INPLASY

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

INPLASY202490002
doi: 10.37766/inplasy2024.9.0002
Received: 31 August 2024
Published: 1 September 2024

Corresponding author:
Philippe Genereux

philippe.genereux@atlantichealth.org

Author Affiliation:
Gagnon Cardiovascular Institute at Morristown Medical Center.

Genereux, P; Seyedin, R.

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 20 January 2025.

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 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. 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 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 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 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 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 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.

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 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, collected the data, analyzed the data, draft the manuscript.
Email: philippe.genereux@atlantichealth.org
Author 2 - Roxanna seyedin - Design the study, collected the data, analyzed the data, draft the manuscript.
Email: roxyseyedin@gmail.com