The CANVAS Program
(CANagliflozin cardioVascular Assessment Study)
The CANVAS Program

Introduction

David R. Matthews, FRCP, DPhil
Photography Prohibited

- Please do not take photos during this presentation per ADA guidelines
- Slides will be available upon conclusion of this presentation at www.georgeinstitute.org
Support

- The CANVAS Program was supported by Janssen Research & Development, LLC
Presentation Outline

- Background       Greg Fulcher
- Design and Methods     Kenneth W. Mahaffey
- Effects on CV Outcomes     Bruce Neal
- Effects on Renal Outcomes     Dick de Zeeuw
- Effects on Safety Outcomes     Vlado Perkovic
- Implications for Clinical Practice     David R. Matthews
- Independent Commentary     Clifford J. Bailey
The CANVAS Program

Background

Greg Fulcher, MD
Presenter Disclosures: Greg Fulcher, MD

- Research support
  - Novo Nordisk

- Advisory boards
  - Janssen, Novo Nordisk, Boehringer Ingelheim, MSD

- Consultant
  - Janssen, Novo Nordisk, Boehringer Ingelheim, MSD
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%

Distal S2/S3 segment of proximal tubule

No glucose

Glucose Metabolism in Diabetes

Glucose

SGLT2
~90%

SGLT1
~10%

Urinary glucose excretion

Inhibition of Renal Glucose Reabsorption

Renal Glucose Reabsorption

- **SGLT2i RTG**: ~3.9-5.0 mmol/L, ~70-90 mg/dL
- **Healthy RTG**: ~10 mmol/L, ~180 mg/dL
- **T2DM RTG**: ~13 mmol/L, ~240 mg/dL

**Graph**
- Y-axis: Urinary glucose excretion (g/day)
- X-axis: Plasma glucose (mg/dL)
- Healthy: Black arrow
- SGLT2i: Red arrow
- T2DM: Blue arrow

**Legend**
- Healthy RTG
- SGLT2i RTG
- T2DM RTG
SGLT2 Inhibition

SGLT2 inhibitors

Less glucose reabsorbed

Urinary glucose excretion

CV Risk Factor Reduction

- Lowers blood glucose levels
- Lowers BP via osmotic diuresis
- Increases urinary caloric loss with reductions in body weight
- Reduces albuminuria possibly due to alterations in tubuloglomerular feedback

Less glucose reabsorbed
Glucose Reabsorption From the Glomerular Filtrate Through a Proximal Tubule Epithelial Cell Into the Blood

Potential Role of SGLT2 Inhibition in Renoprotection

SGLT2 inhibition

Proximal tubular sodium and glucose absorption and albumin

Proximal tubular fractional reabsorption of sodium

Activation of TGF

Hyperfiltration injury

Proximal tubular cell glucotoxicity and albuminuria

Glucose-mediated inflammation and fibrosis

Proximal tubular hypertrophy and hyperplasia

Progression of CKD

Regulatory Requirements

European Medicines Agency (EMA) and US Food and Drug Administration (FDA): Need for CV Outcomes Studies

• ‘Demonstrate that a new anti-diabetic therapy is not associated with unacceptable increase in cardiovascular risk’

FDA Criteria for Assessing CV Risk

Pre-Approval

Post-Approval

Noninferiority

Superiority

Adequately powered for noninferiority
Canagliflozin

- Orally-active, selective SGLT2 inhibitor
- Half-life of 11 to 13 hours (once-daily dosing)
- Balanced renal and biliary excretion
- Glucuronidation is a major metabolic pathway
  - No active metabolites
- Approved doses 100 mg and 300 mg
Presenter Disclosures: Kenneth W. Mahaffey, MD

- **Research support**
  - Afferent, Amgen, AstraZeneca, Daiichi, Ferring, Google (Verily), Janssen, Medtronic, Merck, Novartis, Sanofi, St. Jude

- **Consultant (including CME)**

- **Equity**
  - BioPrint Fitness
Initial Design

CANVAS

Additional 14,000 for total of 18,500

UL 95% CI <1.8
UL 95% CI <1.3

Evaluate CV safety/protection

Initial 4500
Final Design

- CANVAS trial starts
  - CV safety proved and marketing authorization achieved
  - UL 95% CI <1.8
- UL 95% CI <1.3
  - Evaluate CV safety
  - CANVAS Program
    - N = 10,142
      - CANVAS-R
        - n = 5812
        - n = 4330

Timeline:
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
Randomization

CANVAS

2-week placebo run-in

Placebo

Canagliflozin 300 mg

Canagliflozin 100 mg

CANVAS-R

2-week placebo run-in

Placebo

Canagliflozin 100 mg with optional up-titration to 300 mg
Analytic Approach

2-week placebo run-in

Canagliflozin 300 mg + Canagliflozin 100 mg

Placebo
Organizational Structure

Steering Committee
D. Matthews (Co-chair), B. Neal (Co-chair), G. Fulcher, K. Mahaffey, V. Perkovic, M. Desai (Sponsor), D. de Zeeuw

Independent Data Monitoring Committee
P. Home (Chair), J. Anderson, I. Campbell, J. Lachin (withdrew in September 2015), D. Scharfstein, S. Solomon, R. Uzzo

Cardiovascular Adjudication Committee
G. Fulcher (Chair), J. Amerena, C. Chow, G. Figtree, J. French, G. Hillis, M. Hlatky, B. Jenkins, N. Leeper, R. Lindley, B. McGrath, A. Street, J. Watson

Renal Adjudication Committee
G. Fulcher (Chair), S. Shahinfar, T. Chang, A. Sinha, P. August

Safety Adjudication Committees
Fracture Adjudication: Bioclinica
Diabetic Ketoacidosis Adjudication: Baim Institute for Clinical Research
Pancreatitis Adjudication: A. Cheifetz (Chair), S. Sheth, J. Feuerstein

Data Management
Similar electronic case report forms and same endpoint definitions
Participant Inclusion Criteria

Patients with type 2 diabetes

- HbA1c ≥7.0% to ≤10.5%
- eGFR ≥30 mL/min/1.73 m²
- Age ≥30 years and history of prior CV event
  OR
  Age ≥50 years with ≥2 CV risk factors*

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L.
Statistical Methods - Efficacy

- Integrated data set and intent-to-treat (ITT) principle
- Primary endpoint analysis based on Cox regression model with stratification by trial and CV disease history
- Pooled data from canagliflozin doses compared with placebo
- CV event (90% power) and time (>78 weeks) driven study
- Homogeneity of treatment effects across the two trials was evaluated
- Sequential testing prespecified
## Objectives

<table>
<thead>
<tr>
<th>PRIMARY</th>
<th>CV death, nonfatal MI, or nonfatal stroke</th>
</tr>
</thead>
</table>
| SECONDARY | All-cause mortality  
|          | CV death |
| EXPLORATORY | Nonfatal MI  
|          | Nonfatal stroke  
|          | Hospitalization for HF  
|          | Hospitalization for HF or CV death  
|          | Total hospitalizations  
|          | Albuminuria progression  
|          | Albuminuria regression  
|          | Renal composite: 40% reduction in eGFR, end-stage renal disease, or renal death |
**Hypothesis Testing Plan**

- **Major cardiovascular events (non-inferiority)**
  - Superiority*

- **All-cause mortality**

- **Cardiovascular death**

- **Albuminuria progression**

- **Cardiovascular death or hospitalization for heart failure**

- **Cardiovascular death**

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*Superiority testing was included in the Statistical Analysis Plan.*
The CANVAS Program

Effects on Cardiovascular Outcomes

Bruce Neal, MB, ChB, PhD
Presenter Disclosures: Bruce Neal, MB ChB, PhD

- **Research support**
  - Australian National Health and Medical Research Council Principal Research Fellowship
  - Janssen, Roche, Servier, Merck Schering Plough

- **Advisory boards and/or continuing medical education**
  - Abbott, Janssen, Novartis, Pfizer, Roche, Servier
  - Consultancy, honoraria, or travel support paid to his institution
Global Participation

North America
- Canada
- USA

Latin America
- Argentina
- Brazil
- Colombia
- Mexico

Europe
- Belgium
- Czech Republic
- Estonia
- France
- Germany
- Great Britain
- Hungary
- Israel
- Italy
- Luxembourg
- Netherlands
- Spain
- Sweden
- Norway
- Poland
- Russia
- Ukraine

Asia Pacific
- Australia
- China
- India
- Korea
- Malaysia
- New Zealand
- Taiwan

30 Countries
667 sites
Enrollment and Follow-up

**CANVAS**
4330 randomized

**Integrated CANVAS Program dataset**
10,142 randomized* (ITT population)

**CANVAS-R**
5813 randomized

- **4347 placebo**
  - 4327 (99.5%) vital status known
  - 4163 (95.7%) completed study

- **5795 canagliflozin**
  - 5773 (99.6%) vital status known
  - 5571 (96.1%) completed study

*One participant was randomized at 2 different sites and only the first randomization is included in the ITT analysis set.
Follow-up

CANVAS Program mean follow-up 188 weeks

Patients remaining on randomized treatment:

- Canagliflozin 71%
- Placebo 70%
## 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>
## Demographics (cont)

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Asian</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Central/South America</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Europe</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Rest of world</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>
# Baseline Therapies

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihyperglycemic agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>Insulin</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cardioprotective agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS inhibitor</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Statin</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Diuretic</td>
<td>44</td>
<td>45</td>
</tr>
</tbody>
</table>
## Baseline Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.9</td>
<td>32.0</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Results
Effects on HbA1c

Mean HbA1c (%)

Mean difference  
-0.58%  
(95% CI, -0.61 to -0.56)

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>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

Mean systolic BP (mmHg)

Years since randomization

Mean difference
–3.93 mmHg
(95% CI, –4.30 to –3.56)

No. of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>4247</td>
<td>5652</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>3945</td>
<td>5293</td>
</tr>
</tbody>
</table>

Mixed model for repeated measures (MMRM) analysis
Effects on Body Weight

Mean difference
-1.60 kg
(95% CI, -1.70 to -1.51)

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

Years since randomization
0 1 2 3 4 5 6

Patients with an event (%)
0 2 4 6 8 10 12 14 16 18 20

Placebo
Canagliflozin

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

Intent-to-treat analysis
Primary Cardiovascular Outcome by Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS</td>
<td>0.88 (0.75-1.03)</td>
</tr>
<tr>
<td>CANVAS-R</td>
<td>0.82 (0.66-1.01)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>0.86 (0.75-0.97)</td>
</tr>
</tbody>
</table>
Hypothesis Testing Outcome

Major cardiovascular events (non-inferiority)
- Superiority*

All-cause mortality

Cardiovascular death

Albuminuria progression

Cardiovascular death or hospitalization for heart failure

Cardiovascular death

Exploratory Nominal effect estimates

*Superiority testing was included in the Statistical Analysis Plan.
CV Death Component of Primary Outcome

Hazard ratio 0.87 (95% CI, 0.72-1.06)

Placebo
Canagliflozin

Intent-to-treat analysis
MI Component of Primary Outcome

Hazard ratio 0.85 (95% CI, 0.69-1.05)

No. of patients
Placebo  4347  4187  2986  1255  1207  1146  812
Canagliflozin  5795  5625  4405  2602  2516  2425  1728

Intent-to-treat analysis
Hazard ratio 0.90 (95% CI, 0.71-1.15)

Intent-to-treat analysis
All-Cause Mortality

Hazard ratio 0.87 (95% CI, 0.74-1.01)

<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>4279</td>
<td>5723</td>
</tr>
<tr>
<td>2</td>
<td>3119</td>
<td>4576</td>
</tr>
<tr>
<td>3</td>
<td>1356</td>
<td>2761</td>
</tr>
<tr>
<td>4</td>
<td>1328</td>
<td>2710</td>
</tr>
<tr>
<td>5</td>
<td>1292</td>
<td>2651</td>
</tr>
<tr>
<td>6</td>
<td>924</td>
<td>1904</td>
</tr>
</tbody>
</table>

No. of patients

Placebo 4347 4279 3119 1356 1328 1292 924
Canagliflozin 5795 5723 4576 2761 2710 2651 1904

Intent-to-treat analysis
Hospitalization for Heart Failure

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

Patients with an event (%)

Years since randomization

No. of patients

Placebo  4347  4198  3011  1274  1236  1180  829
Canagliflozin  5795  5653  4437  2643  2572  2498  1782

Intent-to-treat analysis
CV Death or Hospitalization for Heart Failure

**Hazard ratio 0.78 (95% CI, 0.67-0.91)**

- **Placebo**
- **Canagliflozin**

**Intent-to-treat analysis**

No. of patients
- Placebo: 4347, 4202, 3015, 1281, 1242, 1184, 831
- Canagliflozin: 5795, 5655, 4442, 2647, 2577, 2503, 1782
## Demographic Subgroups (Primary outcome)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>0.91 (0.76-1.10)</td>
<td>0.26</td>
</tr>
<tr>
<td>≥65 y</td>
<td>0.80 (0.67-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.86 (0.74-1.00)</td>
<td>0.80</td>
</tr>
<tr>
<td>Female</td>
<td>0.84 (0.66-1.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.84 (0.73-0.96)</td>
<td>0.40</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0.45 (0.19-1.03)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1.08 (0.72-1.64)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.01 (0.57-1.80)</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>0.84 (0.65-1.09)</td>
<td>0.89</td>
</tr>
<tr>
<td>Central/South America</td>
<td>0.84 (0.53-1.33)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>0.80 (0.65-0.99)</td>
<td></td>
</tr>
<tr>
<td>Rest of the world</td>
<td>0.94 (0.75-1.18)</td>
<td></td>
</tr>
</tbody>
</table>

Intent-to-treat analysis

Favors Canagliflozin  Favors Placebo
# Risk Factor Subgroups (Primary Outcome)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>0.79 (0.67-0.93)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>0.97 (0.79-1.20)</td>
<td></td>
</tr>
<tr>
<td><strong>BP control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≥140 mmHg or DBP ≥90 mmHg</td>
<td>0.84 (0.70-1.01)</td>
<td>0.64</td>
</tr>
<tr>
<td>SBP &lt;140 mmHg and DBP &lt;90 mmHg</td>
<td>0.88 (0.74-1.04)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 y</td>
<td>0.96 (0.76-1.22)</td>
<td>0.33</td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>0.81 (0.70-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8%</td>
<td>0.80 (0.68-0.94)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥8%</td>
<td>0.94 (0.77-1.15)</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;60 mL/min/1.73 m²</td>
<td>0.70 (0.55-0.90)</td>
<td>0.20</td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.95 (0.80-1.13)</td>
<td></td>
</tr>
<tr>
<td>≥90 mL/min/1.73 m²</td>
<td>0.84 (0.62-1.12)</td>
<td></td>
</tr>
</tbody>
</table>

*Intent-to-treat analysis*
Disease History Subgroups (Primary Outcome)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes Hazard ratio (95% CI)</th>
<th>No Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV disease</td>
<td>0.82 (0.72-0.95)</td>
<td>0.98 (0.74-1.30)</td>
<td>0.18</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.75 (0.58-0.97)</td>
<td>0.89 (0.77-1.03)</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.80 (0.61-1.05)</td>
<td>0.87 (0.76-1.01)</td>
<td>0.51</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.56 (0.28-1.13)</td>
<td>0.86 (0.76-0.98)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Favors Canagliflozin  
Favors Placebo

Intent-to-treat analysis

CANVAS Program

Hazard ratio (95% CI)
### Background Therapy Subgroups (Primary Outcome)

<table>
<thead>
<tr>
<th>Therapeutic Use</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.85 (0.72-1.00)</td>
<td>0.96</td>
</tr>
<tr>
<td>No</td>
<td>0.87 (0.71-1.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Statin use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.84 (0.72-0.97)</td>
<td>0.45</td>
</tr>
<tr>
<td>No</td>
<td>0.91 (0.71-1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Antithrombotic use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.87 (0.75-1.00)</td>
<td>0.86</td>
</tr>
<tr>
<td>No</td>
<td>0.82 (0.61-1.09)</td>
<td></td>
</tr>
<tr>
<td><strong>RAAS inhibitor use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.88 (0.76-1.01)</td>
<td>0.38</td>
</tr>
<tr>
<td>No</td>
<td>0.77 (0.58-1.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Beta-blocker use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.75 (0.64-0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>1.04 (0.85-1.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretic use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.66 (0.56-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>1.11 (0.93-1.34)</td>
<td></td>
</tr>
</tbody>
</table>

*Intent-to-treat analysis*
### Summary

<table>
<thead>
<tr>
<th>Primary cardiovascular outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death</strong></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>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74-1.01)</td>
</tr>
</tbody>
</table>

**Hazard ratio**

- Favors Placebo
- Favors Canagliflozin

**Intent-to-treat analysis**
The CANVAS Program

Effects on Renal Outcomes

Dick de Zeeuw, MD, PhD
Presenter Disclosures: Dick de Zeeuw, MD, PhD

- Advisory boards and/or speaker for:
  - AbbVie, Astellas, Eli Lilly, Fresenius, Janssen, Boehringer Ingelheim, Bayer, Mitsubishi-Tanabe
  - All consultancy honoraria are paid to his institution
Renal Outcomes

Biomarker outcome
• Change in albuminuria

Renal intermediate outcomes
• Progression of albuminuria
• Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
• 40% decrease in glomerular filtration rate (GFR)
• End-stage renal disease
• Renal death
Measurement of Renal Outcomes

**Albuminuria**
- Urine albumin:creatinine ratio (UACR)

**Progression/Regression of albuminuria**
- Change in albuminuria class (normo-, micro-, macroalbuminuria) plus >30% UACR change from baseline

**40% decrease in GFR**
- Sustained more than 40% decrease in estimated GFR (eGFR)

**End-stage renal disease**
- Reaching dialysis or transplantation or sustained eGFR <15 mL/min/1.73 m²

**Renal death**
- Death due to kidney disease
## Renal Baseline Characteristics

*Similar for Canagliflozin and Placebo*

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean eGFR, mL/min/1.73 m²</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>Median albumin:creatinine ratio, mg/g</td>
<td>12.4</td>
<td>12.1</td>
</tr>
<tr>
<td>ACE inhibitor/ARB use, %</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin (n = 5795)</td>
<td>Placebo (n = 4347)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Mean eGFR, mL/min/1.73 m²</strong></td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>≥90 mL/min/1.73 m², %</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m², %</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>45 to &lt;60 mL/min/1.73 m², %</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>&lt;45 mL/min/1.73 m², %</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>Median albumin:creatinine ratio, mg/g</strong></td>
<td><strong>12.4</strong></td>
<td><strong>12.1</strong></td>
</tr>
<tr>
<td>Normoalbuminuria (&lt;30 mg/g), %</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Microalbuminuria (30 to 300 mg/g), %</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Macroalbuminuria (&gt;300 mg/g), %</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
Results

Biomarker outcome
• Change in albuminuria

Renal intermediate outcomes
• Progression of albuminuria
• Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
• 40% decrease in glomerular filtration rate (GFR)
• End-stage renal disease
• Renal death
Change in Albumin:Creatinine Ratio (UACR)
Percent Change in UACR per Albuminuria Class (inset)

Geometric mean UACR with 95% CI (mg/g)

- Normo: -9%
- Micro: -34%
- Macro: -36%

Mean % difference: -18%
(95% CI, -16 to -20)

No. of patients
Placebo: 4084, 3775, 2556, 753, 652, 594, 618
Canagliflozin: 5500, 5103, 3565, 1689, 1541, 1408, 1534

Mixed model for repeated measures (MMRM) analysis
Excluding those below detection level
Results

Biomarker outcome
• Change in albuminuria

Renal intermediate outcomes
• Progression of albuminuria
• Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
• 40% decrease in glomerular filtration rate (GFR)
• End-stage renal disease
• Renal death
Progression of Albuminuria

Hazard ratio 0.73 (95% CI, 0.67-0.79)

Intent-to-treat analysis

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3819</td>
<td>5196</td>
</tr>
<tr>
<td>1</td>
<td>3096</td>
<td>4475</td>
</tr>
<tr>
<td>2</td>
<td>1690</td>
<td>2968</td>
</tr>
<tr>
<td>3</td>
<td>724</td>
<td>1730</td>
</tr>
<tr>
<td>4</td>
<td>626</td>
<td>1528</td>
</tr>
<tr>
<td>5</td>
<td>548</td>
<td>1354</td>
</tr>
<tr>
<td>6</td>
<td>303</td>
<td>775</td>
</tr>
</tbody>
</table>
Regression of Albuminuria

Hazard ratio 1.70 (95% CI, 1.51-1.91)

Intent-to-treat analysis

No. of patients
Placebo  1257  913  426  163  144  123  59
Canagliflozin  1679  1009  518  276  227  198  112
Results

Biomarker outcome
• Change in albuminuria

Renal intermediate outcomes
• Progression of albuminuria
• Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
• 40% decrease in glomerular filtration rate (GFR)
• End-stage renal disease
• Renal death
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></td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Intent-to-treat analysis

No. of patients

Placebo 4347 4227 3029 1274 1229 1173 819
Canagliflozin 5795 5664 4454 2654 2576 2495 1781
Renal Outcomes Summary

• Canagliflozin compared to placebo
  – Induced sustained lowering of albuminuria
  – Prevented progression in albuminuria
  – Induced regression in albuminuria
  – Reduced renal function loss events

• Conclusion
  – These data suggest a potential renoprotective effect of canagliflozin treatment in patients with type 2 diabetes at high CV risk on top of ACE/ARBs
The CANVAS Program

Effects on Safety Outcomes

Vlado Perkovic, MBBS, PhD
Presenter Disclosures:
Vlado Perkovic, MBBS, PhD

• Research support
  – Senior Research Fellowship and Program Grant from the Australian National Health and Medical Research Council

• Steering Committees
  – Abbvie, Boehringer Ingelheim, GSK, Janssen, Pfizer

• Advisory boards and/or speaker at scientific meetings
  – Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier, Vitae

• All honoraria are paid to employer
Adverse Event Collection in CANVAS Program

Pre-registration
• All adverse events

Post-registration streamlined approach
• All serious adverse events
• Adverse events leading to discontinuation
• Adverse events of interest
Adverse Events of Interest

- Prespecified
  - Male genital mycotic infections
  - Malignancies
  - Photosensitivity
  - Venous thromboembolism
  - Fracture

- Added during trials
  - Diabetic ketoacidosis (health authority surveillance for class)
  - Acute pancreatitis (health authority surveillance for class)
  - Amputation (data monitoring committee advice)
## Serious Adverse Events, Adverse Events Leading to Discontinuation & Hospitalizations

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Hazard Ratio (95% CI)</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Event rate per 1000 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events (n = 3280)</td>
<td>0.93 (0.87-1.00)</td>
<td>104</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to discontinuation (n = 1025)</td>
<td>1.13 (0.99-1.28)</td>
<td>35</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization (n = 3486)</td>
<td>0.94 (0.88-1.00)</td>
<td>119</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse Events (CANVAS)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Canagliflozin</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital mycotic infection (n = 196)</td>
<td>18</td>
<td>69</td>
<td>4.37 (2.78-6.88)</td>
</tr>
<tr>
<td>Urinary tract infection (n = 440)</td>
<td>37</td>
<td>40</td>
<td>1.09 (0.89-1.34)</td>
</tr>
<tr>
<td>Hypoglycemia (n = 551)</td>
<td>46</td>
<td>50</td>
<td>1.13 (0.94-1.35)</td>
</tr>
<tr>
<td>Osmotic diuresis (n = 312)</td>
<td>13</td>
<td>34</td>
<td>2.80 (2.06-3.81)</td>
</tr>
<tr>
<td>Volume depletion (n = 266)</td>
<td>19</td>
<td>26</td>
<td>1.44 (1.09-1.90)</td>
</tr>
<tr>
<td>Severe hypersensitivity/cutaneous reaction (n = 87)</td>
<td>9</td>
<td>6</td>
<td>1.41 (0.87-2.28)</td>
</tr>
<tr>
<td>Hepatic injury (n = 90)</td>
<td>9</td>
<td>7</td>
<td>0.81 (0.53-1.25)</td>
</tr>
</tbody>
</table>
### Adverse Events of Interest Across Program

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male genital mycotic infection (n = 503)</td>
<td>35</td>
<td>11</td>
<td>3.76 (2.91-4.86)</td>
</tr>
<tr>
<td>Venous thromboembolic events (n = 50)</td>
<td>1.7</td>
<td>1.7</td>
<td>0.96 (0.54-1.71)</td>
</tr>
<tr>
<td>Photosensitivity (n = 22)</td>
<td>1.0</td>
<td>0.3</td>
<td>2.71 (0.92-8.03)</td>
</tr>
<tr>
<td>Adjudicated diabetic ketoacidosis (n = 18)</td>
<td>0.6*</td>
<td>0.3</td>
<td>2.33 (0.76-7.17)</td>
</tr>
<tr>
<td>Adjudicated acute pancreatitis (n = 13)</td>
<td>0.5</td>
<td>0.4</td>
<td>1.34 (0.40-4.41)</td>
</tr>
</tbody>
</table>

*5 patients reporting diabetic ketoacidosis (all on canagliflozin) identified as having autoimmune diabetes (positive GADA and mIAA or a reported history of T1DM).
Lower-extremity Amputations

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

Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.
# Highest Level of Amputation

<table>
<thead>
<tr>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canagliflozin</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>All amputations (n = 187)</td>
<td>6.3</td>
</tr>
<tr>
<td>Minor amputation (71%)</td>
<td>4.5</td>
</tr>
<tr>
<td>Toe</td>
<td>3.4</td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.0</td>
</tr>
<tr>
<td>Major amputation (29%)</td>
<td>1.8</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
</tr>
<tr>
<td>Below-knee</td>
<td>1.2</td>
</tr>
<tr>
<td>Above-knee</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Amputation Risk Factors - Multivariate Analysis

<table>
<thead>
<tr>
<th>Risk Factor at Baseline</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>20.9</td>
<td>(14.2-30.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease*</td>
<td>3.1</td>
<td>(2.2-4.5)</td>
</tr>
<tr>
<td>Male</td>
<td>2.4</td>
<td>(1.6-3.5)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2.1</td>
<td>(1.6-2.9)</td>
</tr>
<tr>
<td>HbA1c &gt;8%</td>
<td>1.9</td>
<td>(1.4-2.6)</td>
</tr>
<tr>
<td>Canagliflozin treatment</td>
<td>1.8</td>
<td>(1.3-2.5)</td>
</tr>
<tr>
<td>Presence of CV disease</td>
<td>1.5</td>
<td>(1.0-2.3)</td>
</tr>
</tbody>
</table>

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations
Low-trauma Fracture

Hazard ratio 1.23 (95% CI, 0.99–1.52)

Patients with an event (%)

Years since randomization

No. of patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4344</td>
<td>4182</td>
<td>2987</td>
<td>1263</td>
<td>1217</td>
<td>1162</td>
<td>817</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Canagliflozin</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5790</td>
<td>5606</td>
<td>4376</td>
<td>2566</td>
<td>2467</td>
<td>2373</td>
<td>1692</td>
<td></td>
</tr>
</tbody>
</table>
### Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjudicated low-trauma fractures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program (Heterogeneity p = 0.003)</td>
<td>12 9.2 1.23 (0.99–1.52)</td>
<td></td>
</tr>
<tr>
<td>CANVAS (n = 271)</td>
<td>13 8.3 1.56 (1.18–2.06)</td>
<td></td>
</tr>
<tr>
<td>CANVAS-R (n = 108)</td>
<td>7.9 10 0.76 (0.52–1.12)</td>
<td></td>
</tr>
<tr>
<td><strong>All adjudicated fractures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program (Heterogeneity p = 0.005)</td>
<td>15 12 1.26 (1.04–1.52)</td>
<td></td>
</tr>
<tr>
<td>CANVAS (n = 350)</td>
<td>17 11 1.55 (1.21–1.97)</td>
<td></td>
</tr>
<tr>
<td>CANVAS-R (n = 146)</td>
<td>11 13 0.86 (0.62–1.19)</td>
<td></td>
</tr>
</tbody>
</table>
## Malignancy

<table>
<thead>
<tr>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canagliflozin</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Neoplasms (n = 741)</td>
<td>21</td>
</tr>
<tr>
<td>Renal cancer (n = 17)</td>
<td>0.6</td>
</tr>
<tr>
<td>Bladder cancer (n = 38)</td>
<td>1.0</td>
</tr>
<tr>
<td>Breast cancer (n = 37)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Favors Canagliflozin

Favors Placebo
## Renal Safety

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious renal-related (n = 83)</td>
<td>0.76 (0.49-1.19)</td>
</tr>
<tr>
<td>Serious acute kidney injury (n = 58)</td>
<td>0.68 (0.45-1.02)</td>
</tr>
<tr>
<td>Serious hyperkalemia (n = 15)</td>
<td>0.75 (0.27-2.11)</td>
</tr>
</tbody>
</table>

### Event rate per 1000 patient-years

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious renal-related (n = 83)</td>
<td>2.5</td>
<td>3.3</td>
<td>0.76 (0.49-1.19)</td>
</tr>
<tr>
<td>Serious acute kidney injury (n = 58)</td>
<td>1.6</td>
<td>2.5</td>
<td>0.68 (0.45-1.02)</td>
</tr>
<tr>
<td>Serious hyperkalemia (n = 15)</td>
<td>0.4</td>
<td>0.6</td>
<td>0.75 (0.27-2.11)</td>
</tr>
</tbody>
</table>

Favors Canagliflozin  Favors Placebo
Safety Summary

Canagliflozin use was associated with:

- Newly identified increase in risk of amputation
- Possible increase in fracture risk
- Adverse event profile otherwise consistent with known effects of canagliflozin
The CANVAS Program

Implications for Clinical Practice

David R. Matthews, FRCP, DPhil
Presenter Disclosures:
David R. Matthews, FRCP, DPhil

- Research support
  - Janssen
- Advisory boards
  - Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, Servier
- Consultant
  - Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, Servier
- Lectures
  - Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly, Novartis, Janssen, Aché Laboratories
What Was the Population Studied?

- T2DM ~14 years
- High CV risk
- Hypertensive
- Overweight
- Multiple comorbidities
- 2/3 with prior CV disease
- 1/3 primary prevention
What Did the Trial Assess?

- **Hard outcomes**
  - CV disease
  - Renal protection

- **Biomarkers**
  - $\text{HbA}_{1\text{c}}$
  - Blood pressure
  - Weight
  - Albuminuria

- **Safety and side effects**

  Trial powered for events and time
  Pre-specified

  Measures of microvascular and macrovascular risk

  A measure of multiple health and social risks

  A measure of renal and CV risk

CANVAS Program
Biomarkers

- The CANVAS Program was not designed to maintain a glycemic difference. Even so, the difference in average glycemia was -0.58%.

- Blood pressure was 3.9 mmHg lower than in the placebo group.
Biomarkers (cont)

- Body weight was 1.6 kg lower than in the placebo group

- Urinary albumin:creatinine ratio was 18% lower than in the placebo group
Key Efficacy Outcomes in the CANVAS Program

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
</tr>
</tbody>
</table>

- Favors Placebo
- Favors Canagliflozin

- p < 0.0001 noninferiority
- p = 0.0158 superiority
**Key Efficacy Outcomes in the CANVAS Program**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>1.0</td>
<td>&lt;0.0001 noninferiority</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.5</td>
<td>0.0158 superiority</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal composite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors Placebo

Favors Canagliflozin

Favors Canagliflozin

Favors Placebo

Hazard ratio (95% CI)

Hazard ratio (95% CI)

p <0.0001 noninferiority

p = 0.0158 superiority
Primary and Secondary Prevention?

<table>
<thead>
<tr>
<th>CV death, nonfatal myocardial infarction, or nonfatal stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV disease history (n = 6656)</td>
</tr>
<tr>
<td>No CV disease history (n = 3486)</td>
</tr>
<tr>
<td>All patients (n = 10,142)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV disease history</td>
</tr>
<tr>
<td>No CV disease history</td>
</tr>
<tr>
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</tbody>
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<table>
<thead>
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<tr>
<td>All patients</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)

- Favors Canagliflozin
- Favors Placebo
Comparisons Between Trials

- There is interest in interpreting these data in the context of EMPA-REG OUTCOME

- Comparisons between trials are complicated by differences in:
  - Populations
  - Trial designs
  - Analytic approaches
  - Drug effects

- Comparisons are therefore hazardous, subject to bias, and may be confounded by multiple uncontrolled factors
Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME

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

*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Who Might Benefit?
Patients With High CV Risk

CV death, nonfatal myocardial infarction, or nonfatal stroke
Who Might Benefit?

- **MACE**
  - Placebo: 160 fewer patients per 1000 patients over 5 years
  - Canagliflozin: 23 fewer patients per 1000 patients over 5 years

- **Hospitalization for heart failure**
  - 16 fewer patients

- **Renal composite**
  - 17 fewer patients

*Incidence rate (per 1000 patients over 5 years)*
Newly Identified Risk - Amputation

- The mechanism of increased amputation risk is unknown
- The US FDA issued a drug safety communication regarding increased risk of amputation with canagliflozin
- The European regulatory pharmacovigilance risk assessment committee (PRAC) noted that:
  - ‘An increased amputation risk has only become apparent with canagliflozin so far
  - One large cardiovascular outcome study (DECLARE) is still ongoing for dapagliflozin
  - Amputation events were not been [sic] systematically captured within the completed large cardiovascular outcome study conducted with empagliflozin (EMPA-REG)
  - Hence, it is currently not possible to establish whether the increased amputation risk is a class effect or not’

EMA PRAC assessment report. 9 February 2017.
Clinical Considerations - Amputation

• Caution in patients at high risk

• Canagliflozin EU Summary of Product Characteristics (product label)
  - ‘As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown
  - However, as precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration
  - Consideration may also be given to stopping treatment in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene’

Invokana SmPc. 20 April 2017.
Benefits and Risk

Incidence rate (per 1000 patients over 5 years)

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

Placebo vs Canagliflozin
Benefits and Risk

- **Incidence rate (per 1000 patients over 5 years)**
  - **MACE**
    - Placebo: 160
    - Canagliflozin: 137
    - **23 fewer patients**
  - **Hospitalization for heart failure**
    - Placebo: 40
    - Canagliflozin: 24
    - **16 fewer patients**
  - **Renal composite**
    - Placebo: 30
    - Canagliflozin: 13
    - **17 fewer patients**
  - **Amputation**
    - Placebo: 10
    - Canagliflozin: 5
    - **15 more patients**

Additional information:
- 5 above ankle
- 10 toes and metatarsals
Conclusion

- The CANVAS Program met its primary objective of demonstrating the cardiovascular safety and efficacy of canagliflozin.
- Canagliflozin use was associated with an increased risk of amputation which should be taken into consideration when prescribing this agent.
- These data suggest a favorable benefit/risk profile with canagliflozin treatment in many patients with type 2 diabetes and high cardiovascular risk.
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

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We thank

• All the patients who volunteered to enroll in CANVAS and CANVAS-R

• The Principal Investigators in the 667 centers in 30 countries

We acknowledge the dedicated work involved to achieve the ultimate follow-up of 99.6% percent of the patients since first patient randomized in CANVAS in December 2009.
Acknowledgments (cont)

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Ian Campbell
John Lachin (for early years)
Daniel Scharfstein
Scott D. Solomon
Robert G. Uzzo
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**Diabetic Ketoacidosis Adjudication:**
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**Pancreatitis Adjudication:**
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Ngozi Erondu
Wayne Shaw
Gordon Law

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Lyndal Hones (George Clinical)
...and many others in this long and successful enterprise
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