Sotagliflozin Reduces Total Hospitalizations and Increases Days Alive and Out of Hospital in the SOLOIST-WHF Trial

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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

Diabetes and No Diabetes

0 years
10 years
18-20 years

Normal Ventricular Function
End-stage Heart Failure

HF Prevention
HF Treatment

The Evolution of SGLT2i in HF Management

Normal Ventricular Function

Diabetes

0 years

Pre-clinical (subclinical) stage of the disease

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Detectable cardiac involvement

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10 years

18-20 years

Window of opportunity for treatment

Diabetes Prevention

CANVAS Program

CREDENCE

DAPA-CKD

DECLARE-TIMI 58

EMPA-REG OUTCOME

VERTIS CV

End-stage Heart Failure

HF Treatment

DAPA-HF

DELIVER HFpEF

EMPEROR-Preserved

EMPEROR-Reduced

SOLOIST-WHF

Acute HF?

HF Prevention

HF Treatment

**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
SOLOIST Study Design

1222 patients with diabetes and HF

Double-blind randomization in-hospital or within 3 days after discharge

Placebo QD

Sotagliflozin 200 mg QD

Endpoints used in current analyses:
- Incidence and duration of each hospitalization
- Primary reason for each hospitalization
- All-cause death

Median follow up duration (IQR) = 9.0 (4.9-13.4) months

Key inclusion criteria:
- Admission with signs and symptoms of HF
- Treatment with intravenous diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if afib) or NT-proBNP ≥600 pg/mL (≥1800 pg/mL if afib)
- Type 2 diabetes

Key exclusion criteria:
- End-stage HF
- Recent ACS, stroke, PCI, or CABG
- eGFR <30 mL/min/1.73m²

Goal of dose increase to 400 mg QD

HF or reasons other than HF
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Sotagliflozin (N=608)</th>
<th>Placebo (N=614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), years</td>
<td>69 (63-76)</td>
<td>70 (64-76)</td>
</tr>
<tr>
<td>Female sex, n(%)</td>
<td>198 (32.6)</td>
<td>214 (34.9)</td>
</tr>
<tr>
<td>Geographic Region, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>399 (65.6)</td>
<td>401 (65.3)</td>
</tr>
<tr>
<td>Americas</td>
<td>171 (28.1)</td>
<td>175 (28.5)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>38 (6.3)</td>
<td>38 (6.2)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;50%, n(%)</td>
<td>481 (79.1)</td>
<td>485 (79.0)</td>
</tr>
<tr>
<td>Median estimated GFR (IQR), mL/min/1.73m²</td>
<td>49.2 (39.5-61.2)</td>
<td>50.5 (40.5-64.6)</td>
</tr>
<tr>
<td>Median diabetes duration prior to randomization (IQR), years</td>
<td>10.2 (16.8, 5.0)</td>
<td>10.2 (16.9, 5.2)</td>
</tr>
<tr>
<td>Diagnosis of diabetes during index admission, n(%)</td>
<td>17 (2.8)</td>
<td>14 (2.3)</td>
</tr>
<tr>
<td>Any Glucose Lowering Medication, n(%)</td>
<td>522 (85.9)</td>
<td>522 (85.0)</td>
</tr>
<tr>
<td>First Study Drug Dose Prior to Index Hospitalization Discharge, n(%)</td>
<td>290 (47.7)</td>
<td>306 (49.8)</td>
</tr>
</tbody>
</table>
Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

![Graph showing the comparison between Placebo and Sotagliflozin in terms of events per 100 patients. The graph indicates a hazard ratio (HR) of 0.67 (95% CI 0.52-0.85), P=0.0009. The absolute risk reduction (ARR) is 25 events per 100 patient-years. Treatment patient-years to avoid 1 event is 4.]

Motivation for Current Analysis

Risk of hospitalization among patients with a history of diabetes and HF is an important component of their total disease burden.

SGLT2i treatment reduces first and total hospitalizations for HF (HHF) and in some cases hospitalizations for any reason.

Prior reports only account for the incidence of each admission, but broader effects on health would also account for duration.
Objectives

Comparison of the sotagliflozin and placebo groups in terms of:

- Incidence of total hospitalizations for any reason, for HF, and for reasons other than HF
- Days alive and out of hospital (DAOH), which accounts for incidence and duration

Hypothesis: In SOLOIST-WHF, sotagliflozin reduces the risk of hospitalizations and extends DAOH following index HHF.
Analysis Methods

Total hospitalization incidence: mean cumulative functions (MCF); joint semiparametric model with death

DAOH: Poisson regression

Hospitalizations reported by investigators on designated CRF

All analyses conducted according to intention-to-treat, including all patients and events from randomization to the prespecified common study end date (CSED; May 1, 2020)
Calculation of DAOH for Each Patient

Total potential follow-up: days from randomization until
Calculation of DAOH for Each Patient

**Total potential follow-up:** days from randomization until

- Date last known alive, or
Calculation of DAOH for Each Patient

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\[
\text{DAOH} = \text{total potential follow-up} - \text{days in hospital} - \text{days dead}
\]
## Number and Duration of Hospitalizations

<table>
<thead>
<tr>
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<tr>
<td>Total hospitalizations for any reason, n</td>
<td>464</td>
<td>583</td>
<td></td>
</tr>
<tr>
<td>For heart failure</td>
<td>159</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td>For reasons other than heart failure</td>
<td>305</td>
<td>346</td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations per patient during follow-up, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>347 (61.5)</td>
<td>360 (58.6)</td>
<td></td>
</tr>
<tr>
<td>At least once</td>
<td>234 (38.5)</td>
<td>254 (41.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Once</td>
<td>135 (22.2)</td>
<td>118 (19.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>More than once</td>
<td>99 (16.3)</td>
<td>136 (22.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Median total duration of hospitalization among patients hospitalized at least once (IQR), days</td>
<td>8 (3,21)</td>
<td>10 (3, 24)</td>
<td></td>
</tr>
<tr>
<td>Death during follow-up, n (%)</td>
<td>64 (10.5)</td>
<td>76 (12.4)</td>
<td></td>
</tr>
</tbody>
</table>

Note: P values from Fisher exact tests.
Total Hospitalizations
(Mean Cumulative Functions)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sotagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>614</td>
<td>608</td>
</tr>
<tr>
<td>3</td>
<td>520</td>
<td>537</td>
</tr>
<tr>
<td>6</td>
<td>414</td>
<td>426</td>
</tr>
<tr>
<td>9</td>
<td>301</td>
<td>306</td>
</tr>
<tr>
<td>12</td>
<td>193</td>
<td>208</td>
</tr>
<tr>
<td>15</td>
<td>96</td>
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</tr>
<tr>
<td>18</td>
<td>22</td>
<td>26</td>
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HR (95% CI) = 0.76 (0.63-0.93), P=0.006
## Total Hospitalizations
(Joint Model Results)

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<th>HR (95% CI)</th>
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<tr>
<td>Total hospitalizations for any reason</td>
<td>97.6</td>
<td>126.6</td>
<td>0.76 (0.63, 0.93)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total hospitalizations for HF</td>
<td>33.4</td>
<td>51.4</td>
<td>0.61 (0.45, 0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total hospitalizations for reasons other than HF</td>
<td>64.2</td>
<td>75.1</td>
<td>0.81 (0.65, 1.02)</td>
<td>0.074</td>
</tr>
</tbody>
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CI, confidence interval; DAOH, HR, hazard ratio; p-y, patient-years.

29.0 (95% CI: 5.2, 52.8) total hospitalizations were avoided with sotagliflozin per 100 patient-years of follow-up.
## DAOH Results
*(Poisson regression)*

<table>
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<tr>
<th></th>
<th>Sotagliflozin (N=608)</th>
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<th>Rate per 100 p-y</th>
<th>RR (95% CI)</th>
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<td>DAOH</td>
<td>91.8 years</td>
<td>88.9 years</td>
<td>1.03 (1.00, 1.06)</td>
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CI, confidence interval; DAOH, days alive and out of hospital; p-y, patient-years; RR, rate ratio; SD, standard deviation.

For every 100 patient-years of follow-up, patients in the sotagliflozin group were alive and out of the hospital for 2.9 years more in absolute terms and 3% in relative terms.
## DAOH Results (Poisson regression)

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<td><strong>DAOH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Days dead</strong></td>
<td>6.3 years</td>
<td>8.9 years</td>
<td>0.71 (0.52, 0.99)</td>
<td>0.041</td>
</tr>
<tr>
<td><strong>Days in hospital</strong></td>
<td>1.9 years</td>
<td>2.2 years</td>
<td>0.86 (0.69, 1.08)</td>
<td>0.21</td>
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For every 100 patient-years of follow-up, patients in the sotagliflozin group were alive and out of the hospital for 2.9 years more in absolute terms and 3% in relative terms.
Limitations

• Other than HF, the primary reason for each hospitalization was unspecified; reduction in hospitalizations for reasons other than HF may be due to benefits on ischemic events.

• May have been other events that could have been included in days hospitalized that either were not recorded or were unknown, resulting in underreporting of hospitalizations.

• Study enrollment and duration of follow-up was curtailed due to loss of funding, which may have reduced statistical power.

• While DAOH was a prespecified outcome in the study analysis plan, total hospitalizations was not, and neither was prespecified in the study protocol.
Conclusions

In patients with type 2 diabetes and at high risk for recurrent hospitalization due to recent admission for worsening HF, sotagliflozin:
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**sotagliflozin:**

- Reduced subsequent hospitalizations, with 29.0 total hospitalizations avoided per 100 patient-years of follow-up
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- Reduced subsequent hospitalizations, with 29.0 total hospitalizations avoided per 100 patient-years of follow-up
- Extended DAOH by 2.9 years per 100 patient-years of follow-up

Beyond the primary efficacy endpoint, these results provide additional patient-centered metrics to capture the totality of disease burden and have important implications for patient quality of life and health care costs.