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Aortic valve replacement in asymptomatic severe aortic stenosis: A protocol for a systematic review and meta-analysis of observational studies and randomized trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - Institutional research grants from Edwards Lifesciences; Consulting fees Abbott, Cordis, Edwards Lifesciences, Egnite, Haemonetics, Medtronic, Opsens, Puzzle Medical, Pi-Cardia, 4C medical; Equity: Puzzle Medical, Pi-Cardia; PI of EARLY TAVR trial, PI of PROGRESS trial, both sponsored by Edwards Lifesciences.Edwards Lifesciences: Consultant.

INPLASY registration number: INPLASY202530112

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 March 2025 and was last updated on 26 March 2025.

INTRODUCTION

Review question / Objective Current guidelines recommend a strategy of clinical surveillance (CS) for patients with asymptomatic severe aortic stenosis (AS) and normal left ventricular ejection fraction. To date, 4 randomized controlled trials (RCTs) have assessed the role of aortic valve replacement (AVR) in this setting. We performed an updated meta-analysis of RCTs and observational studies to characterize the totality of the evidence comparing AVR versus routine CS in patients with asymptomatic severe AS.

Rationale To date, several observational studies and randomized trials assessing the impact of AVR versus CS on patients with asymptomatic severe AS have shown reductions in all-cause mortality and heart failure (HF) hospitalization with AVR. Most recently, two recent randomized controlled trials (RCTs) have evaluated the effects of timely intervention with both transcatheter AVR (TAVR) and surgical AVR (SAVR) in asymptomatic patients with severe AS. Given these new data, we performed an updated meta-analysis of RCTs and observational studies to characterize the totality of the evidence evaluating AVR (TAVR or SAVR) versus routine CS in these patients. The present systematic review includes many of the latest randomized and non-randomized evidence, including more studies compared to previous work to date.

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.1-3 Current guidelines do not recommend aortic valve replacement (AVR) in severe AS until the development of symptoms or reduced left ventricular ejection fraction, but rely

largely on non-randomized data and expert opinion. In addition, the assessment of symptoms in patients with severe AS is challenging, particularly among older patients.

METHODS

Search strategy We searched PubMed, Embase, and clinicaltrials.gov using prespecified criteria from inception until November 11, 2024. To increase the sensitivity of the search, variants of the 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 severe AS.

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

Intervention AVR (SAVR or TAVR).

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 We included both RCTs and observational studies if they fulfilled the following criteria: 1) asymptomatic patients with severe or very severe AS treated with AVR (SAVR or TAVR) or conservative CS 2) availability of clinical outcome data. We excluded abstracts, review articles, case reports, letters, editorials, and non-journal literature. For instances where studies had multiple publications in sequence, we collected the most recent data. 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 We searched PubMed, Embase, and clinicaltrials.gov using prespecified criteria from inception until November 11, 2024.

Main outcome(s) The primary outcome assessed was all-cause mortality.

Additional outcome(s) Secondary outcomes included cardiovascular mortality, unplanned cardiovascular or HF hospitalizations, and stroke.

Data management Two reviewers independently screened against predefined eligibility criteria in two phases, title/abstract screening (Phase 1) and full-text screening (Phase 2) using DistillerSR Version 2.35 (DistillerSR Inc. 2024, Ottawa, Canada). Disputes were resolved by a third independent reviewer.

Quality assessment / Risk of bias analysis The risk of bias (RoB) of each RCT was assessed using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs. The risk of bias for observational studies was assessed by the Newcastle-Ottawa Scale (NOS). Publication bias was assessed using funnel plots and also using Egger's linear-regression test to test for funnel plot asymmetry.

Strategy of data synthesis A meta-analysis using the inverse variance method will be 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) will be calculated using a random-effects (RE) model. Heterogeneity will be assessed using Higgins I2 statistic.

Subgroup analysis The primary cohort analysis will be conducted using only studies that reported either a mean or median follow-up time, with subgroup analyses performed by study design (i.e., RCTs versus observational studies) for all outcomes of interest. All subgroups will be tested for statistical interaction using the $\chi 2$ statistic. A sensitivity analysis of the primary outcome, including all studies that reported either the full study length or a mean or median follow-up time, was also performed.

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

Language restriction No restriction was placed on language.

Country(ies) involved United States.

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

Dissemination plans Upon completion of the analysis, a 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

Author 1 - Philippe Genereux - Design the study. Data analysis. Manuscript drafting.
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