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Original Article



SGLT2 inhibitors and progression of moderate calcific aortic stenosis: Protocol for a prospective multicentre cohort study (SLOW-AS)

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ABSTRACT

Calcific aortic valve stenosis (CAVS) is the most common valve disease in adults, and no drug has been shown to slow it. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) improve outcomes after transcatheter valve replacement, and one retrospective cohort linked them to slower progression of non-severe aortic stenosis (AS). This study will test whether SGLT2i use is associated with slower valve progression and less cardiac damage in moderate CAVS. SLOW-AS is a prospective, multicentre cohort study of 600 adults with moderate CAVS (peak aortic jet velocity 3.0–3.9 m/s or aortic valve area 1.0–1.5 cm^2) and left ventricular ejection fraction of 50% or more. Patients taking an SGLT2i for an approved indication will be compared with patients not taking one (1:2). Echocardiography at baseline, 6, 12 and 24 months will be read by a blinded core laboratory. The primary outcome is the annual change in peak aortic jet velocity. Secondary outcomes include mean gradient, valve area, cardiac damage stage, global longitudinal strain, left ventricular mass index, NT-proBNP, progression to severe AS, and a composite of valve replacement, heart failure hospitalisation or death. Confounding will be handled with propensity-score overlap weighting, and outcomes analysed with mixed-effects and Cox models. The study requires ethics approval and written informed consent, and does not change treatment. Results will be reported following the STROBE statement. SLOW-AS will provide the first prospective, core-laboratory evidence on SGLT2i and progression of moderate AS, and will inform a definitive randomised trial.

KEY WORDS: Aortic stenosis, calcific aortic valve disease, SGLT2 inhibitors, disease progression, echocardiography, cardiac damage staging

Strengths and limitations of this study

- It is the first prospective study of SGLT2i and progression in moderate AS, measured by blinded core-laboratory echocardiography.
- It measures both the valve and the myocardium, using the Généreux cardiac damage stages.
- It uses a target-trial emulation framework with active-comparator and new-user sensitivity analyses.
- As an observational study, unmeasured confounding by indication (diabetes, chronic kidney disease, heart failure) may remain.
- It uses echocardiography only for most patients; CT calcium scoring is optional, which limits direct study of calcification.

Introduction

Burden of calcific aortic valve stenosis

Calcific aortic valve stenosis (CAVS) is the most common valve disease in adults, and it becomes more common with age [1, 2, 3]. More than one-quarter of adults over 65 years in Western populations have aortic valve sclerosis, which can progress to stenosis [1]. Untreated severe AS has a 5-year event-free survival below 40%, and severe AS has been estimated to cause more than 100,000 excess deaths worldwide each year [1, 4]. Populations are ageing, so the number of patients will keep rising [2, 4].

An active disease without a drug

CAVS is no longer seen as passive wear. Oxidative stress from uncoupled nitric oxide synthase, chronic inflammation, lipoprotein deposition and osteogenic signalling through bone morphogenetic protein-2 all drive calcification of the leaflets [1, 5]. The disease has two phases. In the *initiation* phase, endothelial injury, lipid entry and inflammation dominate. In the *propagation* phase, calcification sustains itself and mechanical stress becomes more important [1, 5].

Despite this, no drug has been shown to slow CAVS. Treatment is still surgical or transcatheter aortic valve replacement (AVR), and guidelines make no recommendation for drug therapy in mild or moderate disease [6, 7]. Intensive lipid lowering reduced LDL cholesterol but did not slow AS progression in SEAS, SALTIRE or a pooled analysis of 2,344 patients [8, 9, 10]. Vitamin K2 with vitamin D did not slow valve calcification [11]. The soluble guanylate cyclase activator ataciguat slowed calcium accumulation by about 70% in a small phase 2 trial, and a phase 3 trial (KATALYST-AV) is now enrolling [12, 13]. The Lp(a)-lowering drug pelacarsen reduced lipoprotein(a) but did not reduce cardiovascular events in Lp(a)HORIZON, although valve outcomes were not its target [14]. Desai and Braunwald conclude that new

therapies should target both the valve and the accompanying myocardial damage [1].

Moderate AS is not benign

Patients with moderate AS often spend years in "watchful waiting". This period is not harmless. Moderate AS is linked to higher mortality and a heavy burden of cardiac disease, especially when left ventricular function is reduced [15, 16]. The Généreux staging system grades AS by the damage beyond the valve: left ventricle, left atrium or mitral valve, pulmonary circulation, and right ventricle. Each step up predicts higher mortality (Figure 1) [17]. The same pattern holds in asymptomatic and moderate AS [18, 19], and moderate AS with cardiac damage is now considered to behave like severe AS [20].

Recent trials show that early AVR improves outcomes in asymptomatic *severe* AS [35, 36]. In moderate AS with heart failure and reduced ejection fraction, however, TAVR was not superior to medical therapy (TAVR UNLOAD) [27]. A drug that slows both the valve and the myocardium in moderate AS would fill this gap [1, 38].

Why SGLT2 inhibitors?

SGLT2 inhibitors (SGLT2i) reduce heart failure events and death across the range of ejection fraction [21, 22]. They lower preload and afterload by promoting natriuresis and glycosuria, and experimental and clinical studies suggest antifibrotic, antioxidant and anti-inflammatory effects [1, 24]. These effects match both arms of AS: the valve (inflammation, oxidative stress) and the pressure-loaded ventricle (hypertrophy, fibrosis) (Figure 2).

The clinical evidence so far is promising but limited:

- **After TAVR (DapaTAVI):** dapagliflozin reduced death or worsening heart failure (15.0% vs 20.1%; HR 0.72, 95% CI 0.55–0.95) [23]. This tested the myocardium after valve replacement, not valve progression.
- **Non-severe AS (retrospective):** among 11,698 patients, SGLT2i users were less likely to progress to severe AS (HR 0.61, 95% CI 0.39–0.94), and the association strengthened with longer use (HR 0.27 beyond 12 months) [24]. However, only 11% had moderate AS, median exposure was 0.9 years, and users differed from non-users in diabetes and kidney disease [24, 25].
- **Moderate AS (randomised, ongoing):** a UK trial of 104 patients is testing whether empagliflozin prevents myocardial fibrosis and hypertrophy on cardiac MRI [26]. Its endpoints concern the myocardium, not valve progression.

The gap and the setting

No prospective study has measured valve progression *and* cardiac damage stage in moderate AS according to SGLT2i exposure. A setting with very high diabetes prevalence makes such a study feasible. In Pakistan, for example, the age-standardised prevalence of diabetes in adults was estimated at 31.4% in 2024, the highest in the world [28]. As a result, many patients with AS already take SGLT2i for approved indications.

Aims and hypotheses

Primary aim: to compare the annual change in peak aortic jet velocity between patients with moderate CAVS who do and do not take SGLT2i.

Secondary aims: to compare changes in mean gradient, aortic valve area, cardiac damage stage, myocardial function and clinical events.

Primary hypothesis: SGLT2i use is associated with at least a 30% slower annual increase in peak aortic jet velocity.

Secondary hypothesis: SGLT2i use is associated with fewer patients advancing one or more cardiac damage stages over 24 months.

Methods and analysis

Study design

SLOW-AS (SGLT2 inhibition and Longitudinal Worsening of Aortic Stenosis) is a prospective, multicentre, observational cohort study. Its design follows the target-trial emulation framework: eligibility criteria, exposure groups, time zero and outcomes are defined as they would be in a randomised trial [33]. Reporting will follow the STROBE statement [34]. The protocol will be registered on ClinicalTrials.gov before the first patient is enrolled. Figure 3 shows the study flow.

Setting

Patients will be recruited from the echocardiography laboratories and valve clinics of [number] tertiary cardiac centres in [country/cities — to be specified]. Recruitment will run for 24 months, and each patient will be followed for 24 months.

Participants

Consecutive patients with moderate CAVS on a clinical echocardiogram will be screened. Moderate AS is defined using the ACC/AHA and ESC criteria [6, 7, 29]. Table 1 lists the eligibility criteria.

Exposure groups

- **SGLT2i group:** patients taking dapagliflozin, empagliflozin or another SGLT2i at baseline, prescribed by their own physician for an approved indication (type 2 diabetes, heart failure or chronic kidney disease). Drug, dose, start date and indication will be recorded.
- **Comparison group:** eligible patients not taking an SGLT2i, enrolled in a 1:2 ratio (SGLT2i : comparison), stratified by centre and diabetes status.

The study does not influence prescribing. Adherence will be measured at each visit by self-report and pharmacy refill records; a proportion of days covered of 80% or more defines adherent use. Patients who start or stop an SGLT2i during follow-up remain in their baseline group for the primary analysis and are handled in sensitivity analyses (see Secondary and sensitivity analyses).

Echocardiography

Echocardiograms will follow the EACVI/ASE recommendations for AS [29]. Each study will record:

- **Valve:** peak aortic jet velocity from multiple windows (apical, right parasternal, suprasternal), mean gradient, LVOT diameter, aortic valve area by the continuity equation, Doppler velocity index and stroke volume index.

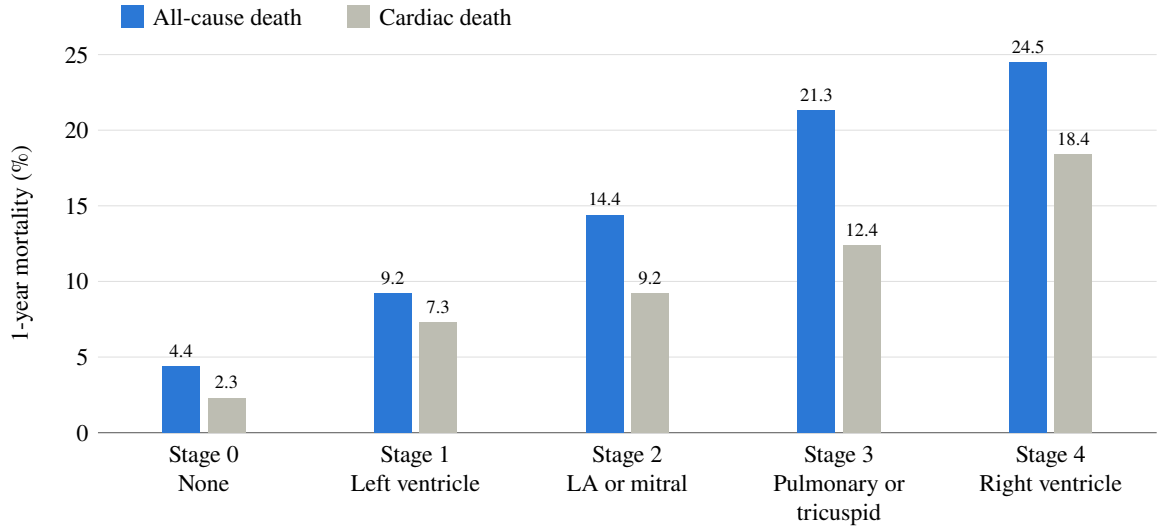


Figure 1: One-year all-cause and cardiac mortality by Généreux cardiac damage stage in patients with severe AS. All-cause mortality rises more than fivefold from stage 0 (4.4%) to stage 4 (24.5%). Data from Généreux et al. [17], as reproduced in Desai and Braunwald [1].

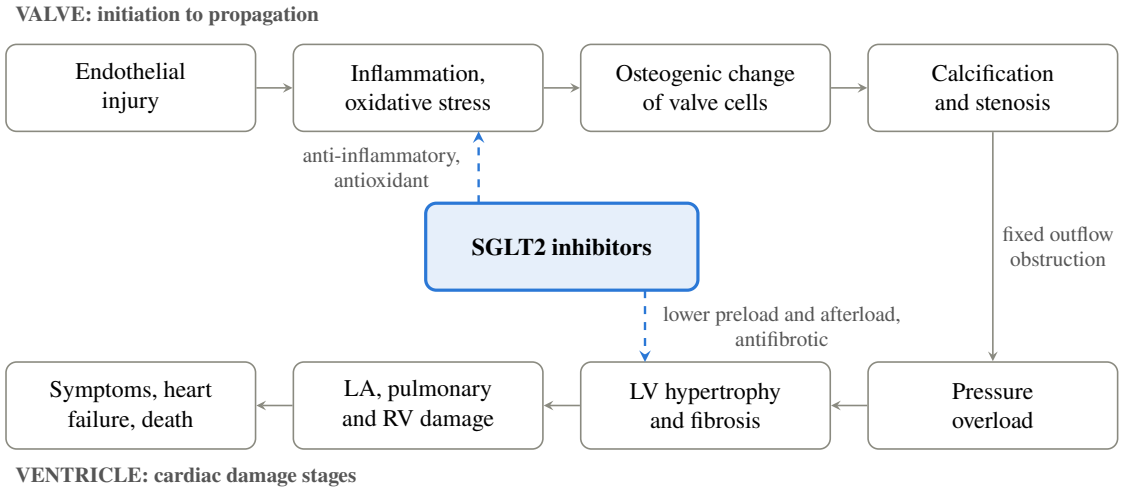


Figure 2: Conceptual model of the study. The valve lesion drives pressure overload and progressive cardiac damage (solid arrows). SGLT2i may act on both the valve (inflammation, oxidative stress) and the ventricle (loading conditions, fibrosis); these hypothesised targets (dashed) are tested in SLOW-AS. Adapted from Desai and Braunwald [1] and Généreux et al. [17].

Table 1: Eligibility criteria

Inclusion criteria	**Exclusion criteria**
Age 50 years or older	Bicuspid or unicuspid aortic valve, suspected or confirmed
Peak aortic jet velocity 3.0–3.9 m/s **or** mean gradient 20–39 mmHg, **and** aortic valve area 1.0–1.5 cm^2 (with consistent indexed values)	Rheumatic valve disease (commissural fusion)
Calcific, trileaflet valve on echocardiography	Previous aortic valve replacement or balloon valvuloplasty, or AVR planned within 6 months
Left ventricular ejection fraction $\geq$50%	More than moderate mitral or aortic regurgitation, or mitral stenosis
Adequate acoustic windows for Doppler assessment	eGFR $<$25 mL/min/1.73 m^2, or on dialysis
Written informed consent	Type 1 diabetes
	Hypertrophic, infiltrative (e.g., amyloid) or other primary cardiomyopathy
	Previous mediastinal or chest radiation
	Life expectancy $<$2 years from non-cardiac disease; pregnancy

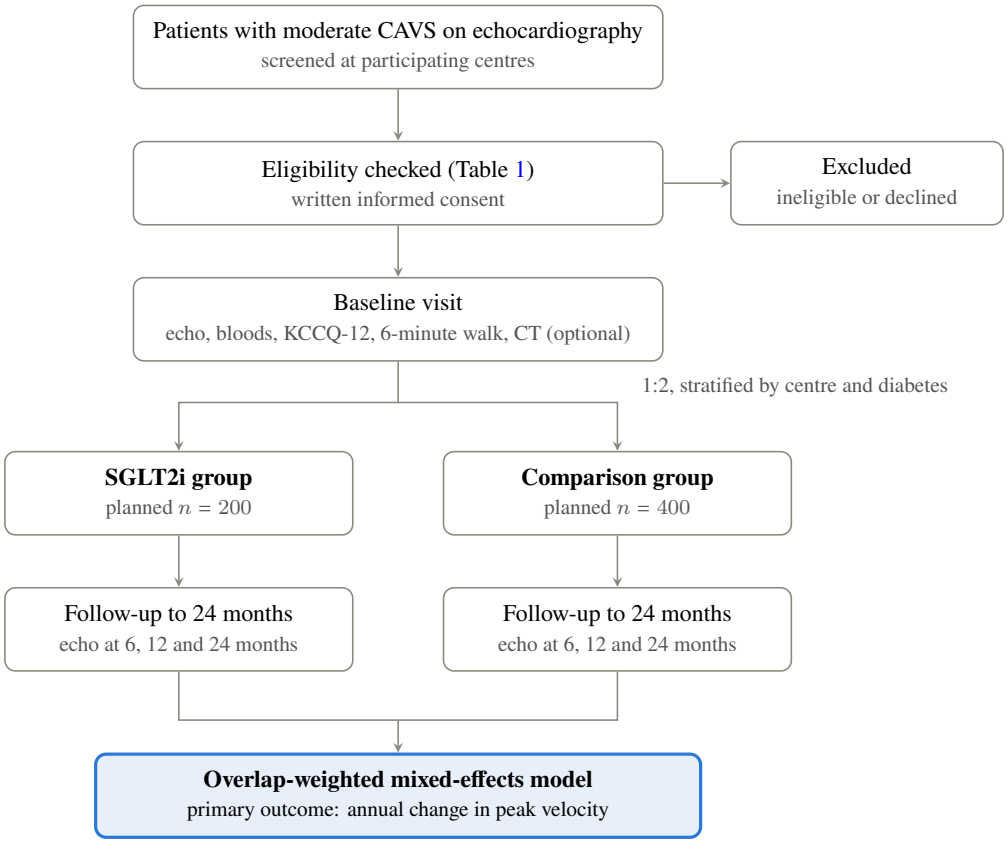


Figure 3: Study flow. Patients are allocated to a group according to whether they already take an SGLT2i. Both groups follow the same visit schedule and are analysed together with overlap weighting. Numbers are planned; actual counts will be reported in a STROBE flow diagram.

- **Left ventricle:** ejection fraction (biplane Simpson), LV mass index, relative wall thickness, global longitudinal strain by speckle tracking [30], and E/e′.
- **Extravalvular:** indexed left atrial volume, mitral regurgitation grade, systolic pulmonary artery pressure, tricuspid regurgitation grade, TAPSE and right ventricular function, and atrial fibrillation on ECG.

All images will be sent to a central core laboratory. Two readers, blinded to SGLT2i status and visit order, will measure each study. Inter- and intra-observer agreement will be assessed on a random 10% of studies using intraclass correlation coefficients. Each patient will be assigned a Généreux cardiac damage stage (0–4) at each visit [17, 18]. **Optional CT sub-study:** where non-contrast CT is available, the aortic valve calcium score (Agatston units) will be measured at baseline and 24 months [31].

Other measurements

- **Laboratory:** NT-proBNP, high-sensitivity troponin, HbA1c, creatinine and eGFR, lipid profile, lipoprotein(a) (once), calcium, phosphate and high-sensitivity C-reactive protein.
- **Function and symptoms:** NYHA class, Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and 6-minute walk distance.
- **Covariates:** age, sex, body mass index, blood pressure, smoking, diabetes duration and treatment, coronary disease, atrial fibrillation, and all cardiovascular drugs, including statins, renin–angiotensin inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors.

Outcomes

Table 2 defines the primary and secondary outcomes. Clinical events will be adjudicated by an events committee blinded to SGLT2i status.

Schedule of assessments

Data management

Data will be entered into a secure electronic database (e.g., REDCap) with built-in range checks. Patient identifiers will be stored separately from study data. A monitor will verify 10% of records against source documents at each site.

Sample size and statistical analysis

Sample size

The study requires 600 patients (200 SGLT2i, 400 comparison) to detect a 30% slower annual rise in peak velocity with 80% power. The calculation uses the natural history reported by Otto et al., in whom peak aortic jet velocity increased by a mean of 0.32 m/s per year with a standard deviation of 0.34 m/s per year [32]. We assumed a slightly lower rate of 0.30 m/s per year in the comparison group and retained the standard deviation of 0.34. A 30% reduction therefore corresponds to a difference (Δ) of 0.09 m/s per year. This target is supported by the retrospective HR of 0.61 for progression to severe AS [24].

For a two-sided test with $\alpha = 0.05$, 80% power and a 1:2

Table 2: Study outcomes

Outcome	Definition	Time point
Primary		
Valve progression	Annual change in peak aortic jet velocity (m/s per year), from all visits	Baseline to 24 months
Secondary: valve		
Mean gradient	Annual change (mmHg per year)	Baseline to 24 months
Aortic valve area	Annual change (cm^2 per year)	Baseline to 24 months
Progression to severe AS	Peak velocity $\geq$4.0 m/s, mean gradient $\geq$40 mmHg, or AVA $<$1.0 cm^2 with consistent findings	Time to event
Valve calcium (CT sub-study)	Annual change in Agatston score	Baseline to 24 months
Secondary: myocardium		
Cardiac damage stage	Advance of one or more stages	24 months
Global longitudinal strain	Change (absolute %)	Baseline to 24 months
LV mass index	Change (g/m^2)	Baseline to 24 months
NT-proBNP	Change (log-transformed)	Baseline to 24 months
Secondary: clinical		
Clinical composite	First of AVR, hospitalisation for heart failure, or cardiovascular death	Time to event
All-cause death	Death from any cause	Time to event
Quality of life and function	Change in KCCQ-12 score and 6-minute walk distance	Baseline to 24 months
Safety		
Adverse events	Genital infection, volume depletion, acute kidney injury, ketoacidosis	Throughout

Table 3: Schedule of assessments

Assessment	Screening	Baseline	6 mo	12 mo	18 mo	24 mo
Eligibility check and consent	✓					
History, medications, NYHA class		✓	✓	✓	✓	✓
SGLT2i use and adherence		✓	✓	✓	✓	✓
Transthoracic echocardiogram	✓	✓	✓	✓		✓
ECG		✓		✓		✓
NT-proBNP and troponin		✓		✓		✓
HbA1c, eGFR, electrolytes		✓	✓	✓	✓	✓
Lipids, Lp(a), CRP, calcium, phosphate		✓				✓[a]
KCCQ-12 and 6-minute walk		✓		✓		✓
CT valve calcium (sub-study)		✓				✓
Clinical events and safety			✓	✓	✓	✓

[a] Lp(a) is measured at baseline only. The 18-month visit may be conducted by telephone. The screening echocardiogram may serve as the baseline study if performed within 30 days and of core-laboratory quality.

allocation ratio ($k = 2$), the number of SGLT2i patients is

$$n_{\mathrm{SGLT2i}} = \left(1 \;\; \frac{1}{k}\right) \frac{\left(z_{1-\alpha 2} \;\; z_{1-\beta}\right)^2 \sigma^2}{\Delta^2} = 1.5 \times \frac{1.960 \;\; 0.842^2 \times 0.34^2}{0.09^2} \approx 169. \tag{1}$$

This gives 169 SGLT2i and 338 comparison patients (507 analysable). Allowing about 15% for death, AVR before the 12-month echocardiogram and loss to follow-up, we will enrol 600 (200 and 400). Because the mixed model (see Primary analysis) uses all repeated echocardiograms, true power should be slightly higher. Figure 4 shows power across plausible effect sizes.

Primary analysis

Confounding control. A propensity score for SGLT2i use will be estimated by logistic regression including age, sex, diabetes and HbA1c, eGFR, heart failure history, coronary disease, hypertension, body mass index, baseline peak velocity, LV mass index, cardiac damage stage, statin use, renin–angiotensin inhibitor use, Lp(a), calcium–phosphate product and centre. The primary analysis will use **overlap weighting**, which provides good balance and stable weights when groups differ substantially. Balance will be accepted if every standardised mean difference is below 0.1.

Model. The primary outcome will be analysed with a weighted linear mixed-effects model:

$$V_{ij} = \beta_0 \;\; \beta_1 t_{ij} \;\; \beta_2 G_i \;\; \beta_3 \left(G_i \times t_{ij}\right) \;\; b_{0i} \;\; b_{1i} t_{ij} \;\; \varepsilon_{ij}, \tag{2}$$

where V_{ij} is the peak velocity of patient i at visit j, t_{ij} is time from baseline in years, G_i is SGLT2i group, b_{0i} and b_{1i} are patient-level random intercept and slope, and ε_{ij} is residual error. The coefficient β_3 is the treatment effect: the between-group difference in annual progression. Robust standard errors will be used. The model will be fitted by restricted maximum likelihood, which gives valid estimates under a missing-at-random assumption.

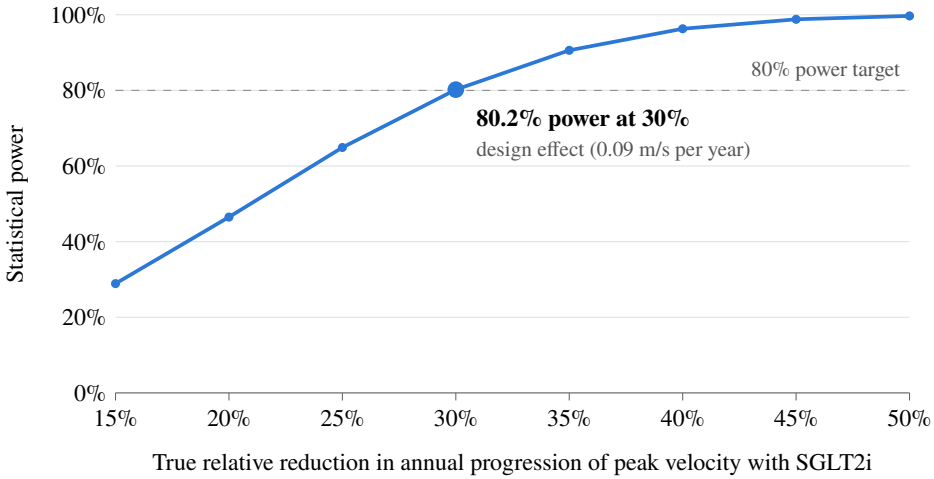


Figure 4: Power to detect slower valve progression with 507 analysable patients (169 SGLT2i vs 338 comparison; control progression 0.30 m/s per year, SD 0.34, two-sided $\alpha = 0.05$). Power is adequate for effects of 30% or more and falls quickly below 25%. Natural-history inputs from Otto et al. [32].

Secondary and sensitivity analyses

- **Continuous secondary outcomes** (gradient, valve area, strain, LV mass index, log NT-proBNP, KCCQ-12) will use the same mixed model.
- **Cardiac damage stage:** advance of one or more stages by 24 months will be analysed with weighted logistic regression; stage over time will also be analysed with an ordinal mixed model.
- **Time-to-event outcomes** (severe AS, clinical composite, death) will use weighted Cox models with Kaplan–Meier curves. AVR and non-cardiovascular death will be treated as competing risks using the Fine–Gray model.
- **Exposure duration:** cumulative SGLT2i exposure will be modelled as a time-varying variable, to examine whether longer use is linked to slower progression, as reported previously [24].
- **Active comparator:** in patients with type 2 diabetes, SGLT2i users will be compared with DPP-4 inhibitor users to limit confounding by diabetes severity.
- **New users:** the analysis will be repeated in patients who started an SGLT2i within 6 months before baseline.
- **Unmeasured confounding:** E-values will be reported.
- **Missing data:** missing covariates will be handled by multiple imputation (20 datasets); a pattern-mixture model will test robustness to data missing not at random.

Pre-specified subgroups

Subgroups are diabetes status, sex, baseline peak velocity (<3.5 vs ≥ 3.5 m/s), baseline cardiac damage stage (0–1 vs ≥ 2), eGFR (<60 vs ≥ 60 mL/min/1.73 m^2) and SGLT2i agent. Effect modification will be tested with interaction terms and displayed as a forest plot.

Interim analysis and software

There will be no efficacy interim analysis. An independent safety monitoring committee will review adverse events every 6 months. Analyses will be performed in R (packages `lme4`, `PSweight`, `survival` and `cmprsk`). The statistical analysis plan will be finalised before database lock.

Results (template for completion)

No data have been collected. The tables below are empty templates for the planned report; they must be completed only with measured study data.

Participant flow

Of [N] patients screened, [N] were eligible and [N] were enrolled: [N] in the SGLT2i group and [N] in the comparison group. [N] completed 24-month follow-up. Reasons for exclusion and loss to follow-up will be shown in a STROBE flow diagram updated from Figure 3.

Baseline characteristics

Primary and secondary continuous outcomes

Clinical and staging outcomes

Additional figures planned for the final report: mean peak velocity by visit and group, Kaplan–Meier curves for progression to severe AS, and a subgroup forest plot.

Discussion

What this study adds

SLOW-AS is designed to test, prospectively and with blinded core-laboratory imaging, whether SGLT2i use is associated with slower progression of moderate AS. Current evidence points in the same direction but comes from different settings and endpoints (Figure 5). DapaTAVI showed a benefit for the myocardium after valve replacement [23]. The retrospective study by Shah et al. suggested slower valve progression, but in a mostly sclerotic population with short exposure [24]. The ongoing UK trial examines only the myocardium [26]. Table 7 compares SLOW-AS with these studies.

Table 4: Baseline characteristics by SGLT2i use (template)

Characteristic	**SGLT2i** (n =)	**Comparison** (n =)	**SMD before weighting**	**SMD after weighting**
Age, years, mean (SD)				
Female sex, n (%)				
Body mass index, kg/m^2, mean (SD)				
Type 2 diabetes, n (%)				
HbA1c, %, mean (SD)				
eGFR, mL/min/1.73 m^2, mean (SD)				
Hypertension, n (%)				
Coronary artery disease, n (%)				
Heart failure history, n (%)				
Statin use, n (%)				
Lipoprotein(a), nmol/L, median (IQR)				
NT-proBNP, pg/mL, median (IQR)				
Peak aortic jet velocity, m/s, mean (SD)				
Mean gradient, mmHg, mean (SD)				
Aortic valve area, cm^2, mean (SD)				
LV ejection fraction, %, mean (SD)				
Global longitudinal strain, %, mean (SD)				
LV mass index, g/m^2, mean (SD)				
Cardiac damage stage 0/1/2/3/4, n (%)				

SMD = standardised mean difference.

Table 5: Valve and myocardial outcomes (template)

Outcome (per year)	**SGLT2i** (95% CI)	**Comparison** (95% CI)	**Weighted difference** (95% CI)	P
Peak aortic jet velocity, m/s (primary)				
Mean gradient, mmHg				
Aortic valve area, cm^2				
Global longitudinal strain, %				
LV mass index, g/m^2				
log NT-proBNP				
Valve calcium score, AU (CT sub-study)				

Table 6: Events at 24 months (template)

Outcome	**SGLT2i** n (%)	**Comparison** n (%)	**Weighted HR or OR** (95% CI)	P
Advance of $\geq$1 cardiac damage stage				
Progression to severe AS				
Clinical composite (AVR, HF hospitalisation, CV death)				
Aortic valve replacement				
Hospitalisation for heart failure				
All-cause death				
Safety events (any)				

How SGLT2i might act on the valve and the myocardium

Two routes are plausible, and the study is designed to distinguish them (Figure 2). First, a **valve route**: reduced inflammation and oxidative stress could slow the osteogenic transformation of valve interstitial cells, the same pathways that Desai and Braunwald identify as drivers of progression [1, 5]. Second, a **myocardial route**: reduced preload and afterload, less hypertrophy and less fibrosis could protect the pressure-overloaded ventricle [21, 22, 23].

If SGLT2i slow cardiac damage staging but not peak velocity, the benefit is mainly myocardial. If both slow, SGLT2i may offer the "two targets with one drug" therapy proposed in the editorial accompanying Shah et al. [25]. Genetic studies linking CAVS to adiposity and metabolic pathways add biological plausibility for a metabolically active drug [37].

Clinical implications

A positive result would not change practice by itself. It would justify a randomised, placebo-controlled trial of SGLT2i in moderate AS, designed using the effect size and variance measured here. A neutral result would also be informative: patients with moderate AS who need an SGLT2i for diabetes or heart failure could take it without expecting a valve benefit, and trial resources could be directed elsewhere. In either

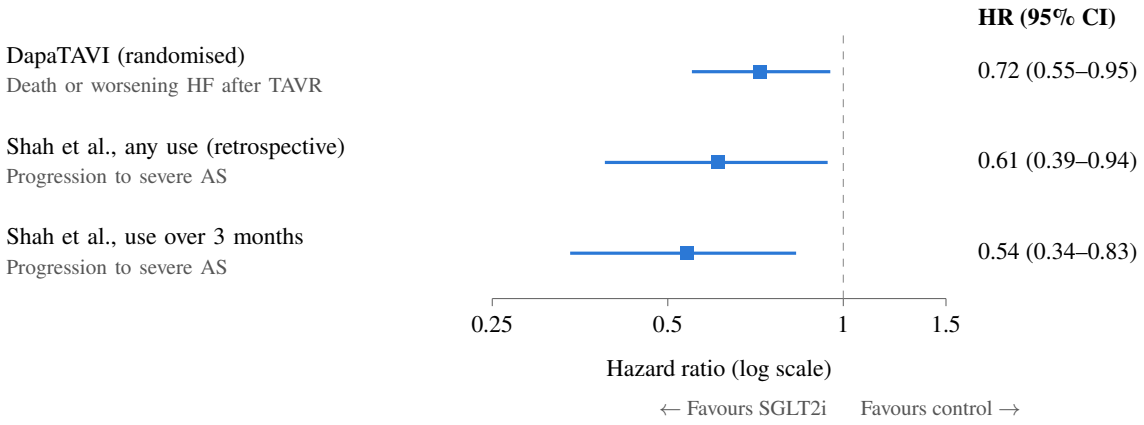


Figure 5: Published hazard ratios for SGLT2i in aortic stenosis. All favour benefit, but none comes from a prospective study of valve progression in moderate AS. Endpoints differ, so estimates are shown side by side and not pooled. Data from Raposeiras-Roubin et al. [23] and Shah et al. [24].

Table 7: SLOW-AS compared with existing and ongoing evidence

Study	Design	Population	Size	Main endpoint	Valve progression?	Damage stage?
DapaTAVI [23]	Randomised trial	Severe AS undergoing TAVR	See [23]	Death or worsening heart failure	No (valve replaced)	No
Shah et al. [24]	Retrospective cohort, target-trial emulation	Sclerosis 66%, mild 23%, moderate 11%	11,698	Progression to severe AS	Yes (routine echo)	No
UEA trial, NCT06469645 [26]	Randomised trial	Moderate AS	104	Myocardial fibrosis and hypertrophy (MRI)	No	No
KATALYST-AV [13]	Randomised trial (ataciguat)	Moderate CAVS	1,276	Valve calcium, valve area, peak VO_2	Yes	No
SLOW-AS	Prospective cohort, target-trial emulation	Moderate CAVS only, LVEF $\geq$50%	600	Annual change in peak velocity	Yes (blinded core lab)	Yes

case, the study will provide the first prospective natural-history data on moderate AS in a South Asian population, where diabetes and kidney disease—both linked to faster progression—are highly prevalent [24, 28].

Strengths

- Only moderate AS is enrolled, using standard guideline thresholds [6, 7].
- Valve and myocardial outcomes are measured together, using the Généreux stages [17].
- Measurements are read by a blinded core laboratory with multi-window Doppler [29].
- Multiple sensitivity analyses address confounding: overlap weighting, an active comparator, a new-user cohort and E-values.

Limitations

- **Confounding by indication.** SGLT2i users will have more diabetes, kidney disease or heart failure. These conditions themselves accelerate AS, which would bias results *toward the null*. Unmeasured differences may persist despite weighting.
- **Non-randomised design.** The study can show association, not causation.
- **Echocardiography only for most patients.** Peak velocity depends on flow and measurement technique. CT calcium scoring, which reflects calcification biology more directly, is optional [31].
- **24-month follow-up.** Progression is slow, and clinical events may be too few for firm conclusions on hard endpoints.
- **Exclusions.** Bicuspid valves are excluded, so results will not apply to them.

Table 8: Study timeline

Phase	Months
Ethics approval, registration, site set-up	1–6
Recruitment	7–30
Follow-up of last patient	31–54
Database lock and analysis	55–58
Manuscript submission	59–60

Timeline

Ethics and dissemination

Ethics. The protocol will be submitted to the ethics review committee of each participating centre and will follow the Declaration of Helsinki. All patients will give written informed consent in their preferred language. The study is observational: SGLT2i are prescribed by treating physicians for approved indications only, and no drug is supplied or withheld for research purposes.

Confidentiality. Data will be pseudonymised. Only the site team will hold the key linking study identifiers to identities. **Dissemination.** Results will be submitted to a peer-reviewed cardiology journal and presented at national and international meetings, regardless of the direction of the findings. De-identified data will be available on reasonable request after publication.

Conclusion

CAVS has no disease-modifying drug, and moderate AS carries real risk to the heart and to survival [1, 15, 16, 17, 18, 19, 20]. SGLT2i act on pathways that drive both the valve lesion and ventricular damage, and early data suggest slower progression [23, 24]. SLOW-AS will provide the first prospective, core-laboratory evidence on whether SGLT2i use is associated with slower valve and myocardial progression in moderate AS, and its results will inform the design of a definitive randomised trial.

Declarations

- **Author contributions:** [to be completed using the CRediT taxonomy]
- **Funding:** [to be completed]
- **Competing interests:** [to be completed]
- **Trial registration:** ClinicalTrials.gov [number pending]
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References

[1] Desai, M. Y., & Braunwald, E. (2025). The pathophysiologic basis and management of calcific aortic valve stenosis: JACC state-of-the-art review. *Journal of the American College of Cardiology, 86*(9), 659–672.

[2] Lindman, B. R., Clavel, M.-A., Mathieu, P., Iung, B., Lancellotti, P., Otto, C. M., & Pibarot, P. (2016). Calcific aortic stenosis. *Nature Reviews Disease Primers, 2*, 16006.

[3] Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., & Enriquez-Sarano, M. (2006). Burden of valvular heart diseases: A population-based study. *The Lancet, 368*(9540), 1005–1011.

[4] Yadgir, S., Johnson, C. O., Aboyans, V., Adebayo, O. M., Adedoyin, R. A., Afarideh, M., Alahdab, F., Alashi, A., Alipour, V., Arabloo, J., Azari, S., Barthelemy, C. M., Benziger, C. P., Berman, A. E., Bijani, A., Carrero, J. J., Carvalho, F., Daryani, A., Durães, A. R., . . . Roth, G. A. (2020). Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990–2017. *Circulation, 141*(21), 1670–1680.

[5] Pawade, T. A., Newby, D. E., & Dweck, M. R. (2015). Calcification in aortic stenosis: The skeleton key. *Journal of the American College of Cardiology, 66*(5), 561–577.

[6] Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P., III, Gentile, F., Jneid, H., Krieger, E. V., Mack, M., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M., III, Thompson, A., & Toly, C. (2021). 2020 ACC/AHA guideline for the management of patients with valvular heart disease: Executive summary. *Journal of the American College of Cardiology, 77*(4), 450–500.

[7] Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S., Bauersachs, J., Capodanno, D., Conradi, L., De Bonis, M., De Paulis, R., Delgado, V., Freemantle, N., Gilard, M., Haugaa, K. H., Jeppsson, A., Jüni, P., Pierard, L., Prendergast, B. D., Sádaba, J. R., . . . Wojakowski, W. (2022). 2021 ESC/EACTS guidelines for the management of valvular heart disease. *European Heart Journal, 43*(7), 561–632.

[8] Rossebø, A. B., Pedersen, T. R., Boman, K., Brudi, P., Chambers, J. B., Egstrup, K., Gerdts, E., Gohlke-Bärwolf, C., Holme, I., Kesäniemi, Y. A., Malbecq, W., Nienaber, C. A., Ray, S., Skjaerpe, T., Wachtell, K., Willenheimer, R., & SEAS Investigators. (2008). Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *New England Journal of Medicine, 359*(13), 1343–1356.

[9] Cowell, S. J., Newby, D. E., Prescott, R. J., Bloomfield, P., Reid, J., Northridge, D. B., & Boon, N. A. (2005). A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *New England Journal of Medicine, 352*(23), 2389–2397.

[10] Teo, K. K., Corsi, D. J., Tam, J. W., Dumesnil, J. G., & Chan, K. L. (2011). Lipid lowering on progression of mild to moderate aortic stenosis: Meta-analysis of the randomized placebo-controlled clinical trials on 2344 patients. *Canadian Journal of Cardiology, 27*(6), 800–808.

[11] Diederichsen, A. C. P., Lindholt, J. S., Møller, S., Øvrehus, K. A., Auscher, S., Lambrechtsen, J., Hosbond, S. E., Alan, D. H., Urbonaviciene, G., Becker, S. W., Fredgart, M. H., Hasific, S., Folkestad, L., Gerke, O., Rasmussen, L. M., Møller, J. E., Mickley, H., & Dahl, J. S. (2022). Vitamin K2 and D in patients with aortic valve calcification: A randomized double-blinded clinical trial. *Circulation, 145*(18), 1387–1397.

[12] Zhang, B., Enriquez-Sarano, M., Schaff, H. V., Michelena, H. I., Roos, C. M., Hagler, M. A., Zhang, H., Casaclang-Verzosa, G., Huang, R., Bartoo, A., Ranadive, S., Joyner, M. J., Pislaru, S., Nkomo, V. T., Kremers, W. K., Araoz, P. A., Singh, G., Walters, M. A., Hawkinson, J., . . . Miller, J. D. (2025). Reactivation of oxidized soluble guanylate cyclase as a novel treatment strategy to slow progression of calcific aortic valve stenosis: Preclinical and randomized clinical trials to assess safety and efficacy. *Circulation, 151*(13), 913–930.

[13] Kardigan, Inc. (2025). *Ataciguat for slowing the progression of moderate calcific aortic valve stenosis (KATALYST-AV)* (ClinicalTrials.gov Identifier NCT07001800).

[14] Novartis. (2026, September 4). *Novartis announces Lp(a)HORIZON Phase III topline results for pelacarsen in patients with elevated Lp(a) and established cardiovascular disease (CVD)* [Press release]. https://www.novartis.com/us-en/news/media-releases/novartis-announces-lpahorizon-phase-iii-topline-results-pelacarsen-patients-elevated-lpa-and-established-cardiovascular-disease-cvd

[15] Morelli, M., Galasso, M., Esposito, G., Soriano, F. S., Nava, S., Da Pozzo, C., Bossi, I., Piccaluga, E., Bruschi, G., Maloberti, A., Oliva, F., Oreglia, J. A., Giannattasio, C., & Montalto, C. (2023). Natural history and clinical burden of moderate aortic stenosis: A systematic review and explorative meta-analysis. *Journal of Cardiovascular Medicine, 24*(9), 659–665.

[16] Khan, K. R., Khan, O. A., Chen, C., Liu, Y., Kandanelly, R. R., Jamiel, P. J., Tanguturi, V., Hung, J., Inglessis, I., Passeri, J. J., Langer, N. B., & Elmariah, S. (2023). Impact of moderate aortic stenosis in patients with heart failure with reduced ejection fraction. *Journal of the American College of Cardiology, 81*(13), 1235–1244.

[17] Généreux, P., Pibarot, P., Redfors, B., Mack, M. J., Makkar, R. R., Jaber, W. A., Svensson, L. G., Kapadia, S., Tuzcu, E. M., Thourani, V. H., Babaliaros, V., Herrmann, H. C., Szeto, W. Y., Cohen, D. J., Lindman, B. R., McAndrew, T., Alu, M. C., Douglas, P. S., Hahn, R. T., . . . Leon, M. B. (2017). Staging classification of aortic stenosis based on the extent of cardiac damage. *European Heart Journal, 38*(45), 3351–3358.

[18] Tastet, L., Tribouilloy, C., Maréchaux, S., Vollema, E. M., Delgado, V., Salaun, E., Shen, M., Capoulade, R., Clavel, M.-A., Arsenault, M., Bédard, É., Bernier, M., Beaudoin, J., Narula, J., Lancellotti, P., Bax, J. J., Généreux, P., & Pibarot, P. (2019). Staging cardiac

damage in patients with asymptomatic aortic valve stenosis. *Journal of the American College of Cardiology, 74*(4), 550–563.

[19] Amanullah, M. R., Pio, S. M., Ng, A. C. T., Sin, K. Y. K., Ajmone Marsan, N., Ding, Z. P., Leon, M. B., Généreux, P., Delgado, V., Ewe, S. H., & Bax, J. J. (2021). Prognostic implications of associated cardiac abnormalities detected on echocardiography in patients with moderate aortic stenosis. *JACC: Cardiovascular Imaging, 14*(9), 1724–1737.

[20] Mihatov, N., & Pibarot, P. (2024). Moderate aortic stenosis with cardiac damage: A new type of severe aortic stenosis. *Structural Heart, 8*(6), 100336.

[21] McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Ponikowski, P., Sabatine, M. S., Anand, I. S., Bělohlávek, J., Böhm, M., Chiang, C.-E., Chopra, V. K., de Boer, R. A., Desai, A. S., Diez, M., Drozdz, J., Dukát, A., Ge, J., . . . Langkilde, A.-M. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. *New England Journal of Medicine, 381*(21), 1995–2008.

[22] Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., Böhm, M., Brunner-La Rocca, H.-P., Choi, D.-J., Chopra, V., Chuquiure-Valenzuela, E., Giannetti, N., Gomez-Mesa, J. E., Janssens, S., Januzzi, J. L., Gonzalez-Juanatey, J. R., Merkely, B., Nicholls, S. J., Perrone, S. V., Piña, I. L., . . . Packer, M. (2021). Empagliflozin in heart failure with a preserved ejection fraction. *New England Journal of Medicine, 385*(16), 1451–1461.

[23] Raposeiras-Roubin, S., Amat-Santos, I. J., Rossello, X., González Ferreiro, R., González Bermúdez, I., Lopez Otero, D., Nombela-Franco, L., Gheorghe, L., Diez, J. L., Baladrón Zorita, C., Baz, J. A., Muñoz García, A. J., Vilalta, V., Ojeda-Pineda, S., de la Torre Hernández, J. M., Cordoba Soriano, J. G., Regueiro, A., Bordes Siscar, P., Salgado Fernández, J., . . . Ibáñez, B. (2025). Dapagliflozin in patients undergoing transcatheter aortic-valve implantation. *New England Journal of Medicine, 392*(14), 1396–1405.

[24] Shah, T., Zhang, Z., Shah, H., Fanaroff, A. C., Nathan, A. S., Parise, H., Lutz, J., Sugeng, L., Bellumkonda, L., Redfors, B., Omerovic, E., Petrie, M. C., Vora, A. N., Fiorilli, P. N., Kobayashi, T., Ahmad, Y., Forrest, J. K., Giri, J. S., Herrmann, H. C., & Lansky, A. J. (2025). Effect of sodium-glucose cotransporter-2 inhibitors on the progression of aortic stenosis. *JACC: Cardiovascular Interventions, 18*(6), 738–748.

[25] Lindman, B. R., & El-Sabawi, B. (2025). SGLT2 inhibition in aortic stenosis: A therapy for the ventricle, the valve, or both? *JACC: Cardiovascular Interventions*.

[26] University of East Anglia. (2024). *The role of sodium glucose co-transporter 2 inhibitors in the management of patients with aortic stenosis* (ClinicalTrials.gov Identifier NCT06469645).

[27] Van Mieghem, N. M., Elmariah, S., Spitzer, E., Pibarot, P., Nazif, T. M., Bax, J. J., Hahn, R. T., Popma, A., Ben-Yehuda, O., Kallel, F., Redfors, B., Chuang, M. L., Alu, M. C., Lindeboom, W., Kolte, D., Zahr, F. E., Kodali, S. K., Strote, J. A., Hermanides, R. S., . . . Leon, M. B. (2025). Transcatheter aortic valve replacement in patients with systolic heart failure and moderate aortic stenosis: TAVR UNLOAD. *Journal of the American College of Cardiology, 85*(9), 878–890.

[28] International Diabetes Federation. (2025). *IDF Diabetes Atlas* (11th ed.): Pakistan country report. https://diabetesatlas.org/data-by-location/country/pakistan

[29] Baumgartner, H., Hung, J., Bermejo, J., Chambers, J. B., Edvardsen, T., Goldstein, S., Lancellotti, P., LeFevre, M., Miller, F., Jr., & Otto, C. M. (2017). Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Journal of the American Society of Echocardiography, 30*(4), 372–392.

[30] Kusunose, K., Goodman, A., Parikh, R., Barr, T., Agarwal, S., Popovic, Z. B., Grimm, R. A., Griffin, B. P., & Desai, M. Y. (2014). Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. *Circulation: Cardiovascular Imaging, 7*(6), 938–945.

[31] Pawade, T., Clavel, M.-A., Tribouilloy, C., Dreyfus, J., Mathieu, T., Tastet, L., Renard, C., Gun, M., Jenkins, W. S. A., Macron, L., Sechrist, J. W., Lacomis, J. M., Nguyen, V., Galian Gay, L., Cuéllar Calabria, H., Ntalas, I., Cartlidge, T. R. G., Prendergast, B., Rajani, R., . . . Dweck, M. R. (2018). Computed tomography aortic valve calcium scoring in patients with aortic stenosis. *Circulation: Cardiovascular Imaging, 11*(3), e007146.

[32] Otto, C. M., Burwash, I. G., Legget, M. E., Munt, B. I., Fujioka, M., Healy, N. L., Kraft, C. D., Miyake-Hull, C. Y., & Schwaegler, R. G. (1997). Prospective study of asymptomatic valvular aortic stenosis: Clinical, echocardiographic, and exercise predictors of outcome. *Circulation, 95*(9), 2262–2270.

[33] Hernán, M. A., & Robins, J. M. (2016). Using big data to emulate a target trial when a randomized trial is not available. *American Journal of Epidemiology, 183*(8), 758–764.

[34] von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & STROBE Initiative. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *The Lancet, 370*(9596), 1453–1457.

[35] Généreux, P., Schwartz, A., Oldemeyer, J. B., Pibarot, P., Cohen, D. J., Blanke, P., Lindman, B. R., Babaliaros, V., Fearon, W. F., Daniels, D. V., Chhatriwalla, A. K., Kavinsky, C., Gada, H., Shah, P., Szerlip, M., Dahle, T., Goel, K., O'Neill, W., Sheth, T., . . . Leon, M. B. (2025). Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *New England Journal of Medicine, 392*(3), 217–227.

[36] Loganath, K., Craig, N. J., Everett, R. J., Bing, R., Tsampasian, V., Molek, P., Botezatu, S., Aslam, S., Lewis, S., Graham, C., White, A. C., MacGillivray, T., Tuck, C. E., Rayson, P., Cranley, D., Irvine, S., Armstrong, R., Milne, L., Chin, C. W. L., . . . Dweck, M. R. (2025). Early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis: The EVOLVED randomized clinical trial. *JAMA, 333*(3), 213–221.

[37] Small, A. M., Peloso, G. M., Linefsky, J., Aragam, J., Galloway, A., Tanukonda, V., Wang, L.-C., Yu, Z., Sunitha Selvaraj, M., Farber-Eger, E. H., Baker, M. T., Setia-Verma, S., Lee, S. S. K., Preuss, M., Ritchie, M. D., Damrauer, S. M., Rader, D. J., Wells, Q. S., Loos, R., . . . O'Donnell, C. J. (2023). Multiancestry genome-wide association study of aortic stenosis identifies multiple novel loci in the Million Veteran Program. *Circulation, 147*(12), 942–955.

[38] Lindman, B. R. (2023). Progression rate of aortic stenosis: Why does it matter? *JACC: Cardiovascular Imaging, 16*(3), 329–331.