SOLOIST

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

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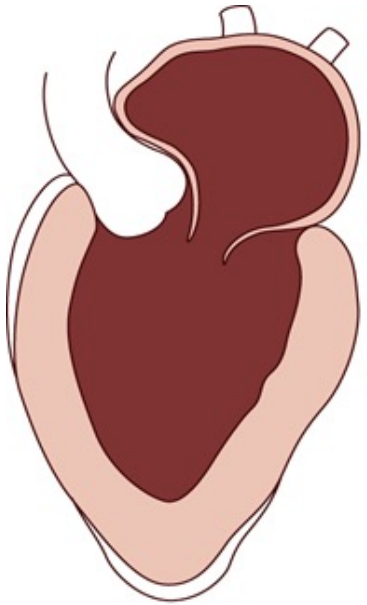
on Behalf of the SOLOIST-WHF Investigators

The Evolution of SGLT2i in HF Management



Normal Ventricular Function

Diabetes

Diabetes and No 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

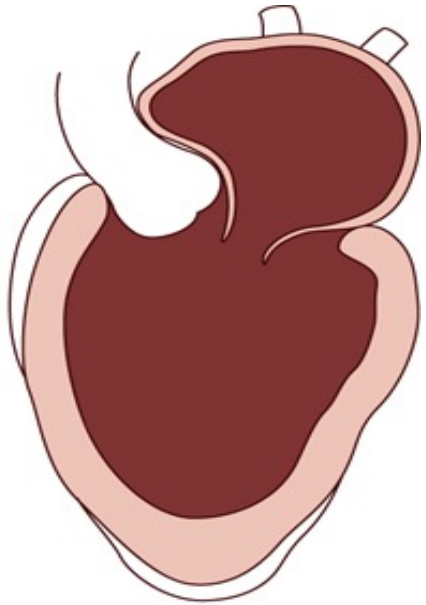
18-20 years

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

DAPA-HF
DELIVER HFpEF
EMPEROR-Preserved
EMPEROR-Reduced

HF Prevention

HF Treatment



End-stage Heart Failure

Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism.* 2019;30:847-849.

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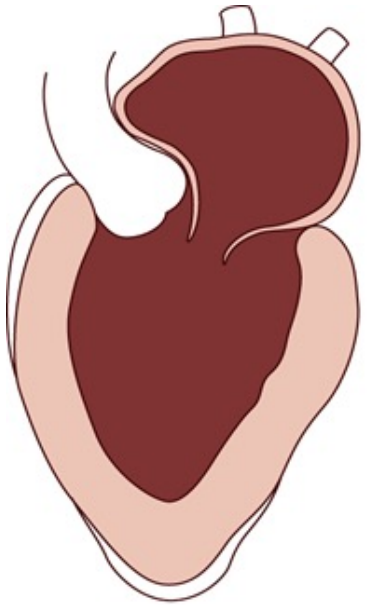

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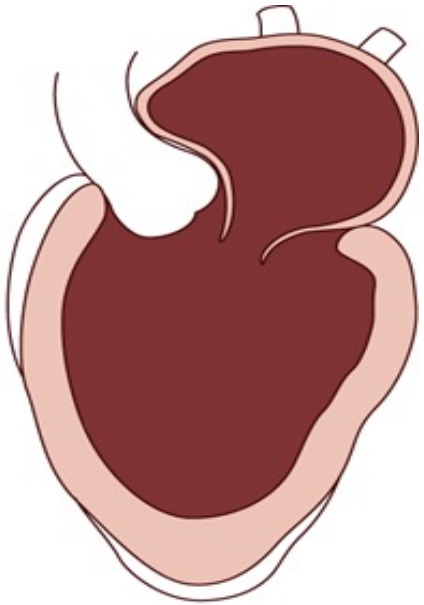
HF Treatment

Acute HF?



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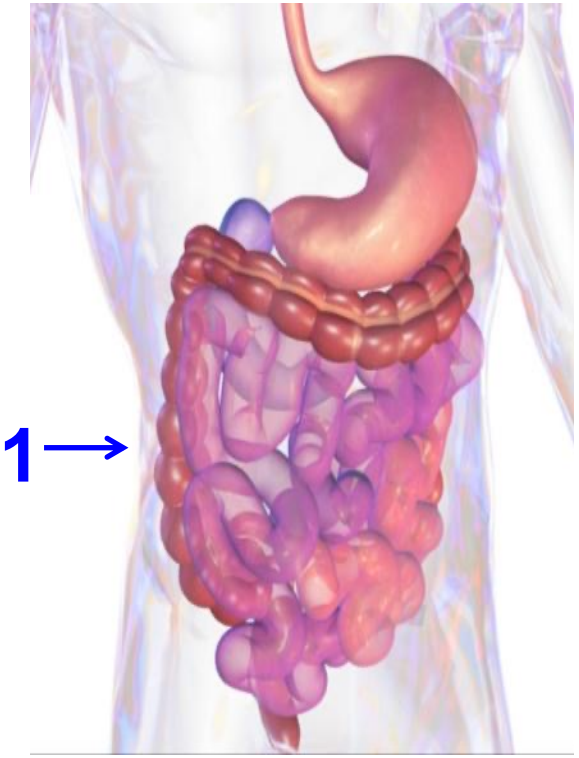
Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor

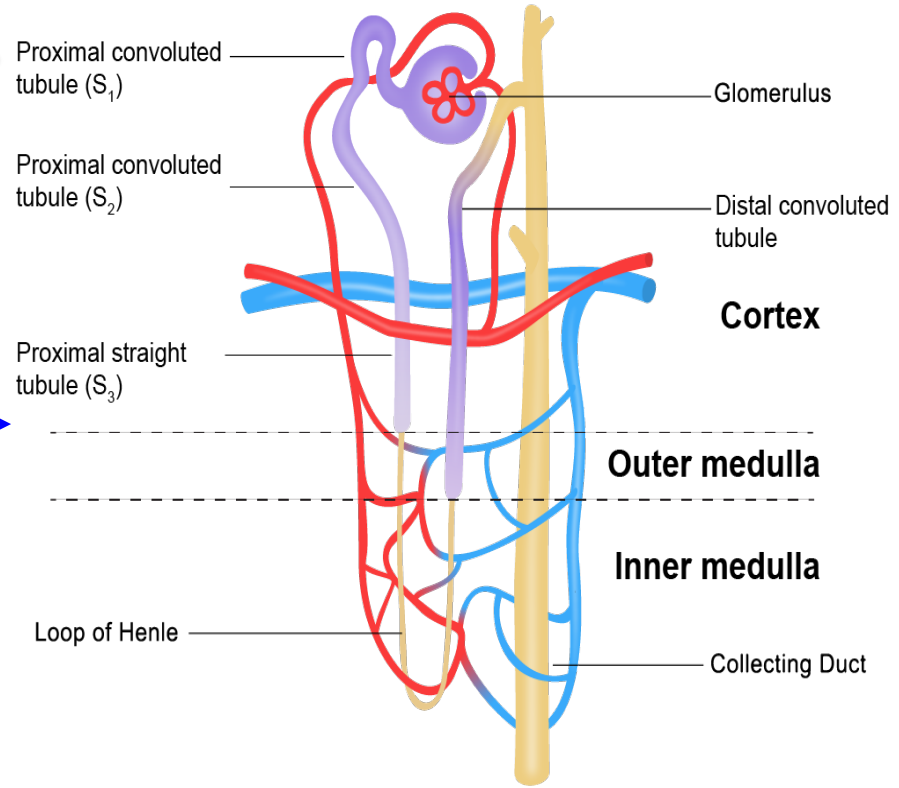
SGLT1 →



- **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

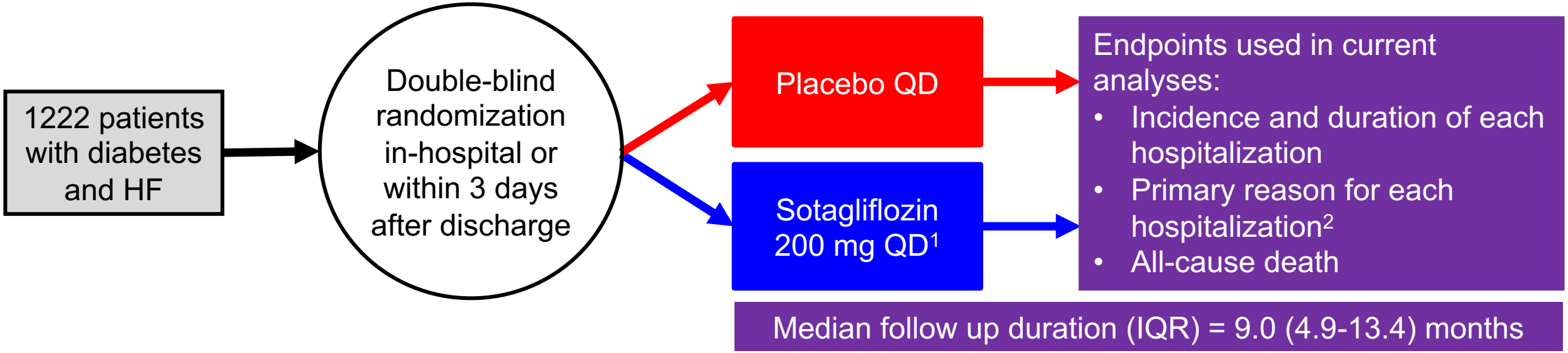
SGLT2 →

SGLT1 →



- **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



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/1.73m^2

[1]Goal of dose increase to 400 mg QD
[2]HF or reasons other than HF

Baseline Characteristics

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	Sotagliflozin (N=608)	Placebo (N=614)
Median age (IQR), years	69 (63-76)	70 (64-76)
Female sex, n(%)	198 (32.6)	214 (34.9)
Geographic Region, n(%)		
Europe	399 (65.6)	401 (65.3)
Americas	171 (28.1)	175 (28.5)
Rest of World	38 (6.3)	38 (6.2)
Left ventricular ejection fraction <50%, n(%)	481 (79.1)	485 (79.0)
Median estimated GFR (IQR), mL/min/1.73m^2	49.2 (39.5-61.2)	50.5 (40.5-64.6)
Median diabetes duration prior to randomization (IQR), years	10.2 (16.8, 5.0)	10.2 (16.9, 5.2)
Diagnosis of diabetes during index admission, n(%)	17 (2.8)	14 (2.3)
Any Glucose Lowering Medication, n(%)	522 (85.9)	522 (85.0)
First Study Drug Dose Prior to Index Hospitalization Discharge, n(%)	290 (47.7)	306 (49.8)

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

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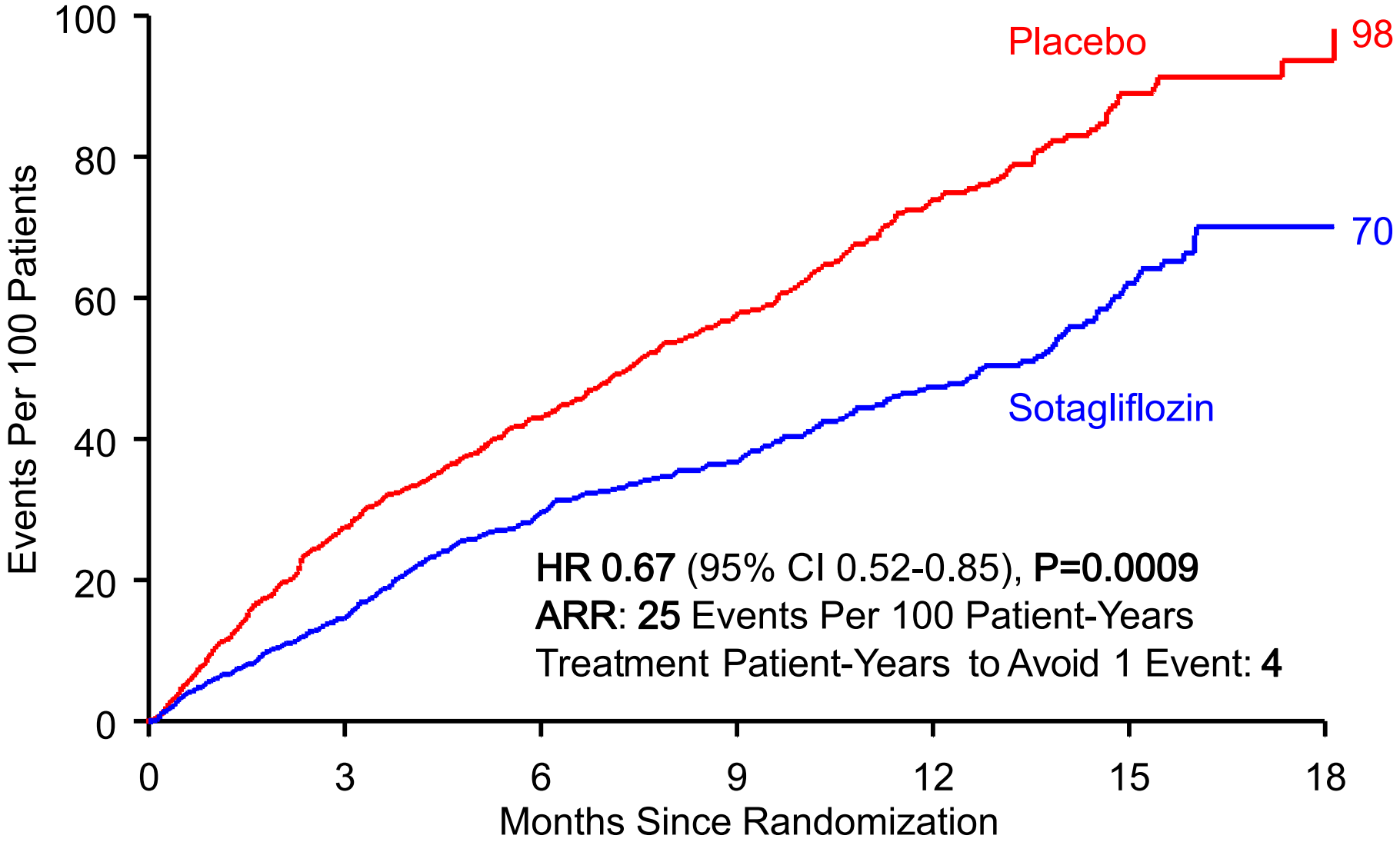

Bhatt DL, Szarek M, Steg PG, et al., *N Engl J Med.* 2021.

Motivation for Current Analysis

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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

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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

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Total potential follow-up: days from randomization until

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Days in hospital was derived from investigator reports

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Days in hospital was derived from investigator reports

If a patient died, days dead was calculated as the time interval between their date of death and the CSED

DAOH = total potential follow-up – days in hospital – days dead

Number and Duration of Hospitalizations

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	Sotagliflozin (N=608)	Placebo (N=614)	P value
Total hospitalizations for any reason, n	464	583	
For heart failure	159	237	
For reasons other than heart failure	305	346	
Number of hospitalizations per patient during follow-up, n(%)			
None	347 (61.5)	360 (58.6)	
At least once	234 (38.5)	254 (41.4)	0.32
Once	135 (22.2)	118 (19.2)	0.20
More than once	99 (16.3)	136 (22.1)	0.011
Median total duration of hospitalization among patients hospitalized at least once (IQR), days	8 (3,21)	10 (3, 24)	
Death during follow-up, n (%)	64 (10.5)	76 (12.4)	

Note: P values from Fisher exact tests.

Total Hospitalizations
(Mean Cumulative Functions)

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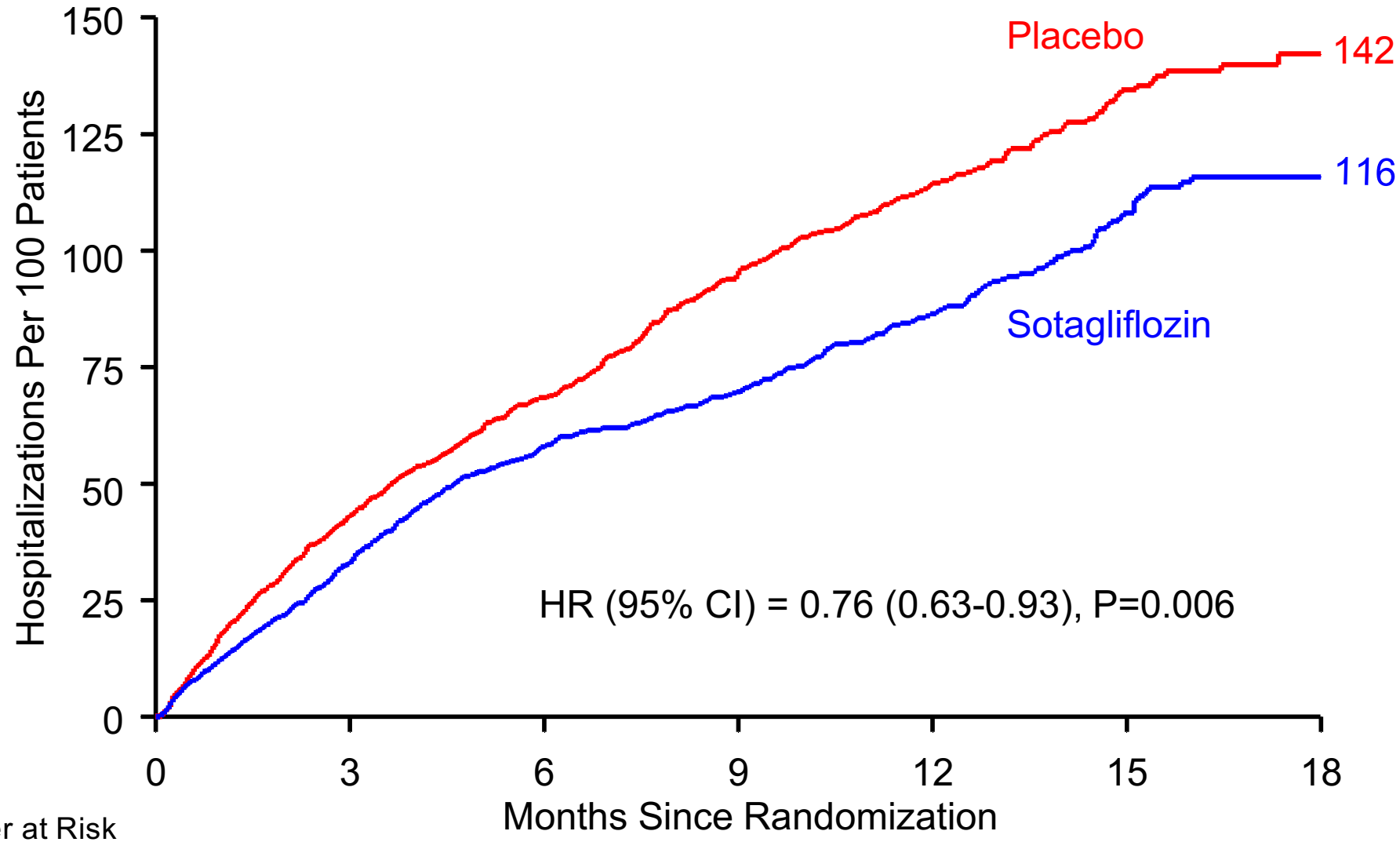

Number at Risk							
Placebo	614	520	414	301	193	96	22
Sotagliflozin	608	537	426	306	208	96	26

Total Hospitalizations
(Joint Model Results)

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	Sotagliflozin (N=608)	Placebo (N=614)		
	Events per 100 p-y		HR (95% CI)	P value
Total hospitalizations for any reason	97.6	126.6	0.76 (0.63, 0.93)	0.006
Total hospitalizations for HF	33.4	51.4	0.61 (0.45, 0.84)	0.002
Total hospitalizations for reasons other than HF	64.2	75.1	0.81 (0.65, 1.02)	0.074

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)

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	Sotagliflozin (N=608)	Placebo (N=614)		
	Rate per 100 p-y		RR (95% CI)	P value
DAOH	91.8 years	88.9 years	1.03 (1.00, 1.06)	0.027

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

CI, confidence interval; DAOH, days alive and out of hospital; p-y, patient-years; RR, rate ratio; SD, standard deviation.

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Limitations

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- 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

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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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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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- Extended DAOH by 2.9 years per 100 patient-years of follow-up

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

- 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.