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

SGLT2 inhibitors

Less glucose reabsorbed

Increased urinary glucose excretion

Renal Glucose Reabsorption

Urinary glucose excretion (g/day)

Plasma glucose (mg/dL)

- **Healthy RT<sub>G</sub>**
  - ~10 mmol/L
  - ~180 mg/dL

- **SGLT2i RT<sub>G</sub>**
  - ~3.9-5.0 mmol/L
  - ~70-90 mg/dL

- **T2DM RT<sub>G</sub>**
  - ~13 mmol/L
  - ~240 mg/dL

**CANVAS Program**
SGLT2 Inhibition

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
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
      - Glucose-mediated inflammation and fibrosis
      - Proximal tubular hypertrophy and hyperplasia
  - Proximal tubular cell glucotoxicity and albuminuria

- 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
- Noninferiority

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
The CANVAS Program

Design and Methods

Kenneth W. Mahaffey, MD
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

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

CV safety proved and marketing authorization achieved

Evaluate CV safety

CANVAS Program
N = 10,142

CANVAS-R
n = 5812

CANVAS n = 4330

Randomization

CANVAS

2-week placebo run-in

- Canagliflozin 300 mg
- Canagliflozin 100 mg
- Placebo

CANVAS-R

2-week placebo run-in

- Canagliflozin 100 mg with optional up-titration to 300 mg
- Placebo
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>
<tbody>
<tr>
<td>SECONDARY</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>CV death</td>
</tr>
<tr>
<td>EXPLORATORY</td>
<td>Nonfatal MI</td>
</tr>
<tr>
<td></td>
<td>Nonfatal stroke</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for HF</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for HF or CV death</td>
</tr>
<tr>
<td></td>
<td>Total hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Albuminuria progression</td>
</tr>
<tr>
<td></td>
<td>Albuminuria regression</td>
</tr>
<tr>
<td></td>
<td>Renal composite: 40% reduction in eGFR,</td>
</tr>
<tr>
<td></td>
<td>end-stage renal disease, or</td>
</tr>
<tr>
<td></td>
<td>renal death</td>
</tr>
</tbody>
</table>
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**

---

*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

30 Countries
667 sites

North America
- Canada
- USA

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

Latin America
- Argentina
- Brazil
- Colombia
- Mexico

Asia Pacific
- Australia
- China
- India
- Korea
- Malaysia
- New Zealand
- Taiwan
Enrollment and Follow-up

**CANVAS**
- 4330 randomized

**CANVAS-R**
- 5813 randomized

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

- 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>
<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>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>Antihyperglycemic agents</th>
<th>Canagliflozin (n = 5795) %</th>
<th>Placebo (n = 4347) %</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardioprotective agents</th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<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></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 difference**: -0.58% (95% CI, -0.61 to -0.56)
- **Mean HbA1c (%):**
  - Placebo: 8.4
  - Canagliflozin: 7.8

**Years since randomization**
- 0
- 1
- 2
- 3
- 4
- 5
- 6

**No. of patients**
- Placebo: 4231, 3854, 2891, 1014, 899, 805, 695
- Canagliflozin: 5644, 5211, 4228, 2206, 2042, 1889, 1661

Mixed model for repeated measures (MMRM) analysis
Effects on Systolic BP

Mean systolic BP (mmHg)

Years since randomization

No. of patients
Placebo 4247 3945 2979 1038 922 828 713
Canagliflozin 5652 5293 4338 2255 2092 1936 1675

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

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

Mean difference

\(-1.60 \text{ kg}\)

(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

Intent-to-treat analysis
Primary Cardiovascular Outcome by Study

Hazard ratio (95% CI)

CANVAS
Favors Placebo
Hazard ratio: 0.88 (0.75-1.03)

CANVAS-R
Favors Canagliflozin
Hazard ratio: 0.82 (0.66-1.01)

CANVAS Program
Favors Placebo
Hazard ratio: 0.86 (0.75-0.97)

Intent-to-treat analysis
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

p < 0.001
p = 0.0158

p = 0.24

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)

Intent-to-treat analysis

No. of patients

<table>
<thead>
<tr>
<th></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>

Years since randomization

Patients with an event (%)
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

Years since randomization

Intent-to-treat analysis
Stroke Component of Primary Outcome

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)

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 5795 5653 4437 2643 2572 2498 1782
Canagliflozin

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

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

Patients with an event (%)

No. of patients

Placebo: 4347, 4202, 3015, 1281, 1242, 1184, 831
Canagliflozin: 5795, 5655, 4442, 2647, 2577, 2503, 1782

Years since randomization

Intent-to-treat analysis
## 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>

Favors Canagliflozin  Favors Placebo

Intent-to-treat analysis

CANVAS Program
## Risk Factor Subgroups (Primary Outcome)

<table>
<thead>
<tr>
<th></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>0.97 (0.79-1.20)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>0.79 (0.67-0.93)</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>0.81 (0.70-0.95)</td>
<td>0.33</td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>0.96 (0.76-1.22)</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8%</td>
<td>0.94 (0.77-1.15)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥8%</td>
<td>0.80 (0.68-0.94)</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**

Favors Canagliflozin  
Favors Placebo
### 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>

**Note:** Intent-to-treat analysis

---

**Favors Canagliflozin** | **Favors Placebo**
### Background Therapy Subgroups (Primary Outcome)

<table>
<thead>
<tr>
<th>Substance</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>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>
<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>

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><strong>Mean eGFR, mL/min/1.73 m²</strong></td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td><strong>Median albumin:creatinine ratio, mg/g</strong></td>
<td>12.4</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>ACE inhibitor/ARB use, %</strong></td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>
Low Renal Risk Population
High Percentage of “Normal” eGFR and Albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean eGFR, mL/min/1.73 m²</strong></td>
<td></td>
<td></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)

Years since randomization

<table>
<thead>
<tr>
<th>Years</th>
<th>No. of patients Placebo</th>
<th>No. of patients Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4084</td>
<td>5500</td>
</tr>
<tr>
<td>1</td>
<td>3775</td>
<td>5103</td>
</tr>
<tr>
<td>2</td>
<td>2556</td>
<td>3565</td>
</tr>
<tr>
<td>3</td>
<td>753</td>
<td>1689</td>
</tr>
<tr>
<td>4</td>
<td>652</td>
<td>1541</td>
</tr>
<tr>
<td>5</td>
<td>594</td>
<td>1408</td>
</tr>
<tr>
<td>6</td>
<td>618</td>
<td>1534</td>
</tr>
</tbody>
</table>

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)

No. of patients
Placebo 3819 3096 1690 724 626 548 303
Canagliflozin 5196 4475 2968 1730 1528 1354 775

Intent-to-treat analysis
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

Years since randomization

Patients with an event (%)

0 0 10 20 30 40 50 60 70 80 90 100

Placebo
Canagliflozin

0 1 2 3 4 5 6

CANVAS Program
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>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
</tr>
</tbody>
</table>

No. of patients

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

Intent-to-treat analysis
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, Relypsy, 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 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 serious adverse events (n = 3280)</td>
<td>104</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation (n = 1025)</td>
<td>35</td>
</tr>
<tr>
<td>All-cause hospitalization (n = 3486)</td>
<td>119</td>
</tr>
</tbody>
</table>

- **Canagliflozin** favors over **Placebo** for all serious adverse events and all-cause hospitalization.
- **Placebo** favors over **Canagliflozin** for adverse events leading to discontinuation.

Favors Canagliflozin  Favors Placebo
<table>
<thead>
<tr>
<th>Event Rate (95% CI)</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital mycotic infection (n = 196)</td>
<td>69</td>
<td>18</td>
<td>4.37 (2.78-6.88)</td>
</tr>
<tr>
<td>Urinary tract infection (n = 440)</td>
<td>40</td>
<td>37</td>
<td>1.09 (0.89-1.34)</td>
</tr>
<tr>
<td>Hypoglycemia (n = 551)</td>
<td>50</td>
<td>46</td>
<td>1.13 (0.94-1.35)</td>
</tr>
<tr>
<td>Osmotic diuresis (n = 312)</td>
<td>34</td>
<td>13</td>
<td>2.80 (2.06-3.81)</td>
</tr>
<tr>
<td>Volume depletion (n = 266)</td>
<td>26</td>
<td>19</td>
<td>1.44 (1.09-1.90)</td>
</tr>
<tr>
<td>Severe hypersensitivity/cutaneous reaction (n = 87)</td>
<td>8</td>
<td>6</td>
<td>1.41 (0.87-2.28)</td>
</tr>
<tr>
<td>Hepatic injury (n = 90)</td>
<td>7</td>
<td>9</td>
<td>0.81 (0.53-1.25)</td>
</tr>
</tbody>
</table>
## Adverse Events of Interest Across Program

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Canagliflozin</th>
<th>Event Rate per 1000 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male genital mycotic infection (n = 503)</td>
<td>11</td>
<td>35</td>
<td></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></td>
<td>0.96 (0.54-1.71)</td>
</tr>
<tr>
<td>Photosensitivity (n = 22)</td>
<td>0.3</td>
<td>1.0</td>
<td></td>
<td>2.71 (0.92-8.03)</td>
</tr>
<tr>
<td>Adjudicated diabetic ketoacidosis (n = 18)</td>
<td>0.3</td>
<td>0.6*</td>
<td></td>
<td>2.33 (0.76-7.17)</td>
</tr>
<tr>
<td>Adjudicated acute pancreatitis (n = 13)</td>
<td>0.4</td>
<td>0.5</td>
<td></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>

Favors Canagliflozin

Favors Placebo
### 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)

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>4344</td>
<td>5790</td>
</tr>
<tr>
<td>1</td>
<td>4182</td>
<td>5606</td>
</tr>
<tr>
<td>2</td>
<td>2987</td>
<td>4376</td>
</tr>
<tr>
<td>3</td>
<td>1263</td>
<td>2566</td>
</tr>
<tr>
<td>4</td>
<td>1217</td>
<td>2467</td>
</tr>
<tr>
<td>5</td>
<td>1162</td>
<td>2373</td>
</tr>
<tr>
<td>6</td>
<td>817</td>
<td>1692</td>
</tr>
</tbody>
</table>
## Fractures

### Adjudicated low-trauma fractures

<table>
<thead>
<tr>
<th></th>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>CANVAS Program</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Heterogeneity p = 0.003)</td>
<td>12</td>
<td>9.2</td>
</tr>
<tr>
<td>CANVAS (n = 271)</td>
<td>13</td>
<td>8.3</td>
</tr>
<tr>
<td>CANVAS-R (n = 108)</td>
<td>7.9</td>
<td>10</td>
</tr>
</tbody>
</table>

### All adjudicated fractures

<table>
<thead>
<tr>
<th></th>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>CANVAS Program</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Heterogeneity p = 0.005)</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>CANVAS (n = 350)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>CANVAS-R (n = 146)</td>
<td>11</td>
<td>13</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>

The figure shows the event rate per 1000 patient-years for different types of malignancies under Canagliflozin and Placebo, along with the hazard ratio and 95% confidence interval.
## Renal Safety

<table>
<thead>
<tr>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Serious renal-related</strong> (n = 83)</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Serious acute kidney injury</strong> (n = 58)</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Serious hyperkalemia</strong> (n = 15)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The chart shows that Canagliflozin favors lower event rates compared to Placebo for each renal-related event.
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**
  - $\text{HbA}_{1c}$
  - 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
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>
<tr>
<td>p &lt; 0.0001 noninferiority</td>
</tr>
<tr>
<td>p = 0.0158 superiority</td>
</tr>
</tbody>
</table>

Favors Canagliflozin
Favors Placebo
**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>p &lt; 0.0001 noninferiority</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>p = 0.0158 superiority</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td></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 Canagliflozin: 0.5
Favors Placebo: 2.0
Primary and Secondary Prevention?

**CV death, nonfatal myocardial infarction, or nonfatal stroke**
- CV disease history (n = 6656)
- No CV disease history (n = 3486)
- All patients (n = 10,142)

**All-cause mortality**
- CV disease history
- No CV disease history
- All patients

**CV death**
- CV disease history
- No CV disease history
- All patients

### Hazard ratio (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>Favors Canagliflozin</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>0.5 (0.4-0.6)</td>
<td>2.0 (1.8-2.2)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.5 (0.4-0.6)</td>
<td>2.0 (1.8-2.2)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.5 (0.4-0.6)</td>
<td>2.0 (1.8-2.2)</td>
</tr>
</tbody>
</table>

Favors Canagliflozin: Lower value on the x-axis
Favors Placebo: Higher value on the x-axis
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>CANVAS Program</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>CANVAS Program</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>CANVAS Program</td>
</tr>
<tr>
<td>Progression to macroalbuminuria*</td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>Renal composite*</td>
<td>CANVAS Program</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

![Graph showing the percentage of patients with an event over time, with a line representing Placebo.](image-url)
Who Might Benefit?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate (per 1000 patients over 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>23 fewer patients per 1000 patients over 5 years</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>16 fewer patients</td>
</tr>
<tr>
<td>Renal composite</td>
<td>17 fewer patients</td>
</tr>
</tbody>
</table>

**Who Might Benefit?**

- Placebo
- Canagliflozin

**Graph:**
- MACE: 23 fewer patients per 1000 patients over 5 years
- Hospitalization for heart failure: 16 fewer patients
- Renal composite: 17 fewer patients

**Legend:**
- Placebo
- Canagliflozin

**Note:**
- The graph shows the incidence rate of MACE, hospitalization for heart failure, and renal composite events per 1000 patients over 5 years, comparing Placebo to Canagliflozin.
- Canagliflozin reduces the incidence of these events compared to Placebo.
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

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

Incidence rate (per 1000 patients over 5 years)

- **Placebo**
- **Canagliflozin**
Benefits and Risk

- **MACE Hospitalization for heart failure**: 23 fewer patients
- **Renal composite**: 17 fewer patients
- **Amputation (5 above ankle, 10 toes and metatarsals)**: 15 more patients

Incidence rate (per 1000 patients over 5 years):
- Placebo
- Canagliflozin
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*

DOI: 10.1056/NEJMoa1611925
Acknowledgments

International Centers – Patients and PIs

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)

Independent Data Monitoring Committee
Philip Home (Chair)
Jeffrey Anderson
Ian Campbell
John Lachin (for early years)
Daniel Scharfstein
Scott D. Solomon
Robert G. 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
Acknowledgments (cont)

CANVAS and CANVAS-R sponsors’ team (Janssen)
Mehul Desai (Steering Committee member)
Ngozi Erondu
Wayne Shaw
Gordon Law

Support team
Kimberly Dittmar (MedErgy)
Lyndal Hones (George Clinical)
...and many others in this long and successful enterprise
CANVAS Investigators


CANVAS-R Investigators