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

Deepak L. Bhatt, MD, MPH, Michael Szarek, PhD, Bertram Pitt, MD, Christopher P. Cannon, MD, Lawrence A. Leiter, MD, Darren K. McGuire, MD, MHS, Julia B. Lewis, MD, Matthew C. Riddle, MD, Silvio E. Inzucchi, MD, Mikhail N. Kosiborod, MD, David Z. I. Cherney, MD, PhD, Jamie P. Dwyer, MD, Benjamin M. Scirica, MD, MPH, Clifford J. Bailey, PhD, Rafael Díaz, MD, Kausik K. Ray, MD, Jacob A. Udell, MD, MPH, Renato D. Lopes, MD, PhD, Pablo Lapuerta, MD, Ph. Gabriel Steg, MD, on Behalf of the SCORED Investigators
Disclosures

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SCORED was initially sponsored by Sanofi and then by Lexicon.

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

Diabetes

Window of opportunity for treatment

Pre-clinical (subclinical) stage of the disease

Clinical stage of the disease

Detectable cardiac involvement

0 years

10 years

18-20 years

Diabetes and No Diabetes

Normal Ventricular Function

End-stage Heart Failure

The Evolution of SGLT2i in HF Management

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Clinical stage of the disease

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0 years

10 years

18-20 years

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Normal Ventricular Function

End-stage 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 effects on 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
The Consequences of the COVID-19 Pandemic on Non-COVID-19 Clinical Trials

Emilia Bagiella, PhD, Deepak L. Bhatt, MD, MPH, Mario Gaudino, MD

- Loss of funding during the onset of the COVID-19 pandemic
- Academic leadership did everything to ensure patient safety and to honor the scientific contribution of the patients
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Michael Szarek, PhD

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Key Inclusion and Exclusion Criteria

Inclusion:
• Type 2 diabetes with HbA1c $\geq$ 7%
• eGFR 25-60 mL/min/1.73m$^2$
  - with no requirement for macro- or micro-albuminuria
• CV risk factors

Exclusion:
• Planned start of SGLT2 inhibitor

CONSORT Diagram

Countries 44
Sites 750

Screen Fails N=8604
Incl./Excl. criteria not met 8305
Death 5
Other 294

Screened N=19,188

Randomized N=10,584 (55%)

Sotagliflozin N=5292 (100%)
(1 never received dose)

Completed Study N=5232 (98.9%)

Early Discontinuation from Study N=60 (1.1%)
Exposed to treatment ≥80% of follow-up 4676 (88.4%)
Known vital status 5270 (99.6%)
Actual vs. potential total follow-up time 99.6%

Placebo N=5292 (100%)
(6 never received dose)

Completed Study N=5210 (98.5%)

Early Discontinuation from Study N=82 (1.5%)
Exposed to treatment ≥80% of follow-up 4661 (88.1%)
Known vital status 5247 (99.1%)
Actual vs. potential total follow-up time 99.3%


Median (Q1-Q3) follow up duration = 15.9 (12.0-20.3) months, maximum 30.0 months
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sotagliflozin (N=5292)</th>
<th>Placebo (N=5292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69 (63-74)</td>
<td>69 (63-74)</td>
</tr>
<tr>
<td>Female</td>
<td>2347 (44.3)</td>
<td>2407 (45.5)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>2324 (43.9)</td>
<td>2322 (43.9)</td>
</tr>
<tr>
<td>Americas</td>
<td>2332 (44.1)</td>
<td>2333 (44.1)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>636 (12.0)</td>
<td>637 (12.0)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60 (51-64)</td>
<td>60 (51-65)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>44.4 (37.0-51.3)</td>
<td>44.7 (37.0-51.5)</td>
</tr>
<tr>
<td>Urine Albumin/Creatinine Ratio, mg/g</td>
<td>74 (18-486)</td>
<td>75 (17-477)</td>
</tr>
<tr>
<td>History of Heart Failure</td>
<td>1640 (31.0)</td>
<td>1643 (31.0)</td>
</tr>
<tr>
<td>Any RAAS Inhibitor</td>
<td>4705 (88.9)</td>
<td>4660 (88.1)</td>
</tr>
<tr>
<td>Any Glucose Lowering Medication</td>
<td>5111 (96.6)</td>
<td>5136 (97.1)</td>
</tr>
</tbody>
</table>

Numbers in table are n (%) or median (Q1, Q3).

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

Placebo

Sotagliflozin

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

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 95 Days

Very early effect:
Significant by 95 days:
HR=0.70, P=0.038

First of CV Death, Non-Fatal MI, or Non-Fatal Stroke

Graph showing cumulative incidence over months since randomization. The graph compares placebo and sotagliflozin treatments. Placebo has an 8.9% cumulative incidence at 24 months, while sotagliflozin has an 8.4% cumulative incidence. The hazard ratio (HR) is 0.84 (95% CI 0.72-0.99), with a p-value of 0.035.

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


HR 0.77 (95% CI 0.65-0.91), P=0.002
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

First of CV Death or HHF


HR 0.77 (95% CI 0.66-0.91), P=0.001

Cumulative Incidence (%)

Months Since Randomization

Placebo 9.5%

Sotagliflozin 8.3%
## Efficacy Testing Hierarchy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Sotagliflozin Rate [Events]</th>
<th>Placebo Rate [Events]</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CV death, HHF, and urgent HF visit</td>
<td>5.6 [400]</td>
<td>7.5 [530]</td>
<td>0.74 (0.63-0.88)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Total HHF and urgent HF visit</td>
<td>3.5 [245]</td>
<td>5.1 [360]</td>
<td>0.67 (0.55-0.82)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>2.2 [155]</td>
<td>2.4 [170]</td>
<td>0.90 (0.73-1.12)</td>
<td>0.35</td>
</tr>
<tr>
<td>Total CV death, HHF, non-fatal MI, and non-fatal stroke</td>
<td>7.6 [541]</td>
<td>10.4 [738]</td>
<td>0.72 (0.63-0.83)</td>
<td>0.000008*</td>
</tr>
<tr>
<td>Total CV death, HHF, urgent HF visit, and HF while hospitalized</td>
<td>6.4 [453]</td>
<td>8.3 [589]</td>
<td>0.76 (0.65-0.89)</td>
<td>0.0005*</td>
</tr>
<tr>
<td>First sustained** ≥50% decrease in eGFR, chronic dialysis, renal transplant or sustained* eGFR &lt;15 mL/min/1.73m²</td>
<td>0.5 [37]</td>
<td>0.7 [52]</td>
<td>0.71 (0.46-1.08)</td>
<td>0.11*</td>
</tr>
<tr>
<td>All-cause death</td>
<td>3.5 [246]</td>
<td>3.5 [246]</td>
<td>0.99 (0.83-1.18)</td>
<td>0.93*</td>
</tr>
<tr>
<td>Total CV death, non-fatal MI, and non-fatal stroke</td>
<td>4.8 [343]</td>
<td>6.3 [442]</td>
<td>0.77 (0.65-0.91)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

**For ≥30 days. *Nominal p-value. Rate = number of events per 100 patient-years.**

## Adverse Events of Special Interest

<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>

## 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>10584</td>
<td>5.6</td>
<td>7.5</td>
<td>0.74 (0.63, 0.88)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4754</td>
<td>5.1</td>
<td>6.5</td>
<td>0.77 (0.60, 0.99)</td>
</tr>
<tr>
<td>Male</td>
<td>5830</td>
<td>6.1</td>
<td>8.3</td>
<td>0.73 (0.59, 0.90)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>3224</td>
<td>3.8</td>
<td>6.4</td>
<td>0.60 (0.43, 0.83)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>7360</td>
<td>6.4</td>
<td>8.0</td>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>3226</td>
<td>6.5</td>
<td>9.0</td>
<td>0.72 (0.57, 0.90)</td>
</tr>
<tr>
<td>Latin America</td>
<td>3172</td>
<td>3.9</td>
<td>5.0</td>
<td>0.77 (0.54, 1.10)</td>
</tr>
<tr>
<td>North America</td>
<td>1493</td>
<td>5.6</td>
<td>6.0</td>
<td>0.92 (0.60, 1.40)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>1273</td>
<td>6.7</td>
<td>9.8</td>
<td>0.68 (0.44, 1.05)</td>
</tr>
<tr>
<td>HF-Related Criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2108</td>
<td>15.9</td>
<td>20.6</td>
<td>0.77 (0.61, 0.96)</td>
</tr>
<tr>
<td>No</td>
<td>8476</td>
<td>3.2</td>
<td>4.4</td>
<td>0.72 (0.57, 0.91)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>813</td>
<td>9.3</td>
<td>14.1</td>
<td>0.68 (0.42, 1.11)</td>
</tr>
<tr>
<td>30 to &lt;45</td>
<td>4655</td>
<td>6.9</td>
<td>9.1</td>
<td>0.74 (0.60, 0.93)</td>
</tr>
<tr>
<td>≥ 45</td>
<td>5116</td>
<td>3.9</td>
<td>5.1</td>
<td>0.76 (0.58, 0.99)</td>
</tr>
<tr>
<td>Urine ACR (mg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>3709</td>
<td>4.4</td>
<td>4.2</td>
<td>1.05 (0.76, 1.46)</td>
</tr>
<tr>
<td>≥30</td>
<td>6875</td>
<td>6.3</td>
<td>9.4</td>
<td>0.67 (0.55, 0.80)</td>
</tr>
</tbody>
</table>

After the initial 4 weeks, sotagliflozin slowed the decline in kidney function

Reductions in HbA1c, Systolic Blood Pressure, and Weight with **Sotagliflozin**

**HbA1c**

- Mean (95% CI) Change in HbA1c, %
  - Sotagliflozin: -0.75
  - Placebo: -1.00
  - P < 0.0001

**SBP**

- Mean (95% CI) Change in SBP, mmHg
  - Sotagliflozin: -4
  - Placebo: -2
  - P < 0.0001

**Weight**

- Mean (95% CI) Change Weight, Kg
  - Sotagliflozin: 0
  - Placebo: -1
  - P < 0.0001

Reduction in HbA1c Across Moderate and Severe eGFR Categories with **Sotagliflozin**

Limitations

Trial was stopped early
  • Nevertheless, robust reduction in primary endpoint
  • Shortened duration limited the statistical power to see significant reductions in CV death or in kidney endpoints

Primary endpoint was changed while blinded to results
  • However, original co-primary endpoints were also positive

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

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%, likely due to the SGLT1 effect of sotagliflozin on MI and also stroke

With careful patient selection, sotagliflozin was generally well tolerated (similar to placebo) and safe

The benefits were consistent across subgroups, including:
  • Not only macro- but also micro-albuminuria
  • In HF with reduced or preserved ejection fraction

Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit

HR 0.72 (95% CI 0.63-0.82), P=0.000002

**ARR:** 3.2 Events Per 100 Patient-Years

Treatment Patient-Years to Avoid 1 Event: 31

Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit Among 1758 Patients with HFrEF

- **HR 0.78 (95% CI 0.63-0.96), P=0.02**
- **ARR: 9.1 Events Per 100 Patient-Years**
- Treatment Patient-Years to Avoid 1 Event: **11**

![Graph showing the comparison between Placebo and Sotagliflozin](image)

Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit Among 739 Patients with HFpEF

- **HR 0.63 (95% CI 0.45-0.89), P=0.009**
- **ARR: 11.6 Events Per 100 Patient-Years**
- Treatment Patient-Years to Avoid 1 Event: 9

**Graph:**
- **Placebo:** 59.0
- **Sotagliflozin:** 37.5

---

Implications of SOLOIST and SCORED

With careful patient selection and monitoring, as a class, SGLT2 inhibitors should be strongly considered in the majority of patients with type 2 diabetes including those:

- Admitted with acute decompensated heart failure
- With heart failure with either reduced or preserved EF
- With CKD across the full range of proteinuria

Unlike with pure SGLT2, the SGLT1 inhibition from sotagliflozin provided glycemic control even at the lower range of eGFR

The lower rate of MI and stroke with sotagliflozin suggests an additional relatively early anti-ischemic effect of SGLT1 inhibition which should be explored further

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., P. Gabriel Steg, M.D.,
Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D.,
Darren K. McGuire, M.D., Julia B. Lewis, M.D., Matthew C. Riddle, M.D.,
Adriaan A. Voors, M.D., Ph.D., Marco Metra, M.D., Lars H. Lund, M.D., Ph.D.,
Michel Komajda, M.D., Jeffrey M. Testani, M.D., M.T.R.,
Christopher S. Wilcox, M.D., Piotr Ponikowski, M.D.,
Renato D. Lopes, M.D., Ph.D., Subodh Verma, M.D., Ph.D.,
Pablo Lapuerta, M.D., and Bertram Pitt, M.D., for the SOLOIST-WHF Trial
Investigators‡

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Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., Matthew C. Riddle, M.D.,
Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D.,
David Z.I. Cherney, M.D., Ph.D., Jamie P. Dwyer, M.D.,
Benjamin M. Scirica, M.D., M.P.H., Clifford J. Bailey, Ph.D., Rafael Díaz, M.D.,
Kausik K. Ray, M.D., Jacob A. Udell, M.D., M.P.H., Renato D. Lopes, M.D., Ph.D.,
Pablo Lapuerta, M.D., and P. Gabriel Steg, M.D., for the SCORED Investigators*