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Early Aortic-Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis With Preserved Left Ventricular Systolic Function: A Systematic Review and Meta-Analysis

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Current guidelines recommend routine clinical surveillance for patients with asymptomatic severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF). However, the role of early aortic valve replacement (AVR) as compared with conservative treatment in these patients remains unclear. We systematically searched PubMed, Embase and Cochrane databases to identify studies comparing early AVR versus conservative treatment in asymptomatic patients with severe AS and preserved LVEF. All statistical analyses were performed using R software version 4.3.1 with a random-effects model. Seven studies comprising 2,531 patients with asymptomatic severe AS and preserved LVEF were included, of whom 1,234 (49%) underwent AVR. Median follow-up time was 49.3 months. Early AVR was associated with significantly lower incidence of all-cause (HR 0.51; 95% CI 0.31 to 0.83) and cardiac mortality (RR 0.51; 95% CI 0.30 to 0.89). There were no significant differences between early AVR and conservative treatment in terms of sudden death, hospitalization for cardiovascular (CV) causes, stroke, or myocardial infarction (MI). However, upon a subanalysis of randomized controlled trials (RCTs) only, patients undergoing early AVR had lower rates of hospitalization for CV causes (RR 0.41; 95% CI 0.27 to 0.63) and stroke (RR 0.62; 95% CI 0.40 to 0.95), with no difference in terms of all-cause mortality, sudden death, MI, or cardiac death. In this meta-analysis, early AVR was associated with reduced rates of all-cause and cardiac mortality, while yielding similar rates of stroke, hospitalization for CV causes, MI, or sudden death in the overall cohort analysis as compared with conservative treatment.

Aortic stenosis (AS) is a common valvular disorder, with a prevalence of over 12% in elderly patients and is projected to double by 2050.[1] Current guidelines recommended aortic valve replacement (AVR) in patients with symptomatic severe AS.[2,3] However, the optimal time to treat truly asymptomatic patients with severe AS, who have an increased risk of progression, remains unclear.[4] Recent studies evaluating early AVR versus conservative treatment have shown potential benefits of early intervention in patients with asymptomatic severe AS, including lower rates of all-cause mortality, cardiac death, or hospitalization for heart failure (HF).[5–8] In contrast, previous meta-analyses reported no significant difference between both groups in terms of stroke and myocardial infarction (MI), yielding conflicting results. Despite that, these meta-analyses have combined data from studies comprising patients with left ventricular ejection fraction (LVEF) < 50%, as well as studies with designs that did not allow for direct comparisons between these groups, which may have less generalizable findings.[9,10] Recently, randomized controlled trials (RCTs) focusing on patients with preserved left ventricular function, such as EARLY-TAVR trial and EVOLVED trial, shed light on more short-term outcomes. Additionally, the AVATAR trial released long-term post-hoc analyses.[11–13] Thus, we aim to perform an updated systematic review and meta-analysis evaluating the efficacy and safety of early AVR compared with

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conservative treatment in asymptomatic patients with severe AS and LVEF > 50%.

Material and Methods

This meta-analysis was performed and reported following the Cochrane Handbook of Systematic Reviews of Interventions recommendations and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[14,15] The prospective meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database, under protocol number CRD42024532509.

Eligibility criteria

We considered studies eligible for inclusion if they: (1) were RCTs or observational studies; (2) compared early AVR with conservative treatment; (3) enrolled patients with asymptomatic severe aortic stenosis and clearly specified LVEF > 50%; and (4) reported any of our outcomes of interest. We excluded studies that (1) did not report any of the outcomes of interest; (2) included patients with LVEF < 50%; (3) studies with overlapping populations; (4) studies without control group; and (5) editorials, conference abstracts, case reports, or case series.

Search strategy and data extraction

We systematically searched PubMed, Embase, and Cochrane in November 2024 using the following search: ("very severe aortic stenosis" OR "asymptomatic severe aortic stenosis" OR "asymptomatic aortic stenosis" OR "asymptomatic AS") AND ("surgical aortic valve replacement" OR SAVR OR AVR OR "transcatheter aortic valve replacement" OR TAVR OR eAVR OR "early surgery" OR "early intervention"). Two authors (V.B.P. and T.T.) independently extracted data following predefined search criteria and quality assessment. Discrepancies were resolved through consensus among the authors.

Endpoints and subanalyses

Our outcomes of interest may be stratified as following: (1) all-cause mortality; (2) cardiac death; (3) hospitalization for cardiovascular (CV) causes, including both hospitalization for HF and unplanned aortic stenosis-related hospitalization; (4) MI; (5) stroke; and (6) sudden death. Major adverse cardiac events (MACE) were not assessed due to considerable discrepancies in MACE definitions among the included studies. The specific definitions employed in each included study are detailed in the Supplementary Material (Table S1). We performed a prespecified subanalysis of RCT-only data.

Quality assessment

We performed the quality assessment using the Cochrane Collaboration's tools for assessing risk of bias in randomized and non-randomized studies.[16,17] Two authors (M.R.C.C. and V.B.) performed the risk of bias assessment independently and disagreements were resolved through consensus.

Statistical analysis

We pooled risk ratios (RR) and hazard ratios (HR) with 95% confidence intervals (CI) for binary endpoints. A random-effects model was applied accounting for demographical and methodological heterogeneity among included randomized and nonrandomized studies, as per Cochrane recommendations.[14] We evaluated heterogeneity through the Cochran's Q test and I^2 statistics; I^2 ≥25% and p-values for superior to 0.10 were considered significant for heterogeneity. High heterogeneity and potential study dominance were explored using leave-one-out analysis. p-values inferior to 0.05 were considered statistically significant for treatment effects. We performed all statistical analyses using the *meta* and *metafor* packages in R software 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection and characteristics

Our literature search identified 455 studies. After removal of duplicate records and ineligible studies by title and abstract, 31 underwent full-text review (Figure 1). Four RCTs and 3 observational studies comprising 2,531 patients with asymptomatic severe AS and preserved left ventricular function were included, of whom 1,234 (49%) underwent early AVR.[5,6,8,11–13,18]

Overall, the mean age was over 60 year-old. Furthermore, 4 studies performed surgical aortic-valve replacement (SAVR) only.[5,6,13,18] One study focused exclusively on transcatheter aortic-valve replacement (TAVR),[12] and 2 studies included both surgery and transcatheter procedures.[8,11] Comorbidities varied among studies, hypertension was more common in the study of Banovic and colleagues (2024),[13] while patients with hyperlipidemia was higher in the study of Généreux and colleagues (2024).[12]

In terms of echocardiography parameters, aortic-valve area (AVA) and aortic-valve peak velocity (AVPV) ranged from 0.61 to 0.90 cm^2 and 4.3 to 5.14 m/s, respectively. The mean LVEF was consistent between included studies, ranging from 62% to 68%. Additional individual studies characteristics are reported in Table 1. The follow-up time and the definitions of severe AS are detailed in the Supplementary Material (Table S1).

Pooled analysis of all studies

Early AVR was associated with a significantly lower all-cause mortality as compared with conservative treatment group (HR 0.51; 95% CI 0.31 to 0.83; p <0.01; I^2 = 70.9%; Figure 2). Further, patients undergoing early intervention had a significantly lower cardiac death compared with conservative treatment (RR 0.51; 95% CI 0.30 to 0.89; p = 0.02; I^2 = 65.6%; Figure 3), with a particularly high between-study heterogeneity in these outcomes.

There were no significant differences between early AVR and conservative treatment with regards to the hospitalization for CV causes (RR 0.46; 95% CI 0.21 to 1.04; p = 0.06; I^2 = 60.5%; Figure S1), MI (RR 0.61; 95% CI 0.22 to 1.69; p = 0.34; I^2 = 0%; Figure S2), sudden death (RR 0.47; 95% CI 0.12 to 1.75; p = 0.26; I^2 = 54.1%; Figure S3), or stroke (RR 0.71; 95% CI 0.47 to 1.07; p = 0.10; I^2 = 31.5%; Figure S4).

Subanalyses in selected populations

In a subanalysis of RCT-only data (1,427 patients), there was no difference between groups in all-cause mortality (HR 0.68; 95% CI 0.39 to 1.19; p = 0.18; I^2 = 61.1%; Figure 1), cardiac death (RR 0.72; 95% CI 0.48 to 1.07; p = 0.10; I^2 = 48%; Figure 2), or MI (RR 0.46; 95% CI 0.09 to 2.37; p = 0.35; I^2 = 14.1%; Figure S2). Nevertheless, early AVR was associated with a significantly lower incidence of stroke (RR 0.62; 95% CI 0.40 to 0.95; p = 0.03; I^2 = 0%; Figure S4), and hospitalization for CV causes (RR 0.41; 95% CI 0.27 to 0.63; p <0.01; I^2 = 26.5%; Figure S1).

In observational studies, there was a lower all-cause mortality rate in the early AVR group (HR 0.34; 95% CI 0.15 to 0.76; p <0.01; I^2 = 73.5%; Figure 1) compared with conservative group, which was consistent with the overall cohort analysis. However, cardiac death remained comparable between groups (RR 0.14; 95% CI 0.01 to 1.92; p = 0.14; I^2 = 72.5%; Figure 2) in nonrandomized and randomized

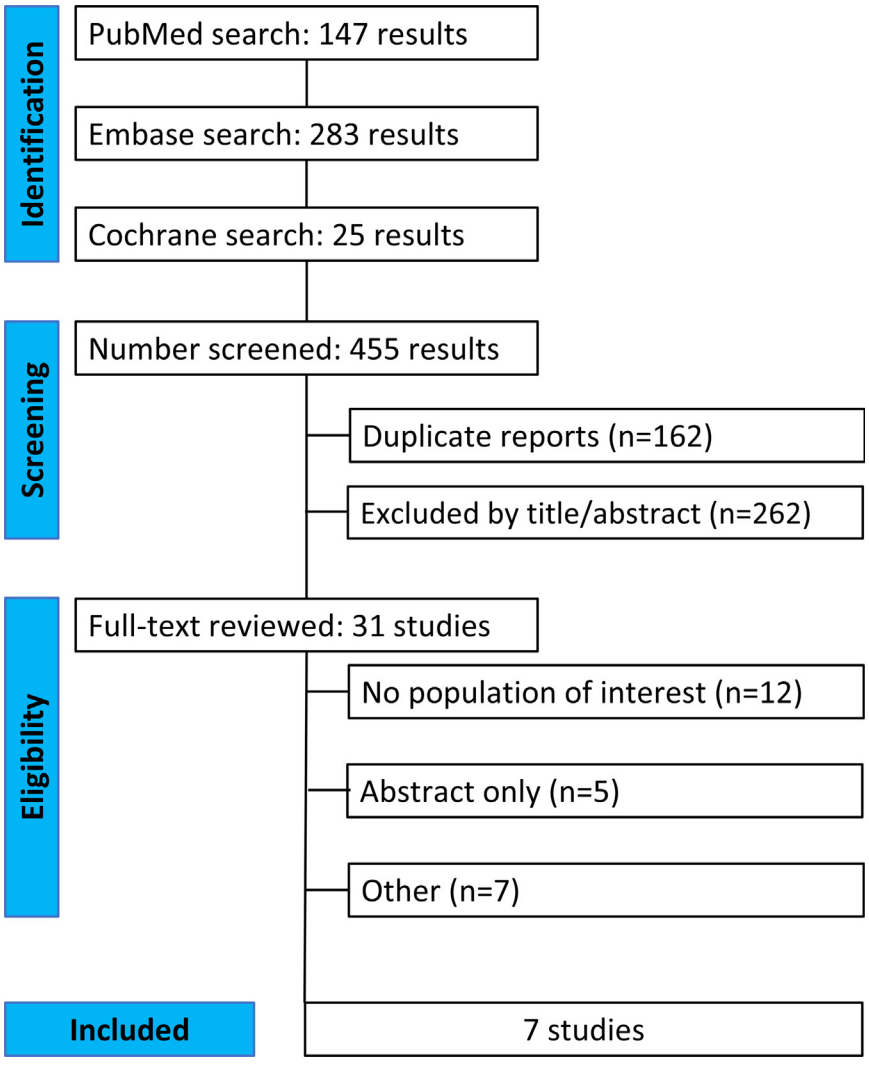

Figure 1. PRISMA flow diagram.

studies analyses. Of note, there were no differences between these subgroups (test for subgroup differences p >0.5).

Quality assessment

The critical appraisal of individual studies and summary of risk of bias are presented in Supplementary Material (Figure S5 and S6, respectively). All RCTs were judged to be at some concerns due to an open-label design. Observational studies were judged to be at low risk of performance bias due to the use of methods to evaluate confound variables, albeit its open-label design. The experimental controls applied in the RCTs, and the statistical controls used in the observational studies were provided in the Supplementary Material (Table S2).

Sensitivity analysis

Sensitivity analyses were conducted to explore high heterogeneity and potential study dominance in the outcomes. Leave-one-out analyses revealed higher contributions to heterogeneity from Kim and colleagues for the outcomes stroke and hospitalization for CV causes (Figures S7 and S8, Supplementary Material) [8]. Moreover, regarding cardiac death – a result that initially showed a significant difference between the 2 groups in the overall cohort analysis – this difference became nonsignificant after omitting the studies by Banovic and Kim (Figure S9, Supplementary Material).[8,13] Nonetheless, results remained consistent with the prior analysis between early AVR and conservative treatment, even though each study has been removed from the analyses (Figures S10, S11 and S12, Supplementary Material).

Discussion

In this systematic review and meta-analysis of 7 studies including 2,531 patients, we compared endpoints of early AVR versus conservative treatment in patients with asymptomatic severe AS and preserved left ventricular function. The main findings with early AVR over conservative treatment include: (1) lower rates of all-cause and cardiac mortality in the pooled analysis of observational and RCT data; (2) comparable incidence of MI and sudden death in the overall cohort and in subanalysis of randomized data; and (3) similar rates of stroke or hospitalization for CV causes, in contrast with the observed lower rates of these outcomes in the subanalysis of RCT-only data as compared with conservative treatment.

Up to 50% of patients with severe AS are asymptomatic at the time of diagnosis, and the progression of the disease is not accurately predictable.[12,19–22] Cardiac remodeling caused by chronic hemodynamic stress can progress to irreversible stages of secondary cardiac damage,

Table 1
Baseline characteristics of included studies

Characteristics	Banovic et al.[13]		Bohbot et al.[5]		Généreux et al.[12]		Loganath et al.[11]		Kang et al.[18]		Kang et al.[6]		Kim et al.[8]	
	Early AVR	CT	Early AVR	CT	Early AVR	CT	Early AVR	CT	Early AVR	CT	Early AVR	CT	Early AVR	CT
Age, years*	68	69	73	73	76	75.6	75	76	63	63	65	63.4	61	67.1
Sample size, n	78	79	192	247	455	446	113	111	102	95	73	72	221	247
Type of procedure	SAVR		SAVR		TAVR		SAVR/TAVR		SAVR		SAVR		SAVR/TAVR	
Female, n (%)	32 (41%)	35 (44%)	NA	NA	131 (29%)	147 (33%)	31 (27%)	32 (29%)	47 (46%)	51 (54%)	36 (49%)	38 (53%)	111 (50%)	121 (49%)
STS score, %*	1.6	1.8	NA	NA	1.8	1.7	NA	NA	NA	NA	NA	NA	NA	NA
BMI, kg/m^2	NA	NA	NA	NA	28.4	28.6	27.2	27.8	23.9	24.1	24.7	24	24.6	23.6
Diabetes mellitus, n (%)	14 (18%)	23 (29%)	NA	NA	119 (26%)	114 (26%)	15 (13%)	26 (23%)	10 (10%)	10 (11%)	13 (18%)	7 (10%)	37 (17%)	66 (27%)
Hypertension, n (%)	69 (88%)	70 (87%)	NA	NA	369 (81%)	365 (82%)	76 (67%)	70 (63%)	37 (36%)	39 (41%)	40 (55%)	39 (54%)	92 (42%)	122 (49%)
Hyperlipidemia, n (%)	NA	NA	NA	NA	375 (82%)	347 (78%)	55 (49%)	56 (50%)	31 (30%)	37 (39%)	41 (56%)	42 (58%)	59 (27%)	61 (25%)
Previous stroke, n (%)	2 (2.5%)	2 (2.5%)	NA	NA	19 (4%)	20 (4.5%)	NA	NA	NA	NA	3 (4%)	3 (4%)	9 (4%)	34 (14%)
Previous MI, n (%)	NA	NA	NA	NA	23 (5%)	18 (4%)	10 (9%)	9 (8%)	NA	NA	NA	NA	4 (2%)	5 (2%)
AVA, cm^2*	0.73	0.74	NA	NA	0.9	0.8	0.8	0.8	0.61	0.62	0.63	0.64	0.74	0.80
AVPV, m/s*	4.5	4.5	NA	NA	4.3	4.4	4.3	4.4	5.1	4.9	5.14	5.04	4.7	4.5
Mean TG, mmHg	51	50	NA	NA	46.5	47.3	45.2	45	65	59	64.3	62.7	55	48.6
LVEF, %*	NA	NA	NA	NA	67.4	67.4	68	68	62	63	64.8	64.8	63.7	63.1

* Mean or median;
AVA = aortic-valve area; AVPV = aortic-valve peak velocity; AVR = aortic-valve replacement; BMI = body mass index; CT = conservative treatment; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SAVR = surgical aortic-valve replacement; STS = Society of Thoracic Surgeons; TG = transaortic gradient; TAVR = transcatheter aortic-valve replacement.

occurring independently of symptom onset or LVEF impairment and significantly impacting the prognosis of AS both before and after AVR. Furthermore, some studies suggested that even asymptomatic patients with severe AS are at increased risk of sudden death.[23–26] In this sense, earlier AVR and clinical surveillance have been compared in patients with asymptomatic severe AS, suggesting that early intervention provide potential benefits as compared with conservative treatment.[11–13] Even so, it remains uncertain whether these benefits will improve the outcomes in patients with preserved left ventricular function.

Meta-analyses have showed that early AVR is associated with reduced all-cause mortality, cardiac death, or hospitalization for HF as compared with conservative treatment, although conflicting results regarding MI and stroke have been reported.[4,9,10,27] Nevertheless, these meta-analyses combined studies comprising patients with LVEF < 50% or without appropriate control group, limiting the ability to accurately assess the efficacy of early intervention in asymptomatic patients with severe AS and preserved left ventricular function. Moreover, current guidelines recommend AVR for patients with asymptomatic severe AS with LVEF < 50%, but 2 additional recent randomized trials suggested earlier TAVR may benefit asymptomatic patients with preserved left ventricular function.[2,3,11,12] Therefore, we conducted an update meta-analysis to address the lack of data focusing on patients with LVEF > 50%.

Although the watchful-waiting strategy to delay surgery until symptoms develop appears to be safe, the conservative treatment is associated with a risk of sudden death and irreversible myocardial damage, increasing periprocedural and potentially affecting long-term prognosis.[22,28,29] In this context, our meta-analysis found no differences between early AVR and conservative care strategy in terms of sudden death. This may be partly attributed to the limited statistical power, given the small sample size in the analysis. However, early AVR was associated with lower rates of all-cause mortality, which is consistent with previous studies.[6,13] Généreux and colleagues reported similar rates of death between both groups, but showed lower rates as compared with previous trials, probably due to the less invasive nature of TAVR as compared with surgery.[12] Our meta-analysis could not specifically evaluate the TAVR procedure due to insufficient data in the available studies.

Despite that, Loganath and colleagues suggested that previous mortality results providing benefits for early AVR cannot be extrapolated to the broader older population with asymptomatic severe AS, particularly those with a greater burden of comorbidities.[11] However, our results were consistent with previous meta-analyses, demonstrating lower rates of cardiac death concomitantly.[30–34] This may be associated with secondary cardiac damage, implying that some initially diagnosed patients may die or suffer from valve-related cardiac events before AVR.[8] Even so, more trials with older patients at high surgical risk are needed.

Our meta-analysis found no significant differences in terms of stroke, while beneficial effect favoring intervention was noticed in RCT-only data. The reason may be differences in confounding in the observational studies. Also, recent evidence suggest a higher incidence of unplanned aortic stenosis-related hospitalizations and hospitalization for HF in patients with guideline-directed conservative management.[35] These findings are particularly significant as they align with primary treatment goals for elderly patients and underscore the value of early intervention, especially given its low procedural risk.[11] Our results showed comparable incidences of hospitalization for CV causes in the overall cohort analysis, but reduced rates were observed for early AVR in subgroup of RCT data, with lower heterogeneity as compared to overall cohort, which may suggest potential source of bias from the observational study, as only patients with a very low risk underwent SAVR or TAVR.

Our study has limitations. First, the robustness of our results may be affected by the constraints of our limited sample size. Second, all

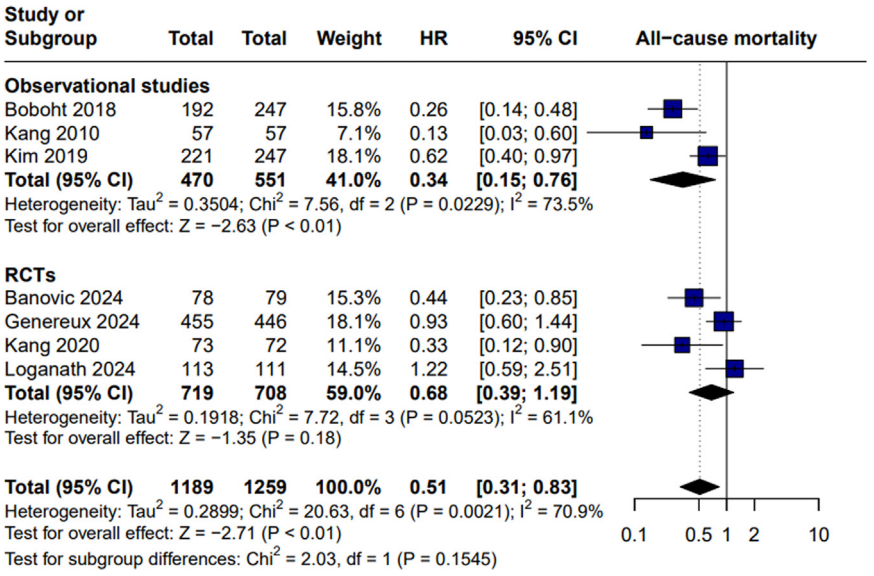

Figure 2. All-cause mortality was significantly lower in the early AVR group as compared to conservative treatment in the overall cohort analysis. *CI = confidence interval; HR = hazard ratio.*

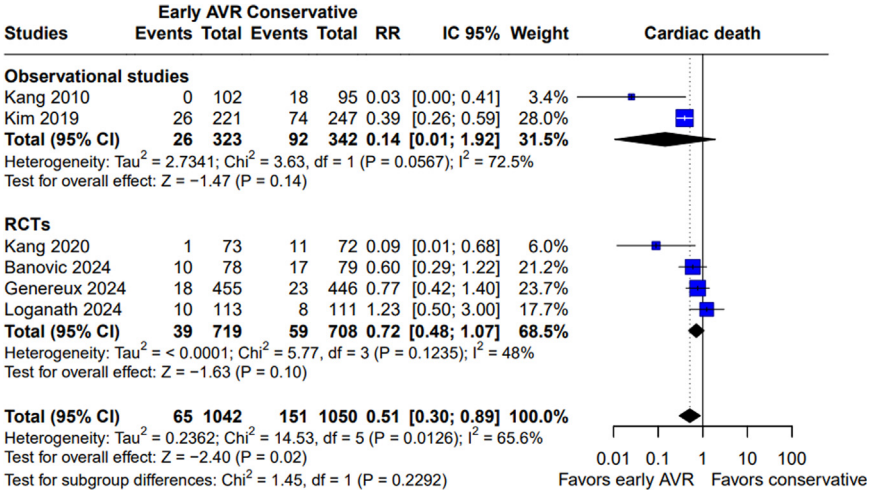

Figure 3. Cardiac death was significantly lower in the early AVR group as compared to conservative treatment in the overall cohort analysis. *AVR = aortic valve replacement; CI = confidence interval; RR = relative risk.*

included studies combined younger patient population, which could be a potential source of selection bias, impairing generalizability to older patients at high surgical risk. Third, most of the studies utilized SAVR as the primary treatment within the AVR group, limiting the generalizability of our findings to patients undergoing TAVR. Fourth, some studies did not routinely perform exercise stress test, or this was performed selectively and, therefore, we were unable to determine whether all patients were truly asymptomatic. Fifth, we were unable to assess midwall myocardial fibrosis or biomarkers of cardiac damage, such as cardiac troponin due to the lack of available data. In addition to, we did not explore the impact of crossover between surveillance and early AVR due to a lack of data and standardization across included studies. Finally, the follow-up time varied among included studies, and we cannot generalize our results to the long-term setting.

Conclusion

In this systematic review and meta-analysis, early AVR by either SAVR or TAVR was associated with reduced rates of all-cause mortality and cardiac death, while yielding similar rates of stroke, hospitalization for CV causes, MI, or sudden death as compared with conservative treatment, albeit beneficial effect favoring early intervention in terms of stroke and hospitalization was noticed in RCT-only data analysis, with no significant differences in mortality rates. This suggests that early AVR may be an effective alternative to clinical surveillance in treating patients with asymptomatic severe AS and preserved left ventricular function.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Vinicius Bittar de Pontes: Writing – original draft, Software, Methodology, Conceptualization. **Mariana R.C. Clemente:** Software, Investigation, Formal analysis. **Thierry Trevisan:** Visualization,

Investigation, Data curation. **Sebastian Jaramillo:** Formal analysis, Data curation. **Mauricio Ferreira Boneli:** Formal analysis, Data curation. **Nicole Felix:** Writing – review & editing, Supervision. **Laura G. S. Gameiro:** Writing – review & editing, Supervision. **Philippe Garot:** Writing – review & editing, Supervision. **Wilton F. Gomes:** Writing – review & editing, Supervision.

Data Sharing

This study-level meta-analysis includes publicly data from published studies; therefore, all of the data and study materials are available in the public domain.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2025.03.039.

References

1 Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Fugar S, Generoso G, Heard DG, Hiremath S, Ho JE, Kalani R, Kazi DS, Ko D, Levine DA, Liu J, Ma J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge MP, Thacker EL, Virani SS, Voeks JH, Wang NY, Wong ND, Wong SS, Yaffe K, Martin SS. Heart disease and stroke statistics-2023 update: A report from the American Heart Association. Circulation 2023;147(8):e93–e621. https://doi.org/10.1161/CIR.0000000000001123.

2 Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43(7):561–632. https://doi.org/10.1093/eurheartj/ehab395.

3 Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin 3rd JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt 3rd TM, Thompson A, Toly C. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143(5):e35–71. https://doi.org/10.1161/CIR.0000000000000932.

4 Gahl B, Çelik M, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ, van Mieghem NM, Kappetein AP, Jüni P, da Costa BR. Natural history of asymptomatic severe aortic stenosis and the association of early intervention with outcomes: a systematic review and meta-analysis. JAMA Cardiol 2020;5(10):1102–12. https://doi.org/10.1001/jamacardio.2020.2497.

5 Bohbot Y, Pasquet A, Rusinaru D, Delabre J, Delpierre Q, Altes A, Maréchaux S, Vanoverschelde JL, Tribouilloy C. Asymptomatic severe aortic stenosis with preserved ejection fraction: early surgery versus conservative management. J Am Coll Cardiol 2018;72(23 Pt A):2938–9. https://doi.org/10.1016/j.jacc.2018.09.049.

6 Kang DH, Park SJ, Lee SA, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, Song JK, Lee JW, Park SW. Early surgery or conservative care for asymptomatic aortic stenosis. New Eng J of Med 2020;382(2):111–9. https://doi.org/10.1056/NEJMoa1912846.

7 Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, Kotrc M, Glaveckaite S, Gasparovic H, Pavlovic N, Velicki L, Salizzoni S, Wojakowski W, Van Camp G, Nikolic SD, Iung B, Bartunek J. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. Circulation 2022;145(9):648–58. https://doi.org/10.1161/CIRCULATIONAHA.121.057639.

8 Kim HJ, Kim JB, Kim HR, Ju MH, Kang DY, Lee SA, Lee S, Ahn JM, Kim DH, Jung SH, Park DW, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Park SJ. Impact of valve replacement on long-term survival in asymptomatic patients with severe aortic stenosis. Am J Cardiol 2019;123(8):1321–8. https://doi.org/10.1016/j.amjcard.2019.01.035.

9 Senguttuvan NB, Srinivasan NV, Panchanatham M, Abdulkader RS, Anandaram A, Polareddy DR, Ramesh S, Singh H, Yallanki H, Kaliyamoorthi D, Chidambaram S, Ramalingam V, Rajendran R, Muralidharan TR, Rao R, Seth A, Claessen B, Krishnamoorthy P. Systematic review and meta-analysis of early aortic valve replacement versus conservative therapy in patients with asymptomatic aortic valve stenosis with preserved left ventricle systolic function. Open Heart 2024;11(1):e002511. https://doi.org/10.1136/openhrt-2023-002511.

10 Yasmin F, Shaikh A, Asghar MS, Moeed A, Najeeb H, Waqar E, Ram MD, Nankani A, Ochani RK, Aamir M, Ullah W, Waqar F, Johnson DM. Early transcatheter or surgical aortic valve replacement versus conservative management in asymptomatic patients with severe aortic stenosis: a systematic review and meta-analysis. Curr Probl Cardiol 2023;48(3):101477. https://doi.org/10.1016/j.cpcardiol.2022.101477.

11 Loganath K, Craig NJ, Everett RJ, Bing R, Tsampasian V, Molek P, Botezatu S, Aslam S, Lewis S, Graham C, White AC, MacGillivray T, Tuck CE, Rayson P, Cranley D, Irvine S, Armstrong R, Milne L, Chin CWL, Hillis GS, Fairbairn T, Greenwood JP, Steeds R, Leslie SJ, Lang CC, Bucciarelli-Ducci C, Joshi NV, Kunadian V, Vassiliou VS, Dungu JN, Hothi SS, Boon N, Prasad SK, Keenan NG, Dawson D, Treibel TA, Motwani M, Miller CA, Mills NL, Rajani R, Ripley DP, McCann GP, Prendergast B, Singh A, Newby DE, Dweck MR. Early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis: the EVOLVED randomized clinical trial. JAMA 2024;333(3):213–21. https://doi.org/10.1001/jama.2024.22730.

12 Généreux P, Schwartz A, Oldemeyer JB, Pibarot P, Cohen DJ, Blanke P, Lindman BR, Babaliaros V, Fearon WF, Daniels DV, Chhatriwalla AK, Kavinsky C, Gada H, Shah P, Szerlip M, Dahle T, Goel K, O'Neill W, Sheth T, Davidson CJ, Makkar RR, Prince H, Zhao Y, Hahn RT, Leipsic J, Redfors B, Pocock SJ, Mack M, Leon MB. Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. N Engl J of Med. 2024;392(3):217-227. doi:10.1056/NEJMoa2405880

13 Banovic M, Putnik S, Da Costa BR, Penicka M, Deja MA, Kotrc M, Kockova R, Glaveckaite S, Gasparovic H, Pavlovic N, Velicki L, Salizzoni S, Wojakowski W, Van Camp G, Gradinac S, Laufer M, Tomovic S, Busic I, Bojanic M, Ristic A, Klasnja A, Matkovic M, Boskovic N, Zivic K, Jovanovic M, Nikolic SD, Iung B, Bartunek J. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: long-term follow-up of the AVATAR trial. Eur Heart J 2024:ehae585. https://doi.org/10.1093/eurheartj/ehae585.

14 Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Repr. with corr, Chichester, West Sussex: John Wiley & Sons; 2009.

15 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

16 Sterne JA, Hernán MA, Reeves BC, Savovi J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.

17 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.

18 Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, Choo SJ, Park SW, Song JK, Lee JW, Park PW. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation 2010;121(13):1502–9. https://doi.org/10.1161/CIRCULATIONAHA.109.909903.

19 Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax JJ, Bonow RO, Leon MB. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2016;67(19):2263–88. https://doi.org/10.1016/j.jacc.2016.02.057.

20 Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, Chambers J, Rosenhek R, Habib G, Lloyd G, Nistri S, Garbi M, Marchetta S, Fattouch K, Coisne A, Montaigne D, Modine T, Davin L, Gach O, Radermecker M, Liu S, Gillam L, Rossi A, Galli E, Ilardi F, Tastet L, Capoulade R, Zilberszac R, Vollema EM, Delgado V, Cosyns B, Lafitte S, Bernard A, Pierard LA, Bax JJ, Pibarot P, Oury C. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiol 2018;3(11):1060–8. https://doi.org/10.1001/jamacardio.2018.3152.

21 Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, Bergler-Klein J, Grimm M, Gabriel H, Maurer G. Natural history of very severe aortic stenosis. Circulation 2010;121(1):151–6. https://doi.org/10.1161/CIRCULATIONAHA.109.894170.

22 Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343(9):611–7. https://doi.org/10.1056/NEJM200008313430903.

23 Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, Svensson LG, Kapadia S, Tuzcu EM, Thourani VH, Babaliaros V, Herrmann HC, Szeto WY, Cohen DJ, Lindman BR, McAndrew T, Alu MC, Douglas PS, Hahn RT, Kodali SK, Smith CR, Miller DC, Webb JG, Leon MB. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J 2017;38(45):3351–8. https://doi.org/10.1093/eurheartj/ehx381.

24 Wang Y, Zhang M, Chen H, Li H. Prognostic value of global longitudinal strain in asymptomatic aortic stenosis: a systematic review and meta-analysis. Front Cardiovasc Med 2022;9:778027. https://doi.org/10.3389/fcvm.2022.778027.

25 Généreux P, Pibarot P, Redfors B, Bax JJ, Zhao Y, Makkar RR, Kapadia S, Thourani VH, Mack MJ, Nazif TM, Lindman BR, Babaliaros V, Vincent F, Russo M, McCabe JM, Gillam LD, Alu MC, Hahn RT, Webb JG, Leon MB, Cohen DJ. Evolution and prognostic impact of cardiac damage after aortic valve replacement. J Am Coll Cardiol 2022;80(8):783–800. https://doi.org/10.1016/j.jacc.2022.05.006.

26 Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Kato T, Ishii K, Nagao K, Nakagawa Y, Toyofuku M, Saito N, Minatoya K, Kimura T. Sudden death in patients with severe aortic stenosis: observations from the CURRENT as registry. J Am Heart Assoc 2018;7(11):e008397. https://doi.org/10.1161/JAHA.117.008397.

27 Costa GNF, Cardoso JFL, Oliveiros B, Gonçalves L, Teixeira R. Early surgical intervention versus conservative management of asymptomatic severe aortic stenosis: a

systematic review and meta-analysis. Heart 2023;109(4):314–21. https://doi.org/10.1136/heartjnl-2022-321411.
28 Carabello BA. Should severe aortic stenosis be operated on before symptom onset? Aortic valve replacement should be operated on before symptom onset. Circulation 2012;126(1):112–7. https://doi.org/10.1161/CIRCULATIONAHA.111.079350.
29 Shah PK. Should severe aortic stenosis be operated on before symptom onset? Severe aortic stenosis should not be operated on before symptom onset. Circulation 2012;126(1):118–25. https://doi.org/10.1161/CIRCULATIONAHA.111.079368.
30 Yuan T, Lu Y, Bian C, Cai Z. Early Aortic valve replacement vs. conservative management in asymptomatic severe aortic stenosis patients with preserved ejection fraction: a meta-analysis. Front Cardiovasc Med 2020;7:621149. https://doi.org/10.3389/fcvm.2020.621149.
31 Yokoyama Y, Takagi H, Kuno T. Early surgery versus conservative management of asymptomatic severe aortic stenosis: a meta-analysis. J Thorac Cardiovasc Surg 2022;163(5):1778–1785.e5. https://doi.org/10.1016/j.jtcvs.2020.06.078.
32 Ullah W, Gowda SN, Khan MS, Sattar Y, Al-Khadra Y, Rashid M, MO Mohamed, Alkhouli M, Kapadia S, Bagur R, Mamas MA, Fischman DL, Alraies MC. Early intervention or watchful waiting for asymptomatic severe aortic valve stenosis: a systematic review and meta analysis. J Cardiovasc Med (Hagerstown) 2020;21(11):897–904. https://doi.org/10.2459/JCM.0000000000001110.
33 Wei C, Li Z, Xu C, Yin T, Zhao C. Timing of surgery for asymptomatic patients with severe aortic valve stenosis: An updated systematic review and meta-analysis. Hellenic J Cardiol 2021;62(4):270–7. https://doi.org/10.1016/j.hjc.2021.01.005.
34 Maziarz M. Is meta-analysis of RCTs assessing the efficacy of interventions a reliable source of evidence for therapeutic decisions? Stud Hist Philos Sci 2022;91:159–67. https://doi.org/10.1016/j.shpsa.2021.11.007.
35 Maznyczka A, Prendergast B, Dweck M, Windecker S, Généreux P, Hildick-Smith D, Bax J, Pilgrim T. Timing of aortic valve intervention in the management of aortic stenosis. JACC Cardiovasc Interv 2024;17(21):2502–14. https://doi.org/10.1016/j.jcin.2024.08.046.