The Role Of SGLT-2 Inhibitors In Clinical Practice

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Director, USC Clinical Diabetes Programs
Disclosure of Potential Conflicts of Interest

Consultantship
- Abbott Diabetes Care
- Astra Zeneca
- Bigfoot Biomedical
- BD, BI
- Janssen, Lexicon, Lilly
- Medscape, Merck
- NovoNordisk
- Science 37

Speaker’s Bureau
- NovoNordisk
Objectives

• Review mechanism of action of SGLT-2 inhibitors
• Summarize outcome data
• Create a paradigm for use in clinical practice
Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical
CV Safety Trials in Type 2 Diabetes

Class of drug of interest being evaluated:
- DPP-4 inhibitor
- GLP-1 receptor agonist
- SGLT2 inhibitor
- Basal insulin
In 1835, French Chemists Isolated Phlorizin From the Bark of the Apple Tree

“Few can foresee whither their road will lead them, till they come to its end” J.R.R. Tolkien

Petersen C. Annales Academie Science Francaise. 1835;15:178.
Normal Renal Glucose Metabolism

Glucose

SGLT2
~90%

SGLT1
~10%

S1 segment of proximal tubule

Distal S2/S3 segment of proximal tubule

No glucose

Inhibition of Renal Glucose Reabsorption

Renal Glucose Reabsorption

- **SGLT2i RT\(_G\)**
  - \(\sim 3.9-5.0\) mmol/L
  - \(\sim 70-90\) mg/dL

- **Healthy RT\(_G\)**
  - \(\sim 10\) mmol/L
  - \(\sim 180\) mg/dL

- **T2DM RT\(_G\)**
  - \(\sim 13\) mmol/L
  - \(\sim 240\) mg/dL

**Plasma glucose (mg/dL)**

- 0
  - 50
  - 100
  - 150
  - 200
  - 250
  - 300

**Urinary glucose excretion (g/day)**

- 0
  - 25
  - 50
  - 75
  - 100
  - 125

**Legend**

- Black arrow: SGLT2i RT\(_G\)
- Red arrow: Healthy RT\(_G\)
- Blue arrow: T2DM RT\(_G\)
SGLT-2 Inhibitors—Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)

Clinical Effects

- Novel mechanism of action/oral agent
- Most will respond—action independent of beta-cell function
- A1C reduction ~1% with 2-3 kg weight loss
- Blood pressure reduction
- CVD benefits
- Renal benefits

Canagliflozin/Dapagliflozin/Empagliflozin Warnings and Precautions

- Hypoglycemia: risk with SU’s and/or insulin
- Genital mycotic infections
- Urinary tract infection, pyelo, urosepsis
- Volume depletion/orthostatic changes
- Acute renal insufficiency/failure
- DKA
- Bladder cancer (dapagliflozin only)
- Increased fracture risk (cana)
- Increased risk for amputation (cana)
## List of SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>US Brand Name</th>
<th>Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>100, 300</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga</td>
<td>5, 10</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
<td>10, 25</td>
</tr>
<tr>
<td>Cana/metformin</td>
<td>Invokamet</td>
<td>50/500, 50/1000, 150/500, 150/1000</td>
</tr>
<tr>
<td>Dapa/metformin</td>
<td>Xigduo XR</td>
<td>5/500, 5/1000, 10/500, 10/1000</td>
</tr>
<tr>
<td>Empa/metformin</td>
<td>Synjardy</td>
<td>5/500, 5/1000, 12.5/500, 12.5/1000</td>
</tr>
<tr>
<td>Empa/linagliptin</td>
<td>Glyxambi</td>
<td>10/5, 25/5</td>
</tr>
<tr>
<td>Ipragliflozin (Japan)</td>
<td>Suglat</td>
<td>25, 50</td>
</tr>
<tr>
<td>Tofogliflozin (Japan)</td>
<td>Apleway, Deberza</td>
<td>30</td>
</tr>
<tr>
<td>Luseogliflozin</td>
<td>Under development</td>
<td></td>
</tr>
<tr>
<td>Remogliflozin Etabonate</td>
<td>Under development</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Under development</td>
<td></td>
</tr>
<tr>
<td>Sotagliflozin</td>
<td>Under development</td>
<td></td>
</tr>
</tbody>
</table>

*Curr Opin Endocrinol Diabetes Obes 2017, 24:73-79*
## SGLT-2 On-Going Outcomes Trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Patients</th>
<th>Primary Endpoint</th>
<th>N</th>
<th>Years</th>
<th>Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-Reg (Empa)</td>
<td>Established CVD</td>
<td>CVD death, nonfatal MI and CVA</td>
<td>7000</td>
<td>~3</td>
<td>Yes</td>
</tr>
<tr>
<td>CANVAS (Cana)</td>
<td>Established CVD or &gt;2RF</td>
<td>As above</td>
<td>4330</td>
<td>6-7</td>
<td>Yes</td>
</tr>
<tr>
<td>CANVAS-R (Cana)</td>
<td>Established CVD or &gt;2RF</td>
<td>Progression of albuminuria</td>
<td>5700</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>CREDENCE (Cana)</td>
<td>Stage 2/3 CKD + albuminuria</td>
<td>ESRD/2X serum creatinine, renal or CV death</td>
<td>3627</td>
<td>~4</td>
<td>2019</td>
</tr>
<tr>
<td>DECLARE-TIMI58 (Dapa)</td>
<td>High risk CVD death</td>
<td>As above</td>
<td>17150</td>
<td>4-5</td>
<td>2018</td>
</tr>
<tr>
<td>Ertugliflozin CVOT</td>
<td>Established CVD</td>
<td>As above</td>
<td>3900</td>
<td>5-7</td>
<td>2021</td>
</tr>
</tbody>
</table>

Diabetes & Vasc Dis Res 2015;12:90-100
Are There Clinically Meaningful Differences Among Available Agents?
SGLT-1 and SGLT-2 Inhibitors

SGLT-1 is a high-affinity low-capacity transporter

SGLT-2 is a low-affinity high-capacity co-transporter

The Lancet Diabetes-Endo 2013:141-151
# SGLT-1 and SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose</th>
<th>IC\textsubscript{50} SGLT1 vs SGLT2</th>
<th>T\textsubscript{max} (h)</th>
<th>T\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective SGLT-2 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cana</td>
<td>300</td>
<td>910 vs 2.2 nmol/L</td>
<td>~1.9</td>
<td>13.1</td>
</tr>
<tr>
<td>Dapa</td>
<td>10</td>
<td>1390 vs 11.0 nmol/L</td>
<td>1.5 – 2.0</td>
<td>~13</td>
</tr>
<tr>
<td>Empa</td>
<td>25</td>
<td>8300 vs 3.1 nmol/L</td>
<td>1.5</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Combined SGLT-1 and SGLT-2 Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotagliflozin</td>
<td>300</td>
<td>36 vs 1.8 nmol/L</td>
<td>0.5 – 2.0</td>
<td>13.5</td>
</tr>
</tbody>
</table>

IC\textsubscript{50} = Half maximal inhibitory concentration

**The Lancet Diabetes-Endo 2013;1:141-151**
A1c Meta-Analysis

### Canagliflozin versus placebo
- Bode 2013: -0.53 (-0.75, -0.31)
- Forst 2014: -0.77 (-0.90, -0.64)
- Gonzalez 2013: -0.77 (-0.91, -0.63)
- Inagaki 2013: -0.99 (-1.10, -0.88)
- Rosenstock 2012: -0.70 (-0.92, -0.48)
- Stenlof 2013: -1.17 (-1.36, -0.98)
- Wilding 2013: -0.97 (-1.18, -0.76)
**Subtotal**: -0.85 (-0.99, -0.71)

### Dapagliflozin versus placebo
- Bailey 2010: -0.80 (-1.09, -0.51)
- Bolinder 2012: -0.42 (-0.61, -0.23)
- Cefalu 2015: -0.66 (-0.80, -0.52)
- Ferrannini 2010: -0.66 (-0.95, -0.37)
- Jabbour 2014: -0.50 (-0.64, -0.36)
- Ji 2014: -0.81 (-1.01, -0.61)
- Kaku 2013: -0.81 (-1.00, -0.62)
- Kaku 2014: -0.39 (-0.56, -0.22)
- LamHeersp 2013: -0.30 (-0.78, 0.18)
- Leiter 2014: -0.50 (-0.64, -0.36)
- List 2009: -0.67 (-0.96, -0.38)
- Mathieu 2015: -0.72 (-0.91, -0.53)
- Matthei 2015: -0.70 (-0.97, -0.43)
- Rosenstock 2012a: -0.67 (-0.89, -0.45)
- Strojek 2011: -0.50 (-0.68, -0.32)
- Wilding 2009: -0.70 (-1.08, -0.32)
- Wilding 2012: -0.54 (-0.71, -0.37)
**Subtotal**: -0.60 (-0.67, -0.53)

### Empagliflozin versus placebo
- Ferrannini 2013: -0.70 (-0.92, -0.48)
- Haring 2014: -0.70 (-0.97, -0.43)
- Häring 2013: -0.70 (-0.98, -0.42)
- Kadowaki 2014: -0.95 (-1.20, -0.70)
- Kovacs 2014: -0.69 (-0.88, -0.50)
- Roden 2013: -0.86 (-1.01, -0.71)
- Rosenstock 2013: -0.70 (-0.91, -0.49)
- Rosenstock 2014: -0.46 (-0.68, -0.24)
- Rosenstock 2015: -0.60 (-0.88, -0.32)
- Ross 2015: -0.50 (-0.67, -0.33)
**Subtotal**: -0.69 (-0.78, -0.59)

**Total**: 100.0% -0.69 (-0.75, -0.62)

Favours SGLT2-i
Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis

Diabetes, Obesity and Metabolism 2016;18:783-794.
Meta-analysis of UTI’s and Genital Tract Infections with SGLT-2 Inhibitors

- Assessment of UTI’s and genital infections in patients on SGLT-2 inhibitors.
- 52 RCT’s with 36,689 patients.
- Cana, dapa, empa all were associated with a higher risk of genital infections than placebo.
- Only dapa 10 mg had more UTI’s than placebo
- No dose-dependent relationship for UTI’s and genital infections except for dapa.
Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes: Pooled Analysis of Phase I–III Clinical Trials

Sven Kohler · Cordula Zeller · Hristo Iliev · Stefan Kaspers
Empa Pooled DataSet

- **Objective:** Characterize the safety and tolerability of empagliflozin in T2D patients using a comprehensive analysis of pooled safety data based on >15,000 patient-years exposure to empagliflozin.

- **Patients:** T2DM—phase I – III Clinical Trials placebo (n = 4203), empa 10 mg (n = 4221), empa 25 mg (n = 4196)
- ~7500 patient years of follow-up in each group

- **Overall results:**
  - Increased risk for hypo only in patients on SU
  - No increase in UTI risk
  - Increase in mycotic genital infections (3.5/100 patient-years vs 0.9/100 patient years)
  - Higher AE incidence in people >= 75 (~3.2/100 pt-yrs vs 2.3/100 pt-yrs)
## Empa Pooled DataSet – Bone Fracture & Amputations*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=4,203)</th>
<th>Empagliflozn 10 mg (N=4,221)</th>
<th>Empagliflozn 25 mg (N=4,196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n or n/N</td>
<td>%</td>
<td>Rate/100 Patient Years</td>
</tr>
<tr>
<td>Bone Fractures</td>
<td>123</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Lower limb amputations</td>
<td>46</td>
<td>1.1</td>
<td>_</td>
</tr>
<tr>
<td>Events potentially related to lower limb amputations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral artery obstructive disease events</td>
<td>96</td>
<td>2.3</td>
<td>_</td>
</tr>
<tr>
<td>Diabetic foot-related events</td>
<td>109</td>
<td>2.6</td>
<td>_</td>
</tr>
<tr>
<td>Relevant infection events</td>
<td>74</td>
<td>1.8</td>
<td>_</td>
</tr>
<tr>
<td>Wound events</td>
<td>57</td>
<td>1.4</td>
<td>_</td>
</tr>
</tbody>
</table>

- Pooled safety data show no increase in bone fractures and lower limb amputations
- In addition generally, no increase in cancer, renal AEs, or DKA

*In the empagliflozin studies, lower limb amputations were not usually captured in AE reports; the frequency of lower limb amputations was assessed on the basis of a manual review of the pooled safety data and AE narratives.
## Amputation/Fracture Rates: CVOT

<table>
<thead>
<tr>
<th>Source</th>
<th>Amputation</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>On Drug</td>
</tr>
<tr>
<td><strong>CDC</strong></td>
<td>2.8/1,000 pt yrs</td>
<td>--</td>
</tr>
<tr>
<td><strong>British Database</strong></td>
<td>1.3/1,000 pt yrs (female)</td>
<td>2.4/1,000 pt yrs (male)</td>
</tr>
<tr>
<td><strong>Canvas--canaglifozin</strong></td>
<td>3.4/1,000 pt yrs</td>
<td>6.3/1,000 pt yrs</td>
</tr>
<tr>
<td><strong>EmpaReg--empagliflozin</strong></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Tecos--sitagliptin</strong></td>
<td>0.9%</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Savor-Timi--saxagliptin</strong></td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*NEJM 2014;370:1514-1523*
Trial design

- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

N Engl J Med 2015; 373:2117-2128
HbA1c

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements.
Primary outcome: 3-point MACE

HR 0.86
(95.02% CI 0.74, 0.99)
p=0.0382*

Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.

N Engl J Med 2015; 373:2117-2128
CV death

HR 0.62
(95% CI 0.49, 0.77)
$p<0.0001$

Cumulative incidence function. HR, hazard ratio

N Engl J Med 2015; 373:2117-2128
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017

Cumulative incidence function. HR, hazard ratio

N Engl J Med 2015; 373:2117-2128
Renal Function over Time

- **Graph A:** Change in eGFR over 192 Wk
  - No. at Risk:
    - Placebo: 2323, 2295, 2267, 2205, 2121, 2064, 1927, 1981, 1763, 1479, 1262, 1123, 977, 731, 448
    - Empagliflozin, 10 mg: 2322, 2290, 2264, 2235, 2162, 2114, 2012, 2064, 1839, 1540, 1314, 1180, 1024, 785, 513
    - Empagliflozin, 25 mg: 2322, 2288, 2269, 2216, 2156, 2111, 2006, 2067, 1871, 1563, 1340, 1207, 1063, 838, 524

- **Table:** No. in Follow-up Analysis
  - Total: 7020, 7020, 6996, 6931, 6864, 6765, 6696, 6651, 6068, 5114, 4443, 3961, 3488, 2707, 1703

**Sources:**
CANVAS: Initial Design

UL 95% CI <1.8

UL 95% CI <1.3

Evaluate CV safety/protection

CANVAS
Additional 14,000 for total of 18,500

Initial 4500


Final Design

CANVAS trial starts

CV safety proved and marketing authorization achieved

UL 95% CI <1.8

Evaluate CV safety

UL 95% CI <1.3

CANVAS Program
N = 10,142

CANVAS-R
n = 5812

CANVAS n = 4330

Randomization

CANVAS

2-week placebo run-in

R

Canagliflozin 300 mg

Canagliflozin 100 mg

Placebo

CANVAS-R

2-week placebo run-in

R

Canagliflozin 100 mg

with optional up-titration to 300 mg

Placebo

Participant Inclusion Criteria

Patients with type 2 diabetes

- HbA1c $\geq 7.0\%$ to $\leq 10.5\%$
- eGFR $\geq 30$ mL/min/1.73 m$^2$
- Age $\geq 30$ years and history of prior CV event
  - OR
  - Age $\geq 50$ years with $\geq 2$ CV risk factors*

*Diabetes duration $\geq 10$ years, SBP $> 140$ mmHg on $\geq 1$ medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol $< 1$ mmol/L.
## Demographics and Disease History

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female, %</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Mean duration of diabetes, y</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Heart failure (NYHA I-III), %</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>65</td>
<td>67</td>
</tr>
</tbody>
</table>
Effects on HbA1c

Mean difference

-0.58%

(95% CI, -0.61 to -0.56)

No. of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>since</td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4231</td>
<td>5644</td>
</tr>
<tr>
<td>1</td>
<td>3854</td>
<td>5211</td>
</tr>
<tr>
<td>2</td>
<td>2891</td>
<td>4228</td>
</tr>
<tr>
<td>3</td>
<td>1014</td>
<td>2206</td>
</tr>
<tr>
<td>4</td>
<td>899</td>
<td>2042</td>
</tr>
<tr>
<td>5</td>
<td>805</td>
<td>1889</td>
</tr>
<tr>
<td>6</td>
<td>695</td>
<td>1661</td>
</tr>
</tbody>
</table>

Mixed model for repeated measures (MMRM) analysis

Effects on Systolic BP

![Graph showing the effects of Placebo and Canagliflozin on systolic blood pressure over 6 years.]

Mean systolic BP (mmHg)

- Placebo
- Canagliflozin

Mean difference

-3.93 mmHg

(95% CI, -4.30 to -3.56)

No. of patients

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4247</td>
<td>5652</td>
</tr>
<tr>
<td>1</td>
<td>3945</td>
<td>5293</td>
</tr>
<tr>
<td>2</td>
<td>2979</td>
<td>4338</td>
</tr>
<tr>
<td>3</td>
<td>1038</td>
<td>2255</td>
</tr>
<tr>
<td>4</td>
<td>922</td>
<td>2092</td>
</tr>
<tr>
<td>5</td>
<td>828</td>
<td>1936</td>
</tr>
<tr>
<td>6</td>
<td>713</td>
<td>1675</td>
</tr>
</tbody>
</table>

Mixed model for repeated measures (MMRM) analysis

Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
p < 0.0001 for noninferiority
p = 0.0158 for superiority

No. of patients
Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661

Hospitalization for Heart Failure

Hazard ratio 0.67 (95% CI, 0.52-0.87)

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4347</td>
<td>5795</td>
</tr>
<tr>
<td>1</td>
<td>4198</td>
<td>5653</td>
</tr>
<tr>
<td>2</td>
<td>3011</td>
<td>4437</td>
</tr>
<tr>
<td>3</td>
<td>1274</td>
<td>2643</td>
</tr>
<tr>
<td>4</td>
<td>1236</td>
<td>2572</td>
</tr>
<tr>
<td>5</td>
<td>1180</td>
<td>2498</td>
</tr>
<tr>
<td>6</td>
<td>829</td>
<td>1782</td>
</tr>
</tbody>
</table>

## Summary

<table>
<thead>
<tr>
<th>Primary cardiovascular outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.85 (0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
</tr>
</tbody>
</table>

- **Hospitalization for heart failure**: 0.67 (0.52-0.87)
- **CV death or hospitalization for heart failure**: 0.78 (0.67-0.91)
- **All-cause mortality**: 0.87 (0.74-1.01)
Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

Hazard ratio 0.60 (95% CI, 0.47-0.77)

<table>
<thead>
<tr>
<th>Events (n)</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
<td>239</td>
<td>2576</td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
<td>21</td>
<td>2495</td>
</tr>
</tbody>
</table>

No. of patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>4347</td>
<td>5795</td>
</tr>
<tr>
<td>4227</td>
<td>5664</td>
</tr>
<tr>
<td>3029</td>
<td>4454</td>
</tr>
<tr>
<td>1274</td>
<td>2654</td>
</tr>
<tr>
<td>1229</td>
<td>2576</td>
</tr>
<tr>
<td>1173</td>
<td>2495</td>
</tr>
<tr>
<td>819</td>
<td>1781</td>
</tr>
</tbody>
</table>

Lower-extremity Amputations

Hazard ratio 1.97 (95% CI, 1.41-2.75)

No. at risk
Placebo  4344  4217  3037  1289  1247  1194  844
Canagliflozin  5790  5634  4420  2618  2536  2460  1765

Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter. N Engl J Med 2017; 377:644-657
Low-trauma Fracture

Hazard ratio 1.23 (95% CI, 0.99–1.52)

Patients with an event (%)

No. of patients
Placebo 4344 4182 2987 1263 1217 1162 817
Canagliflozin 790 5606 4376 2566 2467 2373 1692

Years since randomization

### Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>Favors SGLT2i</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>CANVAS Program</td>
<td></td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
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<td></td>
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<tr>
<td>Hospitalization for heart failure</td>
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<td></td>
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</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to macroalbuminuria*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal composite*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

---


Benefits and Risk

- **MACE**: 23 fewer patients
- **Hospitalization for heart failure**: 16 fewer patients
- **Renal composite**: 17 fewer patients
- **Amputation**: 15 more patients

(N Engl J Med 2017; 377:644-657)

![Graph showing benefits and risk](image-url)
Benefits and Risk

- **MACE**
  - **Placebo**: 180 patients
  - **Canagliflozin**: 157 patients
  - **23 fewer patients**

- **Hospitalization for heart failure**
  - **Placebo**: 120 patients
  - **Canagliflozin**: 104 patients
  - **16 fewer patients**

- **Renal composite**
  - **Placebo**: 100 patients
  - **Canagliflozin**: 83 patients
  - **17 fewer patients**

- **Amputation**
  - **Placebo**: 20 patients
  - **Canagliflozin**: 15 patients
  - **15 more patients**

- **5 above ankle, 10 toes and metatarsals**

INDICATIONS AND USAGE

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,

• to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)
At diagnosis of type 2 diabetes
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

<table>
<thead>
<tr>
<th>A1C &lt;8.5%</th>
<th>A1C ≥8.5%</th>
<th>Symptomatic hyperglycemia with metabolic decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If not at glycemic target (2-3 mos)</td>
<td>Start metformin immediately Consider initial combination with another antihyperglycemic agent</td>
<td></td>
</tr>
<tr>
<td>Start/Increase metformin</td>
<td>If not at glycemic targets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initiate insulin +/- metformin</td>
<td></td>
</tr>
</tbody>
</table>

**PATIENT CHARACTERISTIC**
**CHOICE OF AGENT**

**Priority:** Clinical Cardiovascular Disease → SGLT2 inhibitor with demonstrated CV outcome benefit

- Risk of hypoglycemia
- Overweight or obesity
- Cardiovascular disease or multiple risk factors
- Comorbidities (renal, CHF, hepatic)
- Preferences & access to treatment

- Rare hypoglycemia
- Weight loss or weight neutral
- Effect on cardiovascular outcome
- See therapeutic considerations, consider eGFR
- See cost column; consider access

http://guidelines.diabetes.ca/bloodglucoselowering/pharmacologyt2
• Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

• If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. A

• In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
“Position Statement on the Pharmacologic Treatment of Type 2 Diabetes: Individuals with Pre-existing CVD”

Metformin

Second Line Therapy

eGFR ≥ 45?

- yes
  - Start SGLT-2 I with CVD benefit
- no
  - Start GLP-1 RA with CVD benefit
Additional Considerations

• **Leaner** patients—can have too much weight loss

• Individuals with **renal insufficiency** may also preferentially benefit from these agents

• In patients with **prior CVA** consider pioglitazone/semaglutide (?)
THANK YOU