A Randomized, Double-Blind, Parallel Group Trial to Evaluate the Effect of a Novel Sodium-Glucose Cotransporter 2 Inhibitor, Enavogliflozin Compared with Standard-of-Care Therapy on Reduction of Adverse Clinical Events and Cardiac Reverse Remodeling in Patients with Severe Aortic Stenosis Who Underwent Transcatheter Aortic Valve Replacement

ENAVO-TAVR Trial

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AS is the m/c valve disease in the aging population

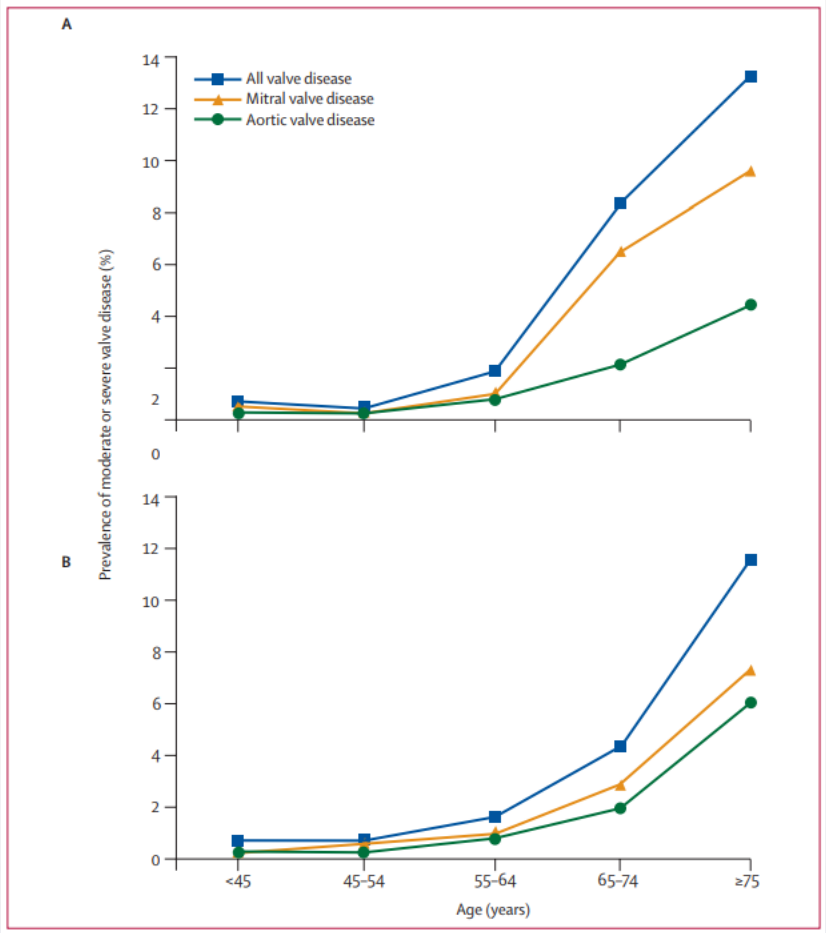


Figure 1: **Prevalence of valvular heart disease by age**
(A) Frequency in population-based studies and (B) in the Olmsted County community.

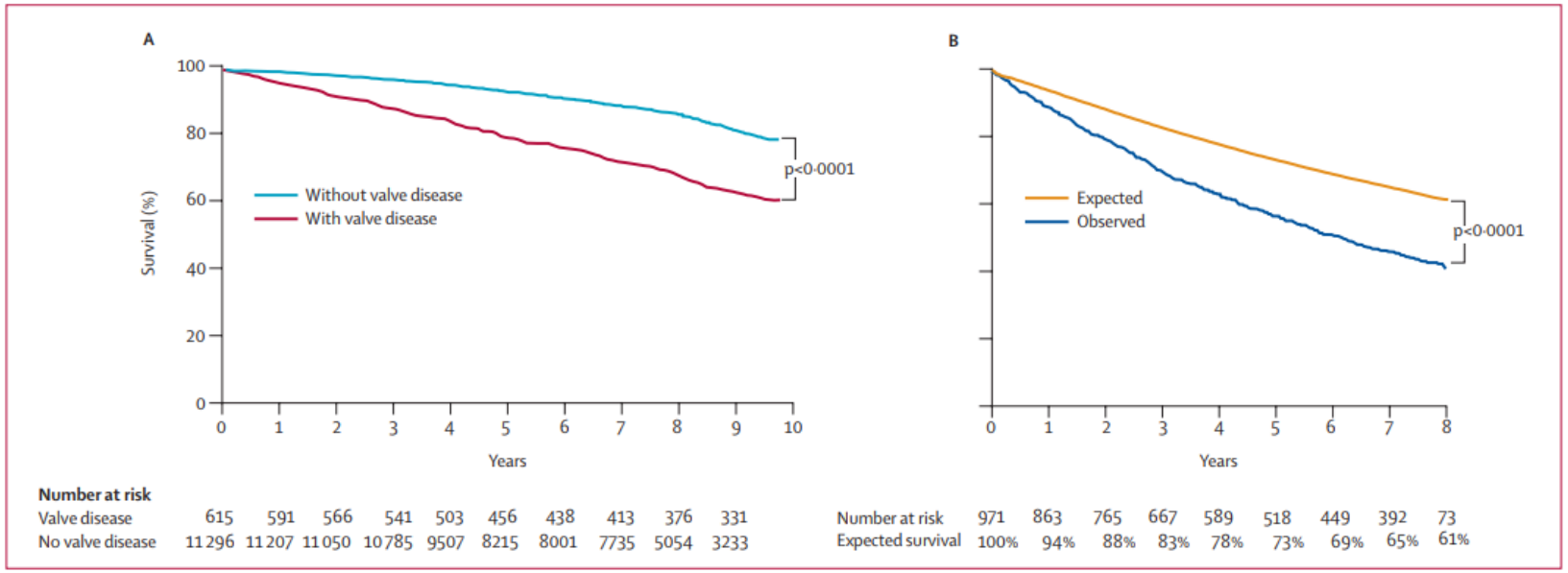


Figure 2: **Survival after detection of moderate or severe valvular heart disease**
(A) Survival in population-based studies. (B) Expected versus observed survival in Olmsted County. The blue line represents survival of 971 residents diagnosed with valve diseases between 1990 and 1995; the yellow line represents the expected survival in the age-matched and sex-matched population of the county.

Nkomo VT, *Lancet*. 2006;368(9540):1005-1011.

Treatment of severe AS

- Aortic valve replacement
  - Surgical or transcatheter (SAVR or TAVR)

- TAVR
  : Recommended in adult ≥ 65years (US guideline) or ≥ 75 years (European guideline)

Post-TAVR outcomes

- Despite of mechanical relief of severe AS after TAVR,

  up to 50% of patients are dead, have residual heart failure (HF) symptoms

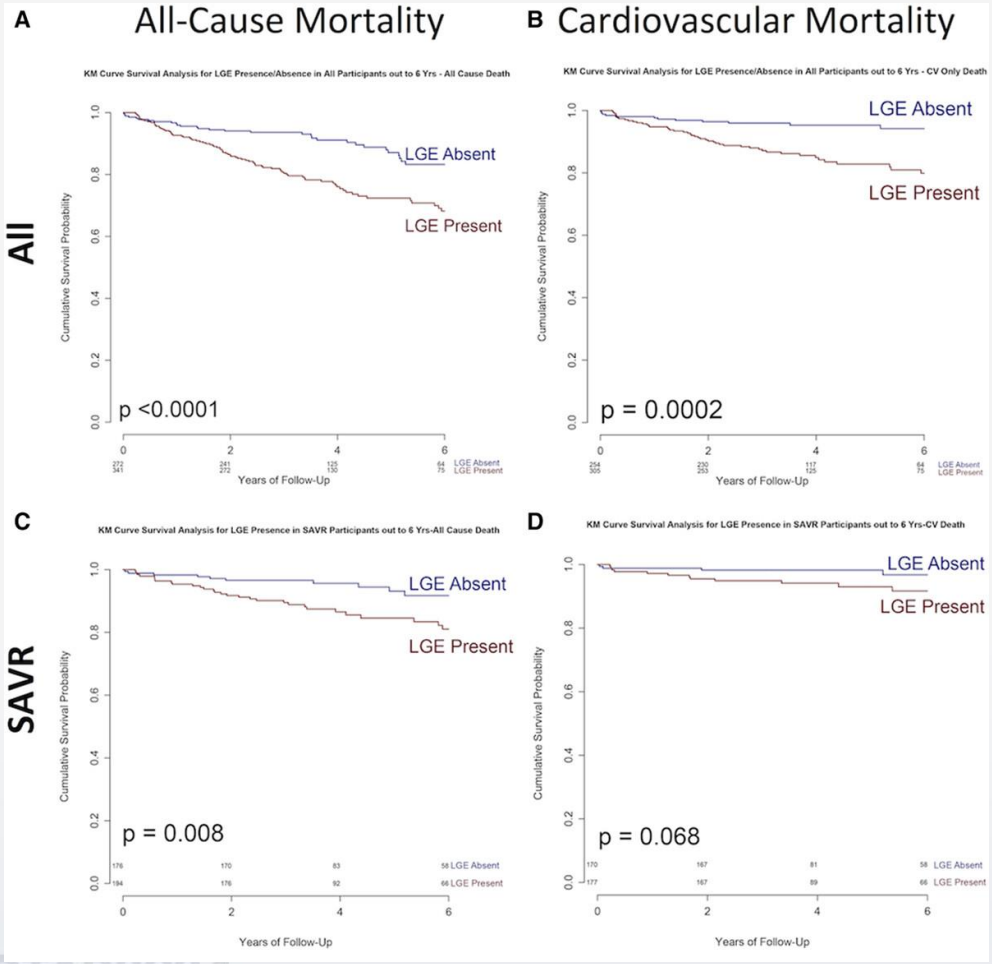
  or poor quality-of-life (QoL) at 1 year.

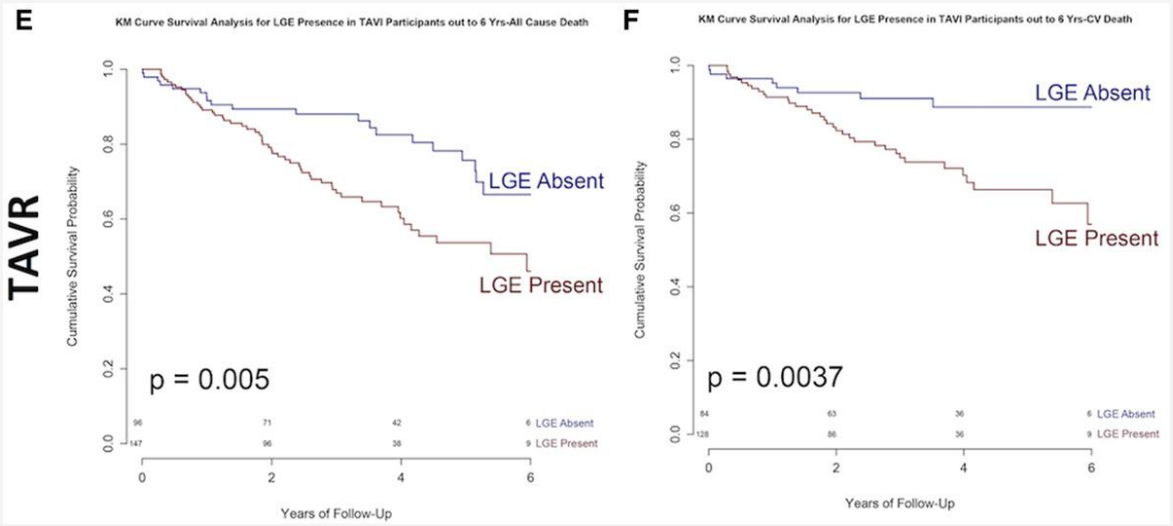
- Especially, patients who underwent TAVR have approximately

  -15~20% rate of readmission for heart failure (HF) within 1 year after

  successful TAVR procedure

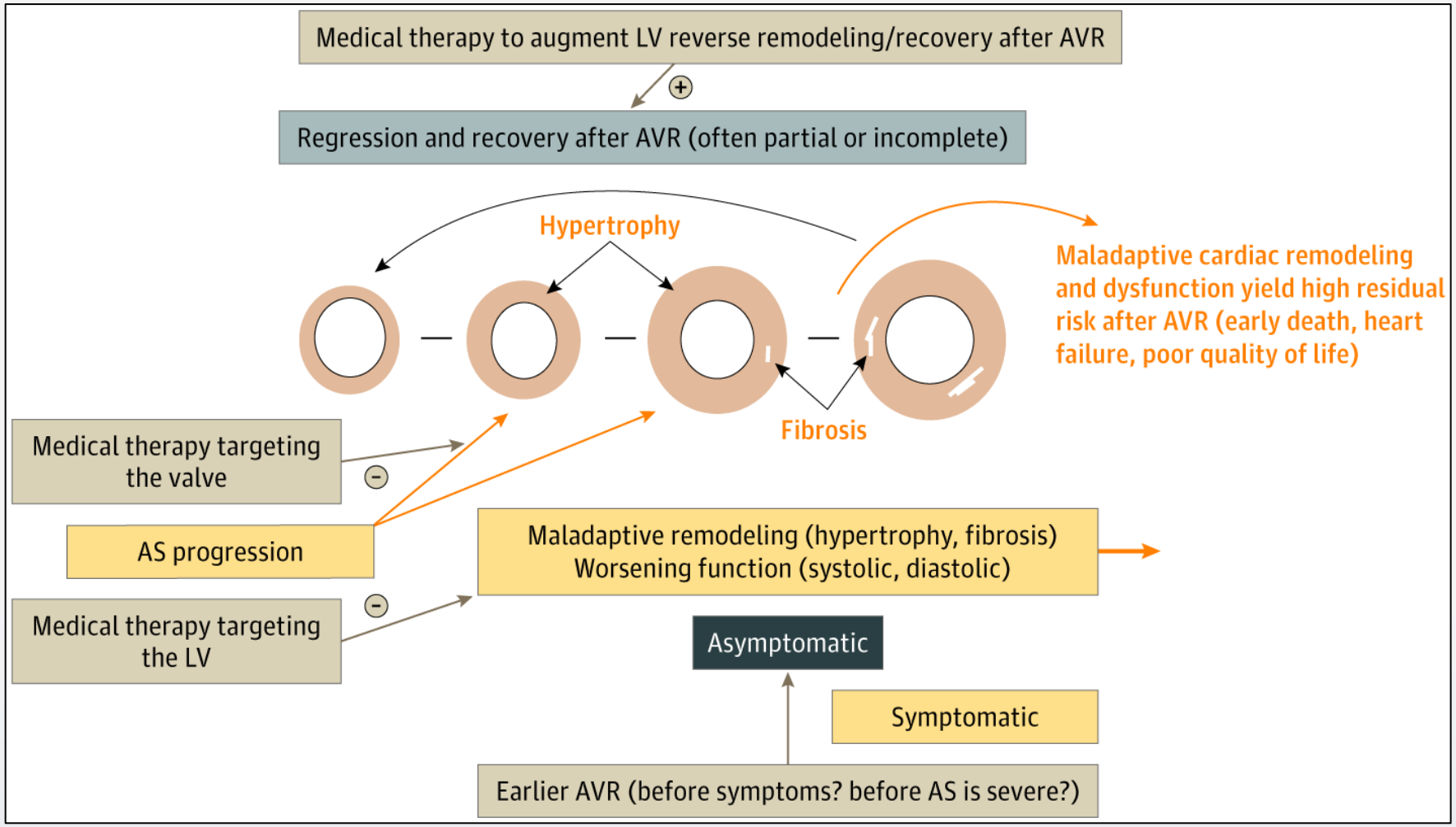
AS – Disease of both the valve & myocardium





Musa TA, et al. Circulation 2018;138:1935-47.

Strategies to Prevent and Mitigate Risk of Heart Failure in Patients With Calcific Aortic Stenosis



JAMA Cardiol. 2021;6(9):993-994

Medical Therapy of AS

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients at risk of developing AS (Stage A) and in patients with asymptomatic AS (Stages B and C), hypertension should be treated according to standard GDMT, started at a low dose, and gradually titrated upward as needed, with appropriate clinical monitoring (66-68).
1	A	2. In all patients with calcific AS, statin therapy is indicated for primary and secondary prevention of atherosclerosis on the basis of standard risk scores (69-71).
2b	B-NR	3. In patients who have undergone TAVI, renin-angiotensin system blocker therapy (ACE inhibitor or ARB) may be considered to reduce the long-term risk of all-cause mortality (72,73).
3: No Benefit	A	4. In patients with calcific AS (Stages B and C), statin therapy is not indicated for prevention of hemodynamic progression of AS (69-71).

- Given myocardial health impacts post-TAVR clinical outcomes
  - Several adjunctive or active pharmacotherapies,
    RAS blockers, ARNI, SGLT2 inhibitors

- Augment myocardial function recovery and to reduce high residual risk (early deaths, HF, or poor quality of life) after TAVR

SGLT2 inhibitor

- SGLT2 inhibitors improves cardiovascular outcomes

Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE–TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

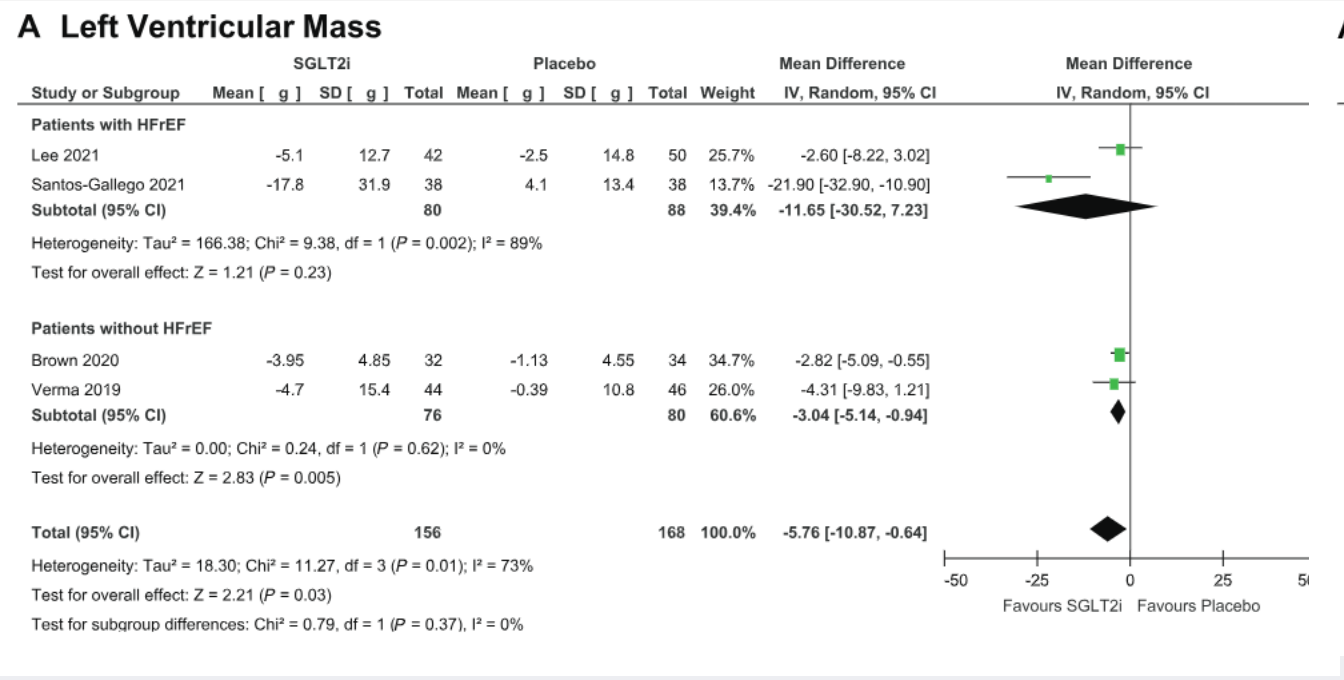
* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.[14]; CANVAS Program, Neal et al.[15]; CREDENCE, Perkovic et al.[16]; DECLARE–TIMI 58, Wiviott et al.[17]; VERTIS CV, Cannon et al.[18]; and SCORED, Bhatt et al.[19] Data are also based on a meta-analysis by McGuire et al.[20]

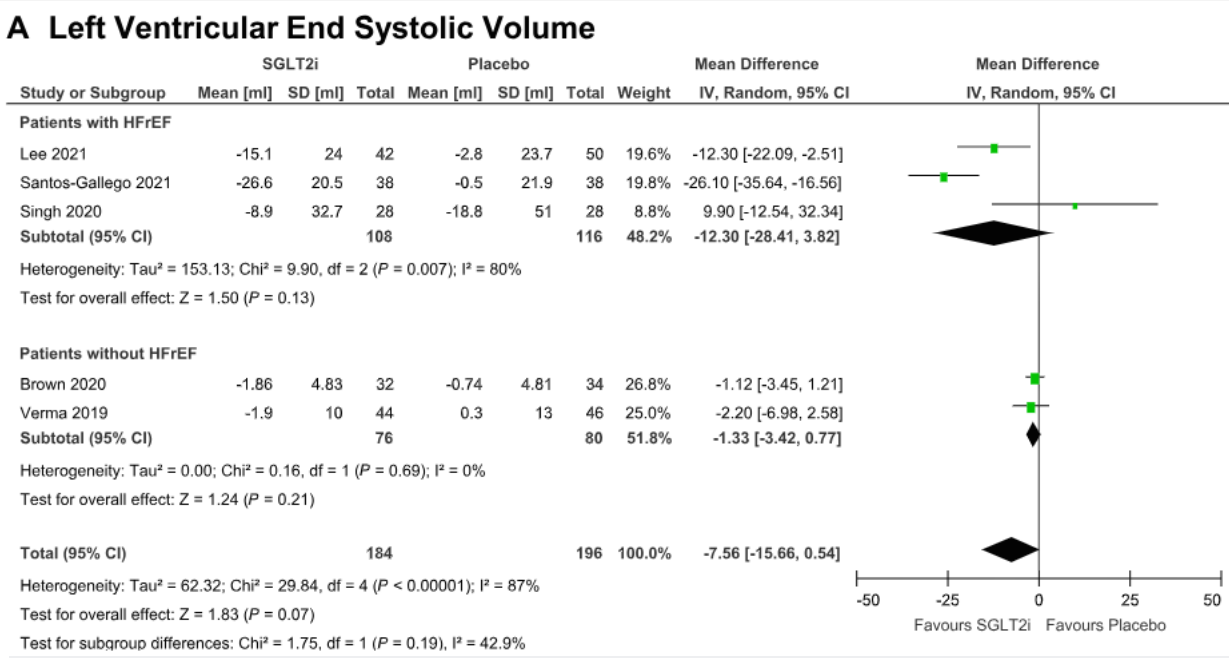
† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

Braunwald E. *N Engl J Med*. 2022;386(21):2024-2034.

SGLT2 inhibitor

- In addition, some imaging and clinical studies proposed that SGLT2 inhibitor was associated with improvements of cardiac volume and function (i.e., reverse cardiac remodeling) owing to several putative mechanisms





Dhingra NK, et al. *ESC Heart Fail*. 2021;8(6):4693-4700.

Hypothesis

- Novel SGLT2 inhibitor, enavogliflozin compared to the standard-of-care therapy would significantly reverse cardiac remodeling and improve clinical outcomes in patients who underwent successful TAVR.

ENAVOgliflozin Outcome Trial in Patient with Severe Aortic Stenosis after Transcatheter Aortic Valve Repacement

ENAVO-TAVR Trial

ENAVOgliflozin Outcome Trial in Patients with Severe Aortic Stenosis after **T**ranscatheter **A**ortic **V**alve **R**eplacement

ENAVO-TAVR Trial

1040 patients with severe AS who underwent successful TAVR

Stratified randomization by (1) baseline LVEF (≤40 or >40%), (2) diabetes status, and (3) eGFR (≤60 or >60 mL/min/1.73m^2),

SGLT2 Inhibitor Group: Enavogliflozin (0.3 mg once daily) (N=520)

Standard-of-Care Group: Matching placebo (N=520)

Primary endpoint: a composite of major adverse cardiovascular events (death from any cause, myocardial infarction, or stroke) or hospitalization for heart failure at 1 year.
Secondary endpoint: changes in measures of cardiac volume and function assessed by echocardiography* and functional status (by NYHA) and quality of life (by KCCQ).

*Left ventricular (LV) EF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), left atrial volume index (LAVI), and ratio of early transmitral Doppler velocity/early diastolic annular velocity (E/e') at 12 months.

Study Design

- Investigator-initiated, multicenter, double-blind, parallel-group, randomized trial

- **Stratification:**
  - Baseline LVEF (≤40 or >40%)
  - Diabetes status (yes or no)
  - eGFR (≤60 or >60 mL/min/1.73m2)

- **Interventions:**
- Enavogliflozin Group :
  - Enavogliflozin 0.3mg once daily
- Standard-of-care Group :
- - Enavogliflozin 0.3mg placebo once daily

Sample Size Estimation

- Superiority trial design
- % of primary endpoint : 30% in the Standard-of-care group base on result from multiple RCTs (PARTNER 1B,2,3 and U.S. CoreValve High Risk Study, SURTAVI, and Evolut Low Risk) and TP-TAVR registry

- Dropout rate : 5%
- Power = 90%; alpha-level = 0.05
- Final N = 1040 (520 vs. 520)

Study Endpoint

- **Primary Endpoint**
  - Composite of major adverse cardiovascular event
    or hospitalization for HF at 1 year after randomization

    1. Death from any causes
    2. Nonfatal myocardial infacrtion
    3. Nonfatal stroke

Secondary Endpoint

1. **Individual components of the primary composite endpoint.**
2. **Composite renal endpoint**

   (1) chronic dialysis; (2) renal transplantation;

   (3) sustained reduction of ≥40% in estimated glomerular filtration rate (GFR); or

   (4) sustained estimated GFR <15 mL/min/1.73 m2 for patients with baseline estimated GFR ≥30 mL/min/1.73 m2 or <10 mL/min/1.73 m2 for patients with baseline eGFR <30 mL/min/1.73 m2.
3. **Rehospitalization for any reason.**
4. **Changes in measures of cardiac volume and function assessed by serial echocardiography;**

   left ventricular (LV) EF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI),

   left atrial volume index (LAVI), and ratio of early transmitral Doppler velocity/early diastolic annular velocity (E/e′) at 1 year.
5. **Changes in New York Heart Association (NYHA) functional class** and the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure).
6. **Serial change in NT-proBNP**
7. **Time from randomization to discontinuation of study medication attributed to side effects or adverse events**

Inclusion Criteria

- **Patients 18 years of age or older**

- **Symptomatic AS patient who underwent successful TAVR**

  A successful TAVI is defined as device success according to the VARC-2 and VARC-3 criteria:

  (1) **Correct positioning of a single prosthetic heart valve into the proper anatomical location**

  (2) **Intended performance of the prosthetic heart valve**

  - mean aortic valve gradient <20 mmHg,
  - peak velocity <3 m/s,
  - no moderate or severe prosthetic valve regurgitation)

  (3) **Absence of periprocedural complications**

  - any type of stroke, life- threatening bleeding,
  - acute coronary artery obstruction requiring intervention,
  - major vascular complication requiring intervention,
  - unresolved acute valve thrombosis, or any requirement of a repeat procedure).

Exclusion Criteria

1.Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomization;

discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor

for the purposes of study enrolment is not permitted.

2. Known allergy, hypersensitivity, or previous intolerance to an SGLT2 inhibitors.

3. Type 1 diabetes or diabetes ketoacidosis

4. Chronic cystitis and/or recurrent urinary tract infection (≥2 times within 1 year).

5. Stroke or transient ischemic attack within 12 weeks prior to enrollment.

6. Symptomatic persistent hypotension and/or a systolic blood pressure (SBP) < 95 mm Hg at screening or at randomization.

Exclusion Criteria

7. SBP ≥180 mmHg irrespective of treatment or SBP ≥160 mmHg with at least ≥3 antihypertensive drugs at screening or randomization.

8. Heart failure due to any of the following: known infiltrative cardiomyopathy (e.g. amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected primary valvular disease.

9. Renal insufficiency (eGFR <30 ml/min/1.73 m2 of body-surface area) or end-stage renal disease or requiring dialysis at the time of screening.

10. Acute or chronic liver disease with severe impairment of liver function (e.g., ascites, esophageal varices, coagulopathy).

11. Significant chronic pulmonary disease requiring home oxygen or primary pulmonary arterial hypertension.

12. Any known or suspected malignancy

13. Subjects with non-cardiac co-morbidities with life expectancy less than 12 months

14. Women of child-bearing potential (i.e., those who are not chemically or surgically sterilized or post-menopausal not willing to use a medically accepted method of contraception considered reliable in the judgment of the investigator or who has a positive pregnancy test at randomization or who is breastfeeding).

15. Participation in another clinical trials

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