 (SGLT2)

- SGLTs move glucose from the urine into the cell via an energy-dependent Na\(^+\)-coupled pump
- Na\(^+\) moves out of the cell into blood as K\(^+\) is pumped into the cell
- Glucose leaves the cell down its concentration gradient into the blood

Zelniker TA. J Am Coll Cardiol 2018
Sodium–glucose co-transporter 2 (SGLT2)

• Inhibiting this transporter forces glucose to be excreted into the urine

• Insulin-independent improvements in glycemic control due to glycosuria of ~70 to 80 g/day

Zelniker TA. J Am Coll Cardiol 2018
Sodium–glucose co-transporter 2 (SGLT2)

- Mechanisms of action of SGLT2is other than their hypoglycemic effects are not fully understood.
SGLT2 Inhibitors

- SGLT2i-mediated natriuresis and glycosuria reduce plasma volume and lower cardiac preload
- Induces an increase in FFA oxidation that stimulates ketogenesis and shifts substrate use toward fat
- Reduces epicardial fat

Scheen AJ. Circ Res 2018
SGLT2 Inhibitors

- 4 SGLT2is (empagliflozin, canagliflozin, dapagliflozin and ertugliflozin) approved by the FDA for treatment of DM 2

- Empagliflozin has the highest (~2,500-fold) selectivity for SGLT2 over SGLT1 compared with
  - Ertugliflozin (~2,000-fold)
  - Dapagliflozin (~1,200-fold)
  - Canagliflozin (~250-fold)
SGLT2 Inhibitors

- Administered orally once daily because of their half-life of >10 h
- Drug-induced urinary glucose excretion requires at least moderately preserved renal function
- SGLT2is are contraindicated in patients with an estimated glomerular filtration rate (GFR)<30 ml/min/1.73
EMPA-Reg: Trial Overview

- 7020 patients
- Established CVD
- Randomized, double-blind, placebo-controlled
- Empaglifozin 10 mg or 25 mg versus placebo

Zinman B. N Engl Med 2015
EMPA-Reg: Mean HbA1c Levels

Zinman B. N Engl Med 2015
EMP A-Reg: Primary Outcome
CV Death, Nonfatal MI, Nonfatal CVA

Zinman B. *N Engl Med* 2015

↓ 14% in Composite Endpoint
EMPA-Reg: CV Death*

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

↓38% in CV death

Zinman B. N Engl Med 2015
EMPA-Reg: Death from Any Cause*

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001

↓ 32% in All-Cause death

Zinman B. N Engl Med 2015
EMPA-Reg: Hospitalization for HF

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

↓35% in HF Hospitalization

Zinman B. N Engl Med 2015
CANVAS: Trial Overview

- CANVAS program: 10,142 participants
  - 4330 in CANVAS
  - 5812 in CANVAS-R
- Randomized, double-blind, placebo-controlled
- ≥30 yo with DM and symptomatic CVD
- ≥50 you with DM and ≥2 RF
- 65.6% had CVD
  - 22.6% had microalbuminuria
  - 7.6% had macroalbuminuria

Neal B. *N Engl Med* 2017
CANVAS: Mean HbA1c ↓ 0.58%

- Body weight –1.60 kg
- SBP –3.93 mm Hg
- DBP –1.39 mm Hg

Neal B. *N Engl Med* 2017
CANTAS: Primary Outcome
CV Death, Nonfatal MI, Nonfatal CVA

14% in Composite Endpoint

Neal B. *N Engl Med* 2017
CANCAS: CV Death

Hazard ratio, 0.87 (95% CI, 0.72–1.06)

Neal B. *N Engl Med* 2017
CANVAS: All-Cause Death

Death from Any Cause

Hazard ratio, 0.87 (95% CI, 0.74–1.01)

Patients with an Event (%)

Placebo
Canagliflozin

Weeks since Randomization

Neal B. N Engl Med 2017
CANVAS: Hospitalization for HF

33% in HF Hospitalization

Neal B. N Engl Med 2017
CANVAS: 2X Increased risk of Amputation

- There was an \( \uparrow \) risk of lower extremity amputation:
  - Canagliflozin: 6.3 participants per 1000 patient years
  - Placebo: 3.4 participants per 1000 patient years
  - HR: 1.97 (95% CI, 1.41 to 2.75)

- Amputations were primarily at the level of the toe or metatarsal

- FDA issued a black box warning for lower limb amputation in May 2017

Neal B. *N Engl Med* 2017
EMPA-Reg: PAD Subgroup

Verma S. Circulation 2018
EMPA-Reg: Lower Limb Amputation

Inzucchi SE. Diabetes Care 2018
CANVAS: Increased fracture risk

FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamide) to include updates on bone fracture risk and new information about bone mineral density.

Canagliflozin use has been associated with increased fracture risk

https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm
Dapaglifozin: DECLARE-TIMI 18

- 17,295 pts in 33 countries with DM 2 and elevated CV risk
  - Multiple CV Risk Factors or CVD
- Demonstrated a reduction in a composite of CV death or hospitalization for HF
- Failed to show a significant difference in MACE (CV death, MI, CVA)
- Will be presented at AHA 11/2018
Dapaglifozin

MACE = CV death, MI, CVA

MACE + UA = MACE + unstable angina

Sonesson C. Cardiovasc Diabetol 2016
SGLT2 Inhibitors: Additional Thoughts

• **Hypoglycemia risk** ↑ when an insulin secretagogue or insulin is given with an SGLT2i, so it may be necessary to reduce the dose of insulin

• **SGLT2i’s may ↓ BP**, so it will be important to monitor for signs and symptoms of hypotension

• **The patient may lose weight with the use of an SGLT2i**

• **SGLT2i-triggered diabetic ketoacidosis** may occur in euglycemic patients who may have delayed diagnosis and therapy

Zelniker TA. J Am Coll Cardiol 2018
SGLT2 Inhibitors

Favorable effects
- Reduction of pre-load (diuretic effects)
- Reduction of afterload (blood pressure, arterial stiffness)
- Improvement of mitochondrial efficiency
- Delay of decline in eGFR
- Delay of micro- and macroalbuminuria
- Weight loss
- Reduction in epicardial adipose tissue
- Improvement in glycemia
- Reduction in uric acid

Unfavorable effects
- Amputations (in particular toe, metatarsal)
- Volume depletion/Hypotension
- Diabetic ketoacidosis
- Fractures
- Urinary and genital infections

Zelniker TA. J Am Coll Cardiol 2018
# SGLT2 Inhibitors Summary

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>CVD</td>
<td>CVD or CV RF</td>
<td>CVD or CV RF</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Reduces</td>
<td>Neutral</td>
<td>?</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>Reduces</td>
<td>Reduces</td>
<td>?</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td>Reduces</td>
<td>Reduces</td>
<td>?</td>
</tr>
</tbody>
</table>
Addition of SGLT-2 Vs Other DM drugs
Denmark, Norway and Sweden

<table>
<thead>
<tr>
<th></th>
<th>SGLT2 Inhibitors (n=22,830)</th>
<th>Other glucose-lowering drugs (n=68,490)</th>
<th>Standardised difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>16,935 (74.2%)</td>
<td>53,006 (77.4%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>6,044 (26.5%)</td>
<td>18,623 (27.2%)</td>
<td>0.013</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>4,398 (19.3%)</td>
<td>12,566 (18.3%)</td>
<td>0.019</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>3,888 (17.0%)</td>
<td>10,105 (14.8%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>343 (1.5%)</td>
<td>948 (1.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Insulin</td>
<td>6822 (29.9%)</td>
<td>20,634 (30.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Short-acting</td>
<td>2,452 (10.7%)</td>
<td>7,257 (10.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>3,143 (13.8%)</td>
<td>9,345 (13.6%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Premixed</td>
<td>1,630 (7.1%)</td>
<td>4,809 (7.0%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Long-acting</td>
<td>2,585 (11.3%)</td>
<td>7,650 (11.2%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Birkeland KI. Lancet Diabetes Endocrinol 2018
Addition of SGLT-2 Vs Other DM drugs
Denmark, Norway and Sweden

Birkeland KI. Lancet Diabetes Endocrinol 2018
Antihyperglycemic Therapy in Adults with T2DM

- European guidelines CVD prevention and the European Society of Cardiology recommended empagliflozin “to prevent or delay the onset of HF in patients with diabetes and to prolong life”

ADA. *Diabetes Care* 2018
Antihyperglycemic Therapy in Adults with DM2 & HF

Heart Failure and Established Type 2 Diabetes Mellitus

HbA1c > 7% Despite Therapy with Metformin

- **Recommended treatment**
  - SGLT-2 inhibitors
    - Potential reduction in CV mortality/HHF

- **High risk for ASCVD**
  - GLP-1RA
    - Potential reduction in CV mortality and ASCVD
  - Caution in recent HHF

- **DPP-4 inhibitors**
  - Neutral benefit on CV and HHF

- **TZD**
  - Increased risk of HHF

Sharma A. J Am Coll Cardiol HF 2018
Conclusions

• DM increases CV risk and risk of death
• Lifestyle changes are crucial for management
• Empagaflozin is FDA-approved for CVD benefit
• Canagliflozin offers CV benefit in select populations
• Dapagliflozin is currently being investigated for CV outcomes