Benefits of SGLT1/2 Inhibition with Sotagliflozin in Heart Failure With Preserved Ejection Fraction

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Disclosures

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SOLOIST-WHF and SCORED were 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

![Diagram showing the evolution of SGLT2i in HF Management]

- **Diabetes**
  - Window of opportunity for treatment
  - Pre-clinical (subclinical) stage of the disease
    - 0 years
    - CANVAS Program
    - CREDENCE
    - DAPA-CKD
    - DECLARE-TIMI 58
    - EMPA-REG OUTCOME
    - VERTIS CV
  - Clinical stage of the disease
    - 10 years
  - Detectable cardiac involvement
    - 18-20 years
    - DAPA-HF
    - DELIVER HFpEF
    - EMPEROR-Preserved
    - EMPEROR-Reduced

- **Diabetes and No Diabetes**

The Evolution of **SGLT2i** in HF Management

**Diabetes** → **Diabetes and No Diabetes**

*Window of opportunity for treatment*

- **Pre-clinical (subclinical) stage of the disease**
  - 0 years
  - CANVAS Program
  - CREDENCE
  - DAPA-CKD
  - DECLARE-TIMI 58
  - EMPA-REG OUTCOME
  - VERTIS CV
  - SCORED

- **Clinical stage of the disease**
  - 10 years
  - DAPA-HF
  - DELIVER HFpEF
  - EMPEROR-Preserved
  - EMPEROR-Reduced
  - SOLOIST-WHF

- **Detectable cardiac involvement**
  - 18-20 years

**Normal Ventricular Function** → **Advanced Heart Failure**

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

**SOLOIST-WHF Trial Design**

1222 patients with diabetes and HF

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

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) = 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

1Goal of dose increase to 400 mg QD

SOLOIST-WHF: Addressing the Vulnerable Period of an Admission for Worsening Heart Failure

Verma S, Anker SD, Butler J, Bhatt DL. ESC Heart Failure. 2020.
**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

**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**

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

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

## Days Alive Out of Hospital (DAOH) (Poisson regression)

<table>
<thead>
<tr>
<th></th>
<th>Sotagliflozin (N=608)</th>
<th>Placebo (N=614)</th>
<th>Rate per 100 p-y</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAOH</td>
<td>91.8 years</td>
<td>88.9 years</td>
<td>1.03 (1.00, 1.06)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Days dead</td>
<td>6.3 years</td>
<td>8.9 years</td>
<td>0.71 (0.52, 0.99)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Days in hospital</td>
<td>1.9 years</td>
<td>2.2 years</td>
<td>0.86 (0.69, 1.08)</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

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.
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

Pooled Data: **SOLOIST and SCORED**

Total CV Death, H HF, and Urgent HF Visit in 11,784 Patients

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**

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Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 1758 Patients with **HFrEF (<40%)**

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**

Bhatt DL. ACC 2021, virtual.
Pooled Data: SOLOIST and SCORED
Total CV Death, H HF, and Urgent HF Visit in 456 Patients with HFmrEF (40% - <50%)*

HR 0.61 (95% CI 0.40-0.94), P=0.02
ARR: 15.2 Events Per 100 Patient-Years
Treatment Patient-Years to Avoid 1 Event: 7

For this analysis, patients from SCORED needed to have a history of HF within 2 years.

*post hoc
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 739 Patients with **HFpEF (≥50%)**

Event Rates:

- **Placebo**: 59.0 Events Per 100 Patient-Years
- **Sotagliflozin**: 37.5 Events Per 100 Patient-Years

Treatment Patient-Years to Avoid 1 Event: **9**

**HR 0.63 (95% CI 0.45-0.89), P=0.009**

**ARR: 11.6 Events Per 100 Patient-Years**

For this analysis, patients from SCORED needed to have a history of HF within 2 years.
SCORED Total CV Death, HHF, and Urgent HF Visit in 6738 Patients with no History of HF (EF≥50%)

HR 0.73 (95% CI 0.54-0.99), P=0.04
ARR: 0.8 Events Per 100 Patient-Years
Treatment Patient-Years to Avoid 1 Event: 121

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Pooled Data: **SOLOIST and SCORED**

Total CV Death, H HF, and Urgent HF Visit in 11,784 Patients

Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST and SCORED**
Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

Bhatt DL. ACC 2021, virtual.

EF<40% (N=1758)  
HR 0.78 (0.63-0.96)  
P=0.02

ARR 9.1/100p-y
Pooled Data: **SOLOIST** and **SCORED**
Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

- **EF<40% (N=1758)**
  - HR 0.78 (0.63-0.96)
  - P=0.02

- **EF 40-50% (N=1357)**
  - HR 0.61 (0.44-0.84)
  - P=0.003

ARR 9.1/100p-y
ARR 6.9/100p-y
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

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<th>EF&lt;40% (N=1758)</th>
<th>EF 40-50% (N=1357)</th>
<th>EF≥50% (N=8669)</th>
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<tr>
<td>HR 0.78 (0.63-0.96)</td>
<td>HR 0.61 (0.44-0.84)</td>
<td>HR 0.70 (0.57-0.86)</td>
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<td>P=0.02</td>
<td>P=0.003</td>
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ARR 9.1/100p-y           ARR 6.9/100p-y           ARR 1.7/100p-y

Bhatt DL. ACC 2021, virtual.
Pooled Data: SOLOIST and SCORED
Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

Bhatt DL. ACC 2021, virtual.

EF<40% (N=1758)
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HR 0.61 (0.44-0.84)
P=0.003

EF≥50% (N=8669)
HR 0.70 (0.57-0.86)
P=0.0008

HR P_{interaction} = 0.46
(by EF category)

RR P_{interaction} = 0.49
(by continuous EF)

HR, hazard ratio; RR, rate ratio
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

Bhatt DL. ACC 2021, virtual. For this analysis, patients from SCORED with any history of HF are included.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

For this analysis, patients from SCORED with any history of HF are included.

- EF<40% (N=1758)
  - HR 0.78 (0.63-0.96)
  - P=0.02

ARR 9.1/100p-y
Pooled Data: **SOLOIST and SCORED**
Total CV Death, HHF, and Urgent HF Visit in 4500 Patients **with History of HF**

**Bhatt DL. ACC 2021, virtual.**

For this analysis, patients from SCORED with any history of HF are included.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

For this analysis, patients from SCORED with any history of HF are included.

**Baseline Ejection Fraction, %**

- **EF<40% (N=1758)**
  - HR 0.78 (0.63-0.96)
  - P=0.02

- **EF 40-50% (N=811)**
  - HR 0.57 (0.40-0.82)
  - P=0.002

- **EF≥50% (N=1931)**
  - HR 0.67 (0.51-0.89)
  - P=0.006
Pooled Data: **SOLOIST and SCORED**

Total CV Death, H HF, and Urgent HF Visit in 4500 Patients with History of HF

Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED with any history of HF are included.

HR, hazard ratio; RR, rate ratio
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

**Intention-to-Treat Analysis**

HR (95% CI)

**Total CV Death, HHF, and Urgent HF Visit**
- **SOLOIST**: 0.67 (0.52, 0.85)
- **SCORED**: 0.74 (0.63, 0.88)
- **Pooled**: 0.72 (0.63, 0.82)

**Total HHF and Urgent HF Visit**
- **SOLOIST**: 0.64 (0.49, 0.83)
- **SCORED**: 0.67 (0.55, 0.82)
- **Pooled**: 0.66 (0.56, 0.78)

**CV Death**
- **SOLOIST**: 0.84 (0.58, 1.22)
- **SCORED**: 0.90 (0.73, 1.12)
- **Pooled**: 0.89 (0.74, 1.07)

Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

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<th>On-Treatment Analysis</th>
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Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

**Intention-to-Treat Analysis**

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**CV Death**

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Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST** and **SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients **with History of HF**

**Intention-to-Treat Analysis**

Total CV Death, HHF, and Urgent HF Visit

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<td>0.75 (0.62, 0.91)</td>
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Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

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<td>Pooled</td>
<td>0.62 (0.52, 0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLOIST</td>
<td>0.86 (0.52, 1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCORED</td>
<td>0.67 (0.47, 0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>0.73 (0.55, 0.98)</td>
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<td></td>
</tr>
</tbody>
</table>

Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

**Intention-to-Treat Analysis**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Sotagliflozin Better</th>
<th>Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total CV Death, HHF, and Urgent HF Visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLOIST</td>
<td>0.67 (0.52, 0.85)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SCORED</td>
<td>0.75 (0.62, 0.91)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.71 (0.61, 0.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total HHF and Urgent HF Visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLOIST</td>
<td>0.64 (0.49, 0.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SCORED</td>
<td>0.71 (0.56, 0.89)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.68 (0.57, 0.81)</td>
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</tr>
<tr>
<td><strong>CV Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLOIST</td>
<td>0.84 (0.58, 1.22)</td>
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</tr>
<tr>
<td>SCORED</td>
<td>0.86 (0.65, 1.15)</td>
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<tr>
<td>Pooled</td>
<td>0.86 (0.69, 1.08)</td>
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</tbody>
</table>

**On-Treatment Analysis**

<table>
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<tr>
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<tr>
<td>SOLOIST</td>
<td>0.62 (0.48, 0.79)</td>
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</tr>
<tr>
<td>SCORED</td>
<td>0.65 (0.52, 0.80)</td>
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</tr>
<tr>
<td>Pooled</td>
<td>0.64 (0.54, 0.75)</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Total HHF and Urgent HF Visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLOIST</td>
<td>0.59 (0.45, 0.77)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SCORED</td>
<td>0.65 (0.51, 0.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.62 (0.52, 0.74)</td>
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Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST and SCORED**

Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

Bhatt DL. ACC 2021, virtual.

**Ejection Fraction <40%**
- Female (n=482): HR = 0.94 (0.60, 1.47)
- Male (n=1276): HR = 0.74 (0.59, 0.94)
- Overall (n=1758): HR = 0.78 (0.63, 0.96)

**Ejection Fraction 40 to 50%**
- Female (n=445): HR = 0.64 (0.36, 1.20)
- Male (n=912): HR = 0.59 (0.40, 0.87)
- Overall (n=1357): HR = 0.61 (0.44, 0.84)

**Ejection Fraction 50%**
- Female (n=4439): HR = 0.71 (0.54, 0.94)
- Male (n=4230): HR = 0.69 (0.51, 0.94)
- Overall (n=8669): HR = 0.70 (0.57, 0.86)

**P collabor**
- 0.37
- 0.75
- 0.90
Pooled Data: SOLOIST and SCORED
Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

HR (95% CI)

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P<sub>interaction</sub>

0.37

0.75

0.90

Bhatt DL. ACC 2021, virtual.
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Total CV Death, H HF, and Urgent HF Visit in 4500 Patients with History of HF

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- Male (n=1276) 0.74 (0.59, 0.94)
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Ejection Fraction 40 to 50%

- Female (n=291) 0.70 (0.37, 1.30)
- Male (n=520) 0.51 (0.33, 0.79)
- Overall (n=811) 0.57 (0.40, 0.82)

Ejection Fraction $\geq$50%

- Female (n=1052) 0.65 (0.46, 0.92)
- Male (n=879) 0.71 (0.45, 1.12)
- Overall (n=1931) 0.67 (0.51, 0.89)

Bhatt DL. ACC 2021, virtual.
Pooled Data: **SOLOIST** and **SCORED**

Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

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- **P_{interaction}**
  - 0.37
  - 0.42
  - 0.77

Bhatt DL. ACC 2021, virtual.
Limitations

Trials were stopped early during the onset of the pandemic
• Nevertheless, robust reduction in primary endpoint

Shortened duration limited the statistical power to see significant reductions in certain endpoints
• Though on-treatment analyses show a significant reduction in CV death

Some of the present analyses were prespecified, others were post hoc
• Both types of analyses were consistent in terms of demonstrating significant benefits

Bhatt DL. ACC 2021, virtual.
Conclusions

Sotagliflozin robustly and significantly reduced the composite of total cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure across the full range of ejection fraction, including in patients with heart failure with preserved ejection fraction.

As well, in on-treatment analyses, sotagliflozin demonstrated a significant reduction in cardiovascular death.

These are the first randomized data from a prespecified analysis of clinical trials to show a significant effect of a therapy on heart failure with preserved ejection fraction, additionally demonstrating a consistent and significant benefit in women.

Bhatt DL. ACC 2021, virtual.
Thank You!

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BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
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