

Aortic valve replacement versus clinical surveillance in asymptomatic severe aortic stenosis: A protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION**Support** - Edwards Lifescience: advisor, consultant, speaker fees. PI of EARLY TAVR trial. PI of PROGRESS trial.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - Consultant for 4C Medical, Abbott Vascular, Abiomed, Boston Scientific, Caranx Medical, Edwards Lifesciences, Medtronic, Opsens, Pi-Cardia, Puzzle Medical, Saranas, Shockwave, Soundbite Medical Inc., egnite, Inc., and Teleflex; advisor to Abbott Vascular, Abiomed, Edwards Lifesciences, egnite, Inc., and Medtronic; speaker fees from Abbott Vascular, Abiomed, Medtronic, Shockwave; principal investigator of 4C Medical for the AltaValve feasibility study, Cardiovascular Systems Inc. for the Eclipse Trial, and Edwards Lifesciences for the EARLY-TAVR and PROGRESS trials; equity in Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc.; and proctor for and received institutional grants from Edwards Lifesciences.**INPLASY registration number:** INPLASY202490002**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 September 2024 and was last updated on 07 September 2024.**INTRODUCTION**

Review question / Objective For patients with severe aortic stenosis (sAS) and no symptoms, current American College of Cardiology/American Heart Association guidelines recommend aortic valve replacement (AVR) for patients with decreased ejection fraction (<50%), symptoms on low level stress-test, or the need for concomitant open-heart surgery. Results from new randomized trials will further inform the role of AVR in the management of asymptomatic patients with sAS, especially including for the first time transcatheter aortic valve replacement (TAVR). We therefore conducted a systematic review and a

meta-analysis to evaluate the impact on clinical outcomes of AVR in asymptomatic patients with sAS versus conservative clinical surveillance (CS).

Rationale Data from several observational studies and two randomized trials suggest that timely AVR may confer a prognostic advantage to guideline-based CS for asymptomatic sAS patients. To date, systematic reviews have only included studies which compared the outcomes of surgical AVR (SAVR) versus CS. The present systematic review includes the latest randomized and non-randomized evidence, including more studies compared to previous work to date. The study is also the first to qualitatively assess the strength of

evidence of both TAVR and SAVR against a CS strategy in these patients.

Condition being studied Aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries, often asymptomatic in early stages leading to delayed treatment and increased risk of complications. Current guidelines do not recommend intervention in patients with asymptomatic sAS unless symptoms appear or left ventricular systolic dysfunction occurs. More recently, randomized trials have demonstrated that timely AVR (with SAVR) is associated with improved clinical outcomes over CS in these patients.

METHODS

Search strategy Searches were performed in PubMed and Embase databases on April 15, 2024, using prespecified criteria. Records were captured using a combination of controlled vocabulary and keywords. Vocabulary and syntax were adjusted across databases. For instance, variants of the following phrases: “asymptomatic aortic stenosis,” “severe aortic stenosis,” “aortic valve replacement,” “surgical aortic valve replacement,” “intervention,” “conservative treatment,” and “conservative management” were developed as either Medical Subject Heading (MeSH) terms in PubMed, Emtree terms in Embase, and text words related to AVR in asymptomatic sAS. To ensure all relevant studies were captured, grey literature searches were conducted in [ClinicalTrials.gov](https://www.clinicaltrials.gov) to identify unpublished trial records. References of excluded reviews were manually reviewed for eligibility.

Participant or population Patients with asymptomatic severe or very severe AS.

Intervention Aortic valve replacement, including transcatheter aortic valve replacement and surgical aortic valve replacement.

Comparator Clinical surveillance.

Study designs to be included The systematic review included randomized controlled trials and observational studies (both prospective and retrospective in design).

Eligibility criteria Randomized controlled trials and observational studies were included if they fulfilled the following criteria: 1) asymptomatic patients with severe or very severe AS (sAS) treated with AVR (SAVR or TAVR) or conservative CS 2) availability of clinical outcome data.

Abstracts, review articles, case reports, letters, editorials, and non-journal literature were excluded. For studies with multiple citations available, data from the publication with the largest sample size or study follow-up were collected. The search strategy did not have any restrictions on language, publication date, age, living setting, gender, race, ethnicity, or geographical region of the patient population.

Information sources PubMed and Embase were searched using prespecified criteria from inception until April 15, 2024. Grey literature searches were conducted in [ClinicalTrials.gov](https://www.clinicaltrials.gov) to identify unpublished trial records. Manual searches of conference proceedings were conducted after the search date to identify additional publicly available and forthcoming data.

Main outcome(s) The primary clinical outcome selected for the pooled analyses was all-cause mortality.

Additional outcome(s) The secondary clinical outcomes were cardiovascular mortality, heart failure hospitalization, and stroke.

Data management Subsequent to the literature search and removal of duplicate citations using EndNote Version 21.3 (Clarivate, EndNote, Chandler, Arizona, United States), studies were selected in two phases, title/abstract screening (Phase 1) and full-text screening (Phase 2). Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR Version 2.35 (DistillerSR Inc. 2024, Ottawa, Canada). Subsequently, data were extracted from eligible articles that passed Phase 2 screening using Nested Knowledge (Nested Knowledge, Inc. 2024, St. Paul, Minnesota, United States). The two independent abstractors resolved any disagreement between them by consulting a third reviewer. Data was abstracted on the study population, baseline demographics, interventions, and outcomes of interest.

Quality assessment / Risk of bias analysis Study quality is assessed using the Cochrane Risk of Bias 2 (RoB2) tool and the Newcastle-Ottawa Scale (NOS) for randomized and non-randomized (observational) studies, respectively. Publication bias for each outcome is also assessed using funnel plots and the Egger's linear-regression test.

Strategy of data synthesis A meta-analysis using the inverse variance method was conducted for outcomes of interest using the ‘metafor’ package (V.4-4-0) from R version 4-0-5 (R Foundation for

Statistical Computing, Vienna, Austria). For all outcomes, pooled incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs) were calculated using a random-effects (RE) model. Heterogeneity among the included studies was tested using the I² statistic, representing the percentage of the total variation between studies that cannot be attributed to chance.

Subgroup analysis Subgroup analyses were performed for the following groups: randomized controlled trials versus observational studies, studies where patients underwent AVR within 90 days of initial diagnosis/randomization (i.e., timely AVR), and studies where patients' asymptomatic status was confirmed with a negative exercise test.

Sensitivity analysis Additional analyses were conducted for the outcome of all-cause mortality. The sensitivity analyses included all studies that report either the full study length or a mean or median follow-up time. The primary analysis only used studies that reported either a mean or median follow-up time.

Language restriction No restriction was placed on language.

Country(ies) involved United States.

Other relevant information NA.

Keywords aortic stenosis; aortic valve replacement; surgical valve replacement; transcatheter valve replacement; transcatheter valve implantation; conservative management; clinical surveillance; systematic review; meta-analysis.

Dissemination plans Upon completion of the analysis, a comprehensive manuscript detailing the research methodology, key results, and implications will be drafted. High-impact and peer-reviewed journals focusing on AS will be identified for dissemination of the work.

Contributions of each author

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