SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

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View faculty bio at https://www.ashpadvantage.com/t2d/sglt2/

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SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

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Disclosure of Relevant Financial Relationships

Ralph J. Riello III

- Consultant: AstraZeneca Pharmaceuticals, Janssen Pharmaceuticals/Johnson & Johnson, Portola Pharmaceuticals
- Research grant: AstraZeneca Pharmaceuticals

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Learning Objectives

At the conclusion of this activity, participants should be able to

• Describe the impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors on the pathophysiology of cardiorenal disease
• Discuss the clinical effects of SGLT2 inhibition on glycemia, major adverse cardiovascular events, hospitalization for heart failure, and renal endpoints in diabetes
• Summarize the evolving landscape of evidence related to SGLT2 inhibition in patients without diabetes

Various Systems Play a Role in Balancing Blood Glucose Levels in Healthy Individuals¹⁻³

SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

Multiple Defects Contribute to the Pathophysiology of Type 2 Diabetes

- Glucose production
- Glucagon secretion
- Lipolysis
- Glucose reabsorption
- Incretin effect
- Neurotransmitter dysfunction

Chronic Hyperglycemia


Normal Glucose Filtration and Reabsorption in the Kidney

- Glucose Filtration
- Glomerulus
- SGLT2
- SGLT1
- Proximal Tubule
- Distal Tubule
- Loop of Henle
- Collecting Duct
- No/Minimal Glucose Excretion


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SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

Glucose Filtration and Reabsorption in Patient With Type 2 Diabetes¹,²

The Concept of SGLT2 Inhibition: Preventing the Reabsorption of Sodium and Glucose

- SGLT2 inhibition compromises transporter function and reduces renal glucose reabsorption to induce glucosuria in adults with T2D
- The effect of pharmacologic inhibition of SGLT2 is not the same as that of naturally occurring mutations

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SGLT2 inhibitors Reduce Threshold for Glucose Excretion and Maximal Glucose Reabsorption¹⁻³

Normal Range²

<table>
<thead>
<tr>
<th>Plasma glucose (mg/dL)</th>
<th>Rate of glucose filtration/reabsorption/excretion (mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>140</td>
<td>20</td>
</tr>
<tr>
<td>200</td>
<td>30</td>
</tr>
<tr>
<td>280</td>
<td>40</td>
</tr>
<tr>
<td>360</td>
<td>50</td>
</tr>
<tr>
<td>440</td>
<td>60</td>
</tr>
<tr>
<td>520</td>
<td>70</td>
</tr>
<tr>
<td>600</td>
<td>80</td>
</tr>
</tbody>
</table>

Simplified from actual data. For illustrative purposes.

Glucose Filtration and Reabsorption in Patient on SGLT2 inhibition (-flozin)

Glucose Filtration

Proximal Tubule

Glomerulus

SGLT2

SGLT1

Distal Tubule

Loop of Henle

Collecting Duct

Simplified from actual data. For illustrative purposes.

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SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

Available SGLT2 Inhibitors in the U.S. Market

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Canagliflozin&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Empagliflozin&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Ertugliflozin&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>First approved</td>
<td>2014</td>
<td>2013</td>
<td>2014</td>
<td>2017</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>T2D, as an adjunct to diet and exercise to improve glycemic control</td>
<td>1. T2D, as an adjunct to diet and exercise to improve glycemic control</td>
<td>1. T2D, as an adjunct to diet and exercise to improve glycemic control</td>
<td>1. T2D, as an adjunct to diet and exercise to improve glycemic control</td>
</tr>
<tr>
<td>2.</td>
<td>Reduce the risk of hHF in adults with T2D with established CV disease or multiple CV risk factors</td>
<td>2. Reduce the risk of MACE in adults with T2D and established cardiovascular disease</td>
<td>2. Reduce the risk of CV death in adult patients with T2D and established CVD.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Reduce the risk of CV death and hHF in HFrEF (NYHA Class II-IV) patients</td>
<td>3. Reduce the risk of ESKD, doubling of serum creatinine, CV death, and hHF in adults T2D and diabetic nephropathy with albuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>QD; AM dosing</td>
<td>QD; take before 1&lt;sup&gt;st&lt;/sup&gt; meal of day</td>
<td>QD; AM dosing</td>
<td>QD; AM dosing</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;45</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

CV = cardiovascular; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes

<sup>1</sup> Farxiga (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; Revised 05/2020.
<sup>2</sup> Invokana (canagliflozin) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; Revised 08/2020.
<sup>3</sup> Jardiance (empagliflozin) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceutical, Inc; Revised 02/2020.

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# Glucose Control with SGLT2 Inhibitors

## Mean Change in HbA1C from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to Insulin +/- OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HbA1C (%)</td>
<td>8.0</td>
<td>7.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Cana 1</td>
<td>-1.03</td>
<td>-0.93</td>
<td>-0.44</td>
</tr>
<tr>
<td>Dapa 2</td>
<td>-0.89</td>
<td>-0.52</td>
<td>-0.96</td>
</tr>
<tr>
<td>Empa 3</td>
<td>-0.78</td>
<td>-0.77</td>
<td>-1.02</td>
</tr>
</tbody>
</table>

*results for the following dose-groups: canagliflozin 300 mg,dapagliflozin 10 mg,empagliflozin 25 mg; mean change from baseline


## Weight Change with SGLT2 Inhibitors

## Mean Change in Body Weight from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to Insulin +/- OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline weight (kg)</td>
<td>86.9</td>
<td>86.6</td>
<td>90.2</td>
</tr>
<tr>
<td>Cana 1</td>
<td>-3.4</td>
<td>-4.0</td>
<td>-1.4</td>
</tr>
<tr>
<td>Dapa 2</td>
<td>-3.2</td>
<td>-3.2</td>
<td>-1.6</td>
</tr>
<tr>
<td>Empa 3</td>
<td>-2.5</td>
<td>-2.5</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

*results for the following dose-groups: canagliflozin 300 mg, dapagliflozin 10 mg, empagliflozin 25 mg; mean change from baseline

Effects on Blood Pressure with SGLT2 Inhibitors

**Mean Change in Systolic Blood Pressure (SBP) from Baseline***

(Not head-to-head trials)

<table>
<thead>
<tr>
<th>Baseline SBP (mm Hg)</th>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to Insulin +/- OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cana¹</td>
<td>Dapa²</td>
<td>Empa³</td>
</tr>
<tr>
<td>Cana¹</td>
<td>128.5</td>
<td>N/A</td>
<td>129.9</td>
</tr>
<tr>
<td>Add-on to Metformin</td>
<td>130.0</td>
<td>132.8</td>
<td>130.0</td>
</tr>
<tr>
<td>Cana⁷</td>
<td>136.7</td>
<td>140.6</td>
<td>132.9</td>
</tr>
</tbody>
</table>

Results for the following dose-groups: canagliflozin 300 mg, dapagliflozin 10 mg, empagliflozin 25 mg; mean change from baseline


Safety Precautions in the Use of SGLT2 Inhibitors

**Warnings and Precautions**

- **Dapagliflozin¹**: Volume depletion, ketoacidosis in patients with T2D, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier’s Gangrene), genital mycotic infections
- **Canagliflozin²**: Volume depletion, ketoacidosis, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier’s Gangrene), genital mycotic infections, hypersensitivity reactions, bone fracture
- **Empagliflozin³**: Hypotension, ketoacidosis, acute kidney injury and impairment of renal function, urosepsis, pyelonephritis, necrotizing fasciitis of the perineum (Fournier’s Gangrene), genital mycotic infections, hypersensitivity reactions, increased LDL-C
- **Ertugliflozin⁴**: Hypotension, ketoacidosis, acute kidney injury, urosepsis, pyelonephritis, lower limb amputation, hypoglycemia, necrotizing fasciitis of the perineum (Fournier’s Gangrene), genital mycotic infections

**Most Common AEs**

- Female genital mycotic infections, nasopharyngitis, urinary tract infections
- Female genital mycotic infections, urinary tract infections, increased urination
- Urinary tract infections and female genital mycotic infections
- Female genital mycotic infections

AE = adverse event; AKI = acute kidney injury; LDL-C = low-density lipoprotein cholesterol; US = United States

SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

Expanding Therapeutic Areas for Treatment with SGLT2 Inhibitors

2015
- EMPA-REG<sup>n=7,020</sup>
- 3-P MACE

2016
- CANVAS Program<sup>n=50,142</sup>
- 3-P MACE

2017
- CREDENCE<sup>*</sup><sup>n=4,464</sup>
- CV death or HF
- HF

2018
- DECLARE-TIMI<sup>58</sup>
- n=17,278
- 3-P MACE; CV death + HF
- VERTIS-CV
- n=8,246
- 3-P MACE

2019
- EMPEROR-Reduced<sup>n=9,730</sup>
- CV death or HF
- DELIVER
- n=6,100
- CV death, HF, urgent HF visit

2020
- EMPEROR-Preserved<sup>n=8,128</sup>
- CV death or HF

2021
- DAPA-HF<sup>n=4,744</sup>
- CV death, HF, urgent HF visit

2022
- EMPA-KIDNEY<sup>n=4,000</sup>
- ESKD, renal death, >40% sustained decline in eGFR, or CV death

All of the following metabolic effects of SGLT2 inhibitors are correct EXCEPT

a. Decrease HbA1c by 0.8-1.0%
b. Lower body weight by 2.5-3.0 kg
c. Decrease LDL-C by 3-10 mg/dL
d. Reduce systolic blood pressure by 3-5 mm Hg

* CREDENCE evaluated patients with diabetic kidney disease. CANVAS was performed per 2008 FDA published guidance to evaluate cardiovascular risk in the treatment of type 2 diabetes.

ACE = acetylcholine esterase; CKD = chronic kidney disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GLP-1 = glucagon-like peptide-1; HF = heart failure; HFHF = hospitalization for HF; MACE = major adverse cardiovascular events; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter 2; ESKD = end stage kidney disease

Review of CVOTs with SGLT2 Inhibitors

Overview of the Study Designs of SGLT2 Inhibitors CVOTs

<table>
<thead>
<tr>
<th>STUDY</th>
<th>EMPA-REG Outcome (1)</th>
<th>CANVAS Program (CANA &amp; CANVAS-R) (2-4)</th>
<th>DECLARE (5,6)</th>
<th>VERTIS CV (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions (randomization)</td>
<td>EMPA/PBO (2:1)</td>
<td>CANA 100/300 mg or PBO (1:1)</td>
<td>DAPA/PBO (1:1)</td>
<td>ERTU 5/15 mg/PBO (1:1)</td>
</tr>
<tr>
<td>Patient Enrollment</td>
<td>7,028</td>
<td>10,142</td>
<td>17,160</td>
<td>8,246</td>
</tr>
<tr>
<td>Key Inclusion Criteria</td>
<td>• Established vascular complications</td>
<td>• Established vascular complications (age ≥30 years) or ≥2 CV risk factors (age ≥50 years)</td>
<td>• Established CVD or multiple CV risk factors</td>
<td>• Established vascular ASCVD</td>
</tr>
<tr>
<td></td>
<td>• HbA1C 7.0–10.0%</td>
<td>• HbA1C 7.0–10.5%</td>
<td>• HbA1C 6.5–12%</td>
<td>• HbA1C 7.0–10.5%</td>
</tr>
<tr>
<td></td>
<td>• Age ≥18 years</td>
<td>• eGFR &gt;30 ml/min/1.73 m²</td>
<td>• Age ≥40 years</td>
<td>• Age ≥40 years</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>CV death, non-fatal MI, non-fatal stroke</td>
<td>CV death, non-fatal MI, non-fatal stroke</td>
<td>CV death, MI, or ischemic stroke</td>
<td>CV death, non-fatal MI, non-fatal stroke</td>
</tr>
<tr>
<td>Secondary Endpoints Include</td>
<td>4P-MACE; 3P-MACE + hospitalization for UA, HHF, microvascular composite, microalbuminuria</td>
<td>Death from any cause, CV death, progression of albuminuria, composite end point of CV death or HHF</td>
<td>Renal composite end point: confirmed sustained ≥40% decrease in eGFR to eGFR &lt;60 ml/min/1.73 m² and/or ESRD and/or renal or CV death</td>
<td>CV death/HHF, CV death, Renal composite (renal death, dialysis/ transplant, doubling of serum creatinine)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>3.1 years</td>
<td>2.4 years</td>
<td>4.2 years</td>
<td>5.7 years</td>
</tr>
<tr>
<td>Target number of events</td>
<td>691</td>
<td>688</td>
<td>1,390</td>
<td>939</td>
</tr>
<tr>
<td>Status</td>
<td>Completed 2015</td>
<td>Completed 2017</td>
<td>Completed 2018</td>
<td>Completed 2020</td>
</tr>
</tbody>
</table>

This chart does not imply comparable or superior efficacy/safety profiles. Each study was placebo-controlled and no direct comparisons to other SGLT2 inhibitor were included. Please refer to study publications and ClinicalTrials.gov for additional information. SCORED (sotagliflozin) not included due to lack of published study baseline data.

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SGLT2 Inhibitors Cardiovascular Outcomes Trials: Percentage of Patients With and Without CVD

- EMPA-REG¹: <1%
- CANVAS Program² ³: ~34%
- DECLARE⁴: ~41%
- VERTIS CV⁵: <1%

Patients without CVD (with multiple CV risk factors)

Patients with ECVD

In the general T2D population, only 20% of patients have established CVD⁶

* Included age ≥55 for men and ≥60 for women, T2D, and at least 1 additional risk factor: dyslipidemia, HTN, or tobacco use.
† Included age ≥50 with T2D and 2 or more additional risk factors: T2D >10 years, HTN, tobacco use, high-density lipoprotein <39 mg/dL, albuminuria.
This chart does not imply comparable or superior efficacy/safety profiles. Each study was placebo controlled, and no direct comparisons to other SGLT2 inhibitors were included. Please refer to study publications and ClinicalTrials.gov for additional information. SCORED (sotagliflozin) is not included due to lack of published study baseline data.

CVD = cardiovascular disease; ECVD = established cardiovascular disease; HDL = high-density lipoprotein; HTN = hypertension; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes


A View Across the CVOTs.....

<table>
<thead>
<tr>
<th></th>
<th>MACE HR (95% CI)</th>
<th>CV Death HR (95% CI)</th>
<th>hHF HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME¹</td>
<td>0.86 (0.74-0.99)</td>
<td>0.62 (0.49-0.77)</td>
<td>0.65 (0.50-0.85)</td>
</tr>
<tr>
<td>CANVAS PROGRAM²</td>
<td>0.86 (0.75-0.97)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58³</td>
<td>0.93 (0.84-1.03)</td>
<td>0.98 (0.82-1.17)</td>
<td>0.73 (0.61-0.88)</td>
</tr>
<tr>
<td>VERTIS CV⁵</td>
<td>0.97 (0.85-1.11)</td>
<td>0.92 (0.77-1.11)</td>
<td>0.70 (0.54-0.90)</td>
</tr>
</tbody>
</table>


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hHF Outcomes in SGLT2 Inhibitors CV Outcomes Trials

**EMPA-REG Outcome**
- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- Placebo
- Empagliflozin

**CANVAS Program**
- Hazard ratio, 0.67 (95% CI, 0.52–0.87)
- Placebo
- Canagliflozin

**DECLARE-TIMI 58**
- Hazard ratio, 0.73 (95% CI, 0.61–0.88)
- Placebo
- Dapagliflozin

**VERTIS CV**
- HR, 0.70 (95% CI, 0.54, 0.90)
- Placebo
- Ertugliflozin

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T2D and HF Often Intersect

- 30.3 million in the United States
- 6.5 million

- 10%–47% of people with HF have T2D
- 9%–22% of people with T2D have HF
- 2- to 4-fold increased risk for HF in T2D


CV Outcomes in Diabetic and Non-diabetic Patients

Patients with T2D were at increased risk of CV events and death, regardless of EF

CV = cardiovascular; EF = ejection fraction; T2D = type 2 diabetes
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**T2D Increases Risk of HF Through Multiple Pathways**

**Diabetes**

- Hyperglycemia, insulin resistance, hyperinsulinemia
  - Inflammation
  - Dyslipidemia
  - Endothelial dysfunction

**CAD**

- Cardiomyocyte hypertrophy/LVH

**RAAS activation**

- Fatty acid utilization
- Formation of AGEs

**Automatic dysfunction**

- Calcium handling

**Fibrosis**

**Diabetic cardiomyopathy**

**Heart failure in diabetes**

- MI, CVA, PAD
- Heart failure
- Kidney disease

**SGLT2 Inhibitor Trials: A Rethink on Diabetes to Pathways of CV Disease**

**Traditional focus**

Type 2 Diabetes

- Obesity

- Insulin
- Renal SGLT2 expression
- Glomerular hyperfiltration
- Tubuloglomerular feedback
- Other mechanisms?

- Lipids
- Glucose
- Blood pressure
- Thrombotic tendency
- Endothelial dysfunctions

**Accelerated atherogenesis**

**Volume status/ hemodynamic and glomerular stress**

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Evidence Supports Glycemic and Nonglycemic Effects of SGLT2 Inhibitor

SGLT2 inhibitors are not indicated for weight loss or hypertension.


Potential mechanisms by which SGLT2 inhibition reduces risk for heart failure hospitalization are not fully understood and basic research is ongoing.

Do SGLT2 Inhibitors Offer Benefits in the Treatment of Patients with HFrEF?1-5

<table>
<thead>
<tr>
<th>DAPA-HF6 (Dapagliflozin)</th>
<th>EMPEROR-Reduced7 (Empagliflozin)</th>
<th>SOLOIST-WHF8 (Sotagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study size, n</strong></td>
<td>4,744 (actual)</td>
<td>3,730 (actual)</td>
</tr>
<tr>
<td><strong>Key inclusion criteria:</strong></td>
<td><strong>HF status</strong></td>
<td><strong>HF status</strong></td>
</tr>
<tr>
<td>Age ≥18 years</td>
<td>NYHA Class II–IV or LVEF ≤40%</td>
<td>Age ≥18 years</td>
</tr>
<tr>
<td>eGFR ≥90 ml/min/1.73 m²</td>
<td>LVEF ≤40% within last 12 mo</td>
<td>eGFR ≥90 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Key exclusion criteria:</td>
<td>Elevated NT-proBNP</td>
<td>Elevated NT-proBNP</td>
</tr>
<tr>
<td>With or without T2D</td>
<td>Optimized/stable HF therapy ≥24 wk</td>
<td>Time to first occurrence of CV death or hHF in patients with LVEF &gt;50% should be on beta-blocker or RAAS inhibitor</td>
</tr>
<tr>
<td>T1D</td>
<td>MI, UA, stroke, TIA, or CV procedure/surgery within 12 wk</td>
<td>MI, CABG, other major CV surgery, stroke, or TIA within 90 d</td>
</tr>
<tr>
<td>Acute decompensated HF</td>
<td>SBP ≥130 mm Hg or symptomatic hypotension</td>
<td>Acute decompensated HF</td>
</tr>
<tr>
<td>SBP ≥180 mm Hg or symptomatic hypotension</td>
<td>Recent treatment/intolerance to SGLT2 inhibitor</td>
<td>SBP ≤180 or &lt;100 mm Hg or symptomatic hypotension</td>
</tr>
</tbody>
</table>

**Primary endpoint**
- Time to first occurrence of any component of the composite of a worsening HF event (HF/HF or urgent HF visit) or CV death
- Time to first occurrence of any component of the composite of CV death or hHF

**Completion Date**
- July 17, 2019 (actual) – positive TLR, ESC 2019
- July 2020 (actual) – positive TLR, ESC 2020
- January 2021 (TBD, AHA 2020) – closed early

*Based on the Chronic Kidney Disease-Epidemiology Collaboration Equation. **T2D years in Japan.

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**DAPA-HF**

First and Largest SGLT2 Inhibitor HFrEF Trial to Successfully Improve Outcomes and Symptoms

**DAPA-HF Overview**

- **N=4744**
- 45% T2D
- 55% No T2D

**Inclusion Criteria:**
- ≥18 years with or without T2D,
- LVEF ≤40%, NYHA class II-IV, elevated NT-proBNP,
- eGFR ≥30 mL/min/1.73 m², stable SoC HFrEF treatment

**DAPA-HF Safety**

- DAPA was well-tolerated in patients with and without T2D
- Adverse events rarely led to discontinuation of treatment
- No events of major hypoglycemia or DKA in patients without T2D

**Significant Reduction in Composite of CV Death or Worsening HF**

- 26% RRR
- HR 0.74 (0.65-0.85)
- p<0.001
- NNT=21

**CV Death**

- 18% RRR
- p=0.029

**hHF**

- 30% RRR
- p=0.00003

**Consistent Benefit Across a Broad and Representative Population**

- T2D/No T2D
- Baseline LVEF
- Background HF therapy
- Diuretic use and dose
- eGFR

**Risk of both first and recurrent hHF events**

- (p=0.022)

**HF symptom improvement**

- more common and deterioration less common

**Significantly reduced risk of CV death or worsening HF**

- as early as

**More data to come in various types of HF trials...**

**Dapagliflozin is the only SGLT2 Inhibitor approved for HFrEF**

---

**EMPEROR-REDUCED**

Second SGLT2 Inhibitor HFrEF Trial to Successfully Improve Outcomes and Symptoms – Class Effect?

**EMPEROR-REDUCED Overview**

- **N=3,730**
- 49.8% T2D
- 50.2% No T2D

**Inclusion Criteria:**
- ≥18 years of age, with or without diabetes who had chronic HFrEF with LVEF ≤40% (NYHA class II–IV) for ≥3 months, Elevated NT-proBNP, Stable SoC HFrEF treatment

**EMPEROR-Reduced Safety**

- EMPA is well-tolerated in patients with and without T2D
- No events of major hypoglycemia or DKA in patients without T2D

**Significant Reduction in Composite of CV Death or First hHF**

- 25% RRR
- HR 0.75 (0.65–0.86)
- P<0.001
- NNT=19

**CV Death**

- 6% RRR
- p=0.002

**First hHF**

- 31% RRR

**Consistent Benefit Across a Broad and Representative Population**

- T2D/No T2D
- baseline LVEF
- Background HF therapy
- NT-proBNP

**Risk of both first and recurrent hHF events**

- HR = 0.70 (0.58–0.85)

**HF symptom improvement**

- more common and deterioration less common

**Significantly reduced risk of composite renal endpoint**

- HR 0.50 (0.32–0.77)

---

*CV = cardiovascular; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

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**Meta-Analysis of DAPA-HF and EMPEROR-Reduced**

### All-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>249/1863 (13.4%)</td>
<td>0.92 (0.77–1.10)</td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>276/2373 (11.6%)</td>
<td>0.83 (0.71–0.97)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.87 (0.77–0.98)</td>
</tr>
</tbody>
</table>

Test for overall treatment effect *p*=0.018  
Test for heterogeneity of effect *p*=0.39

### Cardiovascular death

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>187/1863 (10.0%)</td>
<td>0.92 (0.75–1.12)</td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>227/2373 (9.6%)</td>
<td>0.82 (0.69–0.98)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.86 (0.76–0.98)</td>
</tr>
</tbody>
</table>

Test for overall treatment effect *p*=0.027  
Test for heterogeneity of effect *p*=0.40


**Positive HFrEF Trials 2001 and beyond:**

SGLT2 inhibitors are now a pillar in HFrEF treatment

1. Rate vs. rhythm control in atrial fibrillation (AF)  
2. Exercise prescription

*Angiotensin receptor blocker (ARB); **Implantable cardioverter defibrillator/cardiac resynchronization therapy (ICD/CRT).  
Which of the following SGLT2 inhibitors has been shown to improve overall mortality in HFrEF patients independent of diabetes?

a. Canagliflozin
b. Dapagliflozin
c. Empagliflozin
d. Sotagliflozin

SGLT2 Inhibitors and CKD
Long-Term Progression of Kidney Disease in Patients with T2D\(^1,2\)

United Kingdom Prospective Diabetes Study (UKPDS)\(^1\)
5102 patients with T2D*

- **Normoalbuminuria**
  - Progressed from normo- to microalbuminuria per year: 2.8%
  - Progressed from micro- to macroalbuminuria per year: 2%

- **Microalbuminuria**
  - Progressed from normo- to microalbuminuria per year: 2.8%

- **Macroalbuminuria**
  - Progressed from micro- to macroalbuminuria per year: 28%

*The UKPDS enrolled patients with newly diagnosed T2D; \(\dagger\) Defined as a urinary albumin concentration 50–299 mg/L; \(\ddagger\) Defined as a urinary albumin concentration \(\geq 300\) mg/L; \(\mathsection\) Defined as urinary albumin concentration \(\geq 50\) mg/L.


A substantial proportion of patients with T2D will develop albuminuria and renal impairment.

Potential Effects by which SGLT2 Inhibition Improves Renal Outcomes

- **SGLT2 INHIBITION**
  - Reduce Glomerular Pressure\(^1\)
  - ↑Afferent vasoconstriction
  - ↓Glomerular hyperfiltration
  - Neurohormonal Improvement
  - ↓Intrarenal RAAS activity\(^2\)
  - ↓SNS activity\(^4\)
  - Inflammation/Fibrosis Reductions\(^1,2\)
  - ↓Inflammatory markers
  - ↓Fibrotic markers
  - Decreased Renal Workload and Hypoxia\(^1,2\)
  - ↓Solute transport
  - ↓Oxygen demand

- **CLINICAL EFFECTS**
  - Protection Against Diabetic Nephropathy\(^1,2\)
  - Stabilization of eGFR\(^2\)
  - ↓Blood Pressure\(^1\)
  - ↓Tubular/Glomerular Injury\(^1,2\)
  - ↓Albuminuria
  - ↓Renal Ischemic Injury\(^1\)
  - ↓Hb/hematocrit\(^2\)

*Note: eGFR = estimated glomerular filtration rate; Hb = hemoglobin; RAAS = renin-angiotensin-aldosterone system; SGLT2 = sodium-glucose cotransporter 2; SNS = sympathetic nervous system*

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Meta-Analyses of T2D Treatments in the U.S.: Kidney Outcomes by ASCVD Status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. / total No.</th>
<th>Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
<th>Favors treatment</th>
<th>Favors placebo</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-KIDNEY&lt;sup&gt;5&lt;/sup&gt;</td>
<td>N ~ 6000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS program</td>
<td>NA/3756</td>
<td>4.4</td>
<td>0.63 (0.39-1.02)</td>
<td></td>
<td>1.20</td>
<td>15.72</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>62/5108</td>
<td>3.0</td>
<td>0.51 (0.37-0.69)</td>
<td></td>
<td>1.33</td>
<td>37.41</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>84/1089</td>
<td>29.9</td>
<td>0.68 (0.51-0.89)</td>
<td></td>
<td>1.64</td>
<td>46.87</td>
</tr>
</tbody>
</table>

Fixed-effects model (Q = 1.86; df = 4; P = 0.60; I² = 0%) 0.60 (0.50-0.73)

Patients without ASCVD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. / total No.</th>
<th>Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
<th>Favors treatment</th>
<th>Favors placebo</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDENCE</td>
<td>69/1113</td>
<td>24.1</td>
<td>0.68 (0.51-0.89)</td>
<td></td>
<td>1.64</td>
<td>46.87</td>
</tr>
</tbody>
</table>

Fixed-effects model (Q = 34.4%; df = 3; P = 0.0%) 0.64 (0.56-0.72)

Key Renal Outcome Trials: Do SGLT2 Inhibitors Offer Benefit in Patients with CKD?

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDENCE&lt;sup&gt;1&lt;/sup&gt; N = 4401</td>
<td>DAPA-CKO&lt;sup&gt;4&lt;/sup&gt; N = 4304</td>
</tr>
</tbody>
</table>

Status

- Completed October 2018
- Stopped early due to overwhelming efficacy in March 2020 (presented at ESC 2020)
- Ongoing Est. Completion Date June 2022
- Completed April 2020

Intervention

- EMPA-KIDNEY: Empagliflozin vs Placebo
- CANVAS program: Canagliflozin vs Placebo
- DECLARE-TIMI 58: Dapagliflozin vs Placebo

Patient Population

- T2D
- eGFR ≥ 90 mL/min/1.73 m²
- UACR ≥ 5000 mg/g
- UACR ≥ 57% sustained eGFR decline, kidney failure, or renal death

Primary Endpoint

- Composite: doubling of serum creatinine
- ESKD
- Renal or CV death

Secondary Endpoints

- Composite: eGFR ≥ 25 to <60 mL/min/1.73 m²
- eGFR ≥ 25 to <90 mL/min/1.73 m² and UACR ≥ 300 mg/g
- ≥ 40% sustained eGFR decline, kidney failure, or renal death
- ≥ 40% sustained eGFR decline
- Renal death

ADCA = atherosclerotic cardiovascular disease; 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-KIDNEY = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Patients; NA = not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Participants With Vascular Disease; ASCVD = atherosclerotic cardiovascular disease; T2D = type 2 diabetes; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes; UA = urinary albumin; UAICR = urine albumin to creatinine ratio.

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SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

**CREDENCE** Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

**Patients:**
- ≥18 years of age
- T2D with HbA1c ≥ 6.5%
- Median follow-up: 2.62 years
- Baseline Characteristics:
  - 50% ≥ 75
- ≥18 years of age
- UACR 200 to 5000 mg/g
- ≥18 years of age

**Key Exclusion Criteria**
- History of DKA or T1D, history of hereditary glucose-galactose malabsorption or primary renal glucosuria, treatment with immunosuppressive therapy, liver disease, NYHA Class IV HF, K+ > 5.5 mmol/L
- T1D, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, immunosuppressive therapy ≤6 months prior to enrollment
- End-stage kidney disease, doubling of serum creatinine level, or renal death.

**DAPA-CKD** Overview

**Patients:**
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73 m²
- Baseline Characteristics:
  - 50% ≥ 75
- ≥18 years of age
- UACR 200 to 5000 mg/g
- ≥18 years of age

**Key Exclusion Criteria**
- History of DKA or T1D, history of hereditary glucose-galactose malabsorption or primary renal glucosuria, treatment with immunosuppressive therapy, liver disease, NYHA Class IV HF, K+ > 5.5 mmol/L
- T1D, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, immunosuppressive therapy ≤6 months prior to enrollment
- End-stage kidney disease, doubling of serum creatinine level, or renal death.

**The first trial with a SGLT2 inhibitor to demonstrate an improvement in cardiorenal outcomes and reduce mortality in patients with CKD with or without T2D**

**Participants:**
- N=2202
- N=2199
- Median follow-up: 2.4 years
- Baseline Characteristics:
  - 50% ≥ 75
- ≥18 years of age
- UACR 200 to 5000 mg/g
- ≥18 years of age

**Key Exclusion Criteria**
- History of DKA or T1D, history of hereditary glucose-galactose malabsorption or primary renal glucosuria, treatment with immunosuppressive therapy, liver disease, NYHA Class IV HF, K+ > 5.5 mmol/L
- T1D, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, immunosuppressive therapy ≤6 months prior to enrollment
- End-stage kidney disease, doubling of serum creatinine level, or renal death.

**Safety**
- Fractures: 4.0% vs. 3.2%
- Any SAE due to trial drug: 2.8% vs. 1.9%
- Major hypoglycemia: 0.7% vs. 1.3%
- Amputation: 1.6% vs. 1.8%
- Any SAE: 29.5% vs. 33.9%

**Primary Composite Outcome**
- HR 0.64 (0.52, 0.79)
- 31% RRR in patients with T2D
- HR 0.69 (0.53, 0.88)
- 39% RRR in patients without T2D

**Baseline Characteristics**
- Mean age 62 years
- Mean eGFR 43 mL/min/1.73 m²
- Mean UACR 949 mg/g

**Trial Drug**
- Canagliflozin 100 mg once daily
- Placebo once daily

**Placebo**
- Baseline Characteristics:
  - Mean age 63 years
  - Mean eGFR 56 mL/min/1.73 m²
  - Mean UACR 927 mg/g

**Significant reduction in composite of ESKD, doubling of serum Cr, renal or CV death**

**SAE**
- Volume depletion: 5.9% vs. 4.2%
- Fracture: 4.0% vs. 3.2%
- Any SAE: 29.5% vs. 33.9%

**34% RRR in renal specific outcome**
- HR 0.69 (0.53-0.83); P=0.001

**17% RRR in all-cause mortality**
- HR 0.83 (0.68-1.02)

**44% RRR in composite outcome of sustained 30% eGFR decline, ESKD, renal or CV death**
- HR 0.56 (0.45, 0.72)

**NNT=23**

**NNT=19**

SGLT2 Inhibitors: A Dynamic and Evolving Therapeutic Option

EMPA-KIDNEY: The Study of Heart and Kidney Protection with Empagliflozin

- 6000 patients
  - ≥18 years of age
  - Evidence of CKD at risk of progression defined by CKD-EPI eGFR ≥20 to <45 mL/min/1.73 m² OR CKD-EPI eGFR ≥45 to <90 mL/min/1.73 m² with UACR ≥200 mg/g
  - Clinically appropriate doses of ACEi/ARB unless not tolerant to treatment

Primary Endpoint
- Composite: Time to first occurrence of kidney disease progression* or CV death

Secondary Endpoints
- Time to first hHF or CV death
- Time to occurrences of all-cause hospitalizations (first and recurrent combined)
- Time to death from any cause
- Time to first occurrence of kidney disease progression
- Time to CV death
- Time to CV or ESKD

Empagliflozin 10 mg daily

Placebo

Median follow-up: 3.1 years

All of the following statements regarding the impact of SGLT2 inhibitors on renal function are true EXCEPT

a. Consistently reduce composite worsening nephropathy risk in diabetes by ≥24%
b. Initially decrease eGFR, but delay overall progression of diabetic nephropathy
c. Contraindicated if eGFR <30 mL/min/1.73 m² for safety concerns
d. Improve cardiorenal outcomes in patients with and without type 2 diabetes

*Defined as ESKD, a sustained decline in eGFR to <15 mL/min/1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization. Study NCT03594110. ClinicalTrials.gov website

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### Phase 3 Mortality/Morbidity Trials with SGLT2 Inhibitors in HFpEF

Both trials include patients with and without T2D

<table>
<thead>
<tr>
<th><strong>Hypothesis</strong></th>
<th><strong>EMPEROR-Preserved</strong></th>
<th><strong>Hypothesis</strong></th>
<th><strong>DELIVER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with and without diabetes)</td>
<td></td>
<td>Dapagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with and without diabetes)</td>
<td></td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>5987 patients; symptomatic HF; EF &gt;40%; NT pro BNP &gt;300 pg/mL (&gt;900 pg/mL for patients with AF); structural heart disease or HF hospitalization in prior 12 months.</td>
<td>6100 patients; symptomatic HF: outpatient or inpatient/recently discharged; EF &gt;40%; structural heart disease; NT-proBNP ≥300 pg/L; eGFR ≥30 mL/min/1.73 m²; SBP ≥95 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>CV death or HF hospitalization</td>
<td>CV death or worsening HF event</td>
<td></td>
</tr>
</tbody>
</table>

1. ClinicalTrials.gov Identifier: NCT03057951; 2. ClinicalTrials.gov Identifier: NCT03418213
**SGTL2 Inhibitor Being Formally Evaluated Among Patients After Myocardial Infarction (MI)**

**DAPA-MI**
Dapagliflozin effects in patients without diabetes with Myocardial Infarction
- Dapagliflozin vs. placebo
  - Risk reduction for hHF and CV-related death post-MI
- Acute MI without T2D
- N ~6,400; 100 sites in Sweden and UK
- Two national CV disease quality registries
- Global, multicenter, double-blind, registry-based RCT

**EMPACT-MI**
Empagliflozin for the prevention of chronic heart failure and mortality after an acute Myocardial Infarction
- Empagliflozin vs. placebo
- Acute MI
- N ~3,300; >16 countries

---

**Summary**

SGLT2 Inhibitors Are a Dynamic and Evolving Therapeutic Option for Cardiorenal Protection

- **Heart**
  - ↓Cardiac preload/afterload
  - ↓Cardiac wall stress
  - ↑Cardiac efficiency/output

- **Circulation**
  - ↓Plasma volume
  - ↓Arterial stiffness
  - ↓Systolic blood pressure
  - ↑Hematocrit

- **Kidney**
  - ↓Glucose/sodium reabsorption
  - ↓Intraglomerular pressure
  - ↓Intrarenal RAAS activity
  - ↓Hyperfiltration
  - ↓Inflammation/hypoxia
  - ↓Cardiac preload/afterload
  - ↓Cardiac function
  - ↑Renal function

**Improve Clinical Outcomes**
- ↓CV outcomes
- ↓HF hospitalisation
- Stabilisation of eGFR
- ↓Albuminuria

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