Cardiovascular Protection by SGLT2 Inhibitors – Possible Mechanisms Circa 2019

Kirkwood F. Adams, Jr. MD
Associate Professor of Medicine and Radiology

HF Management 2019
Amelia Island Meeting
Dramatic Benefits of SGLT2 Inhibitors CV On CV Death and CHF Hospitalization

**FIGURE 1** Comparing and Contrasting the Outcome Benefits in the EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 Trials

A. CV death and HF hospitalization

B. MI and Stroke
The cardiovascular benefits with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) in participants with and without a history of heart failure

**EMPA-REG OUTCOME**
- No history of heart failure: HR 0.63 (0.51, 0.78)
- History of heart failure: HR 0.72 (0.50, 1.04)

**CANVAS Program**
- No history of heart failure: HR 0.87 (0.72, 1.06)
- History of heart failure: HR 0.61 (0.46, 0.80)
SGLT2 Inhibitors – Mechanisms CV Protection

Potential mechanisms:
- blood pressure ↓
- body weight ↓
- arterial stiffness ↓
- cardiac function ↑
- cardiac oxygen demand ↓
- lack of sympathetic nerve activation
- sodium depletion
- oxidative stress ↓
- glucagon secretion ↑
- additional unknown mechanisms

SGLT2 inhibition (Empagliflozin) → EMPA-REG OUTCOME

Reduction of:
- CV death
- overall mortality
- HF hospitalization

Figure 3 Potential mechanisms involved in the reduction of cardiovascular events (cardiovascular death, total mortality, and heart failure hospitalization) observed in the EMPA-REG OUTCOME trial for empagliflozin-treated patients with type 2 diabetes mellitus and prevalent atherosclerotic cardiovascular disease.
SGLT2 inhibitors modulate a range of factors related to CV risk
Based on clinical and mechanistic studies

Fig. 2 Diabetes-associated ventricular remodelling (a) is characterised by left ventricular hypertrophy, inflammation, increased extracellular matrix (ECM) production, impaired cardiac metabolism and cardiomyocyte (CMC) apoptosis. SGLT2 inhibitors may offer salutary effects on several of the fundamental molecular and cellular pathways involved in the development and natural history of cardiac failure in diabetes (as illustrated by a healthy heart in b). © G. Oomen 2018. This figure is available as part of a downloadable slideset.
SGLT2 Inhibitors – Potential Role Blocking the Sodium-Hydrogen Exchanger
SGLT2 Inhibitors – Potential Role of Sodium-Hydrogen Exchanger

Figure 1. NHE-dependent pathways that may underlie the interplay of the pathogenesis of heart failure and diabetes.
SGLT2 inhibition and direct effects on Na+/H+ exchange in the myocardium
Benefits on Renal Outcomes with SGLT2 Inhibitors Emap and Cana
<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Patients (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4645</td>
<td>2323</td>
<td>152</td>
<td>6.3</td>
<td>11.5</td>
<td>31.0</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>179</td>
<td>6.4</td>
<td>10.5</td>
<td>35.6</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>183</td>
<td>4.7</td>
<td>8.6</td>
<td>33.4</td>
</tr>
<tr>
<td>Fixed effects model for atherosclerotic cardiovascular disease (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Patients (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>70</td>
<td>4.1</td>
<td>6.6</td>
<td>29.5</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>182</td>
<td>3.0</td>
<td>5.9</td>
<td>70.5</td>
</tr>
<tr>
<td>Fixed effects model for multiple risk factors (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease.
SGLT2 Inhibitors – Renal Protection – Reduce Decline in eGFR

A Change in eGFR over 192 Wk

Adjusted Mean eGFR (ml/min/1.73 m²)

Week

Baseline  4  12  28  52  66  80  94  108  122  136  150  164  178  192

Empagliflozin, 10 mg
Empagliflozin, 25 mg
Placebo
Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load > 180 g/day

SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

SGLT2 inhibitors improve ventricular loading conditions

© G. Oomen 2018
SGLT2 and Tubular Glomerular Feedback

**Natriuresis**
- Tubuloglomerular feedback
  - $P_{c}$
  - $P_{m}$
  - Proximal
- Contraction of plasma volume
  - Blood pressure
  - Heart failure
  - Direct/indirect effect on vascular function (e.g., endothelial function)
  - Use of diuretic agents
  - NHE3 activity – additional natriuresis?
  - Erythropoietin leading to haematocrit
  - Tubular ischaemia/injury/fibrosis
  - Markers of inflammation
  - Oxidative stress

**Glycosuria**
- HbA1c
- Body weight
- Metabolic risk and microvascular complication risk

**Natriuresis + Glycosuria**
- Proximal solute reabsorption
- Energy requirement/utilisation
- Hypoal in the kidney

Diagram:
- DCT
- Glomerulus
- PCT
- Efferent arteriole
- Loop of Henle
- MH
- $P_{c}$
- $P_{m}$
- Na$^+$
- K$^+$
- Na$^+$
- Gluc
- SGLT2i
- Tubuloglomerular feedback leads to afferent constriction
SGLT2 and Tubular Glomerular Feedback

Normal physiology: 
- Normal TGF 
- Appropriate afferent arteriole tone 
- Normal GFR 
- Normal SGLT2 reabsorption

Hyperfiltration in early stages of diabetic nephropathy: 
- Impaired TGF 
- Elevated GFR 
- Decreased Na⁺ delivery to macula densa 
- Increased Na⁺/glucose reabsorption 
- SGLT2 repression

SGLT2 inhibition reduces hyperfiltration via TGF:
- Restored TGF 
- Normalization of GFR 
- Increased Na⁺ delivery to macula densa 
- Glucosuria 
- SGLT2 inhibition in proximal tubule 
- Afferent arteriole constriction
Potential Renal Benefits SGLT2 Inhibitors

**Suggested mechanisms for cardiorenal protection with SGLT2 inhibition.**

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors
  - Natriuresis
  - Glucosuria
    - Glycemic control
    - Weight loss
  - Tubulo-glomerular feedback
    - Blood pressure lowering
    - Amelioration of volume overload
      - Intraglomerular pressure reduction
        - Renal protection
            - Possible direct renal protection
            - Cardiovascular protection

- Recent results in non-diabetic experimental CKD models
  - ↓ Oxidative stress
  - ↓ Fibrosis induction
  - ↓ Local inflammation
  - ↓ Tubular senescence
  - ↓ Glomerular damage
SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics.

© G. Oomen 2018
Favorable **Out Weighs** Unfavorable Effects of SGLT2 Inhibition

**FIGURE 2** Overview of Described Effects of SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Favorable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of pre-load (diuretic effects)</td>
</tr>
<tr>
<td>Reduction of afterload (blood pressure, arterial stiffness)</td>
</tr>
<tr>
<td>Improvement of mitochondrial efficiency</td>
</tr>
<tr>
<td>Delay of decline in eGFR</td>
</tr>
<tr>
<td>Delay of micro- and macroalbuminuria</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Reduction in epicardial adipose tissue</td>
</tr>
<tr>
<td>Improvement in glycemia</td>
</tr>
<tr>
<td>Reduction in uric acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unfavorable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputations (in particular toe, metatarsal)</td>
</tr>
<tr>
<td>Volume depletion/Hypotension</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Fractures</td>
</tr>
<tr>
<td>Urinary and genital infections</td>
</tr>
</tbody>
</table>

Favorable and unfavorable effects that have been reported for sodium-glucose co-transporter (SGLT2) inhibitors. eGFR = estimated glomerular filtration rate.
Broader Potential for SGLT2 Inhibition – At Risk of CVD

Figure: Cardiorenal benefits of SGLT2i in different patient populations
SGLT2i = sodium-glucose cotransporter-2 inhibitors.
SGLT2 Inhibitors – Mechanisms Renal Protection

SGLT2 Inhibitors

- Blood glucose ↓
  - Hyperinsulinemia ↓
  - Glucagon ↑
  - Lipolysis and hepatic gluconeogenesis
  - Sympathetic outflow to kidneys
- Tubuloglomerular feedback
- Correction of glomerular hyperfiltration
- Correction of glucose handling at proximal tubules
- Glucosuria
  - Osmotic diuresis
- NKCC
  - NHE3
- Renal O2 consumption ↓
  - Improving Epo produce cells
- Hematocrit ↑
- Delivery of O2 and nutrition to kidney
- ECV/blood pressure ↓
- Mild ketosis
  - Improving energy consumption
  - Inflammation ↓
  - Oxidative stress ↓
  - Albuminuria ↓
  - Mesangial expansion
- RAAS ↓

Renoprotection
SGLT2 inhibitors modulate a range of factors related to CV risk

Based on clinical and mechanistic studies

## Summary of CV outcome trials with SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Interventions</th>
<th>EMPA-REG OUTCOME&lt;sup&gt;®1&lt;/sup&gt;</th>
<th>CANVAS&lt;sup&gt;2&lt;/sup&gt;</th>
<th>CANVAS-R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CREDENCE&lt;sup&gt;4&lt;/sup&gt;</th>
<th>DECLARE-TIMI 58&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Ertugliflozin CVOT&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main inclusion criteria</td>
<td>Empagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Dapagliflozin/placebo</td>
<td>Ertugliflozin/placebo</td>
</tr>
<tr>
<td>Est. vascular complications</td>
<td>Est. vascular complications</td>
<td>Est. vascular complications or ≥ 2 CV risk factors</td>
<td>Est. vascular complications or ≥ 2 CV risk factors</td>
<td>Stage 2 or 3 CKD + macroalbuminuria</td>
<td>High risk for CV events</td>
<td>Est. vascular complications</td>
</tr>
<tr>
<td>No. of patients</td>
<td>7034</td>
<td>4339</td>
<td>5700</td>
<td>3627</td>
<td>17,150</td>
<td>3900</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>Progression of albuminuria</td>
<td>4P-MACE + HHF</td>
<td>4P-MACE + HHF + revascularisation</td>
<td>3P-MACE</td>
</tr>
<tr>
<td>Key secondary outcome</td>
<td>4P-MACE</td>
<td>Fasting insulin secretion, progression of albuminuria</td>
<td>Regression of albuminuria, change in eGFR</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
</tr>
<tr>
<td>Target no. of events</td>
<td>691</td>
<td>≥ 420</td>
<td>TBD</td>
<td>TBD</td>
<td>1390</td>
<td>TBD</td>
</tr>
<tr>
<td>Estimated median FU</td>
<td>~3 years</td>
<td>6–7 years</td>
<td>3 years</td>
<td>~4 years</td>
<td>4–5 years</td>
<td>5–7 years</td>
</tr>
</tbody>
</table>

Will report EASD 2015

SGLT2 Inhibitors – Mechanisms CV Protection

- Metabolic
  - ↑ Glucose flux to excretion
  - ↓ Glucose toxicity
  - ↑ Ketones
  - Loss of calories & ↓ body fat mass
    - ↓ Adiposity → ↓ CV risk & contributes to ↓ blood pressure
    - ↓ Vascular dysfunction
    - ↓ Denatured proteins
    - ↓ Oxygen free radicals & oxidative stress
    - ↓ Atherosclerosis
  - ↓ Uric acid
  - Significance for CV risk is unclear

- Hormonal
  - ↑ Glucagon
  - Positive inotropic & chronotropic effects
  - Renin-angiotensin-aldosterone system
    - → Nonclassic pathways (AT₂, AT1-7)
      - Vasodilation
        - Positive inotropic effects
        - ↓ Inflammation
  - Plasma volume

- Hemodynamic
  - ↓ Blood pressure
    - ↓ Arterial stiffness
    - ↓ Pre-load & ↓ after-load
    - Hemo-concentration & ↑ oxygen delivery
      - ↑ Cardiac efficiency

- Other
  - Anti-oxidative, anti-inflammatory, anti-apoptotic effects?
  - Cardiac SGLT1?

- Cardiac protection
SGLT2 Inhibitors – Renal Protection

A Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

B Post Hoc Renal Composite Outcome

Hazard ratio, 0.54 (95% CI, 0.40–0.75)
P<0.001

Death, Renal Replacement, Double SCr
Table IV. Cardiovascular outcome trials with sodium-glucose transporter-2 inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>No. of Patients</th>
<th>Cardiovascular Result</th>
<th>HR (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG^68</td>
<td>7020</td>
<td>Better outcome</td>
<td>0.86 (0.74–0.99)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS^70,71</td>
<td>4330</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CREDENCE^72</td>
<td>4200</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DECLARE-TIMI 58^73</td>
<td>17,000</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>VERTIS^74</td>
<td>8000</td>
<td>Ongoing</td>
<td></td>
</tr>
</tbody>
</table>

CANVAS = Canagliflozin Cardiovascular Assessment Study; CREDENCE = Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58 = Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HR = hazard ratio; VERTIS = Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants.

*For a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
Figure 1—Completed and ongoing CVOTs [6–14,39,44–58]. 3-P, 3-point; 4-P, 4-point; 5-P, 5-point. DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; ESRD, end-stage renal disease; HARMONY Outcomes, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; VERTIS CV, Cardiovascular Outcomes Following Erugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.
Filtered glucose load > 180 g/day

SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

1. Improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function) [7, 20, 21, 30–38]

2. Improvement in cardiac metabolism and bioenergetics [39, 40, 44, 45]


4. Reduction of necrosis and cardiac fibrosis [51, 52, 60]

5. Alteration in adipokines, cytokine production and epicardial adipose tissue mass [55–57]
Cardiovascular protection by SGLT2 inhibitors

Diabetes-associated ventricular remodelling

Healthy heart

Left ventricle hypertrophy

Cytokines and inflammation

ECM remodelling

Impaired cardiac metabolism

CMC apoptosis

SGLT2 inhibitors

© G. Oomen 2018