Discussant

Primary and Secondary Prevention of CV Events in the CANVAS Program

M. Angelyn Bethel, MD
Associate Professor of Diabetes and Endocrinology
University of Oxford
UK
Aims & major findings

Aims:
• Compare canagliflozin vs placebo for CV, renal and safety outcomes
  – Primary prevention population
  – Secondary prevention population (established CV disease)

Results:
• Secondary prevention population had higher rates of CV morbidity and mortality (~2-fold), renal (~1.5-fold), and amputation (~2.5-fold) outcomes
• Canagliflozin reduces both CV and renal outcomes overall, with no evidence of statistical heterogeneity between primary and secondary prevention cohorts
• Similar safety outcomes between groups

Why are these results important?
Are they consistent with other evidence?
What other evidence exists? EMPA-REG and CANVAS

**EMPA-REG OUTCOME**

CVD A1c 7-10% n=7,020

Empagliflozin

Placebo

Median follow-up 3.1 years

CV death, nonfatal MI, or nonfatal stroke

**Primary Endpoint**

A1c 7-10.5% ≥30y with CVD, ≥50y with CRFs n=10,142

Canagliflozin

Placebo

Median follow-up 2.4 years*

CV death, nonfatal MI, or nonfatal stroke

*The CANVAS Program (mean follow-up 3.6 years) is comprised of CANVAS: n=4347, mean follow-up 5.7 years CANVAS-R: n=4344, mean follow-up 2.1 years
## Event rates for key outcomes

<table>
<thead>
<tr>
<th>Event Rate per 1000 pt-years</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE-3</strong></td>
<td>Canagliflozin</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.98 (0.74, 1.30)</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td>0.79 (0.58, 1.07)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.74, 0.99)</td>
</tr>
<tr>
<td><strong>Heart failure hospitalization</strong></td>
<td>0.64 (0.35, 1.15)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td><strong>Renal composite</strong>*</td>
<td>0.63 (0.39, 1.02)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.54 (0.40, 0.75)</td>
</tr>
</tbody>
</table>

*The EMPA-REG mortality results were surprising and the mechanisms are debated*

- **Beyond conventional risk factors**
  - Small reductions in weight, SBP, DBP
  - Small increases in LDL and HDL
  - Timeline is too short for glucose- or atherosclerotic processes

- **Diuretic effect/volume status** (mediated via heart failure)

- **Drive toward ketone metabolism**

- Are they relevant to primary prevention?

*CANVAS Renal Composite: 40% reduction in eGFR, renal replacement or renal death*

*EMPA-REG Renal Composite: 2x serum Cr with eGFR ≤45, renal replacement, or renal death*
## Event rates for key outcomes

<table>
<thead>
<tr>
<th>Event Rate per 1000 pt-years</th>
<th>CANVAS 2&lt;sup&gt;o&lt;/sup&gt; Prevention</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>MACE-3</strong></td>
<td>34.1</td>
<td>41.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.98 (0.74, 1.30)</td>
<td>0.82 (0.72, 0.95)</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td>21.1</td>
<td>23.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.79 (0.58, 1.07)</td>
<td>0.89 (0.75, 1.07)</td>
</tr>
<tr>
<td><strong>Heart failure hospitalization</strong></td>
<td>7.3</td>
<td>11.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.35, 1.15)</td>
<td>0.68 (0.51, 0.90)</td>
</tr>
<tr>
<td><strong>Renal composite</strong>*</td>
<td>6.4</td>
<td>10.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.39, 1.02)</td>
<td>0.59 (0.44, 0.79)</td>
</tr>
</tbody>
</table>

*CANVAS Renal Composite: 40% reduction in eGFR, renal replacement or renal death
EMPA-REG Renal Composite: 2x serum Cr with eGFR ≤45, renal replacement, or renal death
Contrasting MACE and renal outcomes

MACE

Secondary Prevention

Primary Prevention

Secondary prevention—curve morphology similar to primary outcome.

No suggestion of difference for primary prevention.
Summary: SGLT-2 in secondary prevention

• Data available from EMPA-REG and CANVAS (prespecified subgroup analysis)
• There are consistent signals for
  – Reduction in MACE, heart failure, and renal outcomes
  – Reduction in all cause mortality (data for CV death not shown), but size of benefit is unclear
• Mechanisms:
  – Beyond conventional risk factors
    • Small changes
    • Timeline is too short for atherosclerotic or glucose mediated mechanisms
  – Partially mediated by heart failure outcomes
• Not all outcomes appear to translate for primary prevention cohorts in the short term (or perhaps at all)

Summary: SGLT-2 in primary prevention

• No statistical heterogeneity between primary & secondary cohort for any outcome...BUT

• Speculation:
  – Effect sizes are comparable for heart failure and renal outcomes
  – Effect size is numerically greater for all cause mortality
  – MACE outcome is inconsistent (HR 0.98) and no separation in the curves

• Limitations
  – Only available evidence is from the CANVAS program which was neither designed nor powered to address the primary prevention cohort
Next steps

• For primary prevention, is this just a power problem?
• How would we see heterogeneity on a forest plot?
  – Divergent effects—point estimate does not lie within the confidence interval of the comparator
  – Non-overlap of 95% confidence intervals
• Could longer follow-up in a larger primary prevention population identify additional long-term benefits?
  – CREDENCE (canagliflozin): ~4500 pts with mixed prior CV status, renal endpoints or CV death, ~5 yr follow-up (2019)*
  – DECLARE (dapagliflozin)~17,000 pts with mixed prior CV status, MACE-3, ~5 yr follow-up (2019)*
• Implications for guidelines?
  – Caution is warranted in extending trial results beyond the enrolled population—may be an overestimate of the benefits
• Amputations & fracture?

THANK YOU