Navigating Through The Latest Diabetes Clinical Trials – The Role of Newer Drugs

Lubaina S. Presswala, D.O.

Assistant Professor
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York
Disclosures

• Not relevant to this presentation
  • Sub-investigator for VESALIUS-CV Study
    • Sponsored by Amgen
  • PCSK9i in patients at **high risk** for CVD
Objectives

- Review landmark clinical trials and outcomes
- Evaluate the success and pitfalls of older medications
- Describe the timeline of emerging newer oral and non-insulin injectable agents
- Understand the cardiovascular and renal outcomes of newer drugs
- Summarize the role of newer drugs with a practical approach to patient care
Prevalence

• Today, an estimated 9.3% of adults aged 20–79 years – a staggering 463 million people – are living with diabetes.

For confidence intervals, see full IDF Diabetes Atlas, Table 3.4.
Several studies have shown that patients with diabetes have higher mortality and morbidity rates than patients without diabetes after an acute myocardial infarction.

Diabetes & Cardiovascular Disease

• The Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry results provided long-term information on 8013 patients with unstable coronary artery disease from 6 different countries and 95 hospitals.
• Mean age was 65 years for patients with and without DM
• They also had significantly more previous cardiovascular events, including MI, congestive heart failure, stroke, and more revascularization procedures.

Diabetes & Cardiovascular Disease

Diabetes & Cardiovascular Disease

## Landmark DM Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>DCCT</th>
<th>EDIC</th>
<th>UKPDS</th>
<th>UKPDS 10-Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>1441</td>
<td>1357</td>
<td>5102</td>
<td>1525</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>6.5 years</td>
<td>10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intensive Arm</strong></td>
<td>Pump or MDI</td>
<td>SU or Insulin or Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conventional Arm</strong></td>
<td>1 or 2 daily insulin injection</td>
<td>Dietary therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median A1c (IA &amp; CA)</strong></td>
<td>7.4% and 9.1%</td>
<td>7.9% and 9.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>41% ↓ in major CV and PVD (NS)</td>
<td>42% ↓ heart disease; 57% ↓ non-fatal MI, stroke, CVD death</td>
<td>16% ↓ in fatal and nonfatal MI and sudden death (NS)</td>
<td>15% ↓ in MI; 13% ↓ in death</td>
</tr>
</tbody>
</table>

# Landmark T2DM Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Duration</td>
<td>3.4 years</td>
<td>5 years</td>
<td>5.6 years</td>
</tr>
<tr>
<td>DM Duration</td>
<td>10 years</td>
<td>7.9 years</td>
<td>11.5 years</td>
</tr>
<tr>
<td>Mean A1c</td>
<td>8.3%</td>
<td>7.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>H/o CV Event</td>
<td>35.2%</td>
<td>32.2%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Intervention Arm</td>
<td>Atleast 2 hypoglycemic agents + other drugs</td>
<td>Gliclazide + other drugs</td>
<td>Glimepiride or Metformin + Roziglitazone OR insulin (max doses)</td>
</tr>
<tr>
<td>Control Arm</td>
<td>Diet or meds or both</td>
<td>Current therapy</td>
<td>Glimepiride or Metformin + Roziglitazone OR insulin (max doses)</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>6.9% vs. 7.2% (NS)</td>
<td>18% vs. 20% (S*)</td>
<td>29.5% vs. (NS)</td>
</tr>
</tbody>
</table>
In Summary: Landmark Trials

- The DCCT/EDIC and the UKPDS did not show any significant reduction in cardiovascular risk until their observational follow-up 10 years later, indicating a "legacy effect"
Existing Favorites – Metformin, Sulfonylureas, and TZDs

• Randomized controlled trials\textsuperscript{1-3} that evaluated metformin in patients with type 2 diabetes indicated significant improvements in cardiovascular outcomes.

• There exists controversial data regarding cardiovascular disease risk with sulfonylureas\textsuperscript{4-5}.

• A meta-analysis of pioglitazone reported lower risk of recurrent MACE, stroke, or MI in patients with vascular disease. Pioglitazone did not lower the risk for all-cause mortality; however, increased the risk for new heart failure\textsuperscript{6}.


Cardiovascular Focus & DM

- In 2007, Rosiglitazone was associated with a significant increase in risk of MI
- In 2008, FDA mandated evaluation of newer DM drugs to show no increase in cardiovascular risk
- All CVOT are industry funded, multicenter, randomized, double-blinded, placebo-controlled trials

Newer DM Drug Categories

Glucagon Like Peptide – 1 Agonists  Dipeptidyl Peptidase 4 Inhibitors
Newer DM Drug Categories

**Glucagon Like Peptide – 1 Agonists**
- Lixisenatide (®Adlyxin)
- Liraglutide (®Victoza)
- Semaglutide (®Ozempic)
- Exenetide (®Byetta)
- Exenatide LAR (®Bydureon)
- Dulaglutide (®Trulicity)
- Oral Semaglutide (®Rybelsus)

**Dipeptidyl Peptidase 4 Inhibitors**
- Sitagliptin (®Januvia)
- Saxagliptin (®Onglyza)
- Linagliptin (®Tradjenta)
- Alogliptin (®Nesina)
GLP-1 CVOT – ELIXA
Lixisenatide (®Adlyxin)

T2DM; N = 6068; Avg A1c 7.7%; Duration = 2yrs
Acute coronary event – 180 days prior to screening
Run-in period of placebo injections

Lixisenatide QD
Placebo QD

Primary Endpoint
Death from CV cause, nonfatal MI, nonfatal stroke or hospitalization for unstable angina

GLP-1 CVOT – ELIXA
Lixisenatide (®Adlyxin)

- Results showed non-inferiority to placebo as primary endpoints were similar in both groups.
- The reduction in HbA1c values was significantly greater among patients in the lixisenatide group vs. placebo.

GLP-1 CVOT – LEADER
Liraglutide (®Victoza)

T2DM; N = 9340; Avg A1c 8.7%; Duration = 3.5yrs
Patients with pre-existing CVD 81.3% and 24.7% with >CKD3
Run-in period of placebo injections

Liraglutide QD
Placebo QD

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke.

A – Primary composite outcome occurred in fewer patients in Liraglutide group (13%) vs. placebo group (14.9%)

B – Death from CV causes occurred in fewer patients in Liraglutide group (4.7%) vs. placebo group (6.9%)

The frequencies of nonfatal myocardial infarction and nonfatal stroke were lower in the liraglutide group than in the placebo group, although the differences were not significant.

E – The rate of death from any cause was lower in the liraglutide group (8.2%) vs. placebo group (9.6%)

F – 18% of patients participating in this trial had NYHA Class I-III HF, the rate of hospitalizations was not significant
GLP-1 CVOT – LEADER
Liraglutide (®Victoza)

• There were also significant mean differences between the liraglutide group and the placebo group in the change from baseline to 36 months in the following variables:
  • Weight loss was 2.3 kg (95% CI, 2.5 to 2.0) higher in the liraglutide group
  • The systolic blood pressure was 1.2 mm Hg (95% CI, 1.9 to 0.5) lower in the liraglutide group

GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)

T2DM; N = 3297; Avg A1c 8.7%; Duration = 2.1yrs
83% patients had CVD and CKD3 or higher
59% patients had CVD without CKD
Run-in period of placebo injections

Semaglutide 0.5 mg or 1.0 mg once/week
Matched Placebo 0.5 mg or 1.0 mg once/week

The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent), or nonfatal stroke.

The primary composite cardiovascular outcome occurred in 6.6% of patients in the semaglutide group vs. 8.9% in the placebo group, which was statistically significant.
There were significantly fewer non-fatal strokes in the semaglutide group (1.6%) vs. placebo group (2.7%).

MACE reduction was primarily due to reduction in non-fatal MI and non-fatal stroke.
GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)

The mean HbA1c level in the semaglutide group vs. placebo group, was 0.7 percentage points lower (for 0.5 mg dose) and 1.0 percentage point lower (for 1.0 mg dose), significant.

The mean body weight in the semaglutide group vs. placebo was 2.9 kg lower in the group receiving 0.5 mg and lower in the group receiving 1.0 mg (P<0.001).

GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)

• The mean systolic blood pressure in the semaglutide group vs. placebo was 1.3 mm Hg lower in the group receiving 0.5 mg (P=0.10) and 2.6 mm Hg lower in the group receiving 1.0 mg (P<0.001)

• New or worsening nephropathy occurred in 3.8% patients in Semaglutide group vs. 6.1% in placebo group (P=0.005)

• In contrast, diabetic retinopathy occurred in 3% patients in Semaglutide group vs. 1.8% in placebo group (P=0.02)

GLP-1 CVOT – EXSCEL
Exenatide LAR (®Bydureon)

T2DM; N = 14,752; Avg A1c 8.0%; Duration = 3.2yrs
73% patients had CVD
NO run-in period of placebo injections

Exenatide 2 mg once/wk
Placebo 2 mg once/wk

The primary outcome was defined as the first occurrence of a component of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (three-component MACE outcome), in a time-to-event analysis.

GLP-1 CVOT – EXSCEL
Exenatide LAR (®Bydureon)

GLP-1 CVOT – EXSCEL
Exenatide LAR (®Bydureon)

GLP-1 CVOT – REWIND
Dulaglutide (®Trulicity)

T2DM; N = 9901; Avg A1c 7.2%; Duration = 5.4 yrs
31.5% patients had CVD
3-week run-in period of placebo injections

Dulaglutide 1.5 mg once/week
Placebo 1.5 mg once/week

The primary outcome was the first occurrence of a composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes.

GLP-1 CVOT – REWIND
Dulaglutide (®Trulicity)

GLP-1 CVOT – PIONEER 6
Semaglutide (®Rybelsus)

T2DM; N = 3183; Avg A1c 8.2%; Duration = 1.3yrs
84.7% patients had CVD

Semaglutide 14 mg PO QD
Placebo 14 mg PO QD

Primary Outcome: The time from randomization to the first occurrence of a major adverse cardiovascular event, a cardiovascular death from cardiovascular causes (including undetermined causes of death), nonfatal myocardial infarction, or nonfatal stroke

GLP-1 CVOT – PIONEER 6
Semaglutide (®Rybelsus)

A Composite Primary Outcome

No. at Risk
Oral semaglutide 1591 1583 1575 1564 1557 1547 1512 1062 735
Placebo 1592 1577 1565 1551 1538 1528 1489 1032 713

GLP-1 Agonist – Class Effects

- GLP-1 agents in general are known to significantly reduce:
  - HbA1c values
  - Weight (in kg)
  - Systolic blood pressure
- Composite cardiovascular outcomes* (LEADER, SUSTAIN-6, and REWIND trials)
# GLP-1 CVOT Comparison

<table>
<thead>
<tr>
<th>GLP-1 RA: Study name</th>
<th>N</th>
<th>Median F/u (yrs)</th>
<th>% with CV disease*</th>
<th>% of statin use</th>
<th>Baseline HbA1c</th>
<th>Baseline BMI</th>
<th>Primary composite CV outcome HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide: ELIXA</td>
<td>6068</td>
<td>2.1</td>
<td>100%</td>
<td>93%</td>
<td>7.70%</td>
<td>30.1</td>
<td>1.02 (0.89 to 1.17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Liraglutide: LEADER</td>
<td>9340</td>
<td>3.8</td>
<td>81%</td>
<td>72%</td>
<td>8.70%</td>
<td>32.5</td>
<td>0.87 (0.78 to 0.97)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Semaglutide: SUSTAIN-6</td>
<td>3297</td>
<td>2.1</td>
<td>60%</td>
<td>73%</td>
<td>8.70%</td>
<td>32.8</td>
<td>0.74 (0.58 to 0.95)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Exenatide QW: EXSCEL</td>
<td>14752</td>
<td>3.2</td>
<td>73.10%</td>
<td>74%</td>
<td>8.00%</td>
<td>31.8</td>
<td>0.91 (0.83 to 1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dulaglutide: REWIND</td>
<td>9901</td>
<td>5.4</td>
<td>31.50%</td>
<td>66%</td>
<td>7.20%</td>
<td>32.3</td>
<td>0.88 (0.79 to 0.99)</td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>Semaglutide Oral: PIONEER 6</td>
<td>3183</td>
<td>1.3</td>
<td>84.70%</td>
<td>85%</td>
<td>8.20%</td>
<td>32.3</td>
<td>0.79 (0.57 to 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

Newer DM Drug Categories

Glucagon Like Peptide – 1 Agonists

- Lixisenatide (®Adlyxin)
- Liraglutide (®Victoza)
- Semaglutide (®Ozempic)
- Exenetide (®Byetta)
- Exenatide LAR (®Bydureon)
- Dulaglutide (®Trulicity)
- Oral Semaglutide (®Rybelsus)

Dipeptidyl Peptidase 4 Inhibitors

- Sitagliptin (®Januvia)
- Saxagliptin (®Onglyza)
- Linagliptin (®Tradjenta)
- Alogliptin (®Nesina)
DPP4-I CVOT

- EXAMINE Trial – Alogliptin (®Nesina)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N = 2679)</th>
<th>Alogliptin (N = 2701)</th>
<th>Hazard Ratio for Alogliptin Group (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point†</td>
<td>316 (11.8)</td>
<td>305 (11.3)</td>
<td>0.96 (≤1.16)‡</td>
<td>0.32</td>
</tr>
<tr>
<td>Components of primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>111 (4.1)</td>
<td>89 (3.3)</td>
<td>0.79 (0.60–1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>173 (6.5)</td>
<td>187 (6.9)</td>
<td>1.08 (0.88–1.33)</td>
<td>0.47</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>32 (1.2)</td>
<td>29 (1.1)</td>
<td>0.91 (0.55–1.50)</td>
<td>0.71</td>
</tr>
<tr>
<td>Principal secondary end point§</td>
<td>359 (13.4)</td>
<td>344 (12.7)</td>
<td>0.95 (≤1.14)‡</td>
<td>0.26</td>
</tr>
<tr>
<td>Other end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>173 (6.5)</td>
<td>153 (5.7)</td>
<td>0.88 (0.71–1.09)</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes¶</td>
<td>130 (4.9)</td>
<td>112 (4.1)</td>
<td>0.85 (0.66–1.10)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Prespecified Clinical End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Saxagliptin (N=8280)</th>
<th>Placebo (N=8212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point</td>
<td>613 (7.3)</td>
<td>609 (7.2)</td>
<td>1.00 (0.89–1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point</td>
<td>1059 (12.8)</td>
<td>1034 (12.4)</td>
<td>1.02 (0.94–1.11)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalization for heart failure</th>
<th>289 (3.5)</th>
<th>228 (2.8)</th>
<th>1.27 (1.07–1.51)</th>
<th>P=0.007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for coronary revascularization</td>
<td>423 (5.2)</td>
<td>459 (5.6)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.18</td>
</tr>
<tr>
<td>Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine &gt;6.0 mg/dl (530 μmol/liter)</td>
<td>194 (2.2)</td>
<td>178 (2.0)</td>
<td>1.08 (0.88–1.11)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for hypoglycemia</td>
<td>53 (0.6)</td>
<td>43 (0.5)</td>
<td>1.22 (0.82–1.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Event rates and percentages are 2-year Kaplan–Meier estimates.

DPP4-I CVOT

- TECOS – Sitagliptin (®Januvia)
- CARMELINA – Linagliptin (®Tradjenta)

<table>
<thead>
<tr>
<th>TECOS</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14671</td>
<td>N=6979</td>
</tr>
<tr>
<td>A1c 6.5% - 8%</td>
<td>A1c 6.5% - 10%</td>
</tr>
<tr>
<td>Duration = 3 years</td>
<td>Duration = 2.2 years</td>
</tr>
<tr>
<td>4-point MACE</td>
<td>3-point MAC</td>
</tr>
</tbody>
</table>

## DPP4-I CVOT

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>CV risk</th>
<th>HR, OR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXAMINE [8]</td>
<td>Alogliptin versus placebo</td>
<td>3-point MACE</td>
<td>↔</td>
<td>HR 0.96 (≤ 1.16)a</td>
</tr>
<tr>
<td>N = 5380</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53 [7]</td>
<td>Saxagliptin versus placebo</td>
<td>3-point MACE</td>
<td>↔</td>
<td>HR 1.00 (0.89–1.12)</td>
</tr>
<tr>
<td>N = 16,492</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TECOS [5]</td>
<td>Sitagliptin versus placebo</td>
<td>4-point MACE</td>
<td>↔</td>
<td>HR 0.98 (0.88–1.09)</td>
</tr>
<tr>
<td>N = 14,671</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARMELINA [6]</td>
<td>Linagliptin versus placebo</td>
<td>3-point MACE</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>N = 6979</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT2 - Inhibitors

The kidneys play a major role in the regulation of glucose, reabsorbing 99% of the plasma glucose that filters through the renal glomerular tubules.
# SGLT2 - Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (@Invokana)</th>
<th>Dapagliflozin (@Farxiga)</th>
<th>Empagliflozin (@Jardiance)</th>
<th>Ertugliflozin (@Steglatro)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doses</strong></td>
<td>100 mg, 300 mg</td>
<td>5 mg, 10 mg</td>
<td>10 mg, 25 mg</td>
<td>5 mg, 15 mg</td>
</tr>
<tr>
<td><strong>eGFR &gt; 60</strong></td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td><strong>eGFR 45-60</strong></td>
<td><strong>100 mg only</strong></td>
<td>Don’t start</td>
<td><strong>No change</strong></td>
<td>Consider stopping</td>
</tr>
<tr>
<td><strong>eGFR 30-45</strong></td>
<td>Don’t start</td>
<td>Don’t start</td>
<td>Stop</td>
<td>Consider stopping</td>
</tr>
<tr>
<td><strong>eGFR &lt; 30</strong></td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>FDA Approved</strong></td>
<td>March 2013</td>
<td>January 2014</td>
<td>August 2014</td>
<td>D</td>
</tr>
</tbody>
</table>
SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

T2DM
N = 10, 142
A1c 7% - 10.5%
GFR >30 ml/min
Age 30 + symptomatic CAD
Age 50 + 2CAD/Renal risks
Duration 3.6 years

CANVAS
1:1:1
Canagliflozin 100 mg:
Canagliflozin 300 mg:
Matching Placebo

CANVAS - R
1:1
Canagliflozin 100 mg:
13 w >> :
Matching Placebo

SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

Hazard ratio, 0.86 (95% CI, 0.75–0.97)
P < 0.001 for noninferiority
P = 0.02 for superiority

No. at Risk
Placebo: 4347, 4239, 4153, 4061, 2942, 2462, 1240, 1217, 1187, 1156, 1120, 1095, 789, 216
Canagliflozin: 5795, 5672, 5566, 5447, 4343, 2843, 2555, 2513, 2460, 2419, 2363, 2311, 1661, 448

Weeks since Randomization

B Death from Cardiovascular Causes

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

No. at Risk
Placebo: 4347, 4316, 4279, 4236, 3119, 1579, 1366, 1344, 1328, 1310, 1292, 1280, 924, 258
Canagliflozin: 5795, 5768, 5723, 5679, 4576, 3182, 2761, 2736, 2710, 2687, 2651, 2615, 1904, 332

Weeks since Randomization

C Nonfatal Stroke

Hazard ratio, 0.90 (95% CI, 0.71–1.15)

No. at Risk
Placebo: 4347, 4270, 4197, 4123, 3004, 1667, 1274, 1235, 1232, 1208, 1177, 1155, 829, 232
Canagliflozin: 5795, 5702, 5616, 5530, 4414, 3043, 2621, 2588, 2543, 2511, 2464, 2415, 1751, 481

Weeks since Randomization

D Nonfatal Myocardial Infarction

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

No. at Risk
Placebo: 4347, 4256, 4187, 4109, 2986, 1647, 1253, 1233, 1207, 111
Canagliflozin: 5795, 5711, 5625, 5513, 4405, 3029, 2602, 2565, 2516, 24
SGLT2-I CVOT – CANVAS & CANVAS-R

**Canagliflozin (®Invokana)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>nonfatal stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td></td>
</tr>
</tbody>
</table>

## SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis (adjudicated)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.3</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fracture (adjudicated)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15.4</td>
<td>11.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Low-trauma</td>
<td>11.6</td>
<td>9.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>1.7</td>
<td>1.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Infection of male genitalia§</td>
<td>34.9</td>
<td>10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serious and nonserious adverse events of interest collected in CANVAS alone¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>34.5</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>26.0</td>
<td>18.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>50.0</td>
<td>46.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3.0</td>
<td>4.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6.9</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>40.0</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>Mycotic genital infection in women</td>
<td>68.8</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>Severe hypersensitivity or cutaneous reaction</td>
<td>8.5</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>7.4</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Renal-related (including acute kidney injury)</td>
<td>19.7</td>
<td>17.4</td>
<td></td>
</tr>
</tbody>
</table>
**SGLT2-I CVOT – CREDENCE**

Canagliflozin (®Invokana)

- The study was designed to formally test whether canagliflozin - reduced the risk of kidney failure and cardiovascular events in patients with T2DM and markers of established kidney disease compared to placebo when used in addition to standard of care.

The primary outcome was a composite of:
- end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m² sustained for at least 30 days),
- doubling of the serum creatinine level from baseline sustained for at least 30 days,
- death from renal or cardiovascular disease.

SGLT2-I CVOT – CREDENCE
Canagliflozin (®Invokana)

A Primary Composite Outcome
- Hazard ratio, 0.70 (95% CI, 0.59–0.82)
- P=0.00001

B Renal-Specific Composite Outcome
- Hazard ratio, 0.66 (95% CI, 0.53–0.81)
- P<0.001

C End-Stage Kidney Disease
- Hazard ratio, 0.68 (95% CI, 0.54–0.86)
- P=0.002

D Dialysis, Kidney Transplantation, or Renal Death
- Hazard ratio, 0.72 (95% CI, 0.54–0.97)

No. at Risk
- Placebo: 2199, 2178, 2132, 2047, 1725, 1129, 621, 170
- Canagliflozin: 2202, 2181, 2145, 2081, 1786, 1211, 646, 196
### Table 2. Efficacy and Safety.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no.</td>
<td>events/1000 patient-yr</td>
<td>no./total no.</td>
<td>events/1000 patient-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>245/2202</td>
<td>340/2199</td>
<td>43.2</td>
<td>61.2</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Doubling of serum creatinine level</td>
<td>118/2202</td>
<td>188/2199</td>
<td>20.7</td>
<td>33.8</td>
<td>0.60 (0.48–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>116/2202</td>
<td>165/2199</td>
<td>20.4</td>
<td>29.4</td>
<td>0.68 (0.54–0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Estimated GFR &lt;15 ml/min/1.73 m²</td>
<td>78/2202</td>
<td>125/2199</td>
<td>13.6</td>
<td>22.2</td>
<td>0.60 (0.45–0.80)</td>
<td>NA</td>
</tr>
<tr>
<td>Dialysis initiated or kidney transplantation</td>
<td>76/2202</td>
<td>100/2199</td>
<td>13.3</td>
<td>17.7</td>
<td>0.74 (0.55–1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Renal death</td>
<td>2/2202</td>
<td>5/2199</td>
<td>0.3</td>
<td>0.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>110/2202</td>
<td>140/2199</td>
<td>19.0</td>
<td>24.4</td>
<td>0.78 (0.61–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>179/2202</td>
<td>253/2199</td>
<td>31.5</td>
<td>45.4</td>
<td>0.69 (l)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td>217/2202</td>
<td>269/2199</td>
<td>38.7</td>
<td>48.7</td>
<td>0.80 (l)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>89/2202</td>
<td>141/2199</td>
<td>15.7</td>
<td>25.3</td>
<td>0.61 (l)</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease, doubling of serum creatinine level, or renal death</td>
<td>153/2202</td>
<td>224/2199</td>
<td>27.0</td>
<td>40.4</td>
<td>0.66 (l)</td>
<td></td>
</tr>
</tbody>
</table>

Empagliflozin (®Jardiance)

Adult with T2DM
BMI ≤ 45 kg/m²
Established cardiovascular disease (prior MI, CAD, stroke, unstable angina or occlusive PAD)
A1C 7-10%

N=7020
3.1 years

Empagliflozin 10mg
Empagliflozin 25mg
Placebo

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.

SGLT2-I CVOT – EMPA-REG OUTCOMES
Empagliflozin (®Jardiance)

A Primary Outcome

B Death from Cardiovascular Causes

C Death from Any Cause

D Hospitalization for Heart Failure

No. at Risk
Empagliflozin
Placebo

No. at Risk
Empagliflozin
Placebo

No. at Risk
Empagliflozin
Placebo

No. at Risk
Empagliflozin
Placebo
At baseline, the eGFR was 45 – 59 ml/min in 17.8% of the patients and 30 - 44 ml/min in 7.7% patients

- 28.7% had microalbuminuria, and 11.0% had macroalbuminuria
- In total, 80.7% of the patients were taking ACEi or ARBs at baseline

SGLT2-I Renal – EMPA-REG OUTCOMES
Empagliflozin (®Jardiance)

# SGLT2-I Renal – EMPA-REG OUTCOMES

**Empagliflozin (®Jardiance)**

<table>
<thead>
<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. with event/ no. analyzed (%)</td>
<td>rate/1000 patient-yr</td>
<td>no. with event/ no. analyzed (%)</td>
<td>rate/1000 patient-yr</td>
</tr>
<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2)</td>
<td>60.7</td>
<td>497/2102 (23.6)</td>
<td>55.9</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124 (12.7)</td>
<td>47.8</td>
<td>388/2061 (18.8)</td>
<td>76.0</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>459/4091 (11.2)</td>
<td>41.8</td>
<td>330/2033 (16.2)</td>
<td>64.9</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²</td>
<td>70/4645 (1.5)</td>
<td>5.5</td>
<td>60/2323 (2.6)</td>
<td>9.7</td>
</tr>
<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3)</td>
<td>1.0</td>
<td>14/2333 (0.6)</td>
<td>2.1</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7)</td>
<td>6.3</td>
<td>71/2323 (3.1)</td>
<td>11.5</td>
</tr>
<tr>
<td>Incident albuminuria in patients with a normal albumin level at baseline</td>
<td>1430/2779 (51.5)</td>
<td>252.5</td>
<td>703/1374 (51.2)</td>
<td>266.0</td>
</tr>
</tbody>
</table>

SGLT2-I CVOT – DECLARE-TIMI 58
Dapagliflozin (®Farxiga)

T2DM (A1c 6.5 – 12%)
CAD or Risk
GFR > 60 ml/min
N = 17,160

Dapagliflozin 10 mg QD

Placebo

4.2 yrs

SGLT2-I CVOT – DECLARE-TIMI
Dapagliflozin (®Farxiga)

### SGLT2-I CVOT – DECLARE-TIMI

**Dapagliflozin (®Farxiga)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin (N=8582)</th>
<th>Placebo (N=8578)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>417 (4.9)</td>
<td>496 (5.8)</td>
<td>0.83 (0.73–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>MACE</td>
<td>756 (8.8)</td>
<td>803 (9.4)</td>
<td>0.93 (0.84–1.03)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 ml/min/1.73 m², ESRD, or death from renal</td>
<td>370 (4.3)</td>
<td>480 (5.6)</td>
<td>0.76 (0.67–0.87)</td>
<td></td>
</tr>
<tr>
<td>or cardiovascular cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>529 (6.2)</td>
<td>570 (6.6)</td>
<td>0.93 (0.82–1.04)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>212 (2.5)</td>
<td>286 (3.3)</td>
<td>0.73 (0.61–0.88)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>393 (4.6)</td>
<td>441 (5.1)</td>
<td>0.89 (0.77–1.01)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>235 (2.7)</td>
<td>231 (2.7)</td>
<td>1.01 (0.84–1.21)</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>245 (2.9)</td>
<td>249 (2.9)</td>
<td>0.98 (0.82–1.17)</td>
<td></td>
</tr>
<tr>
<td>Death from noncardiovascular cause</td>
<td>211 (2.5)</td>
<td>238 (2.8)</td>
<td>0.88 (0.73–1.06)</td>
<td></td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 ml/min/1.73 m², ESRD, or death from renal</td>
<td>127 (1.5)</td>
<td>238 (2.8)</td>
<td>0.53 (0.43–0.66)</td>
<td></td>
</tr>
<tr>
<td>or renal cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

SGLT2-I CVOT – DECLARE-TIMI
Dapagliflozin (®Farxiga)

• This trial included more than 10,000 patients without evident atherosclerotic cardiovascular disease
  • Dapagliflozin prevented cardiovascular events, particularly hospitalization for heart failure, regardless of a history of atherosclerotic cardiovascular disease or heart failure.
  • Majority of patients did not have a history of heart failure, so the prevention of new clinical heart failure is notable.

SGLT2-I CVOT – DAPA – HF Trial
Dapagliflozin (®Farxiga)

• In the DAPA-HF trial, 4443 patients were involved with NYHA Class II HF and EF <40%, optimally treated for HF.
• Only 42% of patients in this trial had a h/o T2DM.
• Patients also completed a Kansas City Cardiomyopathy Questionnaire (23 item questionnaire).

### SGLT2-I CVOT – DAPA – HF Trial

**Dapagliflozin (®Farxiga)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>162/768</td>
<td>209/719</td>
<td>0.70 (0.57, 0.86)</td>
<td>0.52</td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>119/773</td>
<td>152/791</td>
<td>0.77 (0.61, 0.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>73/693</td>
<td>116/699</td>
<td>0.62 (0.46, 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Death or Hospitalization for Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>160/768</td>
<td>205/719</td>
<td>0.71 (0.57, 0.87)</td>
<td></td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>118/773</td>
<td>150/791</td>
<td>0.77 (0.61, 0.99)</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>73/693</td>
<td>115/699</td>
<td>0.62 (0.46, 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization for Heart Failure or Urgent Heart Failure Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>99/768</td>
<td>134/719</td>
<td>0.67 (0.51, 0.86)</td>
<td></td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>78/773</td>
<td>101/791</td>
<td>0.76 (0.56, 1.02)</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>43/693</td>
<td>78/699</td>
<td>0.54 (0.37, 0.78)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization for Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>96/768</td>
<td>130/719</td>
<td>0.67 (0.51, 0.87)</td>
<td></td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>76/773</td>
<td>98/791</td>
<td>0.76 (0.56, 1.03)</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>43/693</td>
<td>77/699</td>
<td>0.55 (0.38, 0.79)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Death</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>107/768</td>
<td>121/719</td>
<td>0.84 (0.64, 1.09)</td>
<td></td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>63/773</td>
<td>81/791</td>
<td>0.78 (0.56, 1.09)</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>39/693</td>
<td>54/699</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Death from Any Cause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65.6 (n=1487)</td>
<td>134/768</td>
<td>142/719</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>65.7-87.5 (n=1564)</td>
<td>76/773</td>
<td>99/791</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;87.5 (n=1392)</td>
<td>46/693</td>
<td>67/699</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

[Graph showing the comparison between Dapagliflozin and Placebo for different outcomes]
SGLT2-I CVOT – VERTIS CV
Ertugliflozin (®Steglatro)

Multicenter, randomized, double-blind, placebo-controlled, event-driven trial

Randomization 1:1:1

- Placebo
- Ertugliflozin 5 mg
- Ertugliflozin 15 mg

**Primary endpoint** (non-inferiority):
- Composite outcome of MACE (CV death, nonfatal MI, nonfatal stroke)

**Secondary endpoints** (superiority):
- Composite outcome of CV death/HHF
- CV death
- Renal composite (renal death, dialysis/transplant, doubling of serum creatinine)

**Other prespecified endpoints**:
- Individual components of MACE
- Composite of MACE-plus (MACE plus hospitalization for unstable angina)
- Fatal or non-fatal MI
- Fatal or non-fatal CV death
- HHF
- All-cause mortality
SGLT2-I CVOT – VERTIS CV
Ertugliflozin (®Steglatro)

HbA1c

Difference in LS mean (95% CI) at Week 18:
- Ertugliflozin 5 mg: -0.5% (-0.8, -0.3); P=0.004
- Ertugliflozin 15 mg: -0.3% (-0.6, -0.03); P=0.001

Body Weight

Mean decrease (SD) in body weight at Week 52:
- Ertugliflozin 5 mg: -2.4 kg (-3.5, -1.2)
- Ertugliflozin 15 mg: -2.6 kg (-4.0, -1.2)
- Placebo: 0.4 kg (-3.6)

Systolic BP

Difference in LS mean (95% CI) at Week 52:
- Ertugliflozin 5 mg: -2.6 mmHg (-3.3, -1.9); P<0.001
- Ertugliflozin 15 mg: -3.2 mmHg (-3.9, -2.5); P<0.001
### SGLT2-I CVOT – VERTIS CV
Ertugliflozin (®Steglatro)

<table>
<thead>
<tr>
<th>Event</th>
<th>Ertugliflozin</th>
<th>Placebo</th>
<th>HR (CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE(^a)</td>
<td>3.9</td>
<td>4.0</td>
<td>0.97 (0.85, 1.11)</td>
<td>&lt;0.001 (for non-inferiority)</td>
</tr>
<tr>
<td>CV Death/HHF(^†)</td>
<td>2.3</td>
<td>2.7</td>
<td>0.88 (0.75, 1.03)</td>
<td>0.11</td>
</tr>
<tr>
<td>CV Death(^†)</td>
<td>1.8</td>
<td>1.9</td>
<td>0.92 (0.77, 1.11)</td>
<td>0.39</td>
</tr>
<tr>
<td>HHF(^†)</td>
<td>0.7</td>
<td>1.1</td>
<td>0.70 (0.54, 0.90)</td>
<td>0.006</td>
</tr>
<tr>
<td>Renal Composite(^†)</td>
<td>0.9</td>
<td>1.2</td>
<td>0.81 (0.63, 1.04)</td>
<td></td>
</tr>
</tbody>
</table>

Rate/100 patient-years

- **Favors Ertugliflozin**: 0.5 to 1
- **Favors Placebo**: 1.3 to 2
SGLT-2 Inhibition Leads to Benefits in Cardiorenal Outcome in Several Patient Populations

- According to a recent meta-analysis of three randomized CVOTs in patients with T2D with either established CVD or multiple risk factors (~60% with established CVD), SGLT-2i reduced the risk of:
  - Hospitalization for HF by 31% (HR=0.69; 95% CI, 0.61-0.79; P<.0001)
  - CV death or hospitalization for HF by 23% (HR=0.77; 95% CI, 0.71-0.84; P<.0001)
  - Major MACE by 11% (HR=0.89; 95% CI, 0.83-0.96; P=.0014)
  - Progression of renal disease by 45% (HR=0.55; 95% CI, 0.48-0.64; P<.0001)

CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; MACE= major adverse cardiovascular event.
In Summary

• All the DPP4 inhibitor trials met the non-ninferiority criteria but none of them met superiority criteria for CV outcomes

• Among the GLP-1 agents, Liraglutide (Victoza), Semaglutide (Ozempic), and Dulaglutide (Trulicity) showed statistically significant and real world clinically significant benefits for CV disease and nephropathy

• Among the SGLT-2 inhibitors, Canagliflozin (Invokana), Empagliflozin (Jardiance), and Dapagliflozin (Farxiga) are noted to significantly reduce hospitalizations for progression of renal disease, and MACE outcomes
In Clinical Practice

• 65 y/o male with poorly controlled T2DM (A1c 8%) complicated with history of CAD s/p 1 stent, CHF (EF 40%), and CKD2 is referred to you by PCP for management of T2DM. His BMI is 32 kg/m2 and BP is 144/94 mm Hg. He admits to a FH of MI in his father at age 40. He is adherent to diet and exercise, takes Metformin 1000 mg BID, Lisinopril 5 mg QD, and Atorvastatin 40 mg QHS.

• Which of the following agents would be of consideration for him in addition to Metformin?
  • Pioglitazone (Actos)
  • Dulaglutide (Trulicity)
  • Saxagliptin (Onglyza)
  • Empagliflozin (Jardiance)
References

References

THANK YOU

Lubaina S. Presswala
Assistant Professor of Medicine
Division of Endocrinology,
Department of Medicine,
Northwell Health.

Office Address:
560 Northern Blvd, Suite 203, Great Neck, NY 11021
Phone: 516-708-2540
Email: lpresswala@northwell.edu