New Approaches to Transform Outcomes for Kidney Disease and Heart Disease in People with Diabetes

December 10, 2020
Support of the Diabetic Kidney Disease Collaborative is provided by Bayer, Boehringer Ingelheim and Lilly, AstraZeneca, and Janssen Pharmaceuticals, Inc.
Welcome & Opening Remarks

SUSAN QUAGGIN, MD, FASN
Chair, Diabetic Kidney Disease Collaborative
President-Elect, American Society of Nephrology
Disclosures

Employer: Northwestern University
Consultancy Agreements: Lowy Medical Research Foundation, AstraZeneca, Janssen, Roche, Genentech, Novartis, Goldfinch
Ownership Interest: Mannin Research
Research Funding: Mannin Research, AstraZeneca
Honoraria: KAIST (Korean Scientific-plenary lecture)
Patents and Inventions:
Scientific Advisor or Membership: Lowy Medical Research Institute, Mannin, AstraZeneca, JCI, Genentech/Roche, Novartis, Karolinska CVRM Institute
Speakers Bureau:
Other Interests/Relationships: CSO and founder, Mannin Research
New Treatments for Diabetic Kidney Disease

DAVID CHERNEY, MD CM, PHD, FRCP(C)
PROFESSOR OF MEDICINE, UNIVERSITY OF TORONTO
CLINICAL SCIENTIST, DIVISION OF NEPHROLOGY, UNIVERSITY HEALTH NETWORK
DIRECTOR, RENAL PHYSIOLOGY LABORATORY, UNIVERSITY HEALTH NETWORK
SENIOR SCIENTIST, TORONTO GENERAL HOSPITAL RESEARCH INSTITUTE
New Treatments for Diabetic Kidney Disease

David Cherney, MD CM, PhD, FRCP(C)
Professor of Medicine, University of Toronto
Clinician Scientist, Division of Nephrology, UHN
Director, Renal Physiology Laboratory, UHN
Senior Scientist, Toronto General Hospital Research Institute
Disclosures

Relationships with commercial entities:

• Consulting, honoraria: Boehringer Ingelheim, Lilly, Janssen, Merck, AstraZeneca, Mitsubishi-Tanabe, Sanofi, BMS, MAZE, Bayer, Novo Nordisk

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

  – Supported by Boehringer Ingelheim, Lilly, Janssen, Merck, AstraZeneca, Sanofi, Novo Nordisk
Objectives

• Sodium glucose cotransport-2 inhibition: mechanisms for kidney protection, key clinical trial data

• Mineralocorticoid receptor antagonists and DKD

• GLP1RA: rationale for kidney protection, trial data
Risk Factors and Targets to Prevent Renal/CV Disease


- **Glucose**
  - HbA$_{1c}$ target individualized, but generally $\sim 7\%^1$

- **BP**
  - Target of $<130/80$ mmHg$^2$

- **RAAS inhibition**
  - ACE inhibitor or ARBs when albumin excretion $\geq 30$ mg/g$^1$

- **Lipids**
  - Lipid-lowering recommended to reduce risk of atherosclerotic events; statins not recommended in patients on hemodialysis$^1$
Significant residual risk remains following the use of RAAS inhibitors approved for the treatment of CKD – novel therapies are required

SGLT2 inhibition
Proposed renal protective pathways with SGLT2 inhibitors

Protection against diabetic kidney disease

Potential direct cardiovascular effects; improved cardiac function with maintenance of renal perfusion

Intraglomerular pressure due to tubuloglomerular feedback effects

"Loop diuretic sparing" effect – preservation of intravascular volume and reduced volume overload

↓ Albuminuria, reducing possible direct toxic effects on renal tubules

↑ Oxygenation of renal tubular cells based on ↓ demand for solute transport and ↑ hemocrit leading to ↑ oxygen delivery

↓ Ambient pro-inflammatory/pro-fibrotic pathways (experimental evidence only)

 Improved metabolic parameters (↓ HbA1c, weight)

↓ Blood pressure, even in the presence of CKD, ↓ endothelial dysfunction, ↓ arterial stiffness

↓ Intraglomerular pressure due to tubuloglomerular feedback effects

Heerpsink/Cherney. Kidney Int 2018
Evidence for the primary role of the kidney in trials: ESKD, substantial loss of eGFR or renal death (baseline eGFR)

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥90 ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>120</td>
<td>8162</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>17</td>
<td>2476</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>22</td>
<td>1529</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=41.8%; P_heterogeneity=0.18</td>
</tr>
<tr>
<td>eGFR 60–&lt;90 ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE</td>
<td>78</td>
<td>1809</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>186</td>
<td>7732</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>30</td>
<td>5625</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>61</td>
<td>3638</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.0%; P_heterogeneity=0.46</td>
</tr>
<tr>
<td>eGFR 45–&lt;60 ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE</td>
<td>99</td>
<td>1279</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>16</td>
<td>1485</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>39</td>
<td>1238</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.0%; P_heterogeneity=0.52</td>
</tr>
<tr>
<td>eGFR &lt;45 ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE</td>
<td>200</td>
<td>1313</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10</td>
<td>554</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>30</td>
<td>563</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.0%; P_heterogeneity=0.94</td>
</tr>
<tr>
<td>P_merge for eGFR subgroup=0.073</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# CREDENCE Summary

<table>
<thead>
<tr>
<th>Primary</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ESKD, doubling of serum creatinine, or renal or CV death</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. CV death or hospitalization for heart failure</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>3. CV death, MI, or stroke</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
<td>✔</td>
</tr>
<tr>
<td>4. Hospitalization for heart failure</td>
<td>0.61 (0.47–0.80)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>5. ESKD, doubling of serum creatinine, or renal death</td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>6. CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
<td>Not significant</td>
</tr>
<tr>
<td>7. All-cause mortality</td>
<td>0.83 (0.68–1.02)</td>
<td>–</td>
<td>Not formally tested</td>
</tr>
<tr>
<td>8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina</td>
<td>0.74 (0.63–0.86)</td>
<td>–</td>
<td>Not formally tested</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Change in mGFR (mL/min/1.73 m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>−6.0</td>
</tr>
</tbody>
</table>

Mean difference: −6.6 mL/min/1.73 m^2
(95% CI: −9.0, −4.2);
P < 0.0001

**DAPA-CKD: Dapagliflozin in Patients With Chronic Kidney Disease**

To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB.

---

**Objective**

- Composite of sustained ≥50% eGFR decline, ESKD\(^a\), renal or CV death

**Secondary Outcomes**

- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

---

**Key Inclusion Criteria**

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m\(^2\)
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

**Key Exclusion Criteria**

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

---

\(^a\)ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m\(^2\) for at least 28 days.

ACEI = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death

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 <15mL/min/1.73m² 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.


<table>
<thead>
<tr>
<th>Months from Randomization</th>
<th>N at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAPA 10 mg</td>
</tr>
<tr>
<td>0</td>
<td>2152</td>
</tr>
<tr>
<td>4</td>
<td>2001</td>
</tr>
<tr>
<td>8</td>
<td>1955</td>
</tr>
<tr>
<td>12</td>
<td>1898</td>
</tr>
<tr>
<td>16</td>
<td>1841</td>
</tr>
<tr>
<td>20</td>
<td>1701</td>
</tr>
<tr>
<td>24</td>
<td>1288</td>
</tr>
<tr>
<td>28</td>
<td>831</td>
</tr>
<tr>
<td>32</td>
<td>309</td>
</tr>
</tbody>
</table>

Cumulative Incidence %

<table>
<thead>
<tr>
<th>NNT=19</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.61 (0.51-0.72)</td>
<td>0.000000028</td>
</tr>
</tbody>
</table>
## Individual Components of the Primary Composite Outcome

<table>
<thead>
<tr>
<th></th>
<th>Number of Events</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite Outcome</strong></td>
<td></td>
<td>DAPA 10 mg (N=2152)</td>
<td>Placebo (N=2152)</td>
</tr>
<tr>
<td>Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death</td>
<td>197</td>
<td>312</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Components of the Primary Composite Outcome</strong></td>
<td></td>
<td>DAPA 10 mg (N=2152)</td>
<td>Placebo (N=2152)</td>
</tr>
<tr>
<td>≥50% eGFR Decline</td>
<td>112</td>
<td>201</td>
<td>0.53</td>
</tr>
<tr>
<td>ESKD</td>
<td>109</td>
<td>161</td>
<td>0.64</td>
</tr>
<tr>
<td>eGFR &lt;15mL/min/1.73m²</td>
<td>84</td>
<td>120</td>
<td>0.67</td>
</tr>
<tr>
<td>Chronic Dialysis</td>
<td>68</td>
<td>99</td>
<td>0.66</td>
</tr>
<tr>
<td>Transplantation</td>
<td>3</td>
<td>8</td>
<td>NC</td>
</tr>
<tr>
<td>Renal Death</td>
<td>2</td>
<td>6</td>
<td>NC</td>
</tr>
<tr>
<td>CV Death</td>
<td>65</td>
<td>80</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Legend:**
- **DAPA 10 mg Better**
- **Placebo Better**

*CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable*

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
## Primary Composite Outcome: Prespecified Subgroup Analyses

<table>
<thead>
<tr>
<th>Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death</th>
<th>Number of Events</th>
<th>HR (95% CI)</th>
<th>p-value Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>197</td>
<td>312</td>
<td>0.61 (0.51, 0.72)</td>
</tr>
<tr>
<td>T2D at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes T2D at Baseline</td>
<td>152</td>
<td>229</td>
<td>0.64 (0.52, 0.79)</td>
</tr>
<tr>
<td>No T2D at Baseline</td>
<td>45</td>
<td>83</td>
<td>0.50 (0.35, 0.72)</td>
</tr>
<tr>
<td>UACR (mg/g) at Baseline</td>
<td>0.52</td>
<td></td>
<td></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>eGFR (mL/min/1.73m²) at Baseline</td>
<td>0.22</td>
<td></td>
<td></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>

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
### Statistical Significance Achieved for the Primary and All Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Number of Events</th>
<th>DAPA 10 mg (N=2152)</th>
<th>Placebo (N=2152)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of ≥50% eGFR Decline, ESKD, and Renal or CV Death</td>
<td>197</td>
<td>312</td>
<td>0.61</td>
<td>(0.51, 0.72)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of ≥50% eGFR Decline, ESKD, or Renal Death</td>
<td>142</td>
<td>243</td>
<td>0.56</td>
<td>(0.45, 0.68)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Composite of CV Death or Hospitalization for HF</td>
<td>100</td>
<td>138</td>
<td>0.71</td>
<td>(0.55, 0.92)</td>
<td>0.0089</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>101</td>
<td>146</td>
<td>0.69</td>
<td>(0.53, 0.88)</td>
<td>0.0035</td>
<td></td>
</tr>
</tbody>
</table>

**CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.**
Aldosterone and the Mineralocorticoid Receptor in Physiology and Pathophysiology

MR activation

↑ NADPH oxidase activity

Wnt/β-catenin

↑ ROS

↓ NO

Pro-inflammatory cytokines, pro-fibrotic proteins

Endothelial dysfunction

Renal inflammatory and fibrosis

DKD (glomerular hypertrophy, glomerulosclerosis, renal injury)

Inflammation, oxidative stress and fibrosis

Adapted from: Metabolism - Clinical and Experimental 2016 65, 1342-1349DOI: (10.1016/j.metabol.2016.06.001), copyright TX0011429.
MR, mineralocorticoid receptor; ALD, aldosterone; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; ROS, reactive oxygen species.
FIDELIO-DKD was a randomised, double-blind, event-driven, placebo-controlled phase III trial

13,911 patients enrolled

1374 patients switched from FIGARO-DKD

1552 patients switched to FIGARO-DKD

13,911 patients enrolled

5734 patients randomised

Run-in

Screening

Visit 1

Visit 2 (month 1)

Visit 3 (month 4)

Visit n (every 4 months)

End-of-study visit

Post-treatment follow-up

Post-treatment follow-up

Run-in visit

Screening visit

Optimisation of ACEi or ARB therapy

Finerenone (initial dose 10 or 20 mg od#)

Placebo (initial dose 10 or 20 mg od#)

4–16 weeks

≤2 weeks

*: Randomisation was stratified by region (North America, Latin America, Europe, Asia or Other), eGFR category at screening visit (25–<45, 45–<60, or ≥60 ml/min/1.73 m²) and albuminuria category at screening visit (‘moderately elevated’ or ‘severely elevated’); #: Up-titration of study drug was encouraged after visit 2 provided potassium value was ≤4.8 mmol/l or less and eGFR was stable; down-titration was allowed any time after treatment initiation for safety reasons; §: 4 weeks and 5 days after last dose of study drug

Efficacy outcomes included kidney- and CV-specific composites

**Primary kidney-specific outcome**

Time to first occurrence of:

- Onset of kidney failure:
  - ESKD (initiation of chronic dialysis for ≥90 days or kidney transplantation)
  - Sustained eGFR <15 ml/min/1.73 m²
- A sustained ≥40% decrease of eGFR from baseline
- Renal death

*Weighted Bonferroni–Holm procedure applied to control for multiplicity between the primary and key secondary outcomes, resulting in a two-sided alpha of 3.28% and 1.58% (after adjustment for one formal interim analysis), respectively*; *Confirmed by a second measurement at the earliest 4 weeks after the initial measurement; †Events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death

**Key secondary CV outcome**

Time to first occurrence of 4-point MACE, defined as:

- CV death
- Nonfatal MI
- Non-fatal stroke
- Hospitalisation for HF

**Other secondary outcomes**

- Time to death from any cause
- Time to hospitalisation for any cause
- Change in UACR from baseline to month 4
- Time to first occurrence of onset of kidney failure, a sustained ≥57% decrease of eGFR from baseline, or renal death

### At baseline, patients had well-controlled blood pressure and HbA1c

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finerenone (N=2833)</th>
<th>Placebo (N=2841)</th>
<th>Total (N=5674)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>65.4 ± 8.9</td>
<td>65.7 ± 9.2</td>
<td>65.6 ± 9.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1953 (68.9)</td>
<td>2030 (71.5)</td>
<td>3983 (70.2)</td>
</tr>
<tr>
<td>HbA1c, %, mean ± SD</td>
<td>7.7 ± 1.3</td>
<td>7.7 ± 1.4</td>
<td>7.7 ± 1.3</td>
</tr>
<tr>
<td>Duration of T2D, years, mean ± SD</td>
<td>16.6 ± 8.8</td>
<td>16.6 ± 8.8</td>
<td>16.6 ± 8.8</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>31.1 ± 6.0</td>
<td>31.1 ± 6.0</td>
<td>31.1 ± 6.0</td>
</tr>
<tr>
<td>SBP, mmHg, mean ± SD</td>
<td>138.1 ± 14.3</td>
<td>138.0 ± 14.4</td>
<td>138.0 ± 14.4</td>
</tr>
<tr>
<td>DBP, mmHg, mean ± SD</td>
<td>75.8 ± 9.7</td>
<td>75.8 ± 9.7</td>
<td>75.8 ± 9.7</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>1375 (48.5)</td>
<td>1371 (48.3)</td>
<td>2746 (48.4)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1044 (36.9)</td>
<td>1078 (37.9)</td>
<td>2122 (37.4)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>414 (14.6)</td>
<td>392 (13.8)</td>
<td>806 (14.2)</td>
</tr>
</tbody>
</table>

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes

In an exploratory analysis, the acute effect of finerenone is a drop in eGFR but the long-term effect is a slowing of eGFR decline*

---

*Mixed model analysis of eGFR over time. Full analysis set; #LS mean change in eGFR slope from baseline to month 4; ‡LS mean change in eGFR slope from month 4 to the permanent discontinuation or end-of-study visit

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares

Although investigator-reported hyperkalaemia was increased, the clinical impact was minimal

There were no deaths due to hyperkalaemia, and the incidences of treatment discontinuation or hospitalisation due to hyperkalaemia were low

*Investigator-reported AEs using the MedDRA preferred terms ‘hyperkalaemia’ and ‘blood potassium increased’. AE, adverse event; SAE, serious adverse event

GLP1 receptor agonists: Direct, indirect effects of GLP-1 may impact renal outcomes

**Direct effects:**
- Natriuresis
- Haemodynamic effects in the setting of diabetic glomerular hyperfiltration
- Inhibition of RAAS
- Reduced oxidative stress
- Anti-inflammatory effects

**Indirect effects:**
- Improved glycaemic control
- Reduction in blood pressure
- Weight loss

GLP-1, glucagon-like peptide-1; RAAS, renin-angiotensin-aldosterone system
NEW OR WORSENING NEPHROPATHY

LEADER1

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67; 0.92)</td>
</tr>
<tr>
<td>New onset of persistent macroalbuminuria</td>
<td>0.74 (0.60; 0.91)</td>
</tr>
<tr>
<td>Persistent doubling of serum creatinine</td>
<td>0.89 (0.67; 1.19)</td>
</tr>
<tr>
<td>Need for continuous renal-replacement therapy</td>
<td>0.87 (0.61; 1.24)</td>
</tr>
<tr>
<td>Death due to renal disease</td>
<td>1.59 (0.52; 4.87)</td>
</tr>
</tbody>
</table>

SUSTAIN 62

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New of worsening nephropathy</td>
<td>0.64 (0.46; 0.88)</td>
</tr>
<tr>
<td>New onset of persistent macroalbuminuria</td>
<td>0.54 (0.37; 0.77)</td>
</tr>
<tr>
<td>Persistent doubling of serum creatinine</td>
<td>1.28 (0.64; 2.58)</td>
</tr>
<tr>
<td>Need for continuous renal-replacement therapy</td>
<td>0.91 (0.40; 2.07)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.
## Time to categorical eGFR reduction

**POST-HOC POOLED ANALYSIS OF LEADER AND SUSTAIN 6**

<table>
<thead>
<tr>
<th>Reduction in eGFR</th>
<th>Sema/lira pooled (N)</th>
<th>Placebo pooled (N)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall pooled population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>791</td>
<td>848</td>
<td>0.92 (0.84; 1.02)</td>
<td>0.1005</td>
</tr>
<tr>
<td>40%</td>
<td>378</td>
<td>432</td>
<td>0.86 (0.75; 0.99)</td>
<td>0.0386</td>
</tr>
<tr>
<td>50%</td>
<td>185</td>
<td>229</td>
<td>0.80 (0.66; 0.97)</td>
<td>0.0233</td>
</tr>
<tr>
<td>57%</td>
<td>121</td>
<td>135</td>
<td>0.89 (0.69; 1.13)</td>
<td>0.3423</td>
</tr>
<tr>
<td><strong>eGFR ≥30 to &lt;60 mL/min/1.73 m² and micro-or macroalbuminuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>151</td>
<td>196</td>
<td>0.65 (0.53; 0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>40%</td>
<td>89</td>
<td>120</td>
<td>0.64 (0.48; 0.84)</td>
<td>0.0013</td>
</tr>
<tr>
<td>50%</td>
<td>51</td>
<td>78</td>
<td>0.57 (0.40; 0.81)</td>
<td>0.0017</td>
</tr>
<tr>
<td>57%</td>
<td>34</td>
<td>53</td>
<td>0.56 (0.37; 0.87)</td>
<td>0.0093</td>
</tr>
<tr>
<td><strong>eGFR ≥60 mL/min/1.73 m² or normoalbuminuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>579</td>
<td>591</td>
<td>0.99 (0.88; 1.10)</td>
<td>0.7982</td>
</tr>
<tr>
<td>40%</td>
<td>245</td>
<td>270</td>
<td>0.91 (0.76; 1.08)</td>
<td>0.2810</td>
</tr>
<tr>
<td>50%</td>
<td>101</td>
<td>118</td>
<td>0.86 (0.66; 1.12)</td>
<td>0.2598</td>
</tr>
<tr>
<td>57%</td>
<td>58</td>
<td>61</td>
<td>0.95 (0.67; 1.37)</td>
<td>0.7961</td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Presented at the 56th European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Congress, 13-16 June 2019, Budapest, Hungary
<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide (n=4949)</th>
<th>Placebo (n=4952)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td>Incidence rate (number of events per 100 person-years)</td>
<td>Number of patients (%)</td>
<td>Incidence rate (number of events per 100 person-years)</td>
</tr>
<tr>
<td>Main analyses of renal effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite renal outcome</td>
<td>848 (17.1%)</td>
<td>3.47</td>
<td>970 (19.6%)</td>
<td>4.07</td>
</tr>
<tr>
<td>Components of composite renal outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New macroalbuminuria</td>
<td>441 (8.9%)</td>
<td>1.76</td>
<td>561 (11.3%)</td>
<td>2.29</td>
</tr>
<tr>
<td>Sustained decline in eGFR of ≥30%</td>
<td>453 (9.2%)</td>
<td>1.79</td>
<td>500 (10.1%)</td>
<td>2.00</td>
</tr>
<tr>
<td>Chronic renal replacement therapy</td>
<td>16 (0.3%)</td>
<td>0.06</td>
<td>21 (0.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serious renal adverse event*</td>
<td>84 (1.7%)</td>
<td>0.32</td>
<td>93 (1.9%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sensitivity analyses of renal effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained decline in eGFR of ≥40%</td>
<td>169 (3.4%)</td>
<td>0.66</td>
<td>237 (4.8%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Composite renal outcome with this decline</td>
<td>587 (11.9%)</td>
<td>2.36</td>
<td>751 (15.2%)</td>
<td>3.10</td>
</tr>
<tr>
<td>Sustained decline in eGFR of ≥50%</td>
<td>61 (1.2%)</td>
<td>0.24</td>
<td>108 (2.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Composite renal outcome with this decline</td>
<td>496 (10.0%)</td>
<td>1.99</td>
<td>649 (13.1%)</td>
<td>2.66</td>
</tr>
</tbody>
</table>

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Table 2: Effect of treatment allocation on renal outcomes
3160 patients

- T2D, HbA1c ≤10%
- RAAS blocker
- eGFR ≤75 to ≥50* and UACR >300 to <5000 mg/g OR eGFR <50 to ≥25* and UACR >100 to <5000 mg/g

0.25 mg 0.5 mg 1.0 mg semaglutide s.c. OW + T2D and CKD standard-of-care

0.25 mg 0.5 mg 1.0 mg placebo s.c. OW + T2D and CKD standard-of-care

*(mL/min/1.73 m²)
CKD, chronic kidney disease; OW, once weekly; T2D, type 2 diabetes.
Primary endpoint

Time to first occurrence of a composite endpoint consisting of:

- Onset of persistent* ≥50% reduction in eGFR (CKD-EPI) compared with baseline
- Onset of persistent* eGFR (CKD-EPI) <15 mL/min/1.73 m²
- Initiation of chronic renal replacement therapy**
- Renal death
- CV death

*persistent outcome in eGFR is defined as having two consecutive central laboratory assessments at least 4 weeks apart; **dialysis or kidney transplantation. Chronic is defined as at least 4 weeks of intermittent dialysis treatment. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate.
TREATMENT ALGORITHM FOR SELECTING ANTIHYPERGLYCEMIC DRUGS FOR PATIENTS WITH T2D AND CKD

Lifestyle therapy

Physical activity
Nutrition
Weight loss

First-line therapy

Metformin
- eGFR < 45: Reduce dose
- eGFR < 30: Discontinue

SGLT2 inhibitor
- eGFR < 30: Do not initiate
- Dialysis: Discontinue

Dialysis

Additional drug therapy as needed for glycemic control

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

DPP-4 inhibitor
Insulin
Sulfonylurea
TZD
Alpha-glucosidase inhibitor

KDIGO 2020 CLINICAL PRACTICE GUIDELINE ON DIABETES MANAGEMENT IN CKD
Clinical, research implications

1. SGLT2 inhibitors: “pleiotropic effects”, (EMPEROR-reduced, DAPA-HF, DAPA-CKD)
2. FIDELIO: new kidney protective therapy
3. GLP1RA: have potential renal protective effects, FLOW is ongoing
4. Implementation of trial results urgent priority
Acknowledgments

UHN/MSH Research Team
Bruce Perkins
Sunita Singh
Vesta Lai, RN, CDE
   Maria Maione, RN
   Josephine Tse, RN
   Angela Lee, RN
   Leslie Cham, RN
Students:
   Yuliya Lytvyn, PhD
   Marko Skrtic, MD PhD
   Harindra Rajasekeran MSc
   Jaya Aminathan, MD
   Vik Sridhar, MD
   Christine Chen BSc

EMPA-REG OUTCOME
Bernard Zinman
Christoph Wanner
Silvio Inzucchi
Gert Meyer
Subodh Verma

FSGS Study team (Toronto, Ottawa, Winnipeg)
Heather N. Reich
Michelle Hladunewich
Daniel Catran
Ian W. Gibson M
Manish M. Sood
Andrew Advani
Moumita Barua

Sunnybrook
Julie Lovshin

Colorado
Petter Bjornstad
David Maahs

Holland
Hiddo Heerspink
Claire Dekkers
Ron Gansevoort
Daniel van Raalte

University of Ottawa
Dylan Burger
Kevin Burns

Vancouver – DIAMOND trial
Sean Barbour

Kawasaki Medical School, Japan
Kengo Kidokoro
Naoki Kashihara

Laboratory Medicine Program
Paul Yip
Jenny Chung
Vathany Kulasingam

• Grant funding: • Salary support:
KDIGO Clinical Practice Guideline
on Diabetes Management in CKD

IAN DE BOER, MD, MS
PROFESSOR OF MEDICINE
ADJUNCT PROFESSOR OF EPIDEMIOLOGY
ASSOCIATE DIRECTOR, KIDNEY RESEARCH INSTITUTE
UNIVERSITY OF WASHINGTON
SEATTLE, WA
KDIGO Clinical Practice Guideline on Diabetes Management in CKD

KDIGO Guideline Co-Chairs:
Ian de Boer, MD, MS
Peter Rossing, MD, DMSc
DISCLOSURES

• Consulting for Astra Zeneca, Bayer, Boehringer-Ingelheim, Cyclerion Therapeutics, George Clinical, Goldfinch Bio, Ironwood

• Research equipment and supplies from Medtronic, Abbott, DexCom
**Work Group**

- Diverse expertise
- Worldwide scope
- Deep experience
- Patients
- Evidence Review Team

**Work Group Co-Chairs**

- Ian H. de Boer, MD, MS
  Kidney Research Institute
  University of Washington
  Seattle, WA, USA

- Peter Rosing, MD, DMSc
  Steno Diabetes Center Copenhagen
  University of Copenhagen
  Copenhagen, Denmark

- M. Luisa Caramori, MD, PhD, MSc
  University of Minnesota
  Minneapolis, MN, USA

- Wasiu A. Olowu, MBBS, FMCPhysed
  Obafemi Awolowo University
  Teaching Hospitals Complex
  Ile-Ife, Osun State, Nigeria

- Juliana C.N. Chan, MBChB, MD, FHKCP, FHKAM, FRCP
  The Chinese University of Hong Kong
  Hong Kong, China

- Tami Sadusky, MBA
  Patient Representative
  Seattle, WA, USA

- Hiddo J.L. Heerspink, PhD, PharmD
  University of Groningen
  Groningen, The Netherlands

- Nikhil Tandon, MBBS, MD, PhD
  All India Institute of Medical Sciences
  New Delhi, India

- Clint Hurst, BSc
  Patient Representative
  Houston, TX, USA

- Katherine R. Tuttle, MD, FASN, FACP, FNKF
  University of Washington
  Spokane, WA, USA

- Kamlesh Khunti, MD, PhD, FRCP, FRCGP, FMedSci
  University of Leicester
  Leicester, United Kingdom

- Christoph Wanner, MD
  University Hospital of Würzburg
  Würzburg, Germany

- Adrian Liew, MBBS, MRCP (UK), FAMS, FRCP (Edin), FASN, MClinEpid
  Mount Elizabeth Novena Hospital
  Singapore

- Katy G. Wilkens, MS, RD
  Northwest Kidney Centers
  Seattle, WA, USA

- Erin D. Michos, MD, MHS, FAHA, FACC, FASE, FASPC
  Johns Hopkins University School of Medicine
  Baltimore, MD, USA

- Sophia Younous, MBBS, FRACP, PhD
  Monash University
  Melbourne, Australia

- Sankar D. Navaneethan, MD, MS, MPH
  Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center
  Houston, TX, USA

- Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Director
  Martin Howell, PhD, Assistant Project Director
  David J. Tunnicliffe, PhD, Evidence Review Project Team Leader and Project Manager
LITERATURE SEARCH

OCTOBER 2018; UPDATED IN FEBRUARY 2020

Randomized controlled trials
Search 18th October 2018: Cochrane Kidney and Transplant Registry of studies
2628 studies retrieved
Updated search February 2020: Cochrane Kidney and Transplant Registry of studies
3039 citations retrieved
- Antihypertensive therapy: 86 RCTs
  - Potassium binders: 1 RCT
  - Antiplatelet therapy: 2 RCTs
  - Smoking cessation: 1 RCT
  - Bariatric surgery: 0 RCTs
  - Weight loss therapies: 0 RCTs
  - Exercise interventions: 47 RCTs
  - Dietary interventions: 28 RCTs
  - Alternative biomarkers and glucose monitoring: 0 RCTs
  - Glycemic targets: 14 RCTs
  - Glycemic therapies: 58 RCTs
  - Education: 4 RCTs
  - Models of care: 3 RCTs

Observational studies
Alternative biomarkers and glucose monitoring correlation search: February 2019 and updated search February 2020
1373 citations retrieved
- 56 duplicates removed
- 1241 citations excluded
- Title and abstract screening
- 45 citations excluded
- Full-text screening
- Included studies
  - 244 RCTs (n = 150,000)
  - 31 observational studies
  - 50 reviews

Reviews
Search October 2018 and updated search February 2020
2311 citations retrieved
- 66 duplicates removed
- 2148 citations excluded
- Title and abstract screening
- 47 citations excluded
- Full-text screening
SCOPE OF THE CLINICAL PRACTICE GUIDELINE

Include:
• Types 1 and 2 diabetes
• All stages of CKD
  • Kidney transplant recipients
  • Dialysis
• Interventions addressed with rigorous data (RCTs)
  • Lifestyle
  • Pharmacotherapy
  • Systems

Exclude:
• Interventions covered elsewhere
  • Blood pressure
  • Lipids
• Prevention & screening
• Topics with insufficient data
  • Diagnosis
  • Emerging & pipeline therapies
**Diabetes & CKD Guideline Contents**

- **Chapter 1. Comprehensive care in patients with diabetes and CKD**
  - Comprehensive diabetes and CKD management
  - RAS blockade
  - Smoking cessation

- **Chapter 2. Glycemic monitoring and targets in patients with diabetes and CKD**
  - Glycemic monitoring
  - Glycemic targets

- **Chapter 3. Lifestyle interventions in patients with diabetes and CKD**
  - Nutrition intake
  - Physical activity

- **Chapter 4. Antihyperglycemic therapies in patients with diabetes and CKD**
  - Overall approach
  - Metformin
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists

- **Chapter 5. Approaches to management of patients with diabetes and CKD**
  - Self-management education programs
  - Team-based integrated care
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figure 2).
Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).
GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD

Recommendation 2.1.1: We recommend hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD (1C).

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in antihyperglycemic therapy.

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4-G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.
**Glycemic Monitoring and Targets in Patients with Diabetes and CKD**

Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C).*

<table>
<thead>
<tr>
<th>CKD G1</th>
<th>Absent/minor</th>
<th>Few</th>
<th>Long</th>
<th>Present</th>
<th>Available</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of CKD</td>
<td>Macrovascular complications</td>
<td>Comorbidities</td>
<td>Life expectancy</td>
<td>Hypoglycemia awareness</td>
<td>Resources for hypoglycemia management</td>
<td>Propensity of treatment to cause hypoglycemia</td>
</tr>
<tr>
<td>CKD G5</td>
<td>Present/severe</td>
<td>Many</td>
<td>Short</td>
<td>Impaired</td>
<td>Scarce</td>
<td>High</td>
</tr>
</tbody>
</table>
Lifestyle Interventions in Patients with Diabetes and CKD

Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.
Lifestyle Interventions in Patients with Diabetes and CKD

Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g of protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis (2C).

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Recommendation 3.1.2: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD (2C).

Recommendation 3.2.1. We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (1D).
CLINICAL TRIALS OF NEW DIABETES DRUGS

Cefalu W et al, Diabetes Care 2018
### Summary of the Benefits and Harms of SGLT2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors, by Class, as Observed in Large, Placebo-Controlled Clinical Outcomes Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiovascular effects</th>
<th>Kidney effects</th>
<th>Notable adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbA₁c lowering</td>
<td>Major atherosclerotic cardiovascular events</td>
<td>Heart failure</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6–0.9% (CKD G1–G2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3–0.5% (CKD G3a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− (CKD G3b–G4) NA (CKD G5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0–1.2% (CKD G3a–4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5–0.7% (CKD G3a–4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* GFR: Glomerular filtration rate
Figure 18. Treatment algorithm for selecting antihyperglycemic drugs for patients with T2D and CKD

- **Lifestyle therapy**
  - Physical activity
  - Nutrition
  - Weight loss

- **First-line therapy**
  - **Metformin**
    - eGFR < 45: Reduce dose
    - eGFR < 30: Discontinue
    - Dialysis: Discontinue
  - **SGLT2 inhibitor**
    - eGFR < 30: Do not initiate
    - Dialysis: Discontinue

- **Additional drug therapy as needed for glycemic control**
  - GLP-1 receptor agonist (preferred)
  - DPP-4 inhibitor
  - Insulin
  - Sulfonylurea
  - TZD
  - Alpha-glucosidase inhibitor

- **Guided by patient preferences, comorbidities, eGFR, and cost**
- **Includes patients with eGFR < 30 ml/min per 1.73 m² or treated with dialysis**
- **See Figure 20**
Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m² with an SGLT2i (1A).

<table>
<thead>
<tr>
<th>Practical provider guide to initiating SGLT-2 inhibitors in patients with type 2 diabetes and CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment</strong></td>
</tr>
<tr>
<td>Eligible patients:</td>
</tr>
<tr>
<td>• eGFR ≥ 30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>High priority features:</td>
</tr>
<tr>
<td>• ACR ≥ 200 mg/g</td>
</tr>
<tr>
<td>• Heart failure</td>
</tr>
<tr>
<td>Potential contraindications:</td>
</tr>
<tr>
<td>• Genital infection risk</td>
</tr>
<tr>
<td>• Diabetic ketoacidosis</td>
</tr>
<tr>
<td>• Foot ulcers</td>
</tr>
<tr>
<td>• Immunosuppression</td>
</tr>
<tr>
<td><strong>Glycemia</strong></td>
</tr>
<tr>
<td>Hypoglycemia risk?</td>
</tr>
<tr>
<td>• Insulin or sulfonylurea</td>
</tr>
<tr>
<td>• History of severe hypoglycemia</td>
</tr>
<tr>
<td>• HbA1c at or below goal</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td>Volume depletion risk?</td>
</tr>
<tr>
<td>• Concurrent diuretic use</td>
</tr>
<tr>
<td>• Tenuous volume status</td>
</tr>
<tr>
<td>• History of AKI</td>
</tr>
</tbody>
</table>
 Recommendation 4.3.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).
**APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD**

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (Figure 28) *(1C)*.

**Key objectives are to:**

<table>
<thead>
<tr>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve diabetes-related knowledge, beliefs, and skills</td>
</tr>
<tr>
<td>Improve self-management and self-motivation</td>
</tr>
<tr>
<td>Encourage adoption and maintenance of healthy lifestyles</td>
</tr>
<tr>
<td>Improve vascular risk factors</td>
</tr>
<tr>
<td>Increase engagement with medication, glucose monitoring, and complication screening programs</td>
</tr>
<tr>
<td>Reduce risk to prevent (or better manage) diabetes-related complications</td>
</tr>
<tr>
<td>Improve emotional and mental well-being, treatment satisfaction, and quality of life</td>
</tr>
</tbody>
</table>
**APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD**

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, health care assistants, community workers, peer supporters) preferably with knowledge of CKD (Figure 33).
OVERALL SUMMARY

• First KDIGO guideline on Diabetes and CKD now available
• Provide recommendations and practice points on:
  • Comprehensive care
  • Glycemic monitoring and targets
  • Lifestyle interventions
  • Antihyperglycemic therapies
  • Approaches to management of patients
• Patient-centered decision-making and support; and consistent efforts at improving diet and exercise remain the foundation of all glycemic management
• Control of risk factors including RAS blockade remains part of standard of care
• Glycemia is monitored with HbA1c and blood glucose
• Glycemic targets should be individualized with focus on increased risk for hypoglycemia with declining kidney function
• Initial use of both metformin and SGLT2i is recommended for T2D
• Health care organizations should support a coordinated effort
ACKNOWLEDGEMENTS

KDIGO
Michael Cheung
Amy Earley
Melissa Thompson
Wolfgang Winkelmayr
Michel Jadoul
Marcello Tonelli

Evidence Review Team
Jonathan Craig
Martin Howell
David Tunnicliffe

Work Group
Peter Rossing (Denmark), Co-Chair
Luiza Caramori (USA)
Juliana Chan (Hong Kong)
Clint Hurst (USA)
Kamlesh Khunti (United Kingdom)
Hiddo Lambers-Heerspink (Netherlands)
Adrian Liew (Singapore)
Erin Michos (USA)

Comments? deboer@u.washington.edu

Sankar Navaneethan (USA)
Wasiu Olowu (Nigeria)
Tami Sadusky (USA)
Nikhil Tandon (India)
Katherine Tuttle (USA)
Christoph Wanner (Germany)
Katy Wilkens (USA)
Sophia Zoungas (Australia)
Implications of New SLGT2 Inhibitors on Heart Failure Guidelines

**CLYDE W. YANCY, MD, MSC, MACC, FAHA, MACP, FHFSNA**

PROFESSOR OF MEDICINE,
PROFESSOR, MEDICAL SOCIAL SCIENCE
CHIEF, CARDIOLOGY
ASSOCIATE DIRECTOR, BLUHM CV INSTITUTE
&
VICE-DEAN, DIVERSITY & INCLUSION
NORTHWESTERN UNIVERSITY, FSM
&
DEPUTY EDITOR, JAMA CARDIOLOGY
Disclosures

No Relevant Disclosures
Heart Failure Treatment, “where we are now”: the Current Paradigm
Stages, Phenotypes and Treatment of HF

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
- Patients Using cardiotoxins
- With family history of cardiomyopathy

**STAGE B**
Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Strategies
  - Identification of comorbidities
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Treatment
  - Diuresis to relieve symptoms of congestion
  - Beta blockers as appropriate
  - Aldosterone antagonists

**STAGE C**
Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Nitrates
  - ACEI and ARB
  - Digoxin

**STAGE D**
Refractory HF
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

Yancy C, et al. JACC, 2013
**Treatment of HFrEF Stage C and D**

1. **Step 1** Establish Dx of HFrEF; assess volume; initiate GDMT
2. **Step 2** Consider the following patient scenarios
   - NYHA class II–IV, provided est. CrCl >30 mL/min & K+<5.0 mEq/L
   - NYHA class II–III HF
     - Adequate BP on ACEI or ARB*: No C/I to ARB or sacubitril
   - NYHA class III–IV, in black patients
   - NYHA class II–III, LVEF ≤35%: (caveat: >1 y survival, ≥40 d post MI)
   - NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
   - NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker

3. **Step 3** Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred
   - Aldosterone antagonist (COR I)
   - Discontinue ACEI or ARB; initiate ARNI* (COR I)
   - Hydral-Nitrates†† (COR I)
   - ICD‡ (COR I)
   - CRT or CRT-D‡ (COR I)
   - Ivabradine (COR IIa)

4. **Step 4** Reassess symptoms
   - Refractory NYHA class III–IV (Stage D)
   - Symptoms improved
   - Palliative care† (COR I)
   - Transplant‡ (COR I)
   - LVAD‡ (COR IIa)
   - Investigational studies§

5. **Step 5** Consider additional therapy

---

†Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.
‡See 2013 HF guideline.
§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy-device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate-hydralazine; K+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

Yancy C, et al. JACC, 2016
Heart Failure Treatment; new data- “where we are headed now with SGLT2 inhibitors”:
Heart Failure
New trials and new data: SGLT2 inhibitors-prevention
Proposed Mechanism of Cardiorenal Protection With Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors: At the level of the kidney, SGLT2 inhibition promotes glycosuria and natriuresis. It also promotes afferent arterial constriction resulting in a decrease in intraglomerular pressure. A reduction in preload and resultant left ventricular (LV) wall stress improves overall LV filling conditions. Additionally, metabolic effects of SGLT2 inhibition to improve myocardial energetics and reduce afterload have also been proposed as cardioprotective mechanisms. ATP indicates adenosine triphosphate.

This figure was specifically commissioned for this article and has not been reproduced in any form in any media format. Figure created by M. Gail Rudakevich, BSc, MScBMC.
Cardiovascular Outcomes and Death from Any Cause.


A  Primary Outcome

B  Death from Cardiovascular Causes

C  Death from Any Cause

D  Hospitalization for Heart Failure

No. at Risk

Empagliflozin  Placebo

Empagliflozin  Placebo

Northwestern Medicine

The NEW ENGLAND JOURNAL of MEDICINE
SGLT2 Inhibitors Reduce the Risk of Heart Failure Events in Type 2 Diabetes

Lancet 2018 Nov (online)
Heart Failure
New trials and new data: SGLT2 inhibitors-treatment
Cardiovascular Outcomes.

A Primary Outcome

No. at Risk
Placebo: 2371, 2218, 2163, 2105, 1917, 1847, 1766, 1684, 1560, 1468, 1346, 1219, 1066, 935, 793, 612, 210
Dapagliflozin: 2373, 2218, 2163, 2105, 1917, 1847, 1766, 1684, 1560, 1468, 1346, 1219, 1066, 935, 793, 612, 210

Hazard ratio, 0.74 (95% CI, 0.61–0.85)
P < 0.001

B Hospitalization for Heart Failure

No. at Risk
Placebo: 2371, 2264, 2168, 2082, 1924, 1483, 1101, 596, 212
Dapagliflozin: 2373, 2264, 2168, 2082, 1924, 1483, 1101, 596, 212

Hazard ratio, 0.70 (95% CI, 0.59–0.83)

C Death from Cardiovascular Causes

No. at Risk
Placebo: 2371, 2330, 2279, 2230, 2091, 1836, 1219, 664, 234
Dapagliflozin: 2373, 2330, 2279, 2230, 2091, 1836, 1219, 664, 234

Hazard ratio, 0.82 (95% CI, 0.69–0.98)

D Death from Any Cause

No. at Risk
Placebo: 2371, 2330, 2279, 2230, 2092, 1838, 1221, 665, 235
Dapagliflozin: 2373, 2342, 2296, 2251, 2150, 1666, 1243, 672, 233

Hazard ratio, 0.83 (95% CI, 0.71–0.97)
DAPA-HF: Effect of Dapagliflozin in Heart Failure, With or Without Diabetes

No diabetes/diabetes subgroup: Primary endpoint

Effect on Primary Endpoint of Cardiovascular Death and Serious Heart Failure Events

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
</tbody>
</table>

*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.
DAPA-HF: Effect of Dapagliflozin in Heart Failure, With or Without Diabetes

An inflection point in the care of patients with heart failure...

- Benefits seen in those with or without Diabetes
- Once a day therapy; single dose; no need for titration (N.B. low use of ARNI)
- No episodes of hypoglycemia or diabetic ketoacidosis
- Negligible incidence of amputations
- $NNT = 21$; benefits seen even in those >75
- Resolution of mechanism of action is needed
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators*
Primary Outcome and Total Hospitalizations for Heart Failure.
Changes in the Estimated Glomerular Filtration Rate.

### A. 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>DAPA HF</td>
<td>246/1865 (33.4%)</td>
<td>266/1867 (14.2%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>276/2373 (11.6%)</td>
<td>379/2371 (13.9%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.92 (0.77-1.10)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.018</td>
<td></td>
<td>0.83 (0.71-0.97)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.59</td>
<td></td>
<td>0.87 (0.77-0.96)</td>
</tr>
</tbody>
</table>

### B. 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>DAPA HF</td>
<td>177/1853 (10.6%)</td>
<td>260/1867 (10.8%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>227/2373 (9.4%)</td>
<td>275/2371 (11.5%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.92 (0.75-1.12)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.027</td>
<td></td>
<td>0.85 (0.69-0.98)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.40</td>
<td></td>
<td>0.86 (0.76-0.98)</td>
</tr>
</tbody>
</table>

### C. First hospitalisation for heart failure or 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>DAPA HF</td>
<td>384/1865 (19.4%)</td>
<td>462/1867 (24.7%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>385/2373 (16.3%)</td>
<td>502/2371 (21.4%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.75 (0.65-0.86)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.001</td>
<td></td>
<td>0.74 (0.65-0.85)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.59</td>
<td></td>
<td>0.74 (0.68-0.82)</td>
</tr>
</tbody>
</table>

### D. First hospitalisation for heart failure

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA HF</td>
<td>246/1865 (13.2%)</td>
<td>342/1867 (18.3%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>321/2373 (13.4%)</td>
<td>318/2371 (13.4%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.60 (0.50-0.81)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.001</td>
<td></td>
<td>0.69 (0.58-0.83)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.51</td>
<td></td>
<td>0.69 (0.63-0.78)</td>
</tr>
</tbody>
</table>

### E. First kidney outcome composite

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA HF</td>
<td>18/1865 (1.0%)</td>
<td>28/1867 (1.5%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>33/2373 (1.3%)</td>
<td>39/2371 (1.6%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.52 (0.39-0.92)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.001</td>
<td></td>
<td>0.71 (0.44-1.15)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.56</td>
<td></td>
<td>0.62 (0.43-0.90)</td>
</tr>
</tbody>
</table>

### F. All (first and recurrent) hospitalisation for heart failure or cardiovascular death

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA HF</td>
<td>273/1865 (14.9%)</td>
<td>273/1867 (14.9%)</td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>56/2373 (2.3%)</td>
<td>74/2371 (3.1%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.75 (0.65-0.85)</td>
</tr>
<tr>
<td>Test for overall treatment effect p=0.001</td>
<td></td>
<td>0.75 (0.65-0.88)</td>
</tr>
<tr>
<td>Test for heterogeneity of effect p=0.59</td>
<td></td>
<td>0.75 (0.68-0.84)</td>
</tr>
</tbody>
</table>
Are the SGLT-2 inhibitors the answer?

Haemodynamic mechanisms
- Fluid overload and retention of salt and water
- Renal and cardiac congestion (renal venous hypertension)
- Limited organ perfusion (forward failure)
- Vasoconstriction in end organs

(Cardiovascular disease-associated mechanisms
- Chronic inflammation and activation of cellular immunity
- Malnutrition, cachexia and wasting
- Bone–mineral disorder
- Acid–base metabolism disorder
- Anaemia and cardio-renal anaemia

(Neuro)hormonal mechanisms
- Activation of the RAAS
- Activation of the sympathetic nervous system

Nature Reviews | Nephrology
Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., et al. for the DAPA-CKD Trial Committees and Investigators*
Primary and Secondary Outcomes.

The primary outcome: composite of sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 (9.2%) in the dapagliflozin group & 312/2152 (14.5%) in the placebo group (hazard ratio, 0.61; 95% [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]).
Change from Baseline in Estimated GFR.

Heart Failure
New trials and new data: SGLT2 inhibitors - a better diuretic?
Empagliflozin in Heart Failure

Diuretic and Cardiorenal Effects


Originally published 15 May 2020 | https://doi-org.ezproxy.galter.northwestern.edu/10.1161/CIRCULATIONAHA.120.045691 | Circulation. 2020;142:1028-1039
Matthew Griffin. Circulation. Empagliflozin in Heart Failure, Volume: 142, Issue: 11, Pages: 1028-1039, DOI: (10.1161/CIRCULATIONAHA.120.045691)
# Empagliflozin in Heart Failure

## Diuretic and Cardiorenal Effects


Originally published 15 May 2020 | [https://doi.org/ezproxy.y.aalter.northwestern.edu/10.1161/CIRCULATIONAHA.120.045691](https://doi.org/ezproxy.y.aalter.northwestern.edu/10.1161/CIRCULATIONAHA.120.045691) | Circulation. 2020;142:1028–1039

---

## Table 2. Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Change From Beginning to End of Treatment Period</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurohormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>0.09 (−1.39 to 0.71)</td>
<td>0.7 (0.02 to 2.33)</td>
<td>0.023*</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity, ng mL⁻¹·h⁻¹</td>
<td>0.84 (−4.90 to 13.81)</td>
<td>0.56 (−2.07 to 10.69)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Total renin, pg/mL</td>
<td>241.3 (−252.8 to 744.9)</td>
<td>368.5 (−56.3 to 1062.1)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Aldosterone, pg/mL</td>
<td>18.3 (−3.0 to 41.4)</td>
<td>1.7 (−16.4 to 23.9)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Copeptin, pg/mL</td>
<td>−8.19 (−45.15 to 14.81)</td>
<td>−4.94 (−19.09 to 16.31)</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>
Heart Failure
New trials and
new data: SGLT2
inhibitors- the
newest data!
"In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events."

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease; Hospitalizations for Heart Failure, and Urgent Visits for Heart Failure. SCORED Trial
Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease; First Occurrence of Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke.

![Graph showing cumulative incidence of outcomes over time. The graph compares placebo and sotagliflozin groups, with a hazard ratio of 0.84 (95% CI, 0.72–0.99).]

No. at Risk
- Placebo: 5292, 5090, 3817, 1985, 421
- Sotagliflozin: 5292, 5150, 3892, 2034, 432
Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure; SOLOIST WHF Trial: Primary Efficacy End-Point Events.

“In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.”

## The Full Portfolio of Treatment Choices – SGLT2 I in heart failure

<table>
<thead>
<tr>
<th>Heart Failure Phenotype</th>
<th>SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFrEF</strong></td>
<td><em>Not currently supported by HF guidelines</em>; pending 2021 HF Guidelines; BUT multiple positive RCTs: DAPA HF: HR 0.74; CI 0.65 – 0.85; NNT 21 EMPEROR REDUCED; HR 0.75; CI 0.65 – 0.86; NNT 19</td>
</tr>
<tr>
<td><strong>HFpEF</strong></td>
<td>Awaiting EMPEROR PRESERVED; encouraging animal data</td>
</tr>
<tr>
<td><strong>Hospitalized HF</strong></td>
<td>SOLOIST – WHF: HR 0.67; CI 0.52 -0.85; NNT 54</td>
</tr>
<tr>
<td><strong>HF and CKD</strong></td>
<td>DAPA CKD; HR 0.61; CI 0.51 – 0.72; NNT 19 SCORED; (with or without albuminuria) HR 0.74; CI 0.63 – 0.88</td>
</tr>
</tbody>
</table>
2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee

**Expert Consensus Decision Pathway**


*J Am Coll Cardiol.* 2020 Aug, 76 (9) 1117–1145
Patient is ≥18 years old with T2D and has ≥1 of the following: ASCVD*; HF, DKD; at high risk for ASCVD.†

Address concurrently.

- Optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet).

- Recommend starting SGLT2 inhibitor or GLP-1RA with proven CV benefit depending on patient-specific factors and comorbidities.‡

Discuss patient-clinician preferences and priorities.

- No additional action taken at this time.

- SGLT2 inhibitor selected.

- GLP-1RA selected.

Reassess and consider the addition of the alternative class, if benefits outweigh risks.

---

*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

†Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.
Patient is ≥18 years old with T2D and ≥1 of the following: ASCVD†, HF, DKD‡, or at high risk for ASCVD†

Is the patient pregnant or breast feeding?

Yes
Do not start an SGLT2 inhibitor (no safety data available).

No

Is the patient’s eGFR <30 ml/min/1.73m²?

Yes

Consider starting an SGLT2 inhibitor with proven ASCVD, HF, or DKD benefit (see Tables 2 and 5).

No

After a discussion incorporating patient-clinician preferences and priorities (see Table 6), does the patient wish to initiate an SGLT2 inhibitor?

Yes

Initiate an SGLT2 inhibitor with proven ASCVD, HF, or DKD benefit.
• Canagliflozin, dapagliflozin, or empagliflozin is appropriate.
• See Table 2 for dosing and cautions.
• No dose titration is required.
• Adjust other antihyperglycemic therapies if necessary.

No

Do not start an SGLT2 inhibitor.

Monitor response to therapy (see Section 3.4 and Table 7) and consider further therapies for CV risk reduction, as indicated.¹

---

* ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial non-circulatory, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

¹ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

² This may include the addition of a GLP-1RA in the appropriate patient (see Section S.3.3).

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes
Patient is ≥18 years old with T2D and ≥1 of the following: ASCVD* or at high risk for ASCVD.†

Is the patient pregnant or breast feeding?
Yes: Do not start a GLP-1RA (no safety data available).
No: Consider starting a GLP-1RA with proven ASCVD benefit (see Tables 4 and 5).§

After a discussion incorporating patient-clinician preferences and priorities (see Table 6), does patient wish to initiate a GLP-1RA?
Yes: Initiate a GLP-1RA with proven ASCVD benefit.
   - Dulaglutide, liraglutide, or injectable semaglutide is appropriate.
   - See Table 4 for dosing and cautions.
   - Start at lowest dose and follow labelling instructions for dose titration to minimize side effects.
   - Adjust other antihyperglycemic therapies, if necessary.

No: Do not start a GLP-1RA.

Monitor response to therapy (see Section 5.5 and Table 7) and consider further therapies for CV risk reduction, as indicated.¶

---

*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary/heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.
†Patients at high risk for ASCVD include patients with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).
§Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.
¶This may include the addition of an SGLT2 inhibitor in the appropriate patient (see Section 5.3.3).

ASCVD = atherosclerotic cardiovascular disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes
NEW & EMERGING HEART FAILURE THERAPY
How might the guidelines change?

Disclaimer: I am a current member of the 2021 ACC/AHA Heart Failure Clinical Practice Guidelines; I am precluded from releasing any decisions already made by the committee; any inferences from this presentation do not represent official statements from the ACC or AHA
How might the HF guidelines change?

SUMMARY:

1. *Expect a stronger emphasis RE: PREVENTION of Heart Failure*

2. *The SGLT2i class is breakthrough therapy for prevention and treatment of heart failure, hospitalized heart failure and the interaction of CVD/CKD; expect explicit mention but ? COR and LOE?*

3. *Expect prompts to consider health equity in the care of patients with heart failure*
THANK YOU!
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

IAN DE BOER, MD, MS

VLADO PERKOVIC, MBBS, PhD, FASN, FRACP

JANANI RANGASWAMI, MD, FACP, FCRS, FAHA

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

CLYDE YANCY, MD, MSC, MACC, FAHA, MACP, FHFS
Roundtable Discussion

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

KATHERINE R. TUTTLE, MD, FASN, FACP, FNKF
EXECUTIVE DIRECTOR FOR RESEARCH
PROVIDENCE HEALTH CARE

PROFESSOR OF MEDICINE
NEPHROLOGY DIVISION AND KIDNEY RESEARCH INSTITUTE
INSTITUTE OF TRANSLATIONAL HEALTH SCIENCES
UNIVERSITY OF WASHINGTON