VERTIS-CV

IS IT ALL CLASS?

Mark Cooper

from here
CONFLICT OF INTEREST

I have received honoraria for medical educational meetings conducted on behalf of pharmaceutical companies including: Merck/MSD, Lilly, Boehringer-Ingelheim, Astra Zeneca, Novartis and Servier.

I have attended advisory boards of pharmaceutical companies including: Boehringer-Ingelheim, Astra Zeneca, Merck/MSD, MundiPharma and Reata.

I have received research support from Boehringer-Ingelheim & Novo.
WHAT IS CLASS?

Things regarded as high-quality, integrity, status, or style

“a class act”

VERTIS-CV ✔️
WHAT IS A DRUG CLASS?

Drugs that share scientifically documented properties:

- Chemical Structure
  - SGLT2 inhibitors

- Mechanism of Action
  - SGLT2 inhibitors

- Physiological Effect
  - SGLT2 inhibitors

https://www.fda.gov/media/77834
SPOT THE DIFFERENCE?

bridged ketal motif

confers rigidity that could potentially positively impact potency and selectivity for SGLT2. Possibly reduce the rate of phase 2 metabolism and improve potency.

<table>
<thead>
<tr>
<th></th>
<th>SGLT2 IC$_{50}$ (nM)</th>
<th>SGLT1 IC$_{50}$ (nM)</th>
<th>(SGLT2:SGLT1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>1.2</td>
<td>1400</td>
<td>~ 1200-fold</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>0.877</td>
<td>1960</td>
<td>~ 2200-fold</td>
</tr>
</tbody>
</table>
SPOT THE DIFFERENCE?

<table>
<thead>
<tr>
<th>Dapagliflozin 10mg</th>
<th>-0.53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin 10 mg</td>
<td>-0.61</td>
</tr>
<tr>
<td>Canagliflozin 100mg</td>
<td>-0.66</td>
</tr>
<tr>
<td>Empagliflozin 25mg</td>
<td>-0.67</td>
</tr>
<tr>
<td>Ertugliflozin 5mg</td>
<td>-0.7</td>
</tr>
<tr>
<td>Canagliflozin 300mg</td>
<td>-0.77</td>
</tr>
<tr>
<td>Ertugliflozin 15mg</td>
<td>-0.79</td>
</tr>
</tbody>
</table>

Predicted HbA1c response (95% CI) at 26 weeks on background oral treatment baseline HbA1c 8.0% and eGFR = 90ml/min/1.73m2

Fediuk d et al. Diabetes 2019 Jun; 68(Supplement 1): https://doi.org/10.2337/db19-1222-P
Doses of background antihyperglycemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycemic rescue criteria.

CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares.
EMPA-REG Outcomes Change in HbA1c over time

Adjusted mean (SE) HbA1c (%)

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

Week

EMPA-REG Outcomes
SPOT THE DIFFERENCE?

**Weight loss***

<table>
<thead>
<tr>
<th></th>
<th>EMPAREG</th>
<th>VERTIS-CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.81</td>
<td>-0.4</td>
</tr>
<tr>
<td>Low dose</td>
<td>-1.82</td>
<td>-2.4</td>
</tr>
<tr>
<td>High dose</td>
<td>-2.86</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

**Lower SBP***

<table>
<thead>
<tr>
<th></th>
<th>EMPAREG</th>
<th>VERTIS-CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.82</td>
<td>0.76</td>
</tr>
<tr>
<td>Low dose</td>
<td>-4.03</td>
<td>-1.8</td>
</tr>
<tr>
<td>High dose</td>
<td>-3.32</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

*mean values at 12 months
**TIME TO FIRST MACE IN PATIENTS WITH ASCVD**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate/1000 patient-years</th>
<th>Placebo Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>37.4</td>
<td>43.9</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>34.1</td>
<td>41.3</td>
<td>0.82 (0.72-0.95)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>36.8</td>
<td>41.0</td>
<td>0.90 (0.79-1.02)</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>55.6</td>
<td>65.0</td>
<td>0.85 (0.69-1.06)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td>40.0</td>
<td>40.3</td>
<td>0.99 (0.88-1.12)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td></td>
<td><strong>0.89 (0.84-0.95)</strong></td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MACE, major adverse cardiovascular events.
### TIME TO FIRST HOSPITALISATION FOR HEART FAILURE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Rate/1000 patient-years</th>
<th>Placebo Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/1000 patient-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD EMPA-REG OUTCOME</td>
<td>9.4</td>
<td>14.5</td>
<td>0.65 (0.50-0.85)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>7.3</td>
<td>11.3</td>
<td>0.68 (0.51-0.90)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>11.1</td>
<td>14.1</td>
<td>0.78 (0.63-0.97)</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>20.6</td>
<td>33.2</td>
<td>0.61 (0.44-0.85)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td>7.3</td>
<td>10.5</td>
<td>0.70 (0.54-0.90)</td>
</tr>
</tbody>
</table>

**P interaction = 0.63**

**Notes:**
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HHF, hospitalization for heart failure.
Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).

CI, confidence interval; CV, cardiovascular; HFF, hospitalization for heart failure; HR, hazard ratio.

TIME TO FIRST HHF – SPOT THE DIFFERENCE?

Placebo

Ertugliflozin

HR, 0.70 (95% CI, 0.54–0.90)
P=0.006

HR, 0.65 (95% CI, 0.50–0.85)
P=0.0017

Placebo

Empagliflozin

*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo). CI, confidence interval; CV, cardiovascular; HFF, hospitalization for heart failure; HR, hazard ratio.
IS IT ALL JUST CLASS EFFECT?

✓ Chemical Structure
✓ Mechanism of Action
✓ HbA1c, Weight, BP
✓ CV Safety
✓ Reduced HHF
✓ Genital Mycoses, Ketoacidosis
## TIME TO CV DEATH – IS THERE A DIFFERENCE?

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment Rate/1000 patient-years</th>
<th>Placebo Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGLT2 inhibitor</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Patients with ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME®¹,⁴</td>
<td>12.4</td>
<td>20.2</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td>CANVAS Program²,⁴</td>
<td>14.8</td>
<td>16.8</td>
<td>0.86 (0.70, 1.06)</td>
</tr>
<tr>
<td>DECLARE-TIMI 53³,⁴</td>
<td>10.9</td>
<td>11.6</td>
<td>0.94 (0.76, 1.18)</td>
</tr>
<tr>
<td>VERTIS-CV</td>
<td>17.6</td>
<td>19.0</td>
<td>0.92 (0.77, 1.10)</td>
</tr>
<tr>
<td><strong>Pooled analysis (all SGLT2 inhibitors)</strong></td>
<td></td>
<td></td>
<td><strong>0.86 (0.78 – 0.96)</strong></td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular.
IS THERE REALLY ANY DIFFERENCE?

• Unlikely, based on so many similarities
• Not because of different baseline risk
• Not because of obvious trial/pop\(n\) differences
• Not a head to head comparison
• Random fluctuations around a mean?
IS IT ALL JUST CLASS EFFECT?

✓ Cardiovascular Death

Renal Protection?
Doubling of serum creatinine, dialysis, transplantation or renal death

**EMPA-REG Outcomes**
- Absolute event rate (per 1000 PY): 11.5
- HR = 0.54

**CANVAS**
- Absolute event rate (per 1000 PY): 6.3
- HR = 0.53

**CREDENCE**
- Absolute event rate (per 1000 PY): 27
- HR = 0.66
- HR = 0.81 (0.64, 1.03)

**VERTIS-CV**
- Absolute event rate (per 1000 PY): 11.5
- Absolute event rate (per 1000 PY): 9.3
VERTIS-CV change in eGFR over time

Mean change in eGFR from baseline (mL/min/1.73 m²)

Baseline eGFR (mL/min/1.73 m²) 75.7 76.0 76.2

- Placebo
- Ertugliflozin 5 mg
- Ertugliflozin 15 mg

eGFR, estimated glomerular filtration rate.
EMPA-REG OUTCOMES change in eGFR over time

Adjusted mean (SE) eGFR (ml/min/1.73m²)

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg
Full analysis set included all randomized patients who received at least one dose of study medication (N=2746 for ertugliflozin 5 mg, N=2747 for ertugliflozin 15 mg, and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

**Ertugliflozin 5 mg**
HR 0.91  
(95.6% CI, 0.77, 1.07)

**Ertugliflozin 15 mg**
HR 1.04  
(95.6% CI, 0.89, 1.20)

**Placebo**

BUT WHAT HAPPENED TO THE DOSE?
VERTIS-CV – it’s all class

Mark Cooper (ADA 2020)