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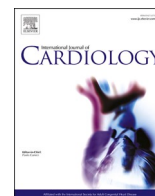
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Early aortic valve replacement versus conservative management in asymptomatic severe aortic stenosis: Meta-analysis of time-to-event data of randomized controlled trials

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ABSTRACT

Background: Current guidelines recommend aortic valve replacement (AVR) for symptomatic patients with severe aortic stenosis (AS), but the optimal timing for intervention in asymptomatic patients is still debated. Recent randomized controlled trials (RCTs) have offered new insights, prompting a reevaluation of the potential benefits of early AVR.

Methods: A systematic review and pooled meta-analysis of Kaplan–Meier-derived reconstructed time-to-event data of RCTs published by November 2024 was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. Outcomes were derived from the primary end-points of the included studies, with the main analysis focusing on all-cause mortality, cardiovascular mortality, and heart failure hospitalization.

Results: Four randomized controlled trials, involving 1427 patients, were included. The early AVR group demonstrated a significant reduction in all-cause mortality (hazard ratio [HR] = 0.72, 95 % confidence interval [CI] 0.53–0.97, $p = 0.031$), cardiovascular mortality (HR = 0.56, 95 % CI 0.36–0.89, $p = 0.014$), and heart failure hospitalization (HR = 0.31, 95 % CI 0.18–0.53, $p < 0.001$). No significant interaction effects between surgical AVR and transcatheter AVR were observed. Additionally, in the conservative management group, the conversion to AVR was substantial, with a median time to conversion of 13.4 months. The cumulative conversion rates were 42.8 % (95 % CI 38.6 %–46.7 %) at 1 year, 82.3 % (95 % CI 78.6 %–85.3 %) at 3 years, and 94.9 % (95 % CI 91.4 %–96.9 %) at 5 years.

Conclusion: Early AVR in asymptomatic patients with severe AS is associated with a significant reduction in all-cause mortality, cardiovascular mortality, and heart failure hospitalization compared to conservative management.

Abbreviations: AS, Aortic stenosis; AVR, Aortic valve replacement; RCT, Randomized clinical trial; IPD, Individual patient data; RMST, Restricted mean survival time; LVEF, Left ventricular ejection fraction.

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1. Introduction

Aortic stenosis (AS) is a progressive and debilitating condition that leads to a significant burden on patients and healthcare systems worldwide [1]. Untreated severe AS is associated with poor long-term outcomes [2]. Current guidelines recommend aortic valve replacement (AVR) for patients with symptomatic severe AS, as this intervention has been shown to reduce morbidity and mortality [3,4]. However, for asymptomatic patients, the decision to perform AVR remains more nuanced, with guidelines suggesting intervention only in certain cases, such as when there is evidence of left ventricular dysfunction or other high-risk features [3–5]. Despite these recommendations, real-world studies have also demonstrated that the adoption of AVR in patients with asymptomatic severe AS remains low [2].

Recent evidence from two new randomized clinical trials (RCT) has expanded our understanding of the optimal timing for AVR, particularly in asymptomatic patients with severe AS [6,7]. These RCTs have prompted a reevaluation of conservative management strategies and have raised questions about whether earlier intervention could provide survival benefits [6,7].

Previous meta-analyses including mostly observational cohort studies have investigated the outcomes of early surgical AVR (SAVR) [8], but critical gaps in evidence remain, particularly regarding the long-term benefits, the comparative effectiveness of surgical versus transcatheter AVR (SAVR vs. TAVR) [9], and the rates of conversion from conservative management to AVR [8]. This study aims to update previous analyses by incorporating data from RCTs only, offering a more robust and comprehensive framework for the current evidence on the effectiveness of early AVR in asymptomatic patients with severe AS.

2. Methods

2.1. Protocol and registration

The present meta-analysis was reported in accordance with published reference guidelines, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplement S1) [10]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024620156). Ethical approval was not required for this study-level meta-analysis.

2.2. Search strategy and selection of studies

Electronic databases (PubMed, Scopus, Embase and CENTRAL) were searched for RCTs published by November 2024. Our search strategy focused on terms related to asymptomatic and severe aortic stenosis, along with keywords associated with aortic valve replacement, transcatheter interventions, and conservative management strategies. The search strategy for each electronic database is available in Supplement S2. In addition, the reference list of eligible studies, and related meta-analyses were searched for additional titles. Titles and abstracts were independently reviewed for eligibility by two authors (X.J, M.P.S). Full-text screening of retrieved reports was performed independently by two authors (X.J, M.P.S), following identical inclusion and exclusion criteria. When there was disagreement, the final decision to include or exclude the study was made in consensus with a third author (I.S).

Inclusion criteria were: (1) the study included patients with severe asymptomatic AS, (2) the patients were randomized to either an AVR strategy or conservative management, and (3) the study must have Kaplan–Meier curves available for individual outcomes. Exclusion criteria consisted of reviews, meta-analyses, case reports/series, one-arm studies, or studies with overlapping samples.

2.3. Endpoints

Outcomes were derived from the primary endpoints of the identified studies. In our analysis, the primary outcome was all-cause mortality, while secondary outcomes included cardiovascular mortality and heart failure-related hospitalization.

2.4. Data extraction and statistical analysis

Data extraction of patient characteristics and Kaplan–Meier curves was performed independently by two reviewers (X.J, M.P.S). Methodologic quality and risk of bias assessment was performed independently by two authors (X.J, M.P.S) using the Cochrane “revised tool for assessing risk of bias in randomised trials” (RoB 2).

The Kaplan–Meier curves were digitized using Web Plot Digitizer software. Reconstructed time-to-event data / individual patient data (IPD) were obtained using the digitized Kaplan–Meier plots and corresponding total number of patients, the total number of events, and the number of patients at risk at various time intervals for each arm respectively [11]. Accuracy of the data was assessed independently by two authors (X.J, M.P.S) (Supplement S3). Hazard ratios (HR) with 95 % confidence intervals (CI) were obtained from a Cox frailty model with robust standard errors. Heterogeneity across trials was assessed for each endpoint by testing for an interaction between the trial and the randomized treatment effect, through the inclusion of a γ frailty term used to account for heterogeneity between trials, with trials modelled as a random effect using random intercepts (Supplement S4). The significance of this variance parameter was assessed with the likelihood ratio test. The respective arms were included in the model as a fixed effect. The proportionality of hazards of each Cox model was checked with the Grambsch–Therneau test and diagnostic plots based on Schoenfeld residuals. The restricted mean survival time (RMST), $\mu(\tau)$, equaling the area under the survival curve from 0 to τ , was calculated for each arm, and the RMST difference, $\Delta(\tau)$, equaling the area between the survival curves, was obtained to provide an absolute dynamic measurement of effect size based on a scale of time [12]. Interaction effects of AVR strategy (surgical AVR or transcatheter AVR) were calculated by the inclusion of an interaction term in the Cox frailty model and the significance of these interaction effects were evaluated using a likelihood ratio test. Significance testing was performed at the two-tailed 5 % significance level. All analyses were completed with R Statistical Software (version 4.1.1, Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Systematic review

A total of 526 publications were identified by the systematic literature search. Of these, 4 studies met the inclusion criteria, with a total of 1427 patients (719 randomized to early AVR, and 708 randomized to conservative management) (Fig. 1) [6,7,13,14]. The study and patient characteristics of the individual RCTs are summarized in Table 1.

In short, the RECOVERY trial (NCT01161732) [13] was a randomized, multicenter study assessing early SAVR versus standard conservative care in asymptomatic patients with very severe AS (aortic valve area ≤ 0.75 cm², aortic valve peak velocity ≥ 4.5 m/s, or mean gradient ≥ 50 mmHg). The primary endpoint—a composite of operative mortality or cardiovascular death during follow-up—showed significantly lower incidence in the early SAVR group. Similarly, the AVATAR trial (NCT02436655) [14] was a randomized, multinational study evaluating early SAVR versus a conservative, watchful waiting approach in asymptomatic patients with severe AS (aortic valve area ≤ 1 cm² or ≤ 0.6 cm²/m², aortic valve peak velocity > 4.0 m/s, or mean gradient ≥ 40 mmHg) and preserved left ventricular ejection fraction (≥ 50 %). The primary endpoint—a composite of all-cause mortality and major adverse

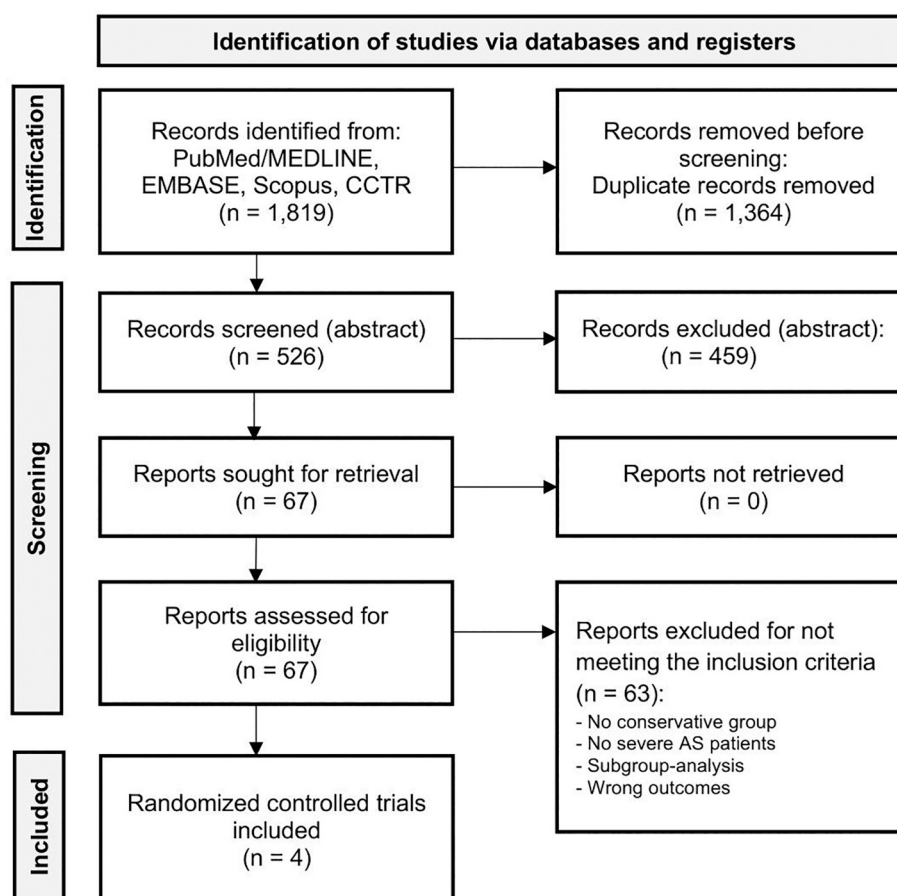


Fig. 1. Flow diagram of included RCTs.

cardiovascular events (MACE), including myocardial infarction, stroke, or unplanned heart failure hospitalization—was significantly lower in the early SAVR group compared to the conservative treatment group. Then, the EARLY TAVR trial (NCT03042104) [7] was a randomized, multicenter study comparing early TAVR with clinical surveillance in patients aged 65 years or older with asymptomatic severe AS and preserved left ventricular ejection fraction ($\geq 50\%$), who met current guideline criteria for watchful waiting. The primary endpoint—a composite of all-cause mortality, stroke, or unplanned cardiovascular hospitalization (including aortic valve intervention within 6 months of randomization)—was significantly reduced in the early TAVR group compared to the clinical surveillance group. Lastly, the EVOLVED trial (NCT03094143) [6] was a randomized, multicenter study comparing early AVR to guideline-directed conservative management in asymptomatic patients with severe AS (aortic valve peak velocity ≥ 4.0 m/s or indexed aortic valve area ≤ 0.6 cm²/m² and aortic valve peak velocity ≥ 3.5 m/s), preserved left ventricular ejection fraction ($\geq 50\%$) and myocardial fibrosis (midwall late gadolinium enhancement). The primary endpoint—a composite of all-cause mortality or unplanned AS-related hospitalization—revealed no significant difference between the early AVR group and the guideline-directed conservative management group. Inclusion and exclusion criteria of all four RCTs are provided in Supplement S5.

These RCTs individually enrolled between 145 and 901 patients from Korea, Europe, North America, the United Kingdom and Australia between 2010 and 2022, with mean ages ranging from 63 to 76 years. Female representation varied from 27 % to 53 %, and mean BMI ranged from 24 to 28.6 kg/m². The risk of bias of each study is shown in Supplement S6.

3.2. Meta-analysis

For the primary outcome of all-cause mortality, reconstructed IPD was available from all four RCTs [6,7,13,14]. In patients randomized to an early AVR strategy, the 8-year cumulative incidence of all-cause mortality was 20.3 % (95 % CI 11.7 %–28.1 %), compared to 35.5 % (95 % CI 20.8 %–47.4 %) in patients randomized to conservative management. The pooled Kaplan–Meier curve is shown in Fig. 2A. Early AVR strategy was associated with a decreased risk of all-cause mortality (HR: 0.72, 95 % CI: 0.53–0.97, $p = 0.031$).

For the secondary outcomes, not all RCTs reported individual KM curves amenable to reconstruction. Specifically, for cardiovascular mortality, only three RCTs made their KM curves available for pooling (RECOVERY, AVATAR and EARLY TAVR) [7,13,14]. Here, in patients randomized for early AVR ($n = 606$), the 8-year cumulative incidence of cardiovascular mortality was 6.6 % (95 % CI 3.4 %–9.7 %), compared to 25.9 % (95 % CI 11.5 %–37.9 %) in patients randomized to conservative management ($n = 597$). The pooled Kaplan–Meier curve is shown in Fig. 2B. The early AVR strategy was associated with a decreased risk of cardiovascular mortality (HR: 0.56, 95 % CI: 0.36–0.89, $p = 0.014$). In the analysis of cardiovascular mortality, the proportional hazards assumption was violated (Schoenfeld residual $p = 0.004$), and a flexible parametric survival models (shown in Supplement S7) demonstrated no significant differences up to 1.92 years, followed by a benefit for the early AVR strategy.

Lastly, for the secondary outcome of heart failure-related hospitalization, two studies were suitable for pooling (AVATAR and EARLY TAVR [7,14]; in the EVOLVED trial only data for unplanned AS-related hospitalization was available and, thus, not eligible for inclusion in our analyses [6] [defined as unplanned admission before or after AVR with

Table 1
Study and patient characteristics.

Study	RECOVERY [13]	AVATAR [14]	EARLY TAVR [7]	EVoLVeD [6]
Country	Korea	Europe	United States and Canada	United Kingdom and Australia
Enrollment years	July 2010 - April 2015	June 2015 - September 2020	March 2017 - December 2021	August 2017 - October 2022
Patients — No	145	157	901	224
Age—Yrs	63.4 ± 10.7 / 65.0 ± 7.8	69 [64–75] / 68 [63–73]	75.6 ± 6.0 / 76.0 ± 6.0	76 [68–80] / 75 [68–79]
Female sex — No. (%)	38 (53) / 36 (49)	35 (44) / 32 (41)	147 (33) / 131 (29)	32 (29) / 31 (27)
BMI — Kg/m2	24.0 ± 2.6 / 24.7 ± 3.4	27.4 [25.4–30.9] / 27.2 [25.6–29.3]	28.6 ± 4.8 / 28.4 ± 4.6	27.8 [24.8–31.1] / 27.2 [24.4–31.1]
STS-PROM score — %	NA	1.8 [1.2–2.7] / 1.6 [1.1–2.2]	1.7 ± 1.0 / 1.8 ± 1.0	NA
EuroSCORE II score — %	0.9 ± 0.4 / 0.9 ± 0.3	NA	NA	NA
BAV — No. (%)	39 (54) / 49 (67)	22 (14)	39 (9) / 37 (8)	28 (25) / 36 (32)
AVA — cm2	0.64 ± 0.09 / 0.63 ± 0.09	0.74 [0.59–0.89] / 0.73 [0.55–0.84]	0.8 ± 0.2 / 0.9 ± 0.2	0.8 ± 0.2 / 0.8 ± 0.2
Vmax — m/s	5.04 ± 0.44 / 5.14 ± 0.52	4.5 [4.2–4.7] / 4.5 [4.3–4.8]	4.4 ± 0.4 / 4.3 ± 0.5	4.4 ± 0.5 / 4.3 ± 0.5
Mean transaortic gradient — mmHg	62.7 ± 12.4 / 64.3 ± 14.4	50 [43–59] / 51 [44–58]	47.3 ± 10.6 / 46.5 ± 10.1	45.0 ± 10.2 / 45.2 ± 11.5
Left ventricular ejection fraction — %	64.8 ± 4.1 / 64.8 ± 5.2	69 [63–75] / 70 [65–76]	67.4 ± 6.7 / 67.4 ± 6.5	68 ± 8* / 68 ± 9*
NT-proBNP — Pg/mL	NA	347 [186–722] / 381 [153–660]	296.8 [147.6–607.7] / 275.6 [138.8–598.9]	NA
Type of AVR	SAVR (50 % mAVR, 50 % bAVR)	SAVR (52.8 % mAVR, 47.2 % bAVR)	TAVR (100 % BEV)	SAVR (75 %; 9 % mAVR, 91 % bAVR) / TAVR (25 %)
Time to AVR — Days	23 [10–36]	55 [36–79]	14 [9–24]	152 [103–243]
Follow-up — Yrs	6.2 [5.0–7.4] / 6.1 [4.5–7.3]	5.3 [4.0–6.3]	3.8 [2.8–5.0]	3.5

Study and patient characteristics in the individual RCTs. *Left ventricular ejection fraction measured using cardiac magnetic resonance imaging instead of echocardiography. Early AVR compared to conservative treatment. Abbreviations: BMI, body mass index; BAV, bicuspid aortic valve; AVA, aortic valve area; Vmax, maximum velocity; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; mAVR, mechanical aortic valve replacement; bAVR, bio-prosthetic aortic valve replacement; TAVR, transcatheter aortic valve replacement; BEV, balloon-expandable valve; NA, not available.

syncope, heart failure, chest pain, ventricular arrhythmia, or second- or third-degree heart block attributed to aortic valve disease)]. For heart failure-related hospitalization, in patients randomized for early AVR (*n* = 533), the 5-year cumulative incidence of heart failure-related hospitalization was 5.2 % (95 % CI 2.4 %–7.8 %), compared to 11.6 % (95 % CI 8.4 %–14.8 %) in patients randomized for conservative management

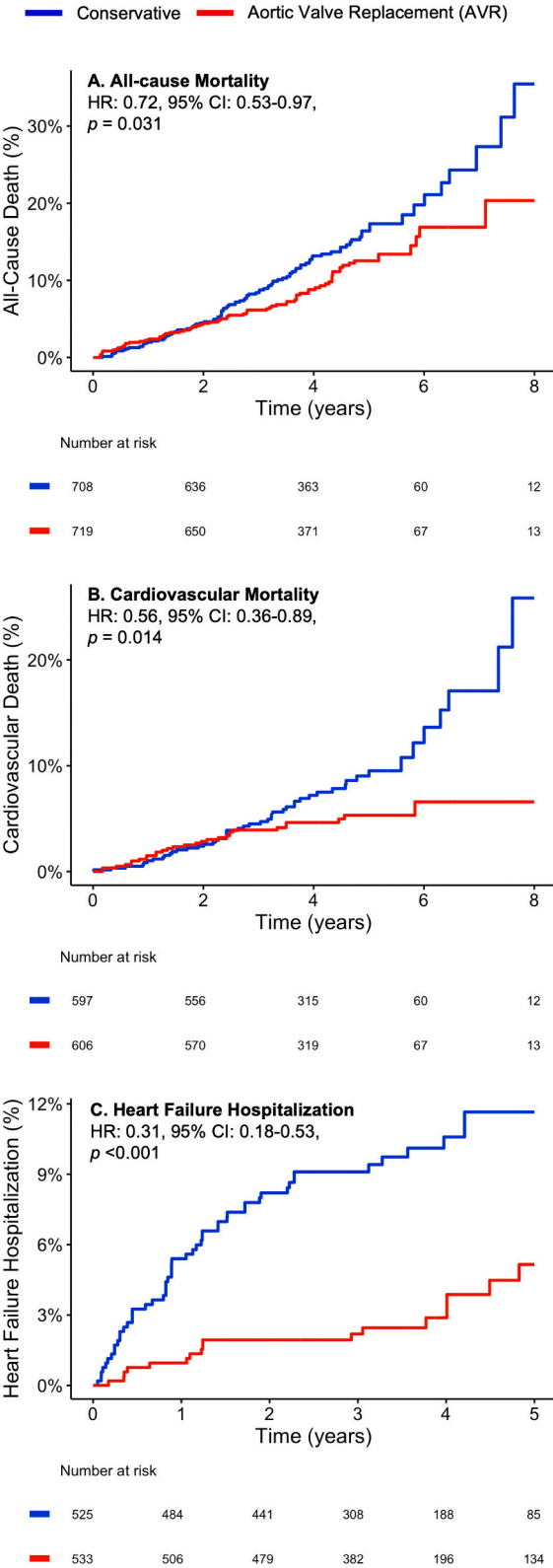


Fig. 2. Time-to-event curves for the primary and secondary outcomes. Cumulative incidence of all-cause mortality (A), cardiovascular mortality (B), and heart failure hospitalization (C), respectively. Studies were pooled from all RCTs (RECOVERY, AVATAR, EARLY TAVR and EVoLVeD) for the analysis of all-cause mortality (A), from 3 RCTs (RECOVERY, AVATAR and EARLY TAVR) for the analysis of cardiovascular mortality (B); and 2 RCTs (AVATAR and EARLY TAVR) for the analysis of heart failure hospitalizations.

($n = 525$). The pooled Kaplan–Meier curve is shown in Fig. 2C. Early AVR was associated with an almost three-fold reduction in risk (HR: 0.31, 95 % CI: 0.18–0.53, $p < 0.001$). The RMST analysis indicated significant benefits for all outcomes associated with an early AVR strategy (Fig. 3).

To assess the interaction effect of choice of AVR type on primary and secondary outcomes, reconstructed IPD from RCTs were stratified according to interventional strategy (RECOVERY and AVATAR for SAVR [13,14]; and EARLY TAVR for TAVR [7], the data from the EVOLVED RCT was not included due to a mixed strategy [SAVR in 75 % and TAVR in 25 %] [6]). For all outcomes, no significant interactions were observed (Fig. 4).

During clinical monitoring across three RCTs (AVATAR, EARLY TAVR and EVOLVED) [6,7,14], 494 patients (83.4 %) in the conservative management group eventually converted to AVR. The pooled Kaplan–Meier curve is shown in Fig. 5. The median time from randomization to conversion to AVR was 13.4 months (interquartile range, 13.2 to 15.1). The cumulative incidence of conversion to AVR was 42.8 % (95 % CI 38.6 %–46.7 %), 82.3 % (95 % CI 78.6 %–85.3 %) and 94.9 % (95 % CI 91.4 %–96.9 %) at 1-, 3- and 5- year follow-up, respectively. No significant differences were observed in the rates of conversion to AVR between the RCTs involving SAVR (AVATAR) and those involving TAVR (EARLY TAVR) (log-rank test, $p = 0.289$) [7,14].

4. Discussion

The main findings of our pooled analyses are as follows: (1) early AVR significantly reduces all-cause mortality, cardiovascular mortality, and heart failure-related hospitalizations compared to conservative management in asymptomatic patients with severe AS; (2) there were no significant interaction effects on the outcomes between SAVR and TAVR; and (3) a large number of asymptomatic patients with severe AS initially randomized to conservative management eventually crossed over to AVR, with a median conversion time of 13.4 months. Specifically, our analysis shows that early AVR significantly reduces mortality and hospitalizations in asymptomatic severe AS. The 8-year number needed to treat (NNT) for all-cause mortality was 6.6 (95 % CI: 2.8–13.5), for cardiovascular mortality was 5.2 (95 % CI: 2.9–6.2), and the 5-year NNT for heart failure-related hospitalization was 15.6 (95 % CI: 8.1–26.3).

The remaining uncertainty about the strategy for patients with asymptomatic severe AS stems from the belief that there is lack of data regarding the natural history of these patients when they remain untreated. However, this so-called gap in the medical literature has been recently addressed by Tan et al. [15] who performed a systematic review with meta-analysis of 46 studies including 9545 patients. Their study revealed poor cardiovascular outcomes for these patients with a

significant proportion eventually requiring AVR. The key findings of their study showed that the median time to the development of symptoms was around 1 year, and by 5 years, nearly 50.0 % of asymptomatic patients had experienced a major adverse cardiovascular event. Furthermore, the median event-free time for heart failure-related hospitalization was 5.5 years, with over one-third of patients having at least one event by year five. By the same time point, almost 80.0 % of patients had developed symptoms such as angina, dyspnea, and syncope, and 12.7 % had died from cardiovascular causes. In terms of overall survival, the median survival time for all-cause mortality was 9.15 years, with nearly 40.0 % of patients dying during 5 year follow-up. Additionally, over 50.0 % of patients required AVR by this time [15]. In line with these findings, looking at a 9 % 2-year mortality rate in asymptomatic severe aortic stenosis and a 50 % relative risk reduction (HR, 0.38; 95 % CI, 0.25–0.58) from prior studies [8], power calculations at $\alpha = 0.05$ and $\beta = 0.2$ suggest a sample size of 974 is adequate. This was achieved by combining the 4 RCTs in our study.

In addition, a recent conventional meta-analysis by G  n  reux et al. [16], including these 4 RCTs, found that early AVR significantly reduced unplanned cardiovascular or HF-related hospitalizations (HR: 0.40, 95 % CI: 0.30–0.53) and stroke rates (HR: 0.62, 95 % CI: 0.40–0.97). However, it did not show significant reductions in all-cause mortality (HR, 0.68; 95 % CI, 0.40–1.17) or cardiovascular mortality (HR: 0.67, 95 % CI: 0.35–1.29) compared to conservative management [16]. While the treatment effect point estimates were consistent with those in our study, our approach-using reconstructed IPD and a more granular analytical method produced narrower confidence intervals, allowing us to demonstrate additional statistical significance for all-cause mortality and cardiovascular mortality.

The latest American ACC/AHA Guidelines established a recommendation for AVR in asymptomatic patients with severe AS and left ventricular ejection fraction (LVEF) < 50 % [4]. However, the optimal threshold of LVEF that should prompt AVR in asymptomatic patients with severe AS is controversial. In a meta-analysis of ten studies including 3332 patients by Perry and Li [17], the authors assessed the relationship between LVEF and mortality benefit in comparing early AVR versus watchful waiting in asymptomatic patients with severe AS [17]. While they found AVR associated with lower mortality in comparison with watchful waiting, there was no statistically significant correlation between LVEF and the size of mortality benefit of AVR, which indicates that AVR was associated with a mortality benefit regardless of LVEF and calls into question the need of an LVEF threshold for recommending AVR in this patient population. Masri et al. also observed AVR associated with improved survival in asymptomatic patients with severe AS despite including only patients with preserved LVEF in their study [18]. Given these findings and the mortality benefit observed in the current study, it is plausible that sudden cardiac death

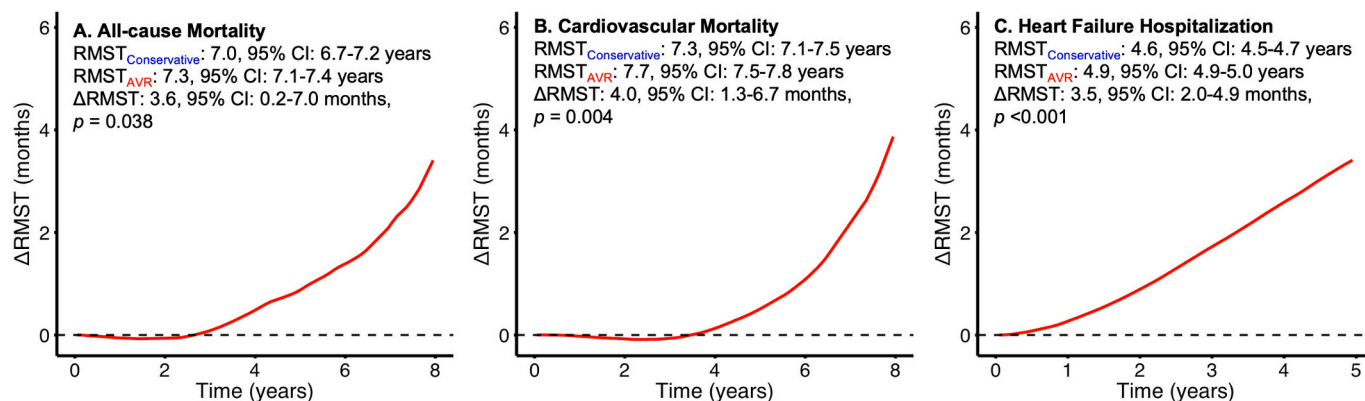


Fig. 3. Restricted mean survival time for all outcomes.

Restricted mean survival time for all-cause mortality (A), cardiovascular mortality (B), and heart failure hospitalization (C), respectively. The difference in restricted mean survival time indicates lifetime gained without occurrence of the outcome.

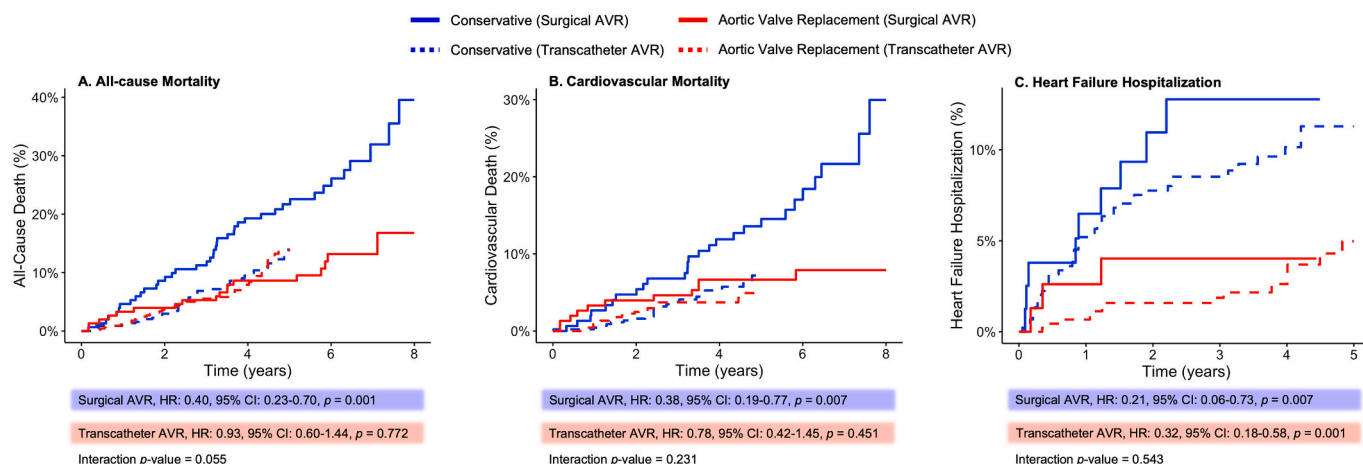


Fig. 4. Time-to-event curves for the primary and the secondary outcomes stratified according to AVR strategy.

Cumulative incidence of all-cause mortality (A), cardiovascular mortality (B), and heart failure hospitalization (C) stratified according to aortic valve replacement strategy at time of randomization, respectively. Studies were pooled from all RCTs (RECOVERY, AVATAR and EARLY TAVR; EVOLVeD was excluded due to the mixed nature of AVR intervention) for the analysis of all-cause mortality (A), from 3 RCTs (RECOVERY, AVATAR and EARLY TAVR) for the analysis of cardiovascular mortality (B); and 2 RCTs (AVATAR and EARLY TAVR) for the analysis of heart failure hospitalizations. The straight lines represent studies with surgical aortic valve replacement, while the dashed lines represent studies with transcatheter aortic valve replacement. The hazard ratio is reported for each individual strategy, along with the significance of the interaction-effect obtained from the likelihood ratio test.

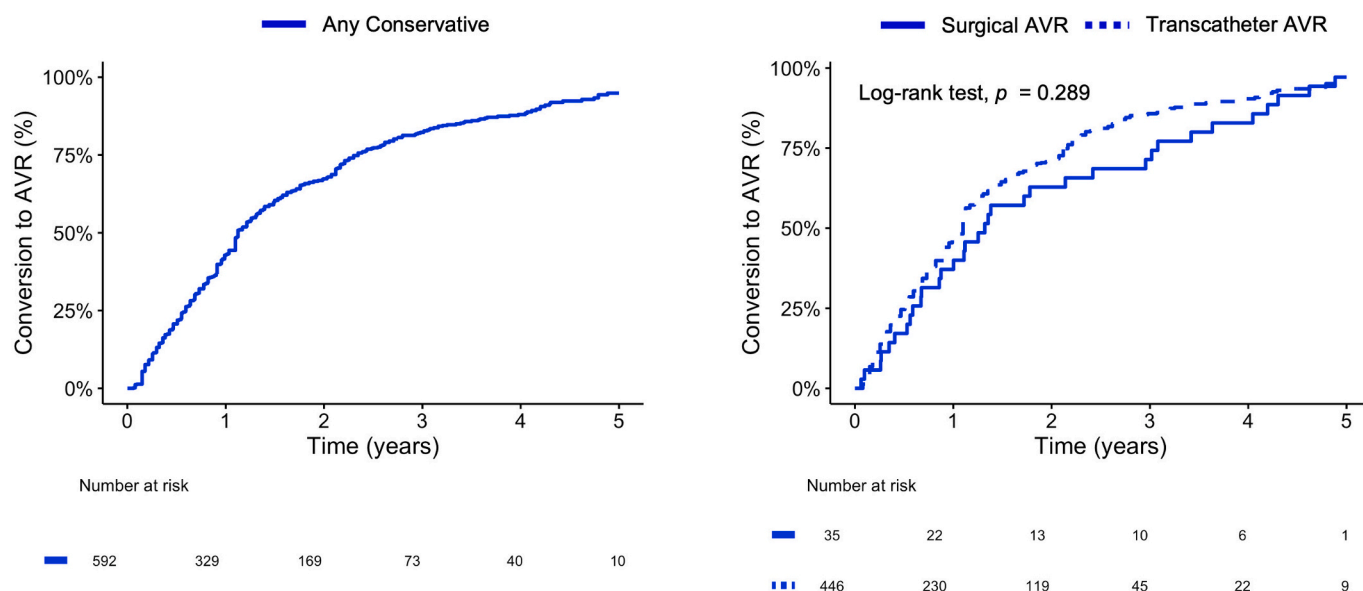


Fig. 5. Time-to-event curves for conversion to aortic valve replacement in the conservative strategy.

Cumulative incidence of conversion to aortic valve replacement in the overall population (A) and stratified according to aortic valve replacement strategy at time of randomization (B). Studies were pooled from 3 RCTs (AVATAR, EARLY TAVR and EVOLVeD) for the overall pooled analysis, for the stratified analysis studies were pooled from 2 RCTs (AVATAR and EARLY TAVR; EVOLVeD was excluded due to the mixed nature of AVR intervention). In the right panel, the straight line represents surgical aortic valve replacement, while the dashed line represents transcatheter aortic valve replacement.

plays a significant role in asymptomatic patients with severe AS, potentially occurring prior to symptom onset, especially in those with left ventricular hypertrophy [19,20].

Another aspect not highlighted in the guidelines (neither ESC/EACTS nor ACC/AHA) is the aortic valve area (AVA) per se as a marker to identify those high-risk patients with asymptomatic severe AS who might benefit from early AVR [3–5]. It stands to reason that, among all patients with severe AS, those with smaller aortic valve areas would be at higher risk of death due to higher pressure afterload. Indeed, the CURRENT AS (*Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis*) Registry Investigators sought to explore the prognostic impact of AVA in asymptomatic patients with severe AS in a large observational database [21]. The investigators

included 3815 consecutive patients with LVEF $\geq 50\%$ and subdivided them into three groups based on AVA (group 1: AVA $> 0.80\text{ cm}^2$, $n = 645$; group 2: $0.8\text{ cm}^2 \geq \text{AVA} > 0.6\text{ cm}^2$, $n = 465$; and group 3: AVA $\leq 0.6\text{ cm}^2$, $n = 199$). The prevalence of patients with very severe AS (peak aortic jet velocity $\geq 5\text{ m/s}$ or mean aortic pressure gradient $\geq 60\text{ mmHg}$) was 2.0 %, 5.8 %, and 26.1 % in groups 1, 2, and 3, respectively. The cumulative 5-year incidence of AVR was not different across the three groups (39.7 %, 43.7 %, and 39.9 %; $p = 0.43$). The cumulative 5-year incidence of the primary outcome measure (a composite of aortic valve-related death or heart failure hospitalization) was incrementally higher with decreasing AVA (24.1 %, 29.1 %, and 48.1 %; $p < 0.001$). After adjusting for confounders, the excess risk of group 3 and group 2 relative to group 1 for the primary outcome measure remained

significant (hazard ratio, 2.21, 95 % CI, 1.56–3.11, $p < 0.001$; and hazard ratio, 1.34, 95 % CI, 1.01–1.78, $P = 0.04$, respectively). These findings revealed that AVA per se (and most importantly when $\leq 0.6 \text{ cm}^2$) should be factored in when evaluating patients with asymptomatic severe AS.

The high rate of conversion to AVR in the conservative group could bias the results toward worse outcomes, and is concerning. Delaying intervention may lead to further adverse cardiac remodeling, which could exacerbate clinical outcomes and dilute the observed benefits of early AVR. As a future perspective, the prognostic value of cardiac damage staging classification based on the extent of extravalvular damage has been proposed in the management of severe AS and might well be included in the decision-making process for asymptomatic patients [22]. Abdelfattah et al. demonstrated that, for patients with asymptomatic severe AS, all-cause mortality was 19.3 %, 36.9 %, 51.7 %, and 67.8 % at 8 years in patients with cardiac damage stage 0, 1, 2, and 3 to 4, respectively (HR in stage 1: 1.70 [95 %CI: 1.21–2.38]; $P = 0.002$; stage 2: 2.20 [95 %CI: 1.60–3.02]; $p < 0.001$; and stage 3 to 4: 3.90 [95 %CI: 2.79–5.47]; $p < 0.001$) [23]. Considering these findings, the assessment of cardiac damage in this population will probably play a role in the management of these patients in the near future.

Considering these potential influencing factors on patient outcomes with early AVR, an initial conservative management strategy with close follow-up may be warranted, with careful monitoring for symptom onset or guideline-directed indications for AVR. In this context, the Heart Team must ensure the selection of the most appropriate therapy for each patient to optimize outcomes. Our findings must not promote over-treatment but instead encourage a multidisciplinary, patient-centered approach to treatment decisions.

4.1. Study limitations

First, it is important to acknowledge that the reconstructed time-to-event data derived from Kaplan-Meier curves were not obtained by pooling original datasets. Instead, our analyses relied on the quality and accuracy of the figures and data points obtained from the published Kaplan-Meier graphs. However, we verified the accuracy of the extracted results by cross-referencing them with the findings reported in the original studies (Supplement S3). Another key limitation is the absence of stroke as an outcome, since only the EARLY TAVR trial provided individual Kaplan-Meier survival curves, preventing data pooling [22]. Notably, while the individual RCTs did not show significant reductions in stroke risk, prior traditional meta-analysis demonstrated a significant reduction (HR: 0.62, 95 % CI: 0.40–0.97) [16]. This suggests that our, more sensitive, analysis could potentially confirm similar findings. Another consideration is the limited mid-term follow-up duration up to 8 years, future follow-up of the trial population is required to observe long-term differences. Furthermore, an important other consideration is that for the secondary outcomes our study may be underpowered due to the relatively small sample size. In line with the considerations regarding sample size, there are concerns about potential publication bias, as only four trials were included, which prevented a formal analysis of bias. Lastly, our analysis also revealed significant between-study heterogeneity, which can be attributed to various factors, including differences in study design, patient demographics and baseline characteristics, interventions, and follow-up durations across the RCTs. For example, differences in AS severity across the trials and the proportion of enrolled women (30 % in recent TAVR trials vs. 40–50 % in SAVR trials) may have contributed to effect modification. Due to the unavailability of stratified data and access to IPD, these hypotheses remain unexplored, and future research should examine their potential impact.

5. Conclusions

The current meta-analysis of reconstructed time-to-event data of RCTs demonstrated that early AVR was associated with significant

reduction in all-cause/cardiovascular mortality (with lifetime gain) and heart failure-related hospitalization in patients with asymptomatic severe AS.

CRediT authorship contribution statement

Xander Jacquemyn: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michel Pompeu Sá:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mateo Marín-Cuarteras:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Jeroen J. Bax:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Michael A. Borger:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Marie-Annick Clavel:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Philippe Pibarot:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Philippe G  n  reux:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Conceptualization. **Ibrahim Sultan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2025.133269>.

Data availability statement

All datasets, statistical methods and study materials will be made available upon request.

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