Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease – The SCORED Trial

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**Disclosures**

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This presentation includes off-label and investigational uses of drugs.
The Evolution of SGLT2i in Heart Failure Management

**Diabetes**

- Pre-clinical (subclinical) stage of the disease
- Clinical stage of the disease
- Detectable cardiac involvement

**Diabetes and No Diabetes**

- Window of opportunity for treatment

**Normal Ventricular Function**

- 0 years
- 10 years
- 18-20 years

**Advanced Heart Failure**

- CANVAS Program
- CREDENCE
- DAPA-CKD
- DECLARE-TIMI 58
- EMPA-REG OUTCOME
- VERTIS CV
- SCORED

- DAPA-HF
- DELIVER HFpEF
- EMPEROR-Preserved
- EMPEROR-Reduced
- SOLOIST-WHF

Diabetes

Na⁺-retention
Hypervolemia
RAAS Activation
Neurohumoral Activation
Inflammation
Ischemia
Altered Energetics

SGLT2 Inhibitors

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor

- **SGLT1** is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential reduction in atherosclerotic risks

- **SGLT2** is expressed in the kidney, where it reabsorbs 90% of filtered glucose
- Pharmacologic inhibition by sotagliflozin is independent of insulin but requires kidney function

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

![Graph showing event rates over time for placebo and Sotagliflozin.](image)

- **Primary Efficacy**:
  - Total CV Death
  - HHF
  - Urgent HF Visit

**Graph Details**:
- **Placebo** event rate: 98 events
- **Sotagliflozin** event rate: 70 events

**Statistical Analysis**:
- **HR 0.67 (95% CI 0.52-0.85), P=0.0009**
- **ARR: 25 Events Per 100 Patient-Years**
- **Months Since Randomization**
- **Treatment Patient-Years to Avoid 1 Event: 4**

References:
## Primary Efficacy Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>Sotagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1222</td>
<td>51.0</td>
<td>76.3</td>
<td>0.67 (0.52, 0.85)</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>966</td>
<td>56.9</td>
<td>79.9</td>
<td>0.72 (0.56, 0.94)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>256</td>
<td>30.6</td>
<td>64.0</td>
<td>0.48 (0.27, 0.86)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>346</td>
<td>68.3</td>
<td>103.0</td>
<td>0.64 (0.43, 0.95)</td>
</tr>
<tr>
<td>Europe</td>
<td>800</td>
<td>44.1</td>
<td>64.7</td>
<td>0.69 (0.50, 0.95)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>76</td>
<td>48.4</td>
<td>78.3</td>
<td>0.60 (0.23, 1.58)</td>
</tr>
<tr>
<td>First Study Drug Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Discharge</td>
<td>596</td>
<td>52.1</td>
<td>76.6</td>
<td>0.71 (0.51, 0.99)</td>
</tr>
<tr>
<td>After Discharge</td>
<td>626</td>
<td>50.0</td>
<td>76.1</td>
<td>0.64 (0.45, 0.90)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>412</td>
<td>41.9</td>
<td>52.0</td>
<td>0.80 (0.51, 1.25)</td>
</tr>
<tr>
<td>Male</td>
<td>810</td>
<td>55.7</td>
<td>89.3</td>
<td>0.62 (0.47, 0.82)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>364</td>
<td>57.1</td>
<td>71.1</td>
<td>0.79 (0.51, 1.23)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>858</td>
<td>48.0</td>
<td>78.5</td>
<td>0.62 (0.47, 0.82)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>854</td>
<td>50.1</td>
<td>85.8</td>
<td>0.59 (0.44, 0.79)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>368</td>
<td>53.1</td>
<td>58.1</td>
<td>0.90 (0.58, 1.37)</td>
</tr>
</tbody>
</table>
**SCORED Trial Design**

Key inclusion criteria:
- Type 2 diabetes with HbA1c ≥ 7%
- eGFR 25-60 mL/min/1.73m²
  - with no requirement for macro- or micro-albuminuria
- CV risk factors

Key exclusion criteria:
- Planned start of SGLT2 inhibitor

10,584 patients with DM + CKD

Double-blind randomization

Placebo QD

Sotagliflozin 200 mg QD

Primary Endpoint: Total Events
- Cardiovascular Death
- Hospitalization for Heart Failure
- Urgent Heart Failure Visit

Median follow up duration (IQR) = 16.0 (12.0-20.3) months


1Goal of dose increase to 400 mg QD
Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

HR 0.74 (95% CI 0.63-0.88), P=0.0004
ARR: 1.9 Events Per 100 Patient-Years
Treatment Patient-Years to Avoid 1 Event: 54

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

Early Effect
Significant by 94 days:
HR=0.69, P=0.045

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fatal or nonfatal MI*</td>
<td>0.68 (0.52-0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total fatal or nonfatal stroke*</td>
<td>0.66 (0.48-0.91)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* Post hoc endpoint

History of Cardiovascular Disease (CVD) Subgroup Analyses

Subgroups

1. History of cardiovascular disease at baseline (N=5144 patients)
2. No history of cardiovascular disease at baseline (N=5440 patients)

The prespecified definition of history of CVD included prior myocardial infarction, prior stroke, coronary revascularization, and peripheral vascular disease; (multiple post hoc sensitivity analyses yielded similar results)

Endpoints

1. Total MACE (first and recurrent events)
2. Total MI (fatal and non-fatal MI)
3. Total stroke (fatal and non-fatal stroke)
Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup


History of CVD: HR 0.79 (95% CI 0.64-0.96), P=0.020
Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup

Placebo

Sotagliflozin

No History of CVD: HR 0.74 (95% CI 0.56-0.99), P=0.046

History of CVD: HR 0.79 (95% CI 0.64-0.96), P=0.020

P_interaction = 0.76

Total MI by CVD Subgroup

History of CVD: HR 0.69 (95% CI 0.51-0.95), P=0.023

History of CVD: HR 0.69 (95% CI 0.51-0.95), P=0.023

No History of CVD: HR 0.66 (95% CI 0.41-1.06), P=0.088

Total MI by CVD Subgroup

Total Stroke by CVD Subgroup

History of CVD: HR 0.69 (95% CI 0.46-1.02), P=0.063
Events Per 100 Patients

History of CVD: HR 0.69 (95% CI 0.46-1.02), P=0.063
No History of CVD: HR 0.62 (95% CI 0.36-1.06), P=0.080

Total Stroke by CVD Subgroup

**Consistent Benefit on MACE Across Vascular Beds**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Sotagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>4943</td>
<td>6.13</td>
<td>7.77</td>
<td>0.79 (0.65, 0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1777</td>
<td>7.03</td>
<td>9.54</td>
<td>0.72 (0.53, 0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>1393</td>
<td>6.76</td>
<td>9.50</td>
<td>0.77 (0.54, 1.09)</td>
<td>0.140</td>
</tr>
</tbody>
</table>

\[ P_{interaction} = NS \text{ for all comparisons} \]

<table>
<thead>
<tr>
<th>Composite Term</th>
<th>Sotagliflozin N=5291 n (%)</th>
<th>Placebo N=5286 n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infections</td>
<td>610 (11.5)</td>
<td>585 (11.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>448 (8.5)</td>
<td>315 (6.0)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>278 (5.3)</td>
<td>213 (4.0)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>111 (2.1)</td>
<td>117 (2.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Genital mycotic infections</td>
<td>125 (2.4)</td>
<td>45 (0.9)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>53 (1.0)</td>
<td>55 (1.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Malignancies</td>
<td>47 (0.9)</td>
<td>42 (0.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Venous thrombotic events</td>
<td>31 (0.6)</td>
<td>37 (0.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Adverse event leading to amputation</td>
<td>32 (0.6)</td>
<td>33 (0.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>30 (0.6)</td>
<td>14 (0.3)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>12 (0.2)</td>
<td>20 (0.4)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Proportions considered serious were similar between groups, and adverse events generally did not lead to treatment discontinuation

## Meta-analysis of MACE Across Sotagliflozin Trials (N>20,000)

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Sotagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCORED (N = 10,584)</strong></td>
<td>N = 5,292</td>
<td>N = 5,292</td>
<td>0.77 (0.65, 0.91)</td>
</tr>
<tr>
<td>Total events (rate/100 PY)*</td>
<td>343 (4.8)</td>
<td>442 (6.3)</td>
<td></td>
</tr>
<tr>
<td><strong>SOLOIST (N = 1,222)</strong></td>
<td>N = 608</td>
<td>N = 614</td>
<td>0.99 (0.72, 1.37)</td>
</tr>
<tr>
<td>Total events (rate/100 PY)*</td>
<td>83 (17.4)</td>
<td>80 (17.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Core Phase 3 T2DM (N = 5,100)</strong></td>
<td>N = 2,904</td>
<td>N = 2,196</td>
<td>0.63 (0.42, 0.94)</td>
</tr>
<tr>
<td>Total events (rate/100 PY)**</td>
<td>55 (1.6)</td>
<td>50 (2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Core Phase 3 T1DM, Phase 2 T2DM (N = 3,386)</strong></td>
<td>N = 1,998</td>
<td>N = 1,388</td>
<td>0.68 (0.25, 1.82)</td>
</tr>
<tr>
<td>Total events (rate/100 PY)**</td>
<td>9 (0.69)</td>
<td>8 (0.87)</td>
<td></td>
</tr>
<tr>
<td><strong>Meta-analysis results (N=20,292)</strong></td>
<td></td>
<td></td>
<td>0.79 (0.68, 0.90)</td>
</tr>
</tbody>
</table>

*Investigator-reported events; **Adjudicated events

Limitations

Trial was stopped early
  • Shortened duration limited the statistical power to see significant reductions in CV death
  • Limited the magnitude of absolute risk reductions in MACE

Investigator-reported events were used instead of adjudication
  • Double-blind trial, with no reason to expect bias
  • Results were generally concordant
Conclusions

In patients with diabetes and chronic kidney disease, **sotagliflozin** significantly reduced the composite of total CV deaths, hospitalizations for HF, and urgent HF visits by **26%**

- With a very early benefit that was **significant by ~3 months**

Total CV deaths, MIs, and strokes were reduced by **23%**, potentially due to the SGLT1 effect of **sotagliflozin** on MI and also stroke; this effect was significant by ~ 3 months

**MACE benefits** were consistent across subgroups, including:

- Prior coronary, cerebral, or peripheral artery disease
- And even without established cardiovascular disease

Thank You!

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