INPLASY

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 12 October 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 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 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) Secondary clinical outcomes were cardiovascular mortality, unplanned cardiovascular or HF 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 of studies comparing AVR to CS using the DerSimonian and Laird 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 HRs and their corresponding 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity among the included studies was tested using the I2 statistic, representing the percentage of the total variation between studies that could not be attributed to chance.

Subgroup analysis None.

Sensitivity analysis None.

Language restriction No restriction was placed on language.

Country(ies) involved United States.

Other relevant information Additional pooled analyses using the inverse variance method were conducted, utilizing both randomized and non-randomized data. For all outcomes, pooled incidence rate ratios (IRRs) and their corresponding 95% Cis were calculated using a random-effects model. Event rates were standardized to IRRs to account for differences in the overall length of follow-up across observational studies and between treatment arms within studies. To derive IRRs, total person-time was extracted or estimated using the median follow-up time of each treatment arm multiplied by each arm's sample size. For studies that reported a mean follow-up time, the median follow-up was estimated assuming an exponential distribution.

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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