

Targeting Outside Myosin: Future Therapies



SOtagliflozi**N** in Patients with
Symptom**A**Tic obstructive **A**nd
non-obstructive **H**ypertrophic
Cardio**M**yopathy

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Disclosures

Bristol Myers Squibb, Cytokinetics, Lexicon, Alexion – unrestricted funding for SHaRe

Lexicon Pharmaceuticals – Co-Chair steering committee (SONATA-HCM)

Cytokinetics – Data safety monitoring board

Pfizer – Data safety monitoring board

Solid BioSciences – Scientific Advisory Board

Ceva Sante Animale – Scientific Advisory Board

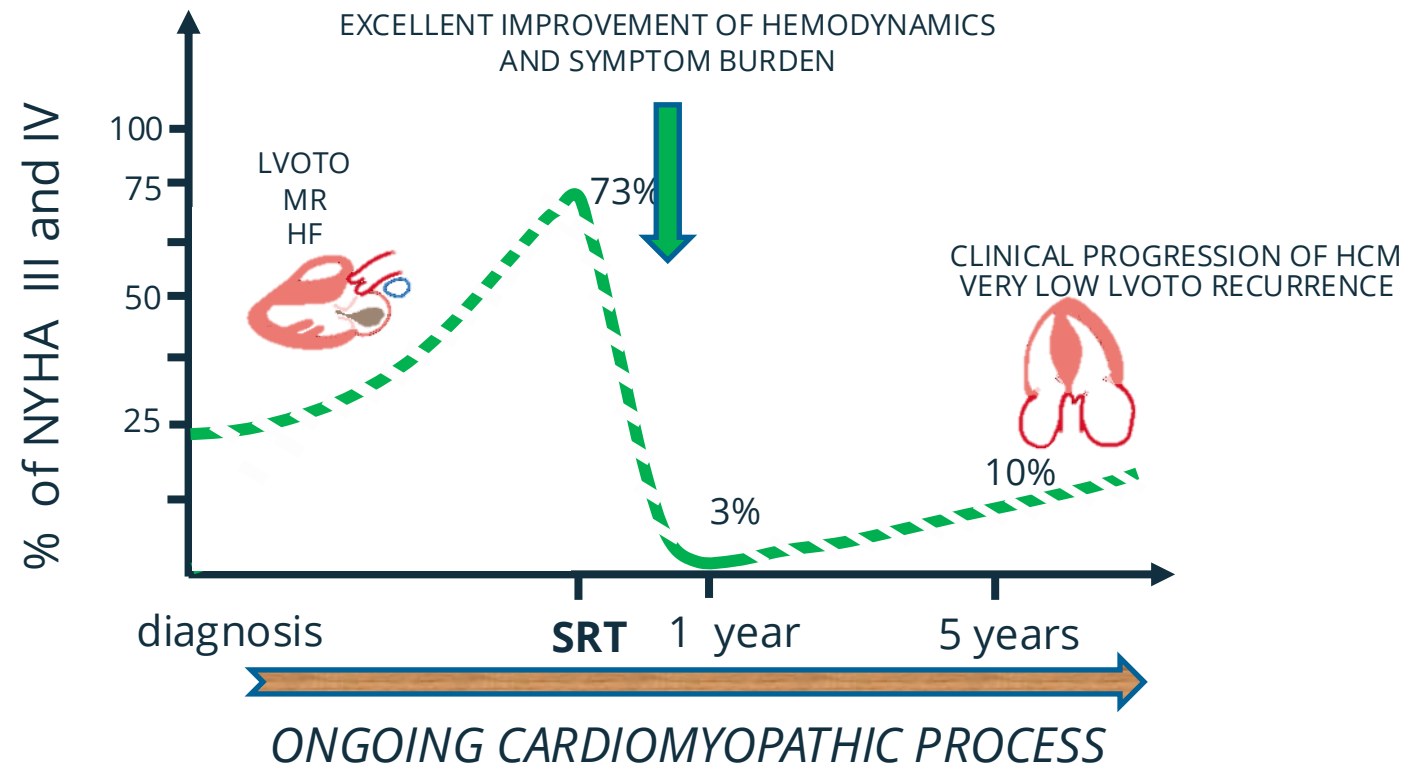
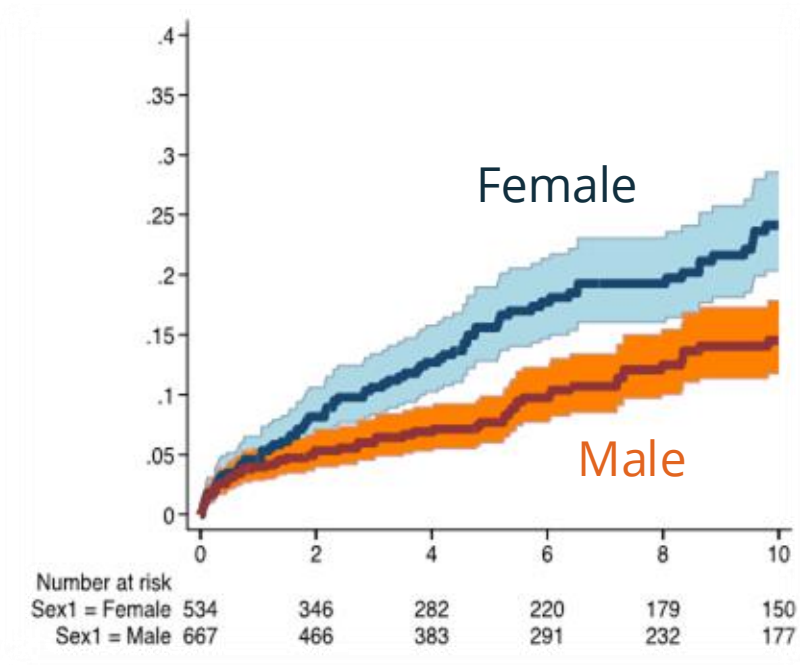
Symptomatic Nonobstructive HCM: the Search for Effective Treatment

- Beta blockers, ACEi, ARBs – no evidence
 - Spironolactone – 1 trial negative
 - Ranolazine – 1 trial negative
 - Eleclazine – trial stopped early for lack of efficacy
 - Perhexiline – toxicity concerns
 - Trimetazine – 1 trial, worse functional capacity
 - **Exercise works!**
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- CMLs – Mixed results from ODYSSEY-HCM and ACACIA-HCM
 - Nineraxstat- Phase 2b ongoing
 - Sarcomere Modulator EDG-7500- Phase 2 ongoing

Symptomatic Obstructive HCM: Still Room for Improvement

- Some patients will have residual symptoms despite elimination of LVOT gradients, either with CMI or after SRT
- Some patients develop heart failure without recurrent obstruction after SRT

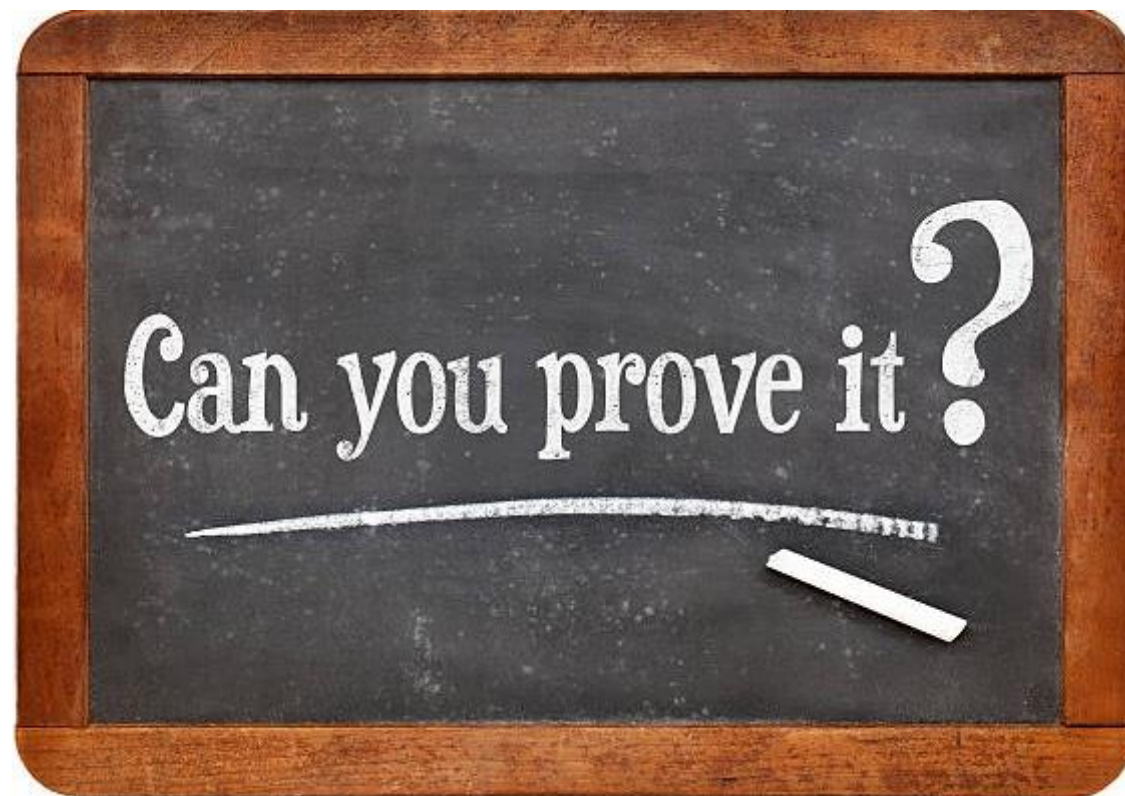
NYHA Class III/IV post SRT



The Importance of Clinical Trials

Expectations ≠ Evidence

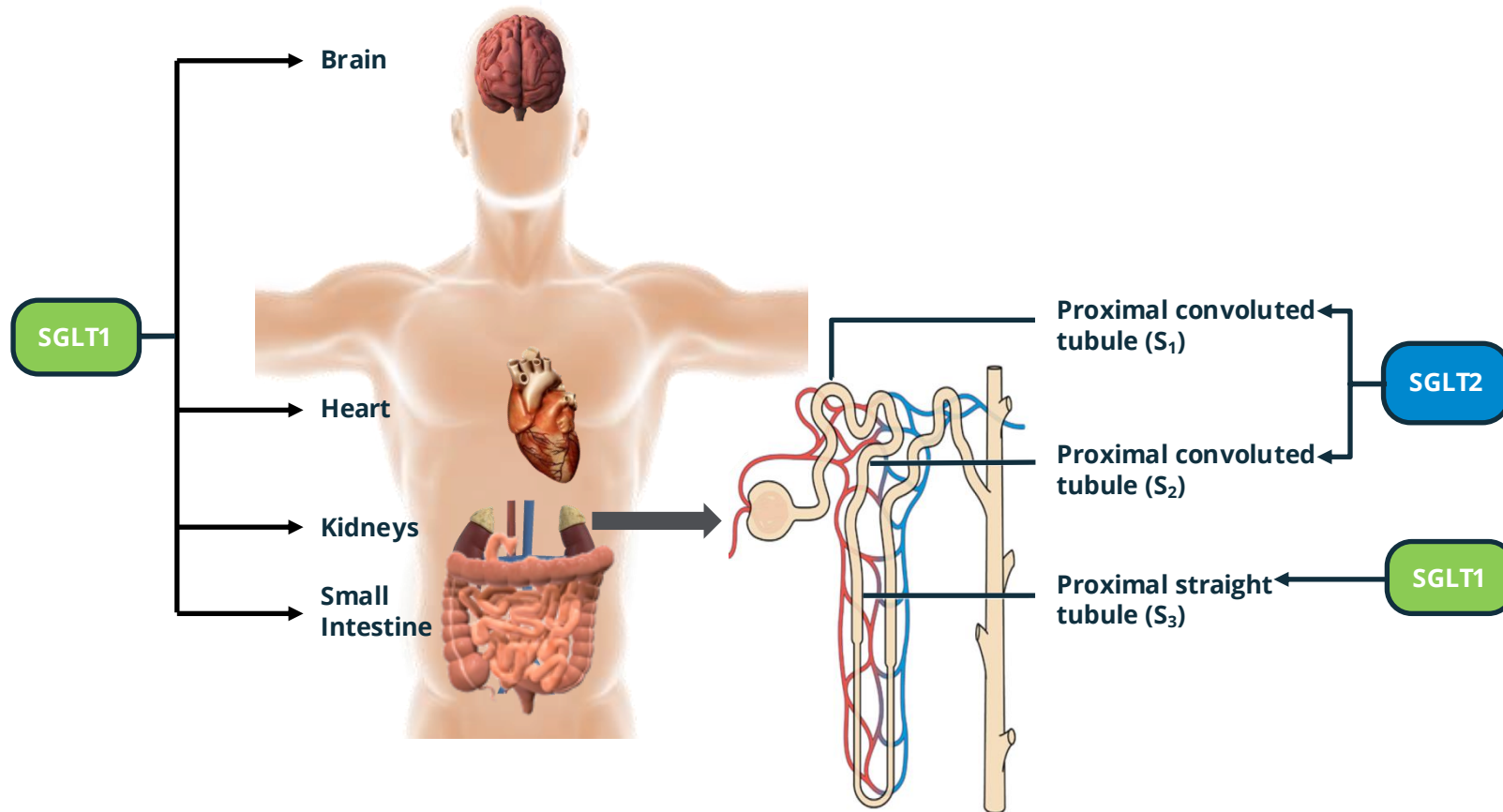
- Enthusiasm for SGLT inhibitors in HCM but not previously tested; benefit needs to be systematically evaluated
- HCM ≠ HFpEF
- Rigorous evidence from clinical trials is needed to guide best practice



Sotagliflozin: Dual SGLT Inhibitor

Sodium-glucose Cotransporter-1 (**SGLT1**) and Sodium-glucose Cotransporter-2 (**SGLT2**)

Expression patterns of **SGLT2** and **SGLT1**^{1,2}



SGLT2 is expressed exclusively in the **renal proximal tubule**

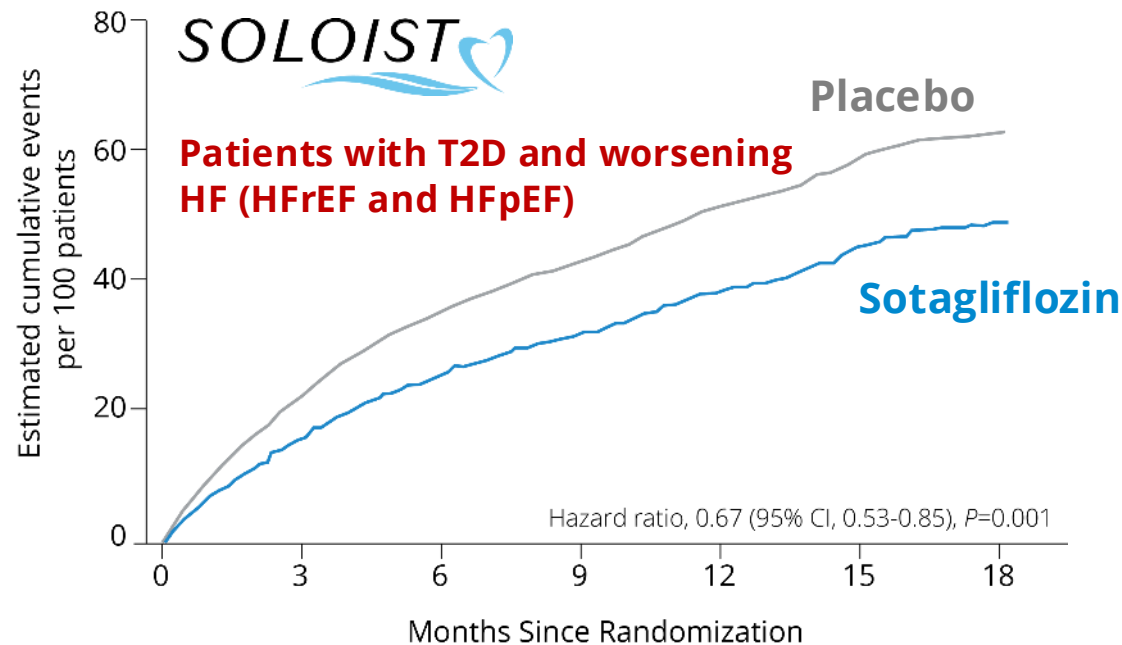
- Co-transport Na⁺ and Glucose (1:1)
- Reuptake of 90-97% glucose in the kidney

SGLT1 is expressed in the **kidney, intestine, heart, platelets, and vascular endothelium**

- Co-transport Na⁺ and Glucose (2:1)
- Primary transporter for absorption of glucose in the GI tract

Sotagliflozin Reduced the Risk of CV Death and Heart Failure Events In High-Risk Patient Populations

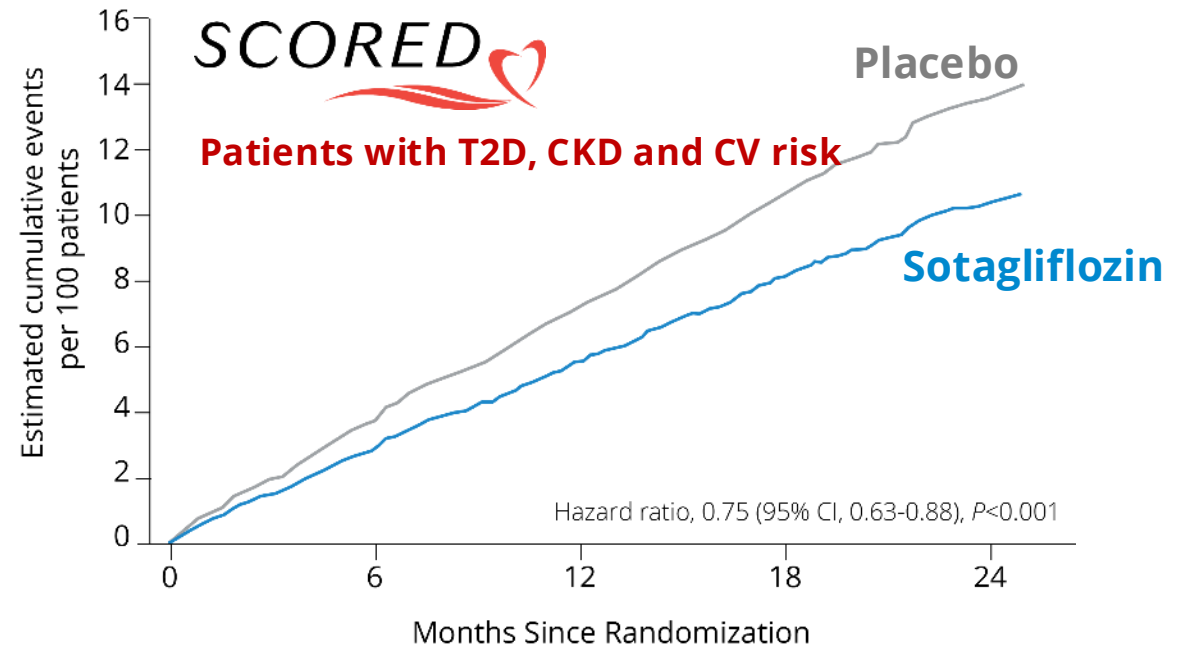
Cumulative Primary Endpoint: Total CV Death, HHF, and Urgent HF Visit



33% Relative Risk Reduction¹

NNT = 4 patient-years²

Placebo: **76.3** events per 100 pt-years sotagliflozin: **51.0** events per 100 pt-years



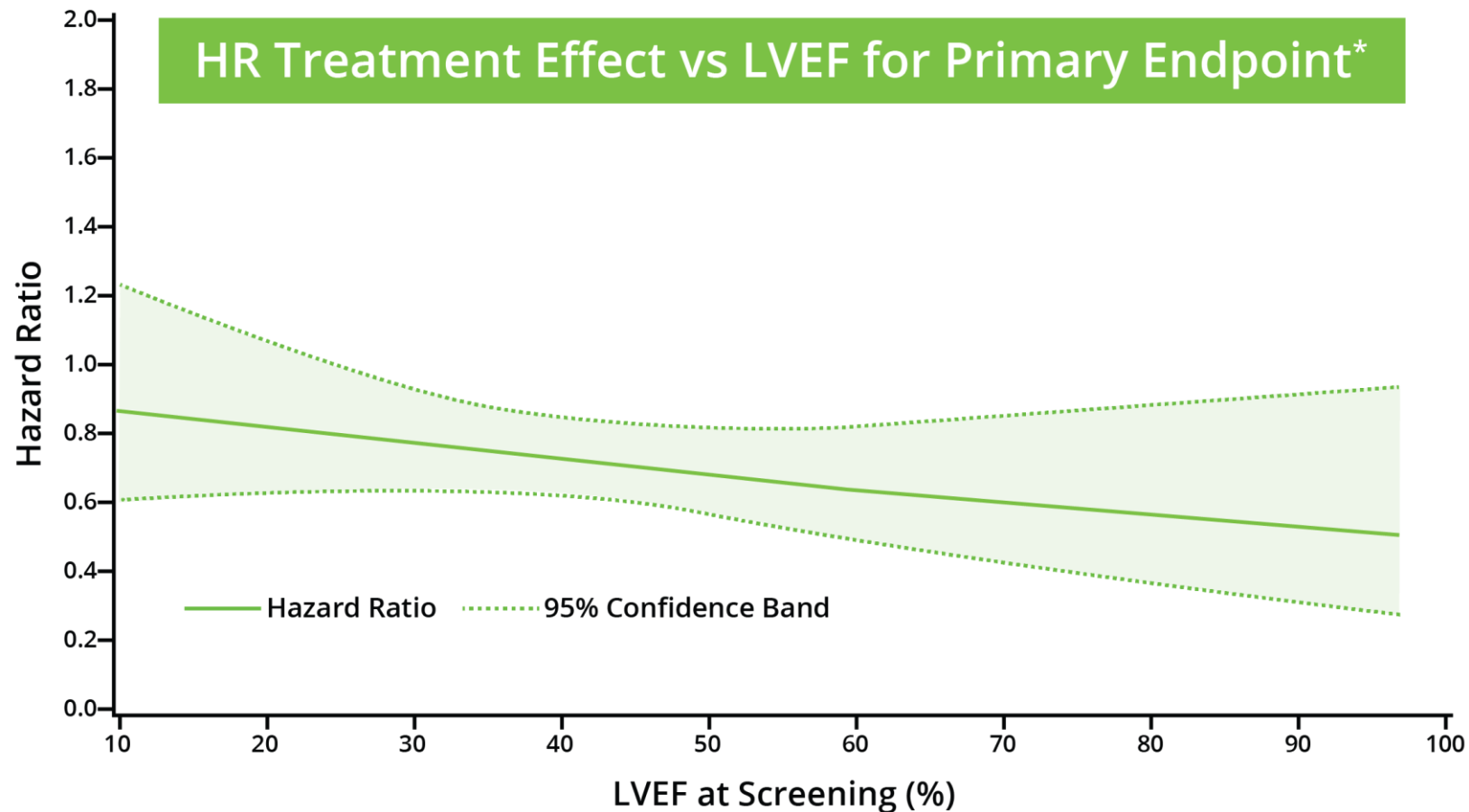
25% Relative Risk Reduction³

Time to Sustained Benefit = 95 days⁴

1. Bhatt et al. N Engl J Med 2021. 2. Verma et al. 2020. 3. Bhatt et al. N Engl J Med 2021. 4. Aggarwal et al. Eur J Heart Fail 2024.

Sotaliflozin Demonstrated Efficacy Across LVEF Range: Greater Efficacy at Higher LVEF

Patients with a History of HF – Pooled Analysis of SOLOIST-WHF and SCORED

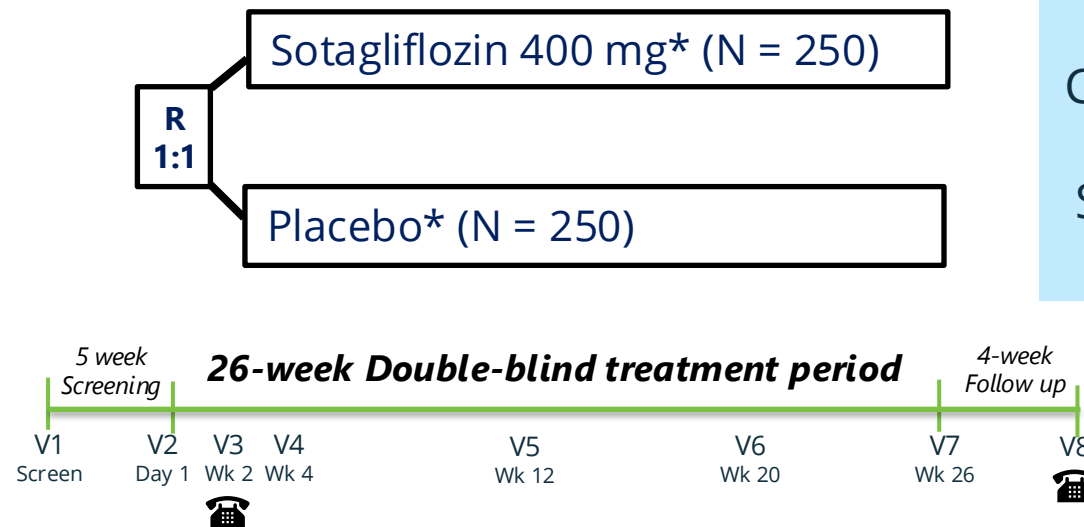


* composite of total occurrence of CV death, hospitalization for heart failure, and urgent visit for heart failure

SONATA-HCM

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of **S**otagliflozin in Patients with Symptom**A**ttic obstructive **A**nd non-obstructive **H**ypertrophic **C**ardio**M**yopathy

- Adults with HCM (o/n)
- LVOT gradient per HCM type:
 - oHCM ≥ 30 mm Hg at rest OR with Valsalva
 - nHCM < 30 mm Hg at rest AND with Valsalva
- KCCQ CSS < 85
- NYHA Class II or III
- LVEF $\geq 50\%$



Primary endpoint:
Change from baseline
in KCCQ Clinical
Summary Scale (CSS)
score

*For patients not tolerating treatment, sotagliflozin or matching placebo down-titrated to 200 mg starting at Week 4.

133 sites in 20 countries (Planned N = 500)

ClinicalTrials.gov: NCT06481891

Baseline Characteristics of Randomized Patients

Characteristic	Overall, N = 542	nHCM, n = 440 (81%)	oHCM, n = 102 (19%)
Age, years (SD)	61 (13)	60 (14)	63 (12)
Females, (%)	274 (50.6)	208 (47.3)	66 (64.7)
BMI, kg/m ²	29.6 (4.9)	29.7 (5.0)	28.9 (4.3)
BMI ≥30 kg/m ² , %	235 (43.4)	199 (45.2)	36 (35.3)
Race (White/Black/Asian), %	91 / 6 / 2	91 / 5 / 2	90 / 7 / 2
Region (US/LATAM/EU), %	22 / 10 / 68	23 / 8 / 69	18 / 18 / 65
Family history of HCM, %	178 (32.8)	154 (35.0)	24 (23.5)
NYHA II/III, % / %	80.1 / 19.4	81.8 / 17.5	72.5 / 27.5
LVEF, %	65.1 (7.5)	64.5 (7.2)	67.9 (8.0)
LV wall thickness, mm	22.4 (5.3)	22.1 (5.2)	23.8 (5.7)
LVOT g at rest, mmHg	8.3 (6.0, 13.3)	7.5 (5.6, 10.2)	27.1 (16.6, 44.4)
LVOT g with Valsalva, mmHg	10.3 (6.5, 21.1)	8.9 (6.1, 13.2)	58.2 (45.7, 91.4)
NTproBNP, pmol/L (pg/mL) median	490 (196, 1123)	439 (178, 998)	749 (328, 1556)
hs cTnI, ng/L median	12.1 (6.5, 22.8)	12.4 (6.2, 23.1)	11.5 (7.4, 19.2)

Baseline Characteristics of Randomized Patients

Characteristic	Overall, N = 542	nHCM, n = 440	oHCM, n = 102
KCCQ CSS	58.7 (20.0)	59.6 (19.8)	55.0 (20.3)
<i>HCM Therapies</i>			
Beta-blocker, %	439 (81.0)	353 (80.2)	86 (84.3)
CCB, %	50 (9.2)	39 (8.9)	11 (10.8)
Disopyramide, %	13 (2.4)	6 (1.3)	7 (6.9)
CMI, %	49 (9.0)	36 (8.2)	13 (12.7)
<i>Selected Medical History</i>			
ICD, %	150 (27.7)	139 (31.6)	11 (10.8)
Septal Myectomy, %	16 (3.0)	13 (3.0)	3 (2.9)
Atrial fibrillation, n (%)	143 (26.4)	127 (28.9)	16 (15.7)

Conclusions

- There continues to be an unmet need for effective and well-tolerated therapies in patients with HCM
- There is strong rationale for testing sotagliflozin for efficacy in improving symptoms in patients with HCM via a mechanism of action independent of LVOT gradient
- Topline results from SONATA-HCM are anticipated to be available in the 1st quarter of 2027