Goal-Directed Medical Therapies (GDMT) for Patients with Diabetic Kidney Disease and Beyond

September 29, 2020
Support of the Diabetic Kidney Disease Collaborative is provided by Bayer, Boehringer Ingelheim and Lilly, AstraZeneca, and Janssen Pharmaceuticals, Inc.
Welcome & Opening Remarks

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Consultant Nephrologist
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Disclosures

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Consultancy Agreements: Johnson and Johnson/ Jansen; Reata; Amgen; Astra Zeneca; Boehringer-Ingelheim
Ownership Interest:
Research Funding: Ortho Biotech; Johnson and Johnson, ; Kidney Foundation of Canada, Canadian Institute of Health Research; Otsuka; Astra Zeneca; Merck;; Janssen; Oxford Clinical Trials, Astra Zeneca; Boehringer-Ingelheim; Otsuka; NIH; NIDDK
Honoraria:
Patents and Inventions:
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Speakers Bureau:
Other Interests/Relationships:
Goal Directed Medical Therapies for Patients with Diabetic Kidney Disease and Beyond

Diabetic Kidney Disease Strategy Conference: Implementing New Diabetic Kidney Disease Treatments
- Time for Nephrologists to Act
January 2020 (the ‘beforetime’)
January 2020 (the ‘beforetime’) 

Diabetic Kidney Disease Strategy Conference: Implementing New Diabetic Kidney Disease Treatments - Time for Nephrologists to Act

• 1 day meeting: Patients, Regulators, Clinicians researchers
• New Therapies: SGLT2i, GLP 1 Receptor Agonists
• Challenges in implementation and Perspectives
• Panel discussion and break out groups
Overview of current state

Context of Executive Order
  - improve outcomes of patients with CKDs

New therapies offering hope

Challenges in implementation

Continued imperative to ensure patients receive best care and how to enable this
Now….September 2020

• What is the Standard of Care for DKD
  – Dr K Tuttle
• Safety and Effectively Prescribing SGLT2i
  – Dr D Cherney
• Paying for New Therapies:
  – Dr C Argyropoulos
• DAPA-CKD Study
  – Prof H Heerspink
• EMPEROR Reduced Study
  – Dr M Packer
The Standard-of-Care for Diabetic Kidney Disease

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Disclosures

**Employer:** Providence Health Care, University of Washington School of Medicine

**Consultancy Agreements:** Eli Lilly; Boehringer Ingelheim; Gilead; AstraZeneca; Goldfinch Bio, Novo Nordisk

**Ownership Interest:**

**Research Funding:** Goldfinch Bio; Bayer

**Honoraria:**

**Patents and Inventions:**

**Scientific Advisor or Membership:** CJASN, NIDDK, Kidney Health Initiative

**Speakers Bureau:**

**Other Interests/Relationships:**
Consultant on therapeutics for diabetes and kidney disease:
- Eli Lilly and Company
- Boehringer Ingelheim
- Gilead
- Astra Zeneca
- Goldfinch Bio
- Novo Nordisk
- Bayer
Consultant on therapeutics for diabetes and kidney disease:
• Eli Lilly and Company
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• Astra Zeneca
• Goldfinch Bio
• Novo Nordisk
• Bayer
Objectives

• Review the current standard-of-care for diabetic kidney disease (DKD).
• Recognize importance of dissemination and implementation of recommended therapies for DKD.
Diabetes and Hypertension
The Most Common Causes of CKD Worldwide

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016

- **Diabetes**: 42%
- **Glomerulonephritis**: 18%
- **Hypertension**: 18%
- **Other**: 22%

~476 MILLION adults are living with diabetes²

of whom ~40% will develop CKD¹

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CKD, chronic kidney disease

Number of People (20-79 years) with Diabetes by Region

- **North America & Caribbean**
  - 2019: 48 million
  - 2030: 56 million
  - 2045: 63 million
  - Increase: 33%

- **South & Central America**
  - 2019: 32 million
  - 2030: 40 million
  - 2045: 49 million
  - Increase: 55%

- **Africa**
  - 2019: 19 million
  - 2030: 29 million
  - 2045: 47 million
  - Increase: 143%

- **Middle East & North Africa**
  - 2019: 55 million
  - 2030: 76 million
  - 2045: 108 million
  - Increase: 96%

- **Europe**
  - 2019: 59 million
  - 2030: 66 million
  - 2045: 68 million
  - Increase: 15%

- **South-East Asia**
  - 2019: 88 million
  - 2030: 115 million
  - 2045: 153 million
  - Increase: 74%

- **Western Pacific**
  - 2019: 163 million
  - 2030: 197 million
  - 2045: 212 million
  - Increase: 31%
Diabetic Kidney Disease Risks

• Progress to ESKD (10 %).
  • Dialysis
  • Kidney transplant

• Die of other causes without reaching ESKD (90 %).
  • CVD 1/2
  • Infections 1/3

Alicic RZ, Rooney MT, Tuttle KR. CJASN 2017;12:2032-2045
Angiotensin Receptor Blockade in Type 2 Diabetes and CKD

Doubling of serum creatinine, ESKD, or death

RENAAL

Absolute residual risk with losartan: ~40%

Risk reduction, 16%
$P=0.02$

IDNT

Absolute residual risk with irbesartan: ~40%

Risk reduction, 20%
$P=0.02$


Medication Use in CKD Stages 3-5 ND
Two Large US Healthcare Systems (N=660,000)

Diabetes with CKD and hypertension: ACE Inhibitor or ARB use 25%

Tuttle KR et al. JAMA Netw Open 2019;2:e1918169
Providence St. Joseph Health and UCLA Health
SGLT2 Inhibitors
Cardiovascular Outcome Trials in Type 2 Diabetes

• Reduce risk of major adverse CVD Events.
  • 3-point MACE (myocardial infarction, stroke, CVD death)
  • Heart failure (empagliflozin, canagliflozin, dapagliflozin)
  • CVD death (empagliflozin, dapagliflozin)

• Decrease macroalbuminuria, decline in eGFR, and ESKD.

• CVD and CKD benefits are present in patients with pre-existing CKD.
Class Effect of SGLT2 Inhibitors on CKD Outcomes


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**EMPA-REG OUTCOME**

HR: 0.54 (95% CI: 0.40, 0.75); *P*<0.001

**DECLARE-TIMI 58**

HR: 0.53 (95% CI: 0.43, 0.66); *P*<0.0001

**CREDENCE**

HR: 0.66 (95% CI: 0.53, 0.81); *P*<0.001

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The composite kidney disease endpoint was defined as: dSCr accompanied by eGFR ≤45 mL/min/1.73 m², RRT, or kidney death; 40% reduction in eGFR, RRT, or death from kidney causes; eGFR decrease ≥40% to <60 mL/min/1.73 m², ESKD or kidney death; ESRD, dSCr, or kidney death.
**Comprehensive Care in Patients with Diabetes and CKD**

**Practice Point 1.1.1:** Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.
ANTIHYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Lifestyle therapy

First-line therapy

Metformin
- eGFR < 45
  - Reduce dose
- eGFR < 30
  - Discontinue
- Kidney failure
  - Discontinue

SGLT-2 inhibitor
- eGFR < 30
  - Do not initiate
- Kidney failure
  - Discontinue

GLP-1 receptor agonist (preferred)
- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 ml/min/1.73 m² or treated with dialysis
- See Figure 12

Additional drug therapy as needed for glycemic control

DPP-4 inhibitor
Insulins
Sulfonylurea
TZD
Alpha-glucosidase inhibitors
**Approaches to Management of Patients with Diabetes and CKD**

**Recommendation 5.2.1:** We suggest that policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD (2B).
Take Home Points

• The standard-of-care for treatment of DKD has been an ACE inhibitor or an ARB, yet these agents remain under utilized in clinical practice.
• SGLT-2 inhibition reduces risks of albuminuria, eGFR decline, ESKD, heart failure, atherosclerotic CVD, and CVD death (empagliflozin, dapagliflozin) in type 2 diabetic and non-diabetic patients.
• SGLT-2 inhibition is now considered a standard-of-care for DKD.
• Team-based, integrated care strategies are needed to improve dissemination and implementation of best practices for DKD care.
Safely and Effectively Prescribing SGLT2 Inhibitors

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CLINICAL SCIENTIST – DIVISION OF NEPHROLOGY, UNIVERSITY HEALTH NETWORK
SENIOR SCIENTIST, TORONTO GENERAL HOSPITAL RESEARCH INSTITUTE
DIRECTOR, RENAL PHYSIOLOGY LABORATORY, UNIVERSITY HEALTH NETWORK
Safely and Effectively Prescribing SGLT2 Inhibitors

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Senior Scientist, Toronto General Hospital Research Institute
Disclosures

Relationships with commercial entities:

• Consulting, honoraria: Boehringer Ingelheim, Lilly, Janssen, Merck, AstraZeneca, Mitsubishi-Tanabe, Sanofi

• Clinical trials: CREDENCE, TRANSLATE, BETWEEN, DIAMOND, DAPA-CKD, EMPA-Kidney, ERADICATE-HF
Objectives

• SGLT2 inhibitors – getting familiar
• Clinical trial evidence illustrating primary role of the kidney
• **Emerging evidence in people without diabetes**
• When to avoid use of SGLT2 inhibitors
Evidence for the primary role of the kidney in trials: ESKD, substantial loss of eGFR or renal death (baseline eGFR)
Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P = 0.00001

Perkovic et al. NEJM 2019
Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death

ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m² for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason. CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

How to avoid clinical inertia: Getting familiar with SGLT2 inhibitors

1. AKI safety and the GFR “dip”
2. Volume effects/hypotension
3. Concern about having to manage glucose, hypoglycemia
4. DKA
5. Genital tract infections
eGFR “dip”: Canagliflozin vs SU – Normal renal function

Change in eGFR over time

- Changes in eGFR also seen in patients with CKD stage 3 and 4, even though less HbA1c lowering

Cherney et al. Lancet Diab Endo 2017 (differences based on CKD stage)
CREDENCE: The Decline in eGFR Was Slower in Each Category of Acute eGFR Change for CANA vs PBO

Adjusted mean (SE) eGFR (mL/min/1.73 m²) vs Months since randomization for CANA and PBO.

- Acute eGFR decrease (>10%) for CANA and PBO.
- Acute modest eGFR decrease (0 to 10%) for CANA and PBO.
- Acute eGFR increase (≥0%) for CANA and PBO.

Mean annual change in eGFR (mL/min/1.73 m²) for each category:
- CANA: -2.01, -1.99, -2.44
- PBO: -4.40, -4.46, -4.72

SE: standard error.

*Multivariable models adjusted for age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, CV disease history, BMI, systolic BP, HbA1c, eGFR, UACR, HDL-LDL cholesterol, triglycerides, and use of diuretic and RAAS inhibitors.
**CREDENCE: Adverse Events Were Consistent Regardless of Initial Drop in eGFR**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>CANA</th>
<th></th>
<th>Hazard ratio (95% CI)*</th>
<th>P interaction</th>
<th>P interaction</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse events</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Acute eGFR decrease†</td>
<td>778</td>
<td>874.2</td>
<td>1.08 (0.96, 1.21)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute modest eGFR decrease‡</td>
<td>480</td>
<td>852.8</td>
<td>1.13 (0.99, 1.29)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute eGFR increase§</td>
<td>454</td>
<td>763.7</td>
<td>1 (reference)</td>
<td></td>
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</tr>
<tr>
<td><strong>Any serious adverse events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute eGFR decrease†</td>
<td>322</td>
<td>175.7</td>
<td>0.96 (0.80, 1.16)</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute modest eGFR decrease‡</td>
<td>188</td>
<td>158.8</td>
<td>0.91 (0.74, 1.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute eGFR increase§</td>
<td>198</td>
<td>177.1</td>
<td>1 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any renal-related events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute eGFR decrease†</td>
<td>133</td>
<td>65.0</td>
<td>1.24 (0.92, 1.66)</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute modest eGFR decrease‡</td>
<td>61</td>
<td>45.6</td>
<td>0.77 (0.55, 1.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute eGFR increase§</td>
<td>74</td>
<td>59.1</td>
<td>1 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Multivariable models adjusted for age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, CV disease history, BMI, systolic BP, HbA1c, eGFR, UACR, HDL- LDL cholesterol, triglycerides, and use of diuretic and RAAS inhibitors.

†Acute eGFR decrease (>10%)
‡Acute modest eGFR decrease (>0 to 10%).
§Acute eGFR increase (≥0%).
How about non-diabetic CKD?

Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

David Z I Chemey*, Claire CJ Dekkers*, Sean J Barbour, Daniel Cattrant, Abdul Halim Abdul Gafor, Peter J Greasley, Gozewijn D Laverman, Soo Kun Lim, Gian Luca Di Tanno, Heather N Reich, Marc GVervoet, Muh Geot Wong, Ron T Gansevoort, Hiddo J L Heerspink, for the DIAMOND investigators

Summary
Background SGLT2 inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These benefits are unlikely to be mediated by improvements in glycaemic control alone. Therefore, we aimed to examine the kidney effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes.
In NDKD patients from the DIAMOND trial, compared with placebo, dapagliflozin causes a reversible decline in mGFR but does not change ACR.

Effect of dapagliflozin, compared with placebo, on mGFR

- Mean difference: –6.6 mL/min/1.73 m²
  (95% CI: –9.0, –4.2); 
  \( P < 0.0001 \)

Effect of dapagliflozin, compared with placebo, on ACR

- Mean difference: –17.0%
  (95% CI: –33.2, 3.4); 
  \( P = 0.095 \)
## Safety Outcomes

<table>
<thead>
<tr>
<th>Safety Outcomes&lt;sup&gt;a&lt;/sup&gt;, n (%)</th>
<th>Dapagliflozin 10 mg (N=2149)</th>
<th>Placebo (N=2149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of study drug</td>
<td>274 (12.8)</td>
<td>309 (14.4)</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>118 (5.5)</td>
<td>123 (5.7)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>633 (29.5)</td>
<td>729 (33.9)</td>
</tr>
</tbody>
</table>

### Adverse events of interest

- Amputation<sup>b</sup>  
  - Dapagliflozin 10 mg: 35 (1.6)  
  - Placebo: 39 (1.8)
- Any definite or probable diabetic ketoacidosis  
  - Dapagliflozin 10 mg: 0  
  - Placebo: 2 (0.1)
- Fracture<sup>c</sup>  
  - Dapagliflozin 10 mg: 85 (4.0)  
  - Placebo: 69 (3.2)
- Renal-related adverse event<sup>c</sup>  
  - Dapagliflozin 10 mg: 155 (7.2)  
  - Placebo: 188 (8.7)
- Major hypoglycemia<sup>d</sup>  
  - Dapagliflozin 10 mg: 14 (0.7)  
  - Placebo: 28 (1.3)
- Volume depletion<sup>c</sup>  
  - Dapagliflozin 10 mg: 127 (5.9)  
  - Placebo: 90 (4.2)
- Serious adverse events of volume depletion  
  - Dapagliflozin 10 mg: 22 (1.0)  
  - Placebo: 18 (0.8)

<sup>a</sup>Safety outcomes reported in participants on and off treatment; <sup>b</sup>Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; <sup>c</sup>Based on pre-defined list of preferred terms; <sup>d</sup>Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
SGLT2 inhibitors are associated with lower risk of AKI

Figure 3: Effect of SGLT2 inhibitors on acute kidney injury
Weights were from random-effects meta-analysis. SGLT2 = sodium-glucose co-transporter-2. RR = relative risk.
AKI risk is also reduced in “Real-World Evidence” studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Observed No. events (%)</th>
<th>Weighted*</th>
<th>RR† (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants taking SGLT2 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 19611</td>
<td>216 (1.10)</td>
<td>−0.29</td>
<td>(0.79, 0.64 to 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Participants taking DPP4 inhibitors</td>
<td>388 (1.99)</td>
<td>(−0.57 to −0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 19483</td>
<td>275 (1.39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants taking SGLT2 inhibitors</td>
<td></td>
<td>−0.28</td>
<td>(0.73, 0.56 to 0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>n = 19611</td>
<td>149 (0.76)</td>
<td>(−0.53 to −0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants taking DPP4 inhibitors</td>
<td>291 (1.49)</td>
<td>0.73</td>
<td>(0.81, 0.49 to 1.33)</td>
<td>0.40</td>
</tr>
<tr>
<td>n = 19775</td>
<td>206 (1.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to hospital with AKI</td>
<td>149 (0.76)</td>
<td>−0.05</td>
<td>(0.33, 0.95 to 1.33)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospital encounter with moderate-to-severe AKI</td>
<td>44 (0.22)</td>
<td>(−0.18 to 0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI in outpatient setting only</td>
<td>573 (2.92)</td>
<td>0.33</td>
<td>(1.13, 0.95 to 1.33)</td>
<td>0.42</td>
</tr>
<tr>
<td>AKI in all settings</td>
<td>716 (3.65)</td>
<td>0.21</td>
<td>(1.06, 0.92 to 1.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>837 (4.30)</td>
<td>(−0.28 to 0.70)</td>
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</tbody>
</table>
Summary: AKI and GFR “dip”

• The GFR dip is reversible and not a sign of injury
• SGLT2 inhibitors may reduce AKI
  – Mechanism?
• Significant volume depletion/hypotension rare
• BP lowering effect quite modest
We Can Finally Stop Worrying About SGLT2 Inhibitors and Acute Kidney Injury

Vikas S. Sridhar, Katherine R. Tuttle, and David Z.I. Cherney

Sodium glucose transporter 2 (SGLT2) inhibitors, originally approved solely as antihyperglycemic agents for the treatment of type 2 diabetes mellitus (T2DM), are increasingly recognized for their distinctive kidney and definition, based on how nonsteroidal anti-inflammatory drugs (NSAIDs) act in the kidney. As described later, SGLT2 inhibitors are clearly not NSAIDs, and drawing parallels between these classes of drugs is both clinically and physiologically incorrect.

The third main reason for concerns around AKI with SGLT2 inhibitors is based on over-categorization of AKI in the UG...
Concern about having to manage glucose, hypoglycemia

• Effects of SGLT2 inhibitors on renal/CV protection – independent of glucose
CREDENCE Post-Hoc Analysis: Outcomes Stratified by A1C

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Participants With an Event, 1000 p-y</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Primary composite outcome, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>39.2</td>
<td>59.8</td>
<td>0.63</td>
</tr>
<tr>
<td>7-&lt;8</td>
<td>44.8</td>
<td>52.3</td>
<td>0.84</td>
</tr>
<tr>
<td>≥8</td>
<td>43.0</td>
<td>66.8</td>
<td>0.63</td>
</tr>
<tr>
<td>ESKD, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>24.8</td>
<td>39.2</td>
<td>0.61</td>
</tr>
<tr>
<td>7-&lt;8</td>
<td>22.8</td>
<td>27.1</td>
<td>0.83</td>
</tr>
<tr>
<td>≥8</td>
<td>17.6</td>
<td>28.1</td>
<td>0.61</td>
</tr>
<tr>
<td>Dialysis initiated or kidney transplant, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>14.1</td>
<td>23.4</td>
<td>0.57</td>
</tr>
<tr>
<td>7-&lt;8</td>
<td>13.5</td>
<td>15.9</td>
<td>0.84</td>
</tr>
<tr>
<td>≥8</td>
<td>12.9</td>
<td>17.1</td>
<td>0.74</td>
</tr>
<tr>
<td>CV death, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>12.8</td>
<td>17.2</td>
<td>0.72</td>
</tr>
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<td>7-&lt;8</td>
<td>17.7</td>
<td>21.1</td>
<td>0.83</td>
</tr>
<tr>
<td>≥8</td>
<td>21.3</td>
<td>28.1</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Favors canagliflozin  Favors placebo
### DAPA-CKD Primary Composite Outcome: Prespecified Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>Number of Events</th>
<th>HR (95% CI)</th>
<th>p-value Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>197</td>
<td>312</td>
<td>0.61 (0.51, 0.72)</td>
</tr>
<tr>
<td><strong>T2D at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>152</td>
<td>229</td>
<td>0.64 (0.52, 0.79)</td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>83</td>
<td>0.50 (0.35, 0.72)</td>
</tr>
<tr>
<td><strong>UACR (mg/g) at Baseline</strong></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>≤1000</td>
<td>44</td>
<td>84</td>
<td>0.54 (0.37, 0.77)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>153</td>
<td>228</td>
<td>0.62 (0.50, 0.76)</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73m²) at Baseline</strong></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>&lt;45</td>
<td>152</td>
<td>217</td>
<td>0.63 (0.51, 0.78)</td>
</tr>
<tr>
<td>≥45</td>
<td>45</td>
<td>95</td>
<td>0.49 (0.34, 0.69)</td>
</tr>
</tbody>
</table>

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
Summary: glucose management, hypoglycemia

- Effects of SGLT2 inhibitors on glycemia decline as GFR declines.
- Rarely have to make adjustments, except in people with tight control on insulin/SU.
- Benefits are independent of glucose (DAPA-CKD, DAPA-HF, EMPEROR-reduced).
**Table 2. Safety Events.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dapagliflozin (N=8574)</th>
<th>Placebo (N=8569)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>2925 (34.1)</td>
<td>3100 (36.2)</td>
<td>0.91 (0.87--0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of trial regimen</td>
<td>693 (8.1)</td>
<td>592 (6.9)</td>
<td>1.15 (1.03--1.28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Major hypoglycemic event</td>
<td>58 (0.7)</td>
<td>83 (1.0)</td>
<td>0.68 (0.49--0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>27 (0.3)</td>
<td>12 (0.1)</td>
<td>2.18 (1.10--4.30)</td>
<td>0.02</td>
</tr>
<tr>
<td>Amputation</td>
<td>123 (1.4)</td>
<td>113 (1.3)</td>
<td>1.09 (0.84--1.40)</td>
<td>0.53</td>
</tr>
<tr>
<td>Fracture</td>
<td>457 (5.3)</td>
<td>440 (5.1)</td>
<td>1.04 (0.91--1.18)</td>
<td>0.59</td>
</tr>
<tr>
<td>Symptoms of volume depletion</td>
<td>213 (2.5)</td>
<td>207 (2.4)</td>
<td>1.00 (0.83--1.21)</td>
<td>0.99</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>125 (1.5)</td>
<td>175 (2.0)</td>
<td>0.69 (0.55--0.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>Genital infection</td>
<td>76 (0.9)</td>
<td>9 (0.1)</td>
<td>8.36 (4.19--16.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>127 (1.5)</td>
<td>133 (1.6)</td>
<td>0.93 (0.73--1.18)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cancer</td>
<td>481 (5.6)</td>
<td>486 (5.7)</td>
<td>0.99 (0.87--1.12)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>26 (0.3)</td>
<td>45 (0.5)</td>
<td>0.57 (0.35--0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>36 (0.4)</td>
<td>35 (0.4)</td>
<td>1.02 (0.64--1.63)</td>
<td>0.92</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>32 (0.4)</td>
<td>36 (0.4)</td>
<td>0.87 (0.54--1.40)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hepatic event</td>
<td>82 (1.0)</td>
<td>87 (1.0)</td>
<td>0.92 (0.68--1.25)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
SGLT2 inhibitors effect on DKA
No heterogeneity between studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment Events per 1000 pt- yrs</th>
<th>Placebo Events per 1000 pt- yrs</th>
<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>5</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>6.6</td>
<td>1.99 [0.22, 17.80]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>18</td>
<td>0.6</td>
<td>0.3</td>
<td>25.2</td>
<td>2.33 [0.76, 7.17]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17143</td>
<td>39</td>
<td>0.9</td>
<td>0.4</td>
<td>68.2</td>
<td>2.18 [1.10, 4.30]</td>
</tr>
</tbody>
</table>

**Fixed Effect Models (p-value = 0.0060)**

Q statistic = 0.02, p=0.99, $I^2$ = 0%

CI, confidence interval; DKA, diabetes ketoacidosis; HR, hazard ratio; SGLT2, sodium-glucose cotransporter-2
Zelniker TA et al. Lancet 2018; doi.org/10.1016/S0140-6736(18)32590-X
Who should not receive SGLT2 inhibition?

1. T2D, history of DKA
2. Frequent genital tract infection
3. Catheterized patients
4. Dynamic volume status, significant concern volume depletion
5. Polycystic kidney disease, immunosuppression (until data available)
Clinical, research implications

1. Glucose lowering plays little or no role in cardiorenal protection with SGLT2 inhibition
2. We should stop thinking about obsolete eGFR thresholds of 45 or 60 ml/min/1.73m²
3. SGLT2 inhibitors: RAAS blockers with "pleiotropic effects", beyond glucose (EMPEROR-reduced, DAPA-HF, DAPA-CKD)
4. Need to work on implementation of the trial data
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Subodh Verma

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Kevin Burns
Paying for New Therapies

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Disclosures

**Employer:** University of New Mexico

**Consultancy Agreements:** Momenta Pharma

**Ownership Interest:**

**Research Funding:** DCI, Inc; University of Pennsylvania

**Honoraria:**

**Patents and Inventions:**

**Scientific Advisor or Membership:** 1) Baxter Healthcare; 2) Health Services Advisory Group; 3) Bayer

**Speakers Bureau:**

**Other Interests/Relationships:** 1) DCI Inc: Medical Director – Outpatient Dialysis Unit in Cuba, New Mexico; 2) Akebia: PI in two Phase 3 trials of an investigational product for the correction and maintenance of anemia in patients with non-dialysis dependent Chronic Kidney Disease and one Phase 3 study of the same agent in dialysis; 3) Abbvie: Sub-I in a Phase 3 study of an experimental agent in diabetic nephropathy; 4) DOPPS: PI for CKD-DOPP
Outline

• When will payors pay for a new drug
• Should the “system” pay for SGLT2i?
• Paying for SGLT2i:
  • tips and suggestions
  • towards universal coverage
Should payors pay for a new drug?

1. Does the drug prolong survival?
2. Does the drug improve quality of life?
3. Does the drug reduce need of renal replacement?
4. Does the drug reduce frequency/severity of costly events?

We currently have published trial data about Q1,Q3,Q4 for SGLT2i
# Hazard Ratios in (diabetic) CKD: SGLT2i vs ARB

<table>
<thead>
<tr>
<th></th>
<th>SGLT2i</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (CREDENCE)</td>
<td>Dapagliflozin (DAPA – CKD)</td>
</tr>
<tr>
<td>All Cause Mortality (Q1)</td>
<td>0.83 (0.68 – 1.02)</td>
<td>0.69 (0.53 – 0.88)</td>
</tr>
<tr>
<td>Composite Kidney Outcome (Q2)</td>
<td>0.66 (0.53-0.81)</td>
<td>0.56 (0.45 – 0.68)</td>
</tr>
<tr>
<td>Heart Failure Hospitalizations (Q4)</td>
<td>0.61 (0.47- 0.80)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.64 – 0.74)*</td>
<td></td>
</tr>
</tbody>
</table>

Composite Kidney Outcome: doubling creatinine/End Stage Kidney Disease/decrease in eGFR > 40%
NR: Not Reported, *meta-analysis from all trials across indications
## SGLT2i vs RASi

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGLT2i</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality (Q1)</td>
<td>0.76</td>
<td>&gt;</td>
</tr>
<tr>
<td>Composite Kidney Outcome ~ESKD (Q2)</td>
<td>0.61</td>
<td>&gt;</td>
</tr>
<tr>
<td>Total Effect on ESKD (Q2)</td>
<td>0.80</td>
<td>~</td>
</tr>
<tr>
<td>Heart Failure Hospitalizations (Q4)</td>
<td>0.69</td>
<td>~</td>
</tr>
</tbody>
</table>

Projected Effect on ESKD must account for the competing outcome of death:

$$ \frac{HR(ESKD)}{HR(Death)} $$

[https://twitter.com/ChristosArgyrop/status/1301706984379482113?s=20](https://twitter.com/ChristosArgyrop/status/1301706984379482113?s=20)

[https://twitter.com/ChristosArgyrop/status/1301736105688014849?s=20](https://twitter.com/ChristosArgyrop/status/1301736105688014849?s=20)
Should the “system” pay for SGLT2?

**YES**
- Improved Survival
- Reduced Hospitalizations
- Reduced ESKD rates

**No**
- Will just end up with older patients (possibly with more comorbidities) needing more costly dialysis
Pharmaco-economic evaluations of ARBs post RENAAL

• AWP (2001) of losartan 25-, 50-, and 100-mg $1.43, $1.43, and $1.95 per tablet

• ESRD related costs only

• Event Rates for the ESKD in RENAAL:
  ➢ 117 events/1000pt years (losartan)
  ➢ 141 events/1000pt years (SoC)

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Net cost savings</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>−137</td>
<td>−1,552 to 1,277</td>
<td>0.849</td>
</tr>
<tr>
<td>2.5</td>
<td>782</td>
<td>−1,238 to 2,801</td>
<td>0.448</td>
</tr>
<tr>
<td>3.0</td>
<td>2,016</td>
<td>−623 to 4,655</td>
<td>0.134</td>
</tr>
<tr>
<td>3.5</td>
<td>3,522</td>
<td>143 to 6,900</td>
<td>0.041</td>
</tr>
<tr>
<td>4.0</td>
<td>5,298</td>
<td>954 to 9,643</td>
<td>0.017</td>
</tr>
</tbody>
</table>

“Moreover, given that the competing mortality rate is so high in this population, it is likely that these savings would persist because individuals would likely die from other causes before reaching ESRD. Regardless, for many decision makers, these near-term savings are meaningful”

Don’t get tempted to multiply the cost savings by the inflation factor (48%)
From ARBs to SGLT2i

Change in costs

• SGLT2i: 5.5 – 11 x more expensive than ARBs after accounting for inflation
  ➢ AWP(2020): dapagliflozin 5,10mg: $20.69
  ➢ AWP (2020) of canagliflozin 100-, 300mg: $20.74
  ➢ AWP (2020) of empagliflozin 10-, 25mg: $20.90
  ➢ AWP (2020) of ertugliflozin 5- 15mg: $11.81

Dialysis costs per patient stable for ~10yrs (w/o accounting for inflation)

Change in Epidemiology

• Event Rates for the ESKD in CREDENCE:
  ➢ 20.4 events/1000pt years (canagliflozin)
  ➢ 29.4 events/1000pt years (SoC)
  ➢ ESKD due to DM: 1.73/1000pt years 33% decline between early 2000s and mid 2010s
  ➢ Prevalence of diabetes type 2 increased by ~26% during the same period

Universal adoption of SGLT2i will stabilize incidence of ESKD over the next 10 years

- DAPA-CKD suggests benefits for non-diabetic forms of CKD
- No subgroup benefits more than others
- Factoring life expectancy benefits, HR for ESKD is ~0.80
- Modelled incidence of ESRD in 2030: 440 ppm
- $440 \times 0.8 = 352$ ppm (2004 incidence rate)
- Factoring population growth, the actual incidence counts after SGLT2i ~127,000 (125,000 in 2017)
SGLT2i will continue to be a hard sell to payors

- **Diminishing returns:**
  - Stable/decreasing ESRD incidence among patients with diabetes
  - Stabilized/reduced per patient dialysis costs due to bundles

- **More expensive** drugs than ARBs
- **More patients who need them** compared to ARBs
- **Lack of total cost/benefit calculations** to account for other effects:
  - QALY
  - Heart Failure Hospitalizations
  - Reduction in non-lethal cardiovascular events
  - *Reduction of Acute Kidney Injury rates* with SGLT2i
  - Cost for DKA complication

- **Medicare Part B** will reap the benefits of SGLT2i, but costs will be born by Medicaid/Medicare Part D/commercial insurance
Paying for SGLT2i

Tips and suggestions

• Know your patient’s formulary (Medscape app to the rescue)
• Prescribe under either the cardiac indications (if your pt meets the criteria) or the renal indication
• Renal benefits are more likely than not class effects (any SGLT2i better than no SGLT2i)

Towards universal SGLT2i coverage

• Detailed cost-benefit calculations that go beyond ESKD to establish a “fair” price
• Educate payors that SGLT2i are not just anti-glycemics
• Legislative action to create a dedicated Part D program (cost share between D and B?) with zero copays (role for Medicare Advantage?)
Dapagliflozin in Patients with Chronic Kidney Disease
DAPA-CKD

HIDDO L. HEERSPINK, PHD, PHARMD
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Disclosures

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**Research Funding:** Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen research support (honoraria directed to employer)

**Honoraria:**

**Patents and Inventions:**

**Scientific Advisor or Membership:**

**Speakers Bureau:** Speaker bureau for AstraZeneca

**Other Interests/Relationships:**
Dapagliflozin in Patients with Chronic Kidney Disease
DAPA-CKD

Hiddo L. Heerspink
Department of Clinical Pharmacy and Pharmacology
University Medical Center Groningen
Life expectancy is significantly reduced in patients with lower eGFR or higher albuminuria

**eGFR categories**

- eGFR normal
- eGFR stage 3A (25–59 mL/min per 1.73 m²)
- eGFR stage 3B (15–29 mL/min per 1.73 m²)
- eGFR stage 4 (<15 mL/min per 1.73 m²)
- eGFR stage 5 or RRT (<15 mL/min per 1.73 m²)

**Albuminuria categories**

- Normal albuminuria
- Albuminuria stage 2
- Albuminuria stage 3

---

Among the successful trials, few therapies have been approved for the treatment of CKD

### Successful trials in DKD and NDKD

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Drug</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>MICRO-HOPE</td>
<td>Captopril</td>
<td>NDKD</td>
</tr>
<tr>
<td>1994</td>
<td>RENAAL</td>
<td>Lisinopril</td>
<td>DKD</td>
</tr>
<tr>
<td>1998</td>
<td>BENEDICT</td>
<td>Benazepril</td>
<td>DKD</td>
</tr>
<tr>
<td>2002</td>
<td>ROAD MAP</td>
<td>BENEDICT</td>
<td>DKD</td>
</tr>
<tr>
<td>2006</td>
<td>IDNT</td>
<td>Benazepril</td>
<td>DKD</td>
</tr>
<tr>
<td>2010</td>
<td>DAPA-CKD</td>
<td>Dapagliflozin</td>
<td>NDKD</td>
</tr>
<tr>
<td>2014</td>
<td>SONAR</td>
<td>Sonataside</td>
<td>NDKD</td>
</tr>
<tr>
<td>2018</td>
<td>CREDENCE</td>
<td>Everolimus</td>
<td>NDKD</td>
</tr>
<tr>
<td>2022</td>
<td>FIDELIO-DKD</td>
<td>Finerenone</td>
<td>NDKD</td>
</tr>
</tbody>
</table>

**DKD**
- ACE inhibitor
- ARB
- ERA
- SGLT2 inhibitor
- MRA

**NDKD**
- ACE inhibitor

---

Rationale for the DAPA-CKD trial

- Despite guideline recommended therapy including ACE inhibitors and ARBs risk of kidney failure and cardiovascular complications remain high in patients with CKD

- The CREDENCE trial showed that canagliflozin reduced the risk of kidney failure and CV outcomes in patients with type 2 diabetes and CKD

- The benefits of SGLT2 inhibitors appear to be independent of their blood glucose-lowering effects and may be mediated by reduction in intra-glomerular pressure which may protect kidney function in patients without diabetes

- We hypothesized that dapagliflozin could also preserve kidney function and improve outcomes in people with chronic kidney disease, independently of the presence of diabetes
Objectives

• To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in people with CKD with or without type 2 diabetes, and who are receiving standard of care including a maximum tolerated dose of an ACE inhibitor or ARB

• Primary outcome
  - Composite outcome of sustained ≥50% eGFR decline, ESKD, renal or CV death

• Secondary outcomes (in hierarchical order)
  - Composite outcome of sustained ≥50% eGFR decline, ESKD or renal death
  - CV death or hospitalizations for heart failure
  - All-cause mortality

**Study Design**

**Key inclusion criteria:**
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73m²
- UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)
- Stable maximum tolerated labelled dose of ACEi or ARB for ≥4 weeks (if not contraindicated)

**Key exclusion criteria:**
- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrollment

**Study End Date**
- Study Closure Visit
  - 2 W
  - Day 0
  - 2 W
  - 2 M
  - 4 M
  - 8 M

Visits every 4 months

Matching Placebo once daily

Dapagliflozin 10 mg once daily

Randomization (1:1)

Screening

• Outcome analysis based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

ANCA, anti-neutrophil cytoplasmatic antibody; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

After a regular review meeting, the Independent DMC recommended on 26 March that the trial be stopped due to overwhelming efficacy, based on 408 primary endpoint events (60% of planned events).
7517 participants enrolled

4304 participants randomized to treatment

Dapagliflozin 10 mg
N=2152

- 3 participants did not receive study drug
- 274 participants discontinued study drug
- 10 participants discontinued study
- 2142 (99.5%) participants completed the study

Placebo
N=2152

- 3 participants did not receive study drug
- 309 participants discontinued study drug
- 5 participants discontinued study
- 2147 (99.8%) participants completed the study

3213 participants not randomized

4299 (99.9%) vital status known; 4289 (99.7%) completed study
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (N=2152)</th>
<th>Placebo (N=2152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Sex, female, %</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Type 2 diabetes, %</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg, mean</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m², mean</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>UACR, mg/g, median</td>
<td>965</td>
<td>934</td>
</tr>
<tr>
<td>ACEi or ARB, %</td>
<td>97</td>
<td>97</td>
</tr>
</tbody>
</table>
Primary outcome:
Sustained ≥50% eGFR decline, ESKD, renal or CV death

Hazard ratio, 0.61 (95% CI, 0.51–0.72)
$p=0.000000028$
NNT=19

Secondary outcome: Sustained ≥50% eGFR decline, ESKD, renal death

Hazard ratio, 0.56 (95% CI, 0.45–0.68)  
$p=0.000000018$

243 Events
142 Events

Placebo
Dapagliflozin

No. at Risk
Dapagliflozin 2152 2001 1955 1898 1841 1701 1288 831 309
Placebo 2152 1993 1936 1858 1791 1664 1232 774 270

Summary of the primary outcome and its components

<table>
<thead>
<tr>
<th>Event</th>
<th>Dapagliflozin events</th>
<th>Placebo events</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>197</td>
<td>312</td>
<td>0.61 (0.51, 0.72)</td>
<td>0.000000028</td>
</tr>
<tr>
<td>≥50% eGFR decline</td>
<td>112</td>
<td>201</td>
<td>0.53 (0.42, 0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESKD</td>
<td>109</td>
<td>161</td>
<td>0.64 (0.50, 0.82)</td>
<td>0.0004</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73m²</td>
<td>84</td>
<td>120</td>
<td>0.67 (0.51, 0.88)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>68</td>
<td>99</td>
<td>0.66 (0.48, 0.90)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Transplantation</td>
<td>3</td>
<td>8</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Renal death</td>
<td>2</td>
<td>6</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>65</td>
<td>80</td>
<td>0.81 (0.58, 1.12)</td>
<td>0.2029</td>
</tr>
</tbody>
</table>

NC, not calculable

## Primary outcome – pre-specified subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin events</th>
<th>Placebo events</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>197</td>
<td>312</td>
<td>0.61 (0.51, 0.72)</td>
<td></td>
</tr>
<tr>
<td>With type 2 diabetes</td>
<td>152</td>
<td>229</td>
<td>0.64 (0.52, 0.79)</td>
<td></td>
</tr>
<tr>
<td>Without type 2 diabetes</td>
<td>45</td>
<td>83</td>
<td>0.50 (0.35, 0.72)</td>
<td>0.24</td>
</tr>
<tr>
<td>UACR ≤1000 mg/g</td>
<td>44</td>
<td>84</td>
<td>0.54 (0.37, 0.77)</td>
<td></td>
</tr>
<tr>
<td>UACR &gt;1000 mg/g</td>
<td>153</td>
<td>228</td>
<td>0.62 (0.50, 0.76)</td>
<td>0.52</td>
</tr>
<tr>
<td>eGFR &lt;45 mL/min/1.73m²</td>
<td>152</td>
<td>217</td>
<td>0.63 (0.51, 0.78)</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥45 mL/min/1.73m²</td>
<td>45</td>
<td>95</td>
<td>0.49 (0.34, 0.69)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

### Primary outcome – pre-specified subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin events</th>
<th>Placebo events</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>197</td>
<td>312</td>
<td>0.61 (0.51, 0.72)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 years</td>
<td>122</td>
<td>191</td>
<td>0.64 (0.51, 0.80)</td>
<td></td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>75</td>
<td>121</td>
<td>0.58 (0.43, 0.77)</td>
<td>0.53</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>126</td>
<td>209</td>
<td>0.57 (0.46, 0.72)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71</td>
<td>103</td>
<td>0.65 (0.48, 0.88)</td>
<td>0.50</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>110</td>
<td>174</td>
<td>0.62 (0.49, 0.79)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>14</td>
<td>0.33 (0.13, 0.81)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>53</td>
<td>77</td>
<td>0.66 (0.46, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>47</td>
<td>0.54 (0.33, 0.86)</td>
<td>0.68</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>50</td>
<td>69</td>
<td>0.70 (0.48, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>57</td>
<td>89</td>
<td>0.60 (0.43, 0.85)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>35</td>
<td>69</td>
<td>0.61 (0.43, 0.86)</td>
<td>0.77</td>
</tr>
<tr>
<td>Latin America</td>
<td>55</td>
<td>85</td>
<td>0.51 (0.34, 0.76)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With type 2 diabetes</td>
<td>152</td>
<td>229</td>
<td>0.64 (0.52, 0.79)</td>
<td></td>
</tr>
<tr>
<td>Without type 2 diabetes</td>
<td>45</td>
<td>83</td>
<td>0.50 (0.35, 0.72)</td>
<td>0.24</td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 mL/min/1.73m²</td>
<td>152</td>
<td>217</td>
<td>0.63 (0.51, 0.78)</td>
<td></td>
</tr>
<tr>
<td>≥45 mL/min/1.73m²</td>
<td>45</td>
<td>95</td>
<td>0.49 (0.34, 0.69)</td>
<td>0.22</td>
</tr>
<tr>
<td>UACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000 mg/g</td>
<td>44</td>
<td>84</td>
<td>0.54 (0.37, 0.77)</td>
<td></td>
</tr>
<tr>
<td>&gt;1000 mg/g</td>
<td>153</td>
<td>228</td>
<td>0.62 (0.50, 0.76)</td>
<td>0.52</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤130 mmHg</td>
<td>46</td>
<td>96</td>
<td>0.44 (0.31, 0.63)</td>
<td></td>
</tr>
<tr>
<td>&gt;130 mmHg</td>
<td>151</td>
<td>216</td>
<td>0.68 (0.56, 0.84)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Secondary outcome: CV death or heart failure hospitalization

Hazard ratio, 0.71 (95% CI, 0.55–0.92)
p=0.0089

No. at Risk
Dapagliflozin 2152 2035 2021 2003 1975 1895 1502 1003 384
Placebo 2152 2023 1989 1957 1927 1853 1451 976 360
Secondary outcome:
All-cause mortality

Hazard ratio, 0.69 (95% CI, 0.53–0.88)
p=0.0035

# Safety

<table>
<thead>
<tr>
<th>Safety outcomes* , n (%)</th>
<th>Dapagliflozin (N=2149)</th>
<th>Placebo (N=2149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of study drug</td>
<td>274 (12.8)</td>
<td>309 (14.4)</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>118 (5.5)</td>
<td>123 (5.7)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>633 (29.5)</td>
<td>729 (33.9)</td>
</tr>
</tbody>
</table>

**Adverse events of interest**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dapagliflozin (N=2149)</th>
<th>Placebo (N=2149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation†</td>
<td>35 (1.6)</td>
<td>39 (1.8)</td>
</tr>
<tr>
<td>Any definite or probable diabetic ketoacidosis</td>
<td>0</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Fracture‡</td>
<td>85 (4.0)</td>
<td>69 (3.2)</td>
</tr>
<tr>
<td>Renal related adverse event‡</td>
<td>155 (7.2)</td>
<td>188 (8.7)</td>
</tr>
<tr>
<td>Major hypoglycaemia §</td>
<td>14 (0.7)</td>
<td>28 (1.3)</td>
</tr>
<tr>
<td>Volume depletion‡</td>
<td>127 (5.9)</td>
<td>90 (4.2)</td>
</tr>
<tr>
<td>Serious adverse events of volume depletion</td>
<td>22 (1.0)</td>
<td>18 (0.8)</td>
</tr>
</tbody>
</table>

---

*Safety outcomes reported in participants on and off treatment; †surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; ‡based on pre-defined list of preferred terms; §AE with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behaviour, ii) need of external assistance, iii) intervention to treat hypoglycaemia, iv) prompt recovery of acute symptoms following the intervention.

Conclusion

In patients with CKD, with and without type 2 diabetes, dapagliflozin compared to placebo:

- Reduced the risk of kidney failure
- Reduced the risk of death from CV causes or hospitalization for heart failure
- Prolonged survival

Dapagliflozin was well tolerated, in keeping with its established safety profile
The DAPA-CKD team would like to thank the following:

Members of the DAPA-CKD Executive Committee
Hiddo J.L. Heerspink, David C. Wheeler, Glenn Chertow, Ricardo Correa-Rotter, Tom Greene, Fan Fan Hou, John McMurray, Peter Rossing, Robert Toto, Bergur Stefansson, and Anna Maria Langkilde

Members of the DAPA-CKD Independent Data Monitoring Committee
Marc A. Pfeffer, Stuart Pocock, Karl Swedberg, Jean L. Rouleau, Nishi Chaturvedi, Peter Ivanovich, Andrew S. Levey, and Heidi Christ-Schmidt

Members of the DAPA-CKD Event Adjudication Committee
Claes Held, Christina Christersson, Johannes Mann, and Christoph Varenhorst

The DAPA-CKD team would also like to thank all participating investigators, the patients and their families!
Conclusion

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  • Reduced the risk of kidney failure
  • Reduced the risk of death from CV causes or hospitalization for heart failure
  • Prolonged survival

• Dapagliflozin was well tolerated, in keeping with its established safety profile
EMPEROR Study

MILTON PACKER, MD
DISTINGUISHED SCHOLAR IN CARDIOVASCULAR SCIENCE
BAYLOR UNIVERSITY MEDICAL CENTER
DALLAS, TEXAS
Disclosures
EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced Executive Committee, Trial Committees, Investigators and Coordinators

Baylor University Medical Center, Dallas TX, Imperial College, London UK
Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France

Disclosures for presenter: Abbvie, Actavis, Akcea, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Eli LillyJohnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance
Diabetes — But Not Prediabetes — Increases the Risk of a Major Heart Failure Event

Risk of cardiovascular death or hospitalization for heart failure

**Diabetes vs. No diabetes**
- Diabetes: 24.6
- No diabetes: 17.6

**Diabetes vs. pre-diabetes vs. no glycaemic disorder**
- Diabetes: 24.6
- Prediabetes: 18.1
- No glycemic disorder: 16.6
Renal Function Progressively Declines in Heart Failure and a Reduced Ejection Fraction in the Absence of Diabetes

**EMPEROR-Reduced Trial**

Change in Estimated Glomerular Filtration Rate

Decline of $\approx 2$ ml/min/1.73m$^2$ per year

**PARADIGM-HF Trial**

Change in Estimated Glomerular Filtration Rate

Decline of $\approx 2$ ml/min/1.73m$^2$ per year
Diabetes Doubles the Rate of Decline in Renal Function in Heart Failure With a Reduced Ejection Fraction

Diabetes

Weeks of follow-up
Change in Estimated Glomerular Filtration Rate

No diabetes
Diabetes

Decline of $\approx 4$ ml/min/1.73m$^2$ per year

Weeks of follow-up
Change in Estimated Glomerular Filtration Rate

No diabetes
Diabetes

Decline of $\approx 4$ ml/min/1.73m$^2$ per year
Diabetes Doubles the Rate of Serious Adverse Renal Event in Patients With Heart Failure and a Reduced Ejection Fraction
### Diabetes — *But Not Prediabetes* — Accelerates the Rate of Decline in Renal Function

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate of Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.0 ml/min/1.73 m(^2) per year</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>2.3 ml/min/1.73 m(^2) per year</td>
</tr>
<tr>
<td>No glycemic disorder</td>
<td>2.6 ml/min/1.73 m(^2) per year</td>
</tr>
</tbody>
</table>
In DAPA-HF, dapagliflozin improved outcomes in patients with heart failure and a reduced ejection fraction (with or without diabetes), largely those mild-to-moderate LV systolic dysfunction and increases in natriuretic peptides.

In the EMPEROR-Reduced trial, we evaluated the effects of empagliflozin in a broad population of patients with chronic heart failure and a reduced ejection fraction (with and without diabetes) that was enriched for patients with more severe left ventricular systolic dysfunction and marked increases in natriuretic peptides.

Eligible patients were randomized double-blind (1:1 ratio) to empagliflozin 10 mg once daily or placebo, in addition to their usual therapy.
EMPEROR-Reduced: Patient Disposition

7220 patients screened for eligibility

3730 were randomized

1863 assigned to empagliflozin
- Drug discontinued
  - Nonfatal adverse event (158)
  - Request by patient (92)
  - Other reasons (53)

1867 assigned to placebo
- Drug discontinued
  - Nonfatal adverse event (167)
  - Request by patient (124)
  - Other reasons (44)

Final vital status known in 1852
Final vital status unknown in 11

Final vital status known in 1857
Final vital status unknown in 10

Median follow-up 16 months
Final vital status known in 99.4%
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EMPEROR-Reduced</th>
<th>Placebo</th>
<th>DAPA-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1863)</td>
<td>(n=1867)</td>
<td>(n=2373)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>67.2 ± 10.8</td>
<td>66.5 ± 11.2</td>
<td>66.2 ± 11.0</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>437 (23.5)</td>
<td>456 (24.4)</td>
<td>564 (23.8)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus (%)</strong></td>
<td>927 (49.8)</td>
<td>929 (49.8)</td>
<td>993 (41.8)</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>983 (52.8)</td>
<td>946 (50.7)</td>
<td>1316 (55.5)</td>
</tr>
<tr>
<td><strong>NYHA functional class II (%)</strong></td>
<td>1399 (75.1)</td>
<td>1401 (75.0)</td>
<td>1606 (67.7)</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>27.7 ± 6.0 (72% ≤30%)</td>
<td>27.2 ± 6.1 (75% ≤30%)</td>
<td>31.2±6.7</td>
</tr>
<tr>
<td><strong>NT-proBNP (median, IQR), pg/mL</strong></td>
<td>1887 (1077, 3429) (79% ≥1000)</td>
<td>1926 (1153, 3525) (80% ≥1000)</td>
<td>1428 (857-2655)</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure within 12 months</strong></td>
<td>577 (31.0)</td>
<td>574 (30.7)</td>
<td>647 (27.3)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>664 (35.6)</td>
<td>705 (37.8)</td>
<td>916 (38.6)</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (ml/min/1.73 m^2)</strong></td>
<td>61.8 ± 21.7</td>
<td>62.2 ± 21.5</td>
<td>66.0 ± 19.6</td>
</tr>
<tr>
<td><strong>Treatment for heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS inhibitor without neprilysin inhibitor</td>
<td>1314 (70.5)</td>
<td>1286 (68.9)</td>
<td>2007 (84.6)</td>
</tr>
<tr>
<td><strong>RAS inhibitor with neprilysin inhibitor</strong></td>
<td>340 (18.3)</td>
<td>387 (20.7)</td>
<td>250 (10.5)</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>1306 (70.1)</td>
<td>1355 (72.6)</td>
<td>1696 (71.5)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>1765 (94.7)</td>
<td>1768 (94.7)</td>
<td>2278 (96.0)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>578 (31.0)</td>
<td>593 (31.8)</td>
<td>622 (26.2%)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>220 (11.8)</td>
<td>222 (11.9)</td>
<td>190 (8.0%)</td>
</tr>
</tbody>
</table>
EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)

Placebo

Empagliflozin

Cumulative incidence (%)

Days after randomization

Patients at risk

Placebo 1867 1715 1612 1345 1108 854 611 410 224 109
Empagliflozin 1863 1763 1677 1424 1172 909 645 423 231 101

462 patients with event
Rate: 21.0/100 patient-years

361 patients with event
Rate: 15.8/100 patient-years

HR 0.75
(95% CI 0.65, 0.86)

P < 0.0001

Packer et al.
## EMPEROR-Reduced: Primary Endpoint Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>361/1863</td>
<td>462/1867</td>
<td>0.75 (0.65, 0.86)</td>
</tr>
<tr>
<td><strong>Baseline diabetes status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>200/927</td>
<td>265/929</td>
<td>0.72 (0.60, 0.87)</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>161/936</td>
<td>197/938</td>
<td>0.78 (0.64, 0.97)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>128/675</td>
<td>193/740</td>
<td>0.71 (0.57, 0.89)</td>
</tr>
<tr>
<td>≥65</td>
<td>233/1188</td>
<td>269/1127</td>
<td>0.78 (0.66, 0.93)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>294/1426</td>
<td>353/1411</td>
<td>0.80 (0.68, 0.93)</td>
</tr>
<tr>
<td>Female</td>
<td>67/437</td>
<td>109/456</td>
<td>0.59 (0.44, 0.80)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>264/1325</td>
<td>289/1304</td>
<td>0.88 (0.75, 1.04)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>24/123</td>
<td>48/134</td>
<td>0.46 (0.28, 0.75)</td>
</tr>
<tr>
<td>Asian</td>
<td>62/337</td>
<td>99/335</td>
<td>0.57 (0.41, 0.78)</td>
</tr>
<tr>
<td>Other</td>
<td>5/51</td>
<td>14/63</td>
<td>0.41 (0.15, 1.14)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>226/1263</td>
<td>322/1300</td>
<td>0.70 (0.59, 0.83)</td>
</tr>
<tr>
<td>≥30</td>
<td>135/600</td>
<td>140/567</td>
<td>0.85 (0.67, 1.08)</td>
</tr>
<tr>
<td><strong>Baseline eGFR (CKD-EPI), ml/min/1.73 m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>159/969</td>
<td>224/960</td>
<td>0.67 (0.55, 0.83)</td>
</tr>
<tr>
<td>&lt;60</td>
<td>202/893</td>
<td>237/906</td>
<td>0.83 (0.69, 1.00)</td>
</tr>
</tbody>
</table>
Empagliflozin Reduced Cardiovascular Death or Hospitalization for Heart Failure Similarly in Diabetics and Nondiabetics

**With diabetes**

HR 0.72 (0.60, 0.87)  
p=0.0006

**Without diabetes**

HR 0.78 (0.64, 0.97)  
p=0.0225
Empagliflozin Eliminated the Excess Risk of Major Heart Failure Events Attributable to Diabetes

**With diabetes**

Event rate in the empagliflozin group: 17.7/100 patient years

HR 0.72 (0.60, 0.87)  
p=0.0006

**Without diabetes**

Event rate in the placebo group: 17.6/100 patient years

HR 0.78 (0.64, 0.97)  
p=0.0225
EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3

**During double-blind treatment**

Mean change from baseline in eGFR (ml/min/1.73 m²)

**Difference in slope**

1.7 ml/min/1.73m²/year (95% CI: 1.1 – 2.4)  
P < 0.0001

Packer et al.  
During double-blind treatment

In 966 patients, eGFR was reassessed at the end of the trial 23-45 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

- 4.2 ml/min/1.73 m² on placebo
- 0.9 ml/min/1.73 m² on empagliflozin

P < 0.0001
EMPEROR-Reduced: Composite Renal Endpoint

Cumulative incidence (%) vs Days After Randomization

- Placebo: 58 patients with event, Rate: 3.1/100 patient-years
- Empagliflozin: 30 patients with event, Rate: 1.6/100 patient-years

HR 0.50 (95% CI 0.32, 0.77)

Packer et al. Under review
Empagliflozin Slowed the Rate of Decline in eGFR
Similarly in Patients With or Without Diabetes

The rate of decline in diabetic patients treated with empagliflozin was similar to rate of decline in nondiabetic patients treated with placebo.
Empagliflozin Reduced the Risk of Serious Adverse Renal Outcomes Similarly in Diabetics and Nondiabetics

With diabetes

HR 0.53 (0.31, 0.90)

Empagliflozin eliminated the excess risk of major adverse events attributable to diabetes

Without diabetes

HR 0.42 (0.19, 0.97)
### Trials in Heart Failure and a Reduced Ejection Fraction (With or Without Diabetes)

<table>
<thead>
<tr>
<th></th>
<th>DAPA-HF (dapagliflozin)</th>
<th>EMPEROR-Reduced (empagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>0.75 (0.65 – 0.85) [877 events]</td>
<td>0.75 (0.65 – 0.86) [823 events]</td>
</tr>
<tr>
<td>First hospitalization for heart failure</td>
<td>0.70 (0.59 – 0.83) [549 events]</td>
<td>0.69 (0.59 – 0.81) [588 events]</td>
</tr>
<tr>
<td>Renal composite endpoint</td>
<td>0.71 (0.44 – 1.16) [67 events]</td>
<td>0.50 (0.32 – 0.77) [88 events]</td>
</tr>
</tbody>
</table>

### Trials in Type 2 Diabetes (With or Without Heart Failure)

<table>
<thead>
<tr>
<th></th>
<th>DECLARE-TIMI58 (dapagliflozin)</th>
<th>EMPA-REG OUTCOME (empagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>0.83 (0.73 – 0.95) [913 events]</td>
<td>0.66 (0.55 – 0.79) [463 events]</td>
</tr>
<tr>
<td>First hospitalization for heart failure</td>
<td>0.73 (0.61 – 0.88) [498 events]</td>
<td>0.65 (0.50 – 0.85) [221 events]</td>
</tr>
<tr>
<td>Renal composite endpoint</td>
<td><strong>0.53 (0.43 – 0.66)</strong> [365 events]</td>
<td><strong>0.54 (0.40 – 0.75)</strong> [152 events]</td>
</tr>
</tbody>
</table>
• The 25% decrease in the risk of the composite of cardiovascular death and heart failure hospitalization observed with empagliflozin in EMPEROR-Reduced was identical to that seen with dapagliflozin in DAPA-HF. Importantly, empagliflozin slowed the rate of progression of renal disease and reduced the risk of major adverse renal events.

• Empagliflozin reduced both heart failure and renal events similarly in patients with or without diabetes. The effect of empagliflozin on heart failure events and renal disease was to bring the risks seen in patients with diabetes to levels seen in the placebo group in patients without diabetes.

• The EMPEROR-Reduced trial is the first heart failure trial that has shown a favorable effect of any treatment on the evolution of chronic kidney disease.
Roundtable

ADEERA LEVIN, MD, FRCPC, FCAHS CM - MODERATOR
Professor of Medicine
Head Division of Nephrology
University of British Columbia

Consultant Nephrologist
Providence Health Care / St. Paul’s Hospital
Vancouver
Panelist Introductions

CHRISTOS ARGYROPOULOS, MD, PhD, FASN

DAVID CHERNEY, MD CM, PhD, FRCP(C)

HIDDO HEERSPINK, PhD, PharmD

MILTON PACKER, MD

KATHERINE R. TUTTLE, MD, FASN, FACP, FNKF
Roundtable Discussion

Please send questions to the panelists using the questions panel on your screen.
Closing Remarks

ADEERA LEVIN, MD, FRCPC, FCAHS CM - MODERATOR
Professor of Medicine
Head Division of Nephrology
University of British Columbia

Consultant Nephrologist
Providence Health Care / St. Paul’s Hospital
Vancouver
Supplemental slides
**Risk Mitigation Strategies for SGLT2 Inhibitors**

- Don’t reduce or stop insulin, the best defense against ketoacidosis.
- If hypoglycemia is an issue, reduce or stop metformin.
  - Even though metformin and SGLT2 inhibitors do not cause hypoglycemia *per se*, they can facilitate it in users of insulin or insulin secretagogues.
- If hypoglycemia is problematic after stopping metformin, reduce the SGLT2 inhibitor dose.
  - Heart and kidney protection appear to be dose independent.
- Hold SGLT2 inhibitor and metformin and check for urine ketones on “sick days.”
- Recommend hygienic measures to prevent genital mycotic infection or urinary tract infection.
  - Daily bathing, clean clothes, frequent voiding
- Monitor volume status due to diuretic effect of SGLT2 inhibition.
  - Consider decreasing or stopping conventional diuretic if patient is at-risk for volume depletion.
Estimates and Projections of the Global Prevalence of Diabetes in the 20-79 Year Age Group (millions)
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Initiate ACEi or ARB

Monitor serum creatinine and potassium (within 2–4 weeks after starting or changing dose)

- Normokalemia
  - < 30% increase in creatinine
    - Increase dose of ACEi or ARB or continue on maximally tolerated dose

- Hyperkalemia
  - Review concurrent drugs
  - Moderate potassium intake
    - Consider: diuretics
    - sodium bicarbonate
    - Gl cation exchangers

- > 30% increase in creatinine
  - Review for causes of AKI
    - Correct volume depletion
    - Reassess concomitant medications (e.g., diuretics, NSAIDs)
    - Consider renal artery stenosis

Reduce dose or stop ACEi or ARB as last resort
DAPA-CKD
DKD and Non-Diabetic CKD

- Participants with eGFR 25-75 mL/min/1.73m² and UACR 200-5000 mg/g (n=4304).
- Dapagliflozin 10 mg daily versus placebo.
- Primary endpoint (eGFR decline ≥50%, ESKD, kidney or CVD death) reduced by 39%.
- Outcomes were similar in participants with or without type 2 diabetes.