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META-ANALYSIS

Aortic Valve Replacement vs Clinical Surveillance in Asymptomatic Severe Aortic Stenosis

A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND Current guidelines recommend a strategy of clinical surveillance (CS) for patients with asymptomatic severe aortic stenosis (AS) and a normal left ventricular ejection fraction.

OBJECTIVES The aim of this study was to conduct a study-level meta-analysis of randomized controlled trials (RCTs) evaluating the effect of early aortic valve replacement (AVR) compared with CS in patients with asymptomatic severe AS.

METHODS Studies were quantitatively assessed in a meta-analysis using random-effects modeling. Prespecified outcomes included all-cause and cardiovascular mortality, unplanned cardiovascular or heart failure (HF) hospitalization, and stroke. The meta-analysis is registered at the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY202490002).

RESULTS Four RCTs were identified, including a total of 1,427 patients (719 in the early AVR group and 708 in the CS group). At an average follow-up time of 4.1 years, early AVR was associated with a significant reduction in unplanned cardiovascular or HF hospitalization (pooled rate 14.6% vs 31.9%; HR: 0.40; 95% CI: 0.30-0.53; $I^2 = 4\%$; $P < 0.01$) and stroke (pooled rate 4.5% vs 7.2%; HR: 0.62; 95% CI: 0.40-0.97; $I^2 = 0\%$; $P = 0.03$). No differences in all-cause mortality (pooled rate 9.7% vs 13.7%; HR: 0.68; 95% CI: 0.40-1.17; $I^2 = 61\%$; $P = 0.17$) and cardiovascular mortality (pooled rate 5.1% vs 8.3%; HR: 0.67; 95% CI: 0.35-1.29; $I^2 = 50\%$; $P = 0.23$) were observed with early AVR compared with CS, although there was a high degree of heterogeneity among studies.

CONCLUSIONS In this meta-analysis of 4 RCTs, early AVR was associated with a significant reduction in unplanned cardiovascular or HF hospitalization and stroke and no differences in all-cause and cardiovascular mortality compared with CS. (JACC. 2025;85:912-922) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CS = clinical surveillance

HF = heart failure

RCT = randomized controlled trial

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

Aortic stenosis (AS) is a progressive disease associated with substantial morbidity, mortality, and health care costs.[1-3] Current guidelines recommend aortic valve replacement (AVR) for patients with severe AS with symptoms or a reduced left ventricular ejection fraction.[4,5] The assessment of symptoms in patients with severe AS is challenging, particularly among older individuals.[6] Previous observational studies and randomized controlled trials (RCTs) assessing the impact of surgical AVR (SAVR) vs clinical surveillance (CS) in patients with asymptomatic severe AS have shown reductions in all-cause mortality and heart failure (HF) hospitalization with a strategy of early AVR.[6-26] Recently, 2 RCTs evaluated the effects of early intervention with both transcatheter AVR (TAVR) and SAVR compared with CS in patients with asymptomatic severe AS.[27,28] Therefore, we conducted an updated meta-analysis of the 4 available RCTs evaluating a strategy of early TAVR or SAVR vs routine CS in patients with severe asymptomatic AS.

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METHODS

SEARCH STRATEGY AND SELECTION CRITERIA. A systematic literature review and meta-analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[29] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[30] Full-text publications reporting clinical outcomes from RCTs and observational studies of asymptomatic patients with severe or very severe AS after treatment with either AVR (SAVR or TAVR) or conservative CS were eligible. Searches were performed in the PubMed and Embase databases on April 15, 2024, using prespecified criteria. Records were captured using a combination of controlled vocabulary and keywords, and vocabulary and syntax were adjusted across databases. For instance, variants of the words and 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 terms in PubMed, entree terms in Embase, and text words related to AVR in asymptomatic severe AS. The search strategy had no restrictions on language, publication date, age, living setting, sex, race, ethnicity, or geographic region of the patient population. To ensure that all relevant studies were captured, gray literature searches were conducted at ClinicalTrials.gov to identify unpublished trial records. References of excluded manuscripts were manually screened for eligibility. Manual searches of conference proceedings were conducted after the search date to identify additional publicly available and forthcoming data. Details of the search strategy and prespecified criteria are presented in Supplemental Table 1. All search strategies were generated using the population, intervention, comparator, outcomes, and study design framework (Supplemental Table 2).

Subsequent to the literature search and removal of duplicate citations using EndNote version 21.3 (Clarivate), studies were selected in 2 phases: title and abstract screening (phase 1) and full-text screening (phase 2). Two reviewers (P.G. and R.S.) independently screened the titles and abstracts of all publications identified using DistillerSR version 2.35 (DistillerSR). Reasons for exclusion were categorized according to the population, intervention, comparator, outcomes, and study design elements during full-text review. Disagreements were resolved by a third independent reviewer (G.G.). The review and meta-analysis protocol was registered at the International Platform of Registered Systematic Reviews and Meta-Analysis Protocols (INPLASY202490002).

DATA ANALYSIS. For studies meeting the eligibility criteria, summary estimates relating to study population, baseline demographics, interventions, and outcomes of interest were extracted by 2 independent reviewers (R.S. and G.G.) using Nested Knowledge (Nested Knowledge). Discrepancies in collected data were resolved by consensus or a third independent

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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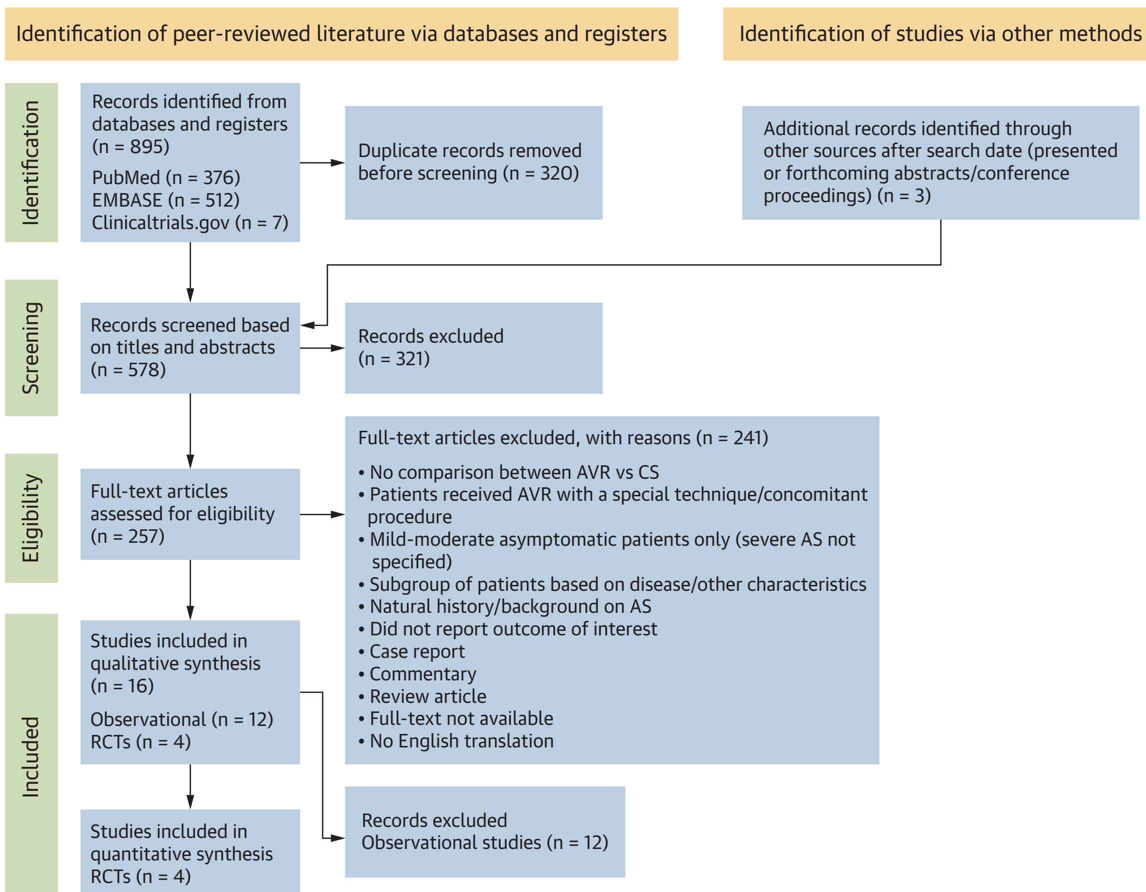
FIGURE 1 **Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart**



Schematic overview of the study selection process. Four randomized controlled trials were included in the main analysis. AS = aortic stenosis; AVR = aortic valve replacement; CS = clinical surveillance; RCT = randomized controlled trial.

reviewer (P.G.). For studies with multiple citations available, data from the publication with the largest sample size or study follow-up were included.

Two reviewers (R.S. and G.G.) independently assessed the risk for bias in the included studies, using the Cochrane Collaboration's Risk of Bias tool for RCTs[31] and the Newcastle-Ottawa Scale for observational studies.[32] Study quality assessment was conducted by a single reviewer, and a second reviewer validated the consistency and integrity of the assessments. Any disagreements were resolved through discussion with a third reviewer.

The primary clinical outcome selected for the pooled analyses was all-cause mortality. Secondary clinical outcomes were cardiovascular mortality, unplanned cardiovascular or HF hospitalization, and stroke. A meta-analysis of studies comparing AVR with CS using the method of DerSimonian and Laird was conducted for outcomes of interest using the metafor package version 4.4-0 for R version 4.0.5 (R Foundation for Statistical Computing).[29,33,34]

For all outcomes, pooled HRs and their corresponding 95% CIs were calculated using a random-effects model. Heterogeneity among the included studies was tested using the I^2 statistic, representing the percentage of the total variation among studies that could not be attributed to chance. Heterogeneity was classified as follows: low, I^2 <40%; moderate, I^2 = 30% to 60%; substantial, I^2 = 50% to 90%; and high, I^2 >75%.[29] Funnel plots depicting standard errors of the HR by summary effect sizes were constructed in accordance with Cochrane guidelines to detect publication bias.[29] Evaluation of statistically significant publication bias was assessed using Egger's linear regression test.[35] Subgroup analyses comparing SAVR and TAVR trials were also performed. The EVoLVeD (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients With Severe Aortic Stenosis) trial was excluded from subgroup analyses because the trial allowed both SAVR and TAVR, and outcomes were not stratified by AVR modality for this study. The chi-square statistic and the interaction *P* value were reported to test for differences between subgroups. To assess the impact of each individual study on the overall all-cause mortality results, a leave-one-out sensitivity analysis was conducted by excluding 1 study at a time and rerunning the meta-analysis on the remaining subset of studies.

RESULTS

A total of 898 records were identified from the PubMed and Embase searches; 7 additional records were identified from the search of ClinicalTrials.gov, as well as 3 identified from supplemental manual searches after the initial search on April 15, 2024. After the exclusion of 320 duplicates, 578 unique records were screened at the title and abstract level, of which 321 were excluded. Of the remaining 257 records considered at full-text screening level, 16 unique studies were deemed eligible for inclusion in the qualitative synthesis (**Figure 1**). Of these, 12 were observational cohort studies[7-18] and 4 were RCTs[25-28] (**Table 1**).

The main quantitative analysis restricted to the 4 RCTs included a total of 1,427 patients with an average follow-up duration of 4.1 years, weighted mean per-patient follow-up duration of 49.8 months, and 5,878 patient-years of follow-up data. The mean age of patients weighted across the trials was 73.3 years (range: 64.5-75.8 years). Female representation varied from 28% to 51% across the trials and bicuspid valve representation from 8% to 61%.

Compared with CS, early AVR was associated with similar rates of all-cause mortality (pooled rate 9.7% vs 13.7%; HR: 0.68; 95% CI: 0.40-1.17; $I^2 = 61\%$; $P = 0.17$; total patient-years = 5,878) (**Figure 2A**) and cardiovascular mortality (pooled rate 5.1% vs 8.3%; HR: 0.67; 95% CI: 0.35-1.29; $I^2 = 50\%$; $P = 0.23$; total patient-years = 5,878) (**Figure 2B**), with a moderate amount of heterogeneity observed for both outcomes. Early AVR was also associated with a significantly lower risk for HF hospitalization, with no heterogeneity (pooled rate 3.0% vs 10.9%; HR: 0.28; 95% CI: 0.17-0.47; $I^2 = 0\%$; $P < 0.01$; total patient-years = 5,054) (**Figure 3A**) and unplanned cardiovascular or HF hospitalization with low heterogeneity (pooled rate 14.6% vs 31.9%; HR: 0.40; 95% CI: 0.30-0.53; $I^2 = 4\%$; $P < 0.01$; total patient-years = 5,878) (**Figure 3B**). A significant reduction in stroke was observed with early AVR compared with CS (pooled rate 4.5% vs 7.2%; HR: 0.62; 95% CI: 0.40-0.97; $I^2 = 0\%$; $P = 0.03$; total patient-years = 5,878) (**Figure 3C**).

Subgroup analyses indicated no significant differences between SAVR and TAVR studies for all outcomes, except for all-cause mortality, for which the 2 studies involving SAVR (RECOVERY [Randomized Comparison of Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis] and AVATAR [Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis]) were associated with a survival benefit compared with CS, while the trial involving TAVR (EARLY TAVR) was not (chi-square = 5.42; $P_{interaction} = 0.02$) (Supplemental Figure 1). However, tests for subgroup differences may be underpowered because of the modest sample size. Additionally, the leave-one-out sensitivity analysis demonstrated that including the EVoLVeD and EARLY TAVR trials in the meta-analysis resulted in a reduced pooled survival benefit for AVR compared with CS (Supplemental Figure 2). Point estimates from these 2 trials showed no differences in survival for AVR vs CS compared with the RECOVERY and AVATAR trials.

Overall risk for bias was considered low for the 4 included RCTs (Supplemental Table 3).[25-28] The funnel plots showed studies generally evenly distributed around the central line to form a symmetrical inverted funnel, suggesting that there was no evidence of systematic bias in the analyses (Supplemental Figure 3). Statistical tests for publication bias (Egger's regression test) could not be performed, because of inadequate power (ie, <10 studies were included).

DISCUSSION

The present study is the largest and most up to date study-level meta-analysis evaluating the effect of AVR compared with CS in patients with asymptomatic severe AS. The main findings are as follows: 1) early AVR was associated with a significant reduction in rates of unplanned cardiovascular or HF-related hospitalization; 2) early AVR was associated with a significant reduction in rates of stroke compared with CS; and 3) a strategy of early AVR was associated with similar all-cause and cardiovascular mortality as CS, with considerable heterogeneity among the 4 trials.

AS is a progressive disease across a continuum ranging from milder forms with no symptoms or hemodynamic effects to more severe forms associated with substantial symptom burden, cardiac damage,

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TABLE 1 Summary of Randomized Controlled Trials Included in the Meta-Analysis

First Author; Study	Country; Period	N; Bicuspid; Female	Early AVR, n	CS, n	Mean Age, y	Follow-Up: Early AVR	Follow-Up: CS	Time to Early AVR	Time to AVR for CS Group: From Randomization	Time to AVR for CS Group: Upon Symptom Development/Indication for AVR
Généreux et al (2024)[27]; EARLY TAVR (NCT03042104)	United States and Canada; 2017-2021	901; 8%; 31%	TAVR, 455	446	75.8	3.7 y (3.0-5.1 y)	3.8 y (2.8-4.8 y)	14.0 d (9.0-24.0 d)	11.1 mo (5.0-19.7 mo)	32 d (18-58 d)
Loganath et al (2024)[28]; EVoLVeD (NCT03094143)	United Kingdom; 2017-2022	224; 29%; 28%	SAVR, 80 TAVR, 26 No AVR, 7 Total, 113	111	73.4	4.0 y (1.0-4.3 y)	3.0 y (1.1-4.1 y)	152.1 d (103.4-243.3 d)	614.4 d (346.8-1,277.5 d)	100 d (43-146 d)
Banovic et al (2024)[26]; AVATAR (NCT02436655)	Europe; 2015-2023	157; 14%; 43%	SAVR, 78	79	67.0	63 mo (48-75 mo)	63 mo (48-75 mo)	55 d (36-79 d)	476 d (226-1,098 d)	123 d (90-297 d)
Kang et al (2020)[25]; RECOVERY (NCT01161732)	Korea; 2010-2015	145; 61%; 51%	SAVR, 73	72	64.5	6.2 y (5.0-7.4 y)	6.1 y (4.5-7.3 y)	23 d (10-36 d)	700 d (277-1,469 d)	NR

Values are N or n, %, mean ± SD, or median (Q1-Q3). [a]Primary endpoint for: 1) EARLY TAVR: all-cause death, all stroke, and unplanned cardiovascular hospitalization when all patients have reached 2-year follow-up; 2) EVoLVeD: composite of all-cause mortality or unplanned AS-related hospitalization from randomization through study completion (mean follow-up expected to be an average of 2.75 years); 3) AVATAR: all-cause mortality or major adverse cardiovascular events composed of acute myocardial infarction, stroke, and unplanned heart failure hospitalization needing intravenous treatment within 5-year follow-up; 4) RECOVERY: operative mortality (during or within 30 days of surgery) or cardiac mortality during entire follow-up (a minimum of 4 years).

AS = aortic stenosis; AVA = aortic valve area; AVR = aortic valve replacement; CMR = cardiac magnetic resonance; CS = clinical surveillance; iAVA = indexed aortic valve area; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MG = mean gradient; NR = not reported; RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; Vmax = maximal systolic aortic flow velocity.

Continued on the next page

and a risk for sudden death.[6,36-41] Although patients with severe AS and clinical symptoms have a guideline-recommended indication for AVR to improve overall survival and quality of life,[5] the optimal timing of AVR in patients with asymptomatic severe AS is unclear. On the basis of observational studies, it is generally accepted that most patients with asymptomatic, severe AS will become symptomatic within 1 to 2 years after the initial diagnosis, with a mortality risk of approximately 1% to 2% per year during the surveillance period.[6] Furthermore, the continuous pressure overload imposed on the left ventricle by severe AS promotes maladaptive remodeling and the development of irreversible structural cardiac damage, which is in turn associated with increased long-term morbidity and mortality.[36,38,42] Previous observational studies suggested a benefit from timely AVR among patients with asymptomatic severe AS, but these studies are limited by the inability to identify the management strategy prospectively as well as immortal time bias.[7-18] Subsequently, 2 RCTs comparing SAVR vs CS demonstrated a benefit from early SAVR among young patients with asymptomatic severe or critical AS.[25,26] TAVR is a less invasive alternative to SAVR and is now a well-established therapy for patients with severe AS across the spectrum of surgical risk[43-49]; however, its role in patients with asymptomatic severe AS remains unknown. With inclusion of the EARLY TAVR and EVoLVeD trials, the present meta-analysis is the largest and most up to date study evaluating the effects of both SAVR and TAVR in patients with asymptomatic severe AS.

Compared with EARLY TAVR and EVoLVeD, the RECOVERY and AVATAR trials demonstrated a survival benefit with early SAVR compared with CS.[25,26]

TABLE 1 Continued

Inclusion Criteria	AVA, cm^2 Early AVR	AVA, cm^2 CS	Vmax, m/s Early AVR	Vmax, m/s CS	MG, mm Hg Early AVR	MG, mm Hg CS	Key Findings
• Age ≥65 y; LVEF ≥50%; AVA ≤1 cm^2 or iAVA ≤0.6 cm^2/m^2 and (Vmax ≥4.0 m/s or MG ≥40 mm Hg); asymptomatic (confirmed exercise testing); STS score ≤10 • LVEF ≥50% • Low-level stress test in 90.6%	0.9 ± 0.23	0.8 ± 0.23	4.3 ± 0.45	4.4 ± 0.43	46.5 ± 10.08	47.3 ± 10.61	• Met primary endpoint (superiority)[a] • Significantly lower incidence of the composite endpoint in early TAVR arm compared with CS arm (26.8% vs 45.3%; HR: 0.50; 95% CI: 0.40-0.63; $P < 0.0001$) • No difference in mortality
• Age ≥18 y; Vmax ≥4.0 m/s or (iAVA <0.6 cm^2/m^2 and Vmax ≥3.5 m/s); midwall LGE on CMR; no symptoms attributable to AS that require AVR • LVEF ≥50% • No stress test reported	0.8 ± 0.2	0.8 ± 0.2	4.3 ± 0.5	4.4 ± 0.5	45.2 ± 11.5	45.0 ± 10.2	• Did not meet primary endpoint[a] • Significantly lower incidence of AS-related hospitalizations in AVR arm compared with CS arm (6.2% vs 17.1%; HR: 0.37; 95% CI: 0.16-0.88; $P = 0.024$) • No difference in mortality
• Age ≥18 y (AVA ≤1 cm^2 or iAVA ≤0.6 cm^2/m^2 at rest) and (Vmax >4.0 m/s or MG ≥40 mm Hg); without reported symptoms; STS score <8% • LVEF ≥50% • Low-level stress test in 100%	0.73 (0.55-0.84)	0.74 (0.59-0.89)	4.5 (4.3-4.8)	4.5 (4.2-4.7)	51 (44-58)	50 (43-59)	• Met primary endpoint (superiority)[a] • Significantly lower incidence of the composite endpoint in SAVR compared with CS arm (23.1% vs 46.8%; HR: 0.42; 95% CI: 0.24-0.73; $P = 0.002$) • Lower rate of mortality with SAVR
• Age 20-80 y; AVA ≤0.75 cm^2 and (Vmax ≥4.5 m/s or MG ≥50 mm Hg); asymptomatic; candidate for early surgery • LVEF ≥50% • Low-level stress test in 17%	0.63 ± 0.09	0.64 ± 0.09	5.14 ± 0.52	5.04 ± 0.44	64.3 ± 14.4	62.7 ± 12.4	• Met primary endpoint (superiority)[a] • Significantly lower incidence of the composite endpoint in SAVR compared with CS arm (1% vs 15%; HR: 0.09; 95% CI: 0.01-0.67; $P = 0.003$) • Lower rate of mortality with SAVR

Although it may be tempting to attribute these differences in survival benefit to the type of AVR, as this was a defining characteristic of 3 of the trials (EVoLVeD included both SAVR and TAVR, and most patients in the early AVR group underwent SAVR). However, given the similar intermediate and long-term survival seen with TAVR and SAVR in multiple randomized trials, it is difficult to believe that differences in the type of AVR explain the differences in trial outcomes. Another potential explanation could be differences in the types of patients included in the studies. In particular, the RECOVERY and AVATAR trials enrolled younger patients (mean age 64.5-67.0 years) with severe or critical AS, a group of patients who might be expected to derive greater survival benefit from AVR. In contrast, EARLY TAVR and EVoLVeD included older patients (mean age 73.4-75.8 years) with asymptomatic severe AS. Given these differences in age, it may be tempting to speculate that competing risks related to both age and comorbidities might have attenuated any a potential survival benefit of early intervention. However, careful inspection of the mortality rates demonstrates that the mortality rates were relatively low in the more recent studies, especially EARLY TAVR.

In our opinion, the most likely explanation for the differences in mortality benefit among the various studies relates more to outcomes in the CS groups than in the early AVR groups. In particular, it seems that the time from onset of AS symptoms to valve replacement differed substantially between the surgery trials and the TAVR trials. For example, among CS patients who underwent AVR in AVATAR, the median time from recognition of symptoms to AVR was 4.0 months; in EVoLVeD, this interval was 3.3 months. In contrast, in EARLY TAVR, the median time from first onset of symptoms to TAVR in the CS group was 32 days. This more prolonged exposure to severe, symptomatic AS in the surgical trials is likely to have led to higher rates of mortality while awaiting AVR in those trials.

There are several potential explanations for the longer delay to AVR seen in the surgical trials. First, patients in the SAVR trials may have been reluctant to undergo surgery because of concerns related to postoperative morbidity and prolonged recuperation. Second, it is possible that the delays to surgical conversion in both surgical trials were related to the health care systems in the countries where the studies were conducted (South Korea, Serbia, and

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FIGURE 2 **Forest Plots for All-Cause Mortality and Cardiovascular Mortality**

A

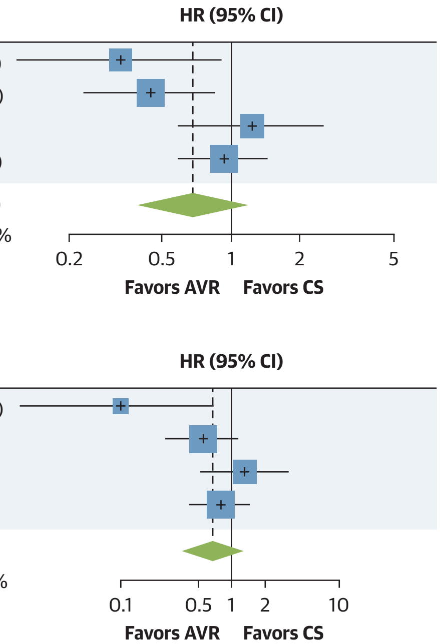
Study	Log (HR)	SE	Weight	HR (95% CI)
Kang 2020[25]	−1.1,087	0.5,140	17.1%	0.33 (0.12-0.90)
Banovic 2024[26]	−0.8,210	0.3,335	26.0%	0.44 (0.23-0.85)
Loganath 2024[28]	0.1,989	0.3,694	24.0%	1.22 (0.59-2.51)
Genereux 2024[27]	−0.0,726	0.2,233	33.0%	0.93 (0.60-1.44)
Total (95% Cl)			**100.0%**	**0.68 (0.40-1.17)**

Heterogeneity: τ^2 = 0.1,805; chi-square = 7.77, df = 3 (P = 0.05); I^2 = 61%
Test for overall effect: Z = −1.38 (P = 0.17)

B

Study	Log (HR)	SE	Weight	HR (95% CI)
Kang 2020[25]	−2.4,079	1.0,726	8.2%	0.09 (0.01-0.67)
Banovic 2024[26]	−0.6,162	0.3,959	30.4%	0.54 (0.25-1.18)
Loganath 2024[28]	0.2,852	0.4,760	25.5%	1.33 (0.52-3.36)
Genereux 2024[27]	−0.2,485	0.3,161	35.9%	0.78 (0.42-1.45)
Total (95% Cl)			**100.0%**	**0.67 (0.35-1.29)**

Heterogeneity: τ^2 = 0.2,115; chi-square = 6.01, df = 3 (P = 0.11); I^2 = 50%
Test for overall effect: Z = −1.20 (P = 0.23)



Forest plots of (A) all-cause mortality and (B) cardiovascular mortality comparing AVR vs CS in RCTs. The sizes of the squares correspond to the weight of each trial in the quantitative synthesis. The diamond and its width represent the pooled HR and the 95% CI, respectively. Abbreviations as in **Figure 1**.

the United Kingdom), which may have less immediate access to highly specialized care than in the United States. Finally, it is worth noting that the time from symptom onset to conversion to AVR in EARLY TAVR was particularly brief, which likely reflects the fact that prior to randomization, all patients had undergone a complete pre-TAVR evaluation. As such, once symptoms developed, these patients were able to bypass much of the usual system delays, resulting in a very brief exposure to the high-risk period of uncorrected, severe, symptomatic AS. Whether this quality of surveillance and timeliness of TAVR treatment that was seen in the EARLY TAVR trial can be replicated outside of the clinical trial setting, even in the United States, is uncertain.

In contrast to the heterogeneous findings with respect to mortality, early AVR was associated with an approximately 50% relative reduction in unplanned cardiovascular or HF-related hospitalizations compared with CS. This finding is important and likely reflects the beneficial effect of relieving the pressure overload imposed by severe AS on the left ventricle, thereby preventing progressive cardiac damage. Furthermore, the evolution of asymptomatic AS is often unpredictable, and many patients present with acute decompensation secondary to the development of left ventricular dysfunction, atrial fibrillation, or pulmonary hypertension.[36] Early treatment of patients with asymptomatic severe AS may allow AVR to be undertaken in stable conditions rather than in an acute phase, when periprocedural risks may be higher and irreversible cardiac damage has ensued.

The reduced incidence of stroke observed among patients undergoing early AVR across the included RCTs was somewhat unexpected. One of the major concerns of performing early AVR is the possibility of procedure-related complications such as stroke, major vascular complications, or bleeding.[50] The incidence of periprocedural disabling stroke using current generation TAVR platforms is about 1% to 2% in real-world registries.[50] Stroke rates are substantial in patients with untreated AS,[51,52] and it is possible that replacement of a diseased aortic valve may reduce the risk for valve-related thromboembolic events or the development of subclinical atrial fibrillation (with an associated high risk for

FIGURE 3 **Forest Plots for HF Hospitalization, Unplanned Cardiovascular or HF Hospitalization, and Stroke**

A

Study	Log (HR)	SE	Weight	HR (95% CI)
Kang 2020[25]	−2.9,957	1.5,513	2.9%	0.05 (0.00-1.05)
Banovic 2024[26]	−1.5,606	0.6,374	17.5%	0.21 (0.06-0.73)
Genereux 2024[27]	−1.1,394	0.2,985	79.6%	0.32 (0.18-0.57)
Total (95% CI)			**100.0%**	**0.28 (0.17-0.47)**

Heterogeneity: τ^2 = 0; chi-square = 1.64, df = 2 (P = 0.44); I^2 = 0%
Test for overall effect: Z = −4.76 (P < 0.01)

B

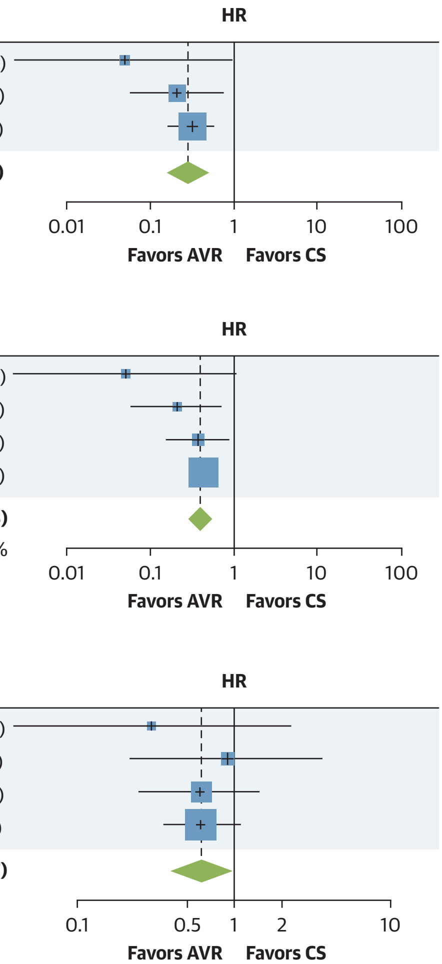
Study	Log (HR)	SE	Weight	HR (95% CI)
Kang 2020[25]	−2.9,957	1.5,513	0.9%	0.05 (0.00-1.05)
Banovic 2024[26]	−1.5,606	0.6,374	5.2%	0.21 (0.06-0.73)
Loganath 2024[28]	−0.9,943	0.4,349	10.8%	0.37 (0.16-0.88)
Genereux 2024[27]	−0.8,440	0.1,303	83.1%	0.43 (0.33-0.55)
Total (95% CI)			**100.0%**	**0.40 (0.30-0.53)**

Heterogeneity: τ^2 = 0.0088; chi-square = 3.13, df = 3 (P = 0.37); I^2 = 4%
Test for overall effect: Z = −6.26 (P < 0.01)

C

Study	Log (HR)	SE	Weight	HR (95% CI)
Kang 2020[25]	−1.2,000	1.0,300	4.8%	0.30 (0.04-2.31)
Banovic 2024[26]	−0.0,900	0.7,100	10.0%	0.91 (0.23-3.65)
Loganath 2024[28]	−0.4,800	0.4,500	25.0%	0.62 (0.26-1.49)
Genereux 2024[27]	−0.4,800	0.2,900	60.2%	0.62 (0.35-1.10)
Total (95% CI)			**100.0%**	**0.62 (0.40-0.97)**

Heterogeneity: τ^2 = 0; chi-square = 0.79, df = 3 (P = 0.85); I^2 = 0%
Test for overall effect: Z = −2.11 (P = 0.03)



Forest plots of (A) heart failure (HF) hospitalization, (B) unplanned cardiovascular or HF hospitalization, and (C) stroke comparing a strategy of AVR vs CS for patients with asymptomatic severe aortic stenosis (AS) in 4 RCTs. Unplanned cardiovascular hospitalization in EARLY TAVR (Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; Généreux et al[27]) is defined as admission through emergency department or same-day admission from a clinic for congestive heart failure or AS-related causes, as well as other cardiovascular causes such as arrhythmia or conduction system disturbance, bleeding, coronary artery disease, stroke or transient ischemic attack, thromboembolic event, and any aortic valve intervention within 6 months of randomization in the CS arm, including conversion to AVR, and any aortic valve reintervention within 6 months of the procedure in the transcatheter AVR arm. Unplanned AS hospitalization in EVoLVeD (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients With Severe Aortic Stenosis; Loganath et al[28]) is defined as any unplanned admission before or after AVR with syncope, HF, chest pain, ventricular arrythmia, or second- or third-degree heart block, attributed to aortic valve disease. Abbreviations as in Figure 1.

thromboembolism) due to prolonged exposure to the AS-related pressure overload on the left ventricle and atrium. Further prospective studies are needed to confirm this finding.

IMPACT ON CLINICAL PRACTICE. The results of the present meta-analysis provide a framework for discussion between patients and caregivers regarding the management of asymptomatic severe AS. Indeed, the benefits of early intervention observed in our meta-analysis, including reductions in HF hospitalization, unplanned cardiovascular hospitalization, and stroke, compared with a strategy of CS, highlights patient-centric and quality of life-related arguments

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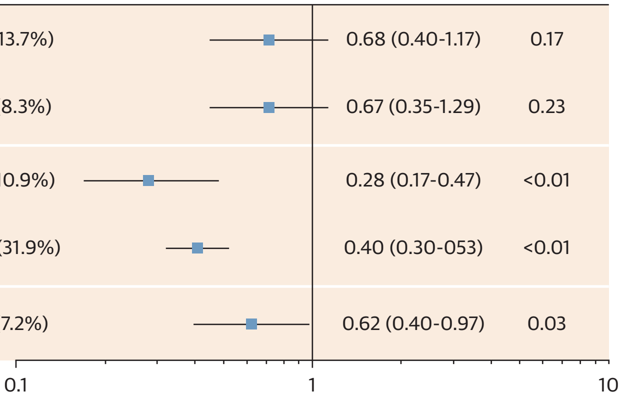
CENTRAL ILLUSTRATION Systematic Review and Study-Level Meta-Analysis of AVR vs Clinical Surveillance in Asymptomatic Severe Aortic Stenosis

	Early AVR n/N (%)	Clinical Surveillance n/N (%)	Pooled HR* (95% CI)	*P* Value
All-Cause Mortality	70/719 (9.7%)	97/708 (13.7%)	0.68 (0.40-1.17)	0.17
Cardiovascular Mortality	37/719 (5.1%)	59/708 (8.3%)	0.67 (0.35-1.29)	0.23
Heart Failure Hospitalization	18/606 (3.0%)	65/597 (10.9%)	0.28 (0.17-0.47)	<0.01
Unplanned CV or HF Hospitalization	105/719 (14.6%)	226/708 (31.9%)	0.40 (0.30-053)	<0.01
Stroke	32/719 (4.5%)	51/708 (7.2%)	0.62 (0.40-0.97)	0.03



Généreux P, et al. JACC. 2025;85(9):912–922.

Among patients with asymptomatic severe aortic stenosis, early aortic valve replacement (AVR) was associated with lower risk for heart failure (HF) or unplanned cardiovascular (CV) hospitalizations and stroke compared with clinical surveillance. There were no significant differences in all-cause or CV mortality between groups. Results are reported as crude proportions (percentage). *Pooled HRs for each endpoint were estimated using random-effects models according to the method of DerSimonian and Laird method.

in favor of early intervention. The absence of benefits in terms of mortality observed in the 2 recent RCTs, especially EARLY TAVR, mainly highlights the benefits of a less invasive approach and prompt conversion to treatment as soon as symptoms occurred if survival is to be preserved. The totality of evidence emerging from the 4 RCTs, and the present meta-analysis, may help change future clinical guidelines (Central Illustration).

STUDY LIMITATIONS. First, we did not have access to individual patient-level data at the time of analysis, which precluded Kaplan-Meier estimates of adverse events, risk adjustment across included studies, and detailed subgroup analyses. Second, there were significant differences in design, intervention, patient selection, and follow-up across studies; however, we used HRs to account for this.

Third, the modality of AVR included both SAVR and TAVR and differed across studies; therefore, these findings, should not inform procedural selection in individual patients with asymptomatic severe AS. Fourth, differences in the timing of AVR after the diagnosis of severe asymptomatic AS may influence the expected benefit of early AVR in this population compared with continuing CS.

Fifth, although there was nominal variability observed in point estimates of studies included in the HF hospitalization and stroke analyses, tests for heterogeneity may not have been sensitive enough to detect real differences among the studies. Therefore, the absence of significant heterogeneity for these outcomes should be interpreted with caution, as it may reflect the limitations of the statistical power rather than true homogeneity across the studies.

Finally, the lack of long-term follow-up precludes definitive conclusions regarding the need for reintervention because of valve failure. Indeed, the benefits of early valve intervention will need to be carefully balanced on a patient-by-patient basis against the potential for structural valve degeneration and the future need for repeat valve interventions, especially in younger patients treated with a bioprosthetic valve.

CONCLUSIONS

Among patients with asymptomatic severe AS, the most recent evidence derived from 4 RCTs demonstrates a reduction in unplanned cardiovascular or HF hospitalization and stroke associated with a strategy of early TAVR or SAVR compared with CS and similar all-cause and cardiovascular mortality. Given the benefits observed and lack of harm, a strategy of prompt AVR may be preferred for patients with asymptomatic severe AS.

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KEY WORDS aortic stenosis, aortic valve replacement, meta-analysis, systematic review, transcatheter aortic valve implantation, transcatheter aortic valve replacement

APPENDIX For supplemental figures and tables, please see the online version of this paper.