CREDENCE
Canagliflozin and Renal Events in Diabetes with Established Nephropathy
Clinical Evaluation
Stanford University Department of Medicine
Medicine Grand Rounds
May 29, 2019
Presentation Outline

• Background and Study Design  Sun H. Kim
• Baseline and Kidney Outcomes  Tara I. Chang
• CV and Safety Outcomes  Kenneth W. Mahaffey
• Implications for Clinical Practice  Group
Presenter Disclosures

**Sun H. Kim, MD MS**

- Consultant
  - Sanofi, GI Dynamics

**Tara I. Chang, MD, MS**

- Consultant
  - Janssen, Novo Nordisk and Tricida

**Kenneth W. Mahaffey, MD**

- Research support
  - Afferent, Amgen, Apple, Inc., AstraZeneca, Cardiva Medical, Inc., Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, NIH, Novartis, Sanofi, St. Jude, and Tenax

- Consultant (speaker fees for CME events only)
  - Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and UCSF
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Background and Study Design

Sun H. Kim, MD, MS
Diabetes and Kidney disease

• ~12% of the US adult population ≥ 18 years has diabetes mellitus\(^1\)
• 30-40% of adults with diabetes will develop diabetic kidney disease (with albuminuria, reduced eGFR, or both).\(^2\)
• Diabetes is the leading cause of kidney failure\(^1\)
• Diabetic kidney disease shortens life span

\(^1\)National Diabetes Statistics Report, 2017
\(^2\)Afkarian et al. JAMA 2016;316:602-610
The Only Proven Treatment for Renoprotection in T2DM: renin-angiotensin system blockade

Doubling of serum creatinine, ESKD, or death

**RENAAL**
- Placebo
- Losartan

Risk reduction, 16%

\[ P = 0.02 \]

**IDNT**
- Irbesartan
- Amlodipine
- Placebo

Risk reduction, 20%

\[ P = 0.02 \]


Sodium-glucose cotransporter 2 (SGLT2) inhibitors

- Newest class of drugs approved for the treatment of type 2 diabetes
- Mechanism: Inhibits sodium glucose transport in the proximal convoluted tubules of the kidneys and promotes glycosuria.
- Currently 4 SGLT2i are approved in the United States for the treatment of type 2 diabetes
  - Canagliflozin, 2013
  - Dapagliflozin, 2014
  - Empagliflozin, 2014
  - Ertugliflozin, 2017
Renal glucose reabsorption in healthy individuals

Glucose

~180 g of glucose per day filtered

SGLT-2

~90%

SGLT-1

~10%

Gerich JE. Diabetic Medicine. 2010;27:136
Renal Threshold for Glucose

Urinary Glucose Excretion (g/day) vs. Plasma Glucose (mg/dL)

- Normal: $R_T \approx 180$ mg/dL
- T2DM: $\approx 240$ mg/dL
SGLT2 Inhibitors

Plasma Glucose (mg/dL)

Urinary Glucose Excretion (g/day)

SGLT2i
~70-90 mg/dL
Many Potential Kidney Benefits of SGLT2 Inhibition

- Glucose
- Blood Pressure
- Weight
- Albuminuria
- Intraglomerular pressure & more
SGLT2i Timeline

1835
Phlorizin isolated from bark of apple tree

2013
First SGLT2i Canagliflozin approved

2015
SGLT2i shows cardiovascular benefits (EMPA-REG)

2017
CREDENCE enrollment CANVAS

2019
CREDENCE stopped

DECLARE
# SGLT2i Trials

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STUDY</th>
<th>MACE*</th>
<th>Kidney Outcomes</th>
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<tr>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>↓</td>
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<tr>
<td>Dapagliflozin</td>
<td>DECLARE</td>
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*MACE = Major Adverse Cardiac Events (CV death, MI, or stroke)*
Available evidence suggested benefits modified by kidney function

- CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function

Composite of worsening of renal function, ESKD, or renal death

<table>
<thead>
<tr>
<th>eGFR &lt;60</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>83</td>
<td></td>
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<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
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<tr>
<td>DECLARE</td>
<td>59</td>
<td></td>
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<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.67 (0.51–0.89)</strong></td>
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<table>
<thead>
<tr>
<th>eGFR 60-&lt;90</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
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<tr>
<td>CANVAS Program</td>
<td>118</td>
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<tr>
<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
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<tr>
<td>DECLARE</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.56 (0.46–0.70)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR ≥90</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DECLARE</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.44 (0.32–0.59)</strong></td>
</tr>
</tbody>
</table>

Interaction

$P$ value = 0.0258

CREDENCE Trial: Objectives

In people with T2DM, eGFR 30 to 90 mL/min/1.73 m$^2$, and UACR 300 to 5000 mg/g who are receiving standard of care including a maximum tolerated dose of an ACEi or ARB, to assess whether canagliflozin compared with placebo reduces

**Primary:**
- Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death

**Secondary:**
- CV death or hospitalization for heart failure
- Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
- Hospitalization for heart failure
- ESKD, doubling of serum creatinine, or renal death
- CV death
- All-cause mortality
- CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina
Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m²
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K⁺ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in

Canagliflozin 100 mg

Placebo

Double-blind randomization (1:1)

Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

Interim Analysis

- Planned interim analysis to occur after 405 confirmed primary efficacy endpoints and 2 years of exposure
- Reviewed by an Independent Data Monitoring Committee
- Prespecified stopping guidance included
  - Primary composite: 2-sided $P < 0.01$
    - AND
    - Composite of ESKD, renal death, or CV death: 2-sided $P < 0.025$
  - Global assessment of benefit and safety

Primary and Kidney Outcomes
Tara I. Chang, MD, MS
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 2202)</th>
<th>Placebo (n = 2199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female, %</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>White race, %</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>Mean duration of diabetes, years</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>CV disease, %</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Prior amputation, %</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mean eGFR, mL/min/1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median urinary albumin-creatinine ratio, mg/g</td>
<td></td>
<td>31% of cohort eGFR&lt;45 (CKD stage 3b or higher)</td>
</tr>
</tbody>
</table>
## Baseline Medications

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 2202)</th>
<th>Placebo (n = 2199)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose-lowering agents, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Metformin</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>28</td>
<td>30</td>
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<tr>
<td>DPP-4 inhibitor</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Renal and CV protective agents, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>&gt;99.9</td>
<td>99.8</td>
</tr>
<tr>
<td>Statin</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Antiplatelet or anticoagulant</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>40</td>
<td>40</td>
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<tr>
<td>Diuretic</td>
<td>47</td>
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</table>
## Effects on Intermediate Outcomes

<table>
<thead>
<tr>
<th></th>
<th>A1C (%)</th>
<th>SBP (mm Hg)</th>
<th>Body Wt (Kg)</th>
<th>ACR (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Values</strong></td>
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<tr>
<td>Canagliflozin</td>
<td>8.3</td>
<td>140</td>
<td>87.3</td>
<td>914</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.3</td>
<td>140</td>
<td>86.9</td>
<td>918</td>
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<tr>
<td><strong>Mean difference</strong></td>
<td>-0.25</td>
<td>-3.3</td>
<td>-0.8</td>
<td>-300</td>
</tr>
</tbody>
</table>
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

Participants with an event (%)

Months since randomization

No. at risk
Placebo 2199 2178 2132 2047 1725 1129 621 170
Canagliflozin 2202 2181 2145 2081 1786 1211 646 196

340 participants
245 participants
<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.60 (0.48–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.68 (0.54–0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m²</td>
<td>0.60 (0.45–0.80)</td>
<td>–</td>
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<tr>
<td>Dialysis initiated or kidney transplantation</td>
<td>0.74 (0.55–1.00)</td>
<td>–</td>
</tr>
<tr>
<td>Renal death</td>
<td>0.39 (0.08–2.03)</td>
<td>–</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
</tr>
<tr>
<td><strong>ESKD, doubling of serum creatinine, or renal death</strong></td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dialysis, kidney transplantation, or renal death</strong></td>
<td>0.72 (0.54–0.97)</td>
<td>–</td>
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</table>

*Post hoc analysis.*
### Primary Outcome by Screening eGFR and Albuminuria

<table>
<thead>
<tr>
<th>Screening eGFR</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;45 mL/min/1.73 m²</td>
<td>0.75 (0.59–0.95)</td>
<td>0.11</td>
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<tr>
<td>45 to &lt;60 mL/min/1.73 m²</td>
<td>0.52 (0.38–0.72)</td>
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<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.82 (0.60–1.12)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Baseline UACR</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1000 mg/g</td>
<td>0.76 (0.55–1.04)</td>
<td>0.49</td>
</tr>
<tr>
<td>&gt;1000 mg/g</td>
<td>0.67 (0.55–0.81)</td>
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</tbody>
</table>
Canagliflozin efficacious across subgroups

- Age
- Sex
- Race/Ethnicity
- Region
- SBP
- BMI
- CV disease
- Heart Failure
- Diabetes duration
- A1C
- Amputation
Effects on eGFR

**Baseline**
- **Canagliflozin**: 56.4
- **Placebo**: 56.0

**Acute eGFR slope (3 weeks)**
Difference: $-3.2$ (95% CI, $-3.9$, $-2.5$)
- **Change in eGFR (mL/min/1.73 m$^2$)**
  - Placebo: $-0.6$
  - Canagliflozin: $-3.7$
- **Acute eGFR slope**: $-1.9$/year

**Chronic eGFR slope**
Difference: $2.7$/year (95% CI, $2.4$–$3.1$)
- **Change in eGFR (mL/min/1.73 m$^2$)**
  - Placebo: $-4.6$/year
  - Canagliflozin: $-0.6$/year

**Months since randomization**

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Placebo</th>
<th>Placebo</th>
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<tr>
<td>6</td>
<td>2178</td>
<td>2084</td>
<td>1985</td>
<td>1882</td>
<td>1720</td>
<td>1536</td>
<td>1006</td>
<td>583</td>
<td>210</td>
<td>2179</td>
<td>2074</td>
<td>2005</td>
<td>1919</td>
<td>1782</td>
<td>1648</td>
<td>1116</td>
<td>652</td>
<td>241</td>
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</table>
Secondary CV Outcomes and Safety Events
Kenneth W. Mahaffey, MD
34 Countries, 690 Sites, 4401 Participants

Europe (n = 1368)
- Bulgaria
- Czech Republic
- France
- Germany
- Hungary
- Italy
- Lithuania
- Poland
- Romania
- Serbia
- Slovakia
- Spain
- Russia*
- Ukraine*
- United Kingdom

Asia Pacific* (n = 848)
- Australia
- China
- India
- Japan
- Korea
- Malaysia
- New Zealand
- Philippines
- Taiwan
- United Arab Emirates

Central/South America (n = 941)
- Argentina
- Brazil
- Chile
- Colombia
- Guatemala

North America (n = 1182)
- Canada
- Mexico
- United States

Africa (n = 62)
- South Africa*

*Analyzed as part of rest of world (n = 1414) in prespecified subgroup analyses.
CV Death or Hospitalization for Heart Failure

Hazard ratio, 0.69 (95% CI, 0.57–0.83)  
*P* < 0.001

Participants with an event (%)

- Placebo
- Canagliflozin

No. at risk
- Placebo: 2199, 2165, 2123, 2044, 1736, 1147, 638, 170
- Canagliflozin: 2202, 2171, 2132, 2077, 1789, 1226, 668, 199

253 participants
179 participants
Major Cardiovascular Events: CV Death, MI, or Stroke

Hazard ratio, 0.80 (95% CI, 0.67–0.95)
P = 0.01

No. at risk
Placebo 2199 2152 2100 2022 1717 1143 635 168
Canagliflozin 2202 2163 2106 2047 1756 1196 642 198

Participants with an event (%)

Months since randomization

269 participants
217 participants
## Summary

<table>
<thead>
<tr>
<th>Primary</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</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>
</tr>
<tr>
<td><strong>Secondary</strong></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>
</tr>
<tr>
<td>3. CV death, MI, or stroke</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>4. Hospitalization for heart failure</td>
<td>0.61 (0.47–0.80)</td>
<td>&lt;0.001</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>
</tr>
<tr>
<td>6. CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
</tr>
<tr>
<td>7. All-cause mortality</td>
<td>0.83 (0.68–1.02)</td>
<td>–</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>
</tr>
</tbody>
</table>
### Other AEs of Interest

<table>
<thead>
<tr>
<th>Event Asiectic mycotic infections</th>
<th>Canagliflozin (N = 2200)</th>
<th>Placebo (N = 2197)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male genital mycotic infections*</td>
<td>28</td>
<td>3</td>
<td>9.30 (2.83–30.60)</td>
</tr>
<tr>
<td>Female genital mycotic infections†</td>
<td>22</td>
<td>10</td>
<td>2.10 (1.00–4.45)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>245</td>
<td>221</td>
<td>1.08 (0.90–1.29)</td>
</tr>
<tr>
<td>Volume depletion-related AEs</td>
<td>144</td>
<td>115</td>
<td>1.08 (0.90–1.29)</td>
</tr>
<tr>
<td>Malignancies‡</td>
<td>98</td>
<td>99</td>
<td>0.98 (0.74–1.30)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1</td>
<td>5</td>
<td>0.20 (0.02–1.68)</td>
</tr>
<tr>
<td>Breast†</td>
<td>8</td>
<td>3</td>
<td>2.59 (0.69–9.76)</td>
</tr>
<tr>
<td>Bladder</td>
<td>10</td>
<td>9</td>
<td>1.10 (0.45–2.72)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>5</td>
<td>2</td>
<td>2.44 (0.47–12.59)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>11</td>
<td>1</td>
<td>10.80 (1.39–83.65)</td>
</tr>
</tbody>
</table>

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.

Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.
Lower Extremity Amputation

Hazard ratio, 1.11 (95% CI, 0.79–1.56)

Participants with an event (%)

Months since randomization

No. at risk
Placebo 2197 2169 2131 2065 1766 1177 658 182
Canagliflozin 2200 2163 2118 2071 1788 1228 667 202

Includes all treated patients through the end of the trial.
## Lower Extremity Amputation

<table>
<thead>
<tr>
<th></th>
<th>Participants with an event</th>
<th>IRD per 1000 patient-years</th>
<th>Hazard ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per 1000 patient-years (n/N)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>12.3 (70/2200)</td>
<td>1.16 (–2.87, 5.18)</td>
<td>1.11 (0.79–1.56)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11.2 (63/2197)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program¹</td>
<td>6.3 (140/5790)</td>
<td>2.93 (1.50, 4.36)</td>
<td>1.97 (1.41–2.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.4 (47/4344)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors Canagliflozin Favors Placebo

Whether the increased risk of lower limb amputation in the CANVAS Program was due to differing trial populations or protocols, or to chance remains unclear.
Summary and Clinical Implications
Higher Renal Risk Population in CREDENCE

GFR categories (mL/min/1.73 m²)

<table>
<thead>
<tr>
<th>Albuminuria categories (mg/g)</th>
<th>A1: &lt;30</th>
<th>A2: 30-300</th>
<th>A3: &gt;300</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-90</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>45-59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sustained RRT Events
- DECLARE: Not reported
- CANVAS Program: 18
- EMPA-REG OUTCOME: 27
- CREDENCE: 176

Median UACR (mg/g): 13, 12, 18, 927
CREDENCE: Summary

- 30% ↓ primary outcome
  NNT: 22

- 32% ↓ ESKD
  NNT: 43

- 31% ↓ heart failure
  NNT: 46

- 20% ↓ CV death, MI, stroke
  NNT: 40

- ↓ SBP
- ↓ A1C
- ↓ Weight
- ↓ GFR decline
Summary

SGLT-2 Inhibitors as Treatment for Diabetes
SGLT-2 Inhibitors as Treatment for Cardiovascular Disease
SGLT-2 Inhibitors as Treatment for Diabetic Nephropathy

C: Cardiology  K: Kidney  D: Diabetes
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy


Slides available:  http://med.stanford.edu/sccr.html

Paper and editorial available at  www.nejm.org
Glucose-lowering medication in type 2 diabetes: overall approach

**FIRST-LINE** therapy is metformin and comprehensive lifestyle (including weight management and physical activity). If HbaA1c above target proceed as below

**ESTABLISHED ASCVD OR CKD**

- **ASCVD PREDOMINATES**
  - GLP1-RA with proven CVD benefit
  - SGLT2i with proven CVD benefit
  - DPP-4i if not on GLP1-RA
  - Basal insulin
  - TZD
  - SU

- If HbaA1c above target
  - Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class (GLP1-RA or SGLT2i) with proven CVD benefit
    - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP1-RA)
    - Basal insulin
    - SU

- If HbaA1c above target
  - Continue with addition of other agents as outlined above

- If HbaA1c above target
  - Consider the addition of SU or basal insulin:
    - Choose later generation SU with lower risk of hypoglycemia
    - Consider basal insulin with lower risk of hypoglycemia

- If HbaA1c above target
  - If triple therapy required or SGLT2i and/or GLP1-RA not tolerated or contraindicated use regimen with lowest risk of weight gain
  - PREFERABLY:
    - DPP-4i (not on GLP1-RA)
    - Based on weight neutrality

- If HbaA1c above target
  - If DPP-4i not tolerated or contraindicated or patient already on GLP1-RA, cautious addition of:
    - SU + TZD + Basal insulin

**HF OR CKD PREDOMINATES**

- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
  - OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate and GLP1-RA with proven CVD benefit

- If HbaA1c above target
  - DPP-4i
  - GLP1-RA
  - SGLT2i

- If HbaA1c above target
  - TZD

**COMPPELLING NEED TO MINIMIZE HYPOGLYCEMIA**

- If HbaA1c above target
  - SGLT2i
  - OR
  - TZD

- If HbaA1c above target
  - GLP1-RA
  - SGLT2i

- If HbaA1c above target
  - SGLT2i
  - OR
  - DPP-4i

- If HbaA1c above target
  - GLP1-RA

**COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**

- If HbaA1c above target
  - GLP1-RA with good efficacy for weight loss
  - SGLT2i

- If HbaA1c above target
  - DPP-4i

**COST IS A MAJOR ISSUE**

- If HbaA1c above target
  - SU
  - TZD

- If HbaA1c above target
  - SU

**NO**

**WITHOUT ESTABLISHED ASCVD OR CKD**

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP1-RA, strongest evidence for lixisenatide > exenatide extended release. For SGLT2i, evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reductions in HF and reduction in CKD progression in CVOTs.
4. Dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter 2 inhibitors have demonstrated CV safety.
5. Low dose may be better tolerated though less well studied for CVD effects.
6. Choose later generation SU with lower risk of hypoglycemia.
7. Dipeptidyl peptidase-4 inhibitors used without weight loss efficacy limitations have demonstrated CV safety.
8. SGLT2i may reduce cardiovascular mortality and CV hospitalization.
9. If no specific comorbidity (e.g., established CVD, low risk of hypoglycaemia, and lower priority to avoid weight gain or no weight-related comorbidities) consider country- and region-specific cost of drugs. In some countries T2DM relative more expensive and DPP-4i relatively cheaper.
10. Consider country- and region-specific cost of drugs. In some countries T2DM relative more expensive and DPP-4i relatively cheaper.

**EASD**

American Diabetes Association (ADA)