Journal of the Society for Cardiovascular Angiography & Interventions 1 (2022) 100383

Contents lists available at ScienceDirect

Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: www.jscai.org

Meta-Analysis

Early Surgery for Patients With Asymptomatic Severe Aortic Stenosis: A Meta-Analysis of Randomized Controlled Trials

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A B S T R A C T

Background: Guidelines provide class I recommendations for aortic valve intervention for patients with symptomatic severe aortic stenosis (AS) or reduced ejection fraction, but the cornerstone of management for asymptomatic patients has been watchful waiting. This is based on historical nonrandomized data, but randomized controlled trials (RCTs) have now been performed of early surgical aortic valve replacement (SAVR) for asymptomatic severe AS. We performed a meta-analysis of RCTs comparing early SAVR to watchful waiting for asymptomatic severe AS, focusing on individual end points of death and heart failure (HF) hospitalization.

Methods: We systematically identified all RCTs comparing early SAVR to watchful waiting in patients with asymptomatic severe AS and synthesized the data in a random-effects meta-analysis. The prespecified primary end point was all-cause mortality.

Results: Two trials randomizing 302 patients were included. Early SAVR lead to a 55% reduction in all-cause mortality (hazard ratio, 0.45; 95% confidence interval, 0.24-0.85; $P = .014$). There was no heterogeneity ($I^2 = 0.0\%$). Early SAVR also lead to a 79% reduction in HF hospitalization (hazard ratio, 0.21; 95% confidence interval, 0.05-0.96; $P = .044$).

Conclusions:: In patients with severe asymptomatic AS and normal ejection fraction, early SAVR reduces death and HF hospitalization compared to initial conservative management. This challenges current treatment standards and has implications for the clinical care of these patients and for guidelines.

Introduction

Guidelines provide class I recommendations for aortic valve intervention for patients with symptomatic severe aortic stenosis (AS) or reduced ejection fraction.[1,2] The cornerstone of management for asymptomatic patients has been watchful waiting, based on historical data from postmortem studies.[3] Randomized controlled trials (RCTs) have now been performed of early surgical aortic valve replacement (SAVR) for asymptomatic severe AS. These trials reported composite outcomes as primary end points and did not provide conclusive results with regard to mortality. We performed a meta-analysis of RCTs of patients with asymptomatic severe AS randomized to either early surgery or watchful waiting, focusing on individual end points of death and heart failure (HF) hospitalization.

Methods

The analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42021293156). This is a study-level meta-analysis of published data, so ethical approval was not required. YA had full access to all the data in the study and takes responsibility for their integrity and the data analysis. The analysis was

Abbreviations: AS, aortic stenosis; AVATAR, Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; HF, heart failure; HR, hazard ratio; IQR, interquartile range; RCT, randomized controlled trial; RECOVERY, Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Keywords: Meta-analysis; randomized controlled trials; severe aortic stenosis.

Data availability statement: The data underlying this article are available in the article and in its online supplementary material.

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https://doi.org/10.1016/j.jscai.2022.100383
Received 14 March 2022; Received in revised form 3 May 2022; Accepted 4 May 2022
Available online 25 May 2022

conducted in accordance with published Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.[4]

We performed a systematic search of electronic databases from December 2010 through December 2021 for all RCTs comparing SAVR to watchful waiting for asymptomatic severe AS. The MEDLINE, Embase, and Cochrane Central Register of Controlled Trial databases were searched. Our search strings are shown in the Supplemental Appendix S1. We hand-searched bibliographies of selected studies, meta-analyses, and reviews to identify any further eligible trials and also searched conference abstracts from American Heart Association, American College of Cardiology, European Society of Cardiology, TCT, TVT, and EuroPCR. There were no language restrictions. Two authors independently performed the searches and extracted the data (YA and JPH), with disputes resolved via consensus. Only randomized trials were considered. Trials had to report clinical outcomes after randomization to early SAVR or watchful waiting.

Both random- and fixed-effects meta-analyses were performed; the I^2 statistic was used to assess heterogeneity.[5] We used the Cochrane risk of bias tool to assess quality of included trials.[6] In accordance with published guidance, tests for publication bias would only be performed if more than 10 suitable trials were included in the meta-analysis.[7] The prespecified primary end point was all-cause mortality; the prespecified secondary end point was HF hospitalization. We also assessed cardiovascular death and clinical thromboembolism. The definitions of all end points utilized in the individual trials were used for this analysis. In both trials, clinical thromboembolism was based on symptoms, signs, and imaging studies. In both trials, the definition of cardiovascular mortality was sudden cardiac death, death from myocardial infarction, congestive HF, complications of cardiac surgery or intervention, stroke, or other cardiovascular disease.

We used hazard ratios (HRs) as our outcome measure to account for time-to-event survival data and differing follow-up durations between trials. A meta-analysis of the natural logarithm of the HRs and their associated standard errors using the restricted maximum likelihood estimator was performed. The standard error was calculated by dividing the difference between the natural logarithms of the upper and lower 95% confidence intervals (CIs) by 2× the appropriate normal score (1.96). Where the lower 95% CI approached zero, the standard error was calculated using only the difference between the natural logarithm of the upper 95% CI and the natural logarithm of the point estimate. We also performed a reconstructed individual

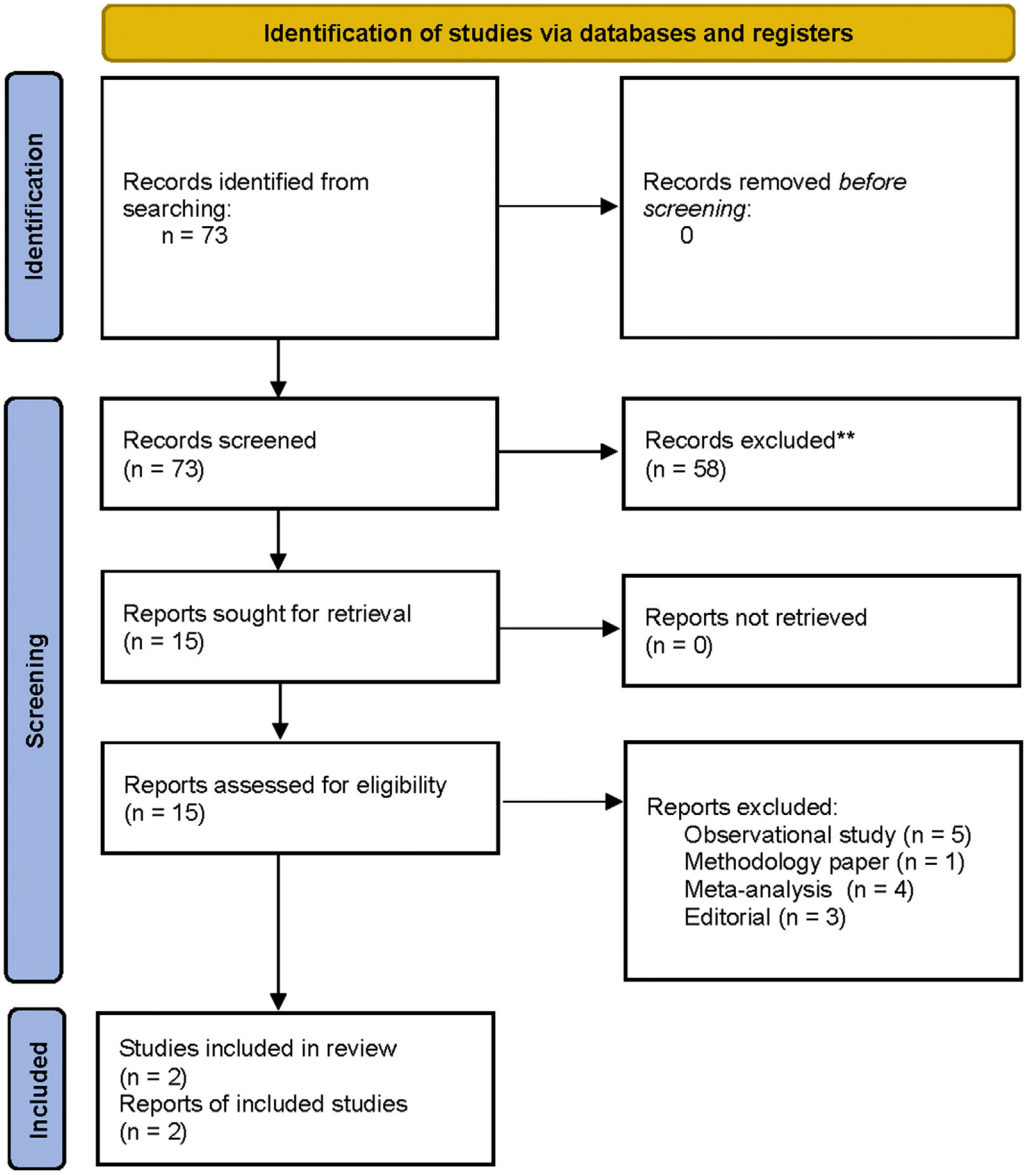


Figure 1. Source of included studies.

Table 1. Characteristics of included trials

Study name	Author	Year	Location	Number of participants	Average age	Follow-up duration	Inclusion criteria	Main exclusion criteria	Primary end point
RECOVERY[11]	Kang et al	2020	Korea (4 centers)	145 (73 randomized to early surgery and 72 randomized to watchful waiting)	64.2 ± 9.4 y	Surgery group: 6.2 y (interquartile range, 5.0-7.4) Watchful waiting group: 6.1 y (interquartile range, 4.5-7.3)	Patients aged 20-80 y with severe aortic stenosis (aortic valve area of 0.75 cm^2 or less with either a peak aortic jet velocity of 4.5 m per second or greater or a mean transaortic gradient of 50 mm Hg or greater)	Symptoms, ejection fraction <50%, clinically significant aortic regurgitation or mitral valve disease, prior cardiac surgery, positive exercise test (performed selectively, not mandated), age >80 y, cancer or other condition making surgery unsuitable	Composite of operative mortality or death from cardiovascular causes
AVATAR[12]	Banovic et al	2021	Europe (9 centers in 7 countries)	157 (78 randomized to early surgery and 79 randomized to watchful waiting)	67 y	Surgery group: 28 mo Watchful waiting group: 35 mo	Patients aged >18 y old with severe asymptomatic aortic stenosis (confirmed with mandatory exercise testing for all patients)	Symptoms, ejection fraction <50%, very severe AS (defined as maximal aortic jet velocity >5.5 m/s at rest), aortic regurgitation ≥3+, dilatation of the ascending aorta requiring replacement of the aortic root or ascending aorta (>5 cm), significant mitral valve disease, prior cardiac surgery, positive exercise test (defined as occurrence of symptoms, fall in systolic blood pressure ≥20 mm Hg from baseline, or evidence of myocardial ischemia), atrial fibrillation, severe lung disease, limited life expectancy	Composite of all-cause mortality or major adverse cardiovascular events (MACE) comprised of acute myocardial infarction, stroke, and unplanned heart failure hospitalization needing intravenous treatment with diuretics or inotropes

AS, aortic stenosis.

patient data analysis by digitizing the survival curves for the outcome of all-cause mortality and combining with the numbers at risk. The digitization and extraction of individual patient data were performed using the Shiny application.[8] Kaplan-Meier analyses and Cox proportional hazard models were fitted using the extracted individual patient data using the "survival" package for R. Kaplan-Meier plots for the pooled data were then generated using the survminer package. All outcomes were assessed by the intention-to-treat principle. Statistical significance was set at $P < .05$. Mean values are expressed as mean ± SD unless otherwise stated. The statistical programming

Table 2. Risk of bias assessment

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall quality
RECOVERY[11]	Low risk: Computer-generated randomization sequence to surgery or watchful waiting in a 1:1 ratio using a web-based interactive response system. The assignment to each treatment group was computer-generated and stratified according to the participating center by means of a permuted block sequence with variable block size.	Low risk: No allocation bias	High risk: Unblinded	High risk: Adverse clinical events were adjudicated by the data safety monitoring board by consensus, but the data and safety monitoring board were not blinded	Low risk: No patients lost to follow-up	Low risk: All end points on CT.gov reported	Moderate quality: well-conducted but modestly sized open-label trial. Participants and investigators not blinded, which is typical for a randomized trial of surgery vs no surgery.
AVATAR	Low risk: Computer-generated randomization to the early surgery or watchful waiting group in a 1:1 ratio using a web-based interactive response system. The assignment to each treatment group was computer-generated and stratified according to the participating centers by means of a permuted block sequence with variable block size.	Low risk: No allocation bias	High risk: Unblinded	High risk: The independent clinical events committee adjudicated all serious adverse events, but they were not blinded to the treatment arm	Low risk: 1 patient lost to follow-up	Low risk: All end points on CT.gov reported	Moderate quality: well-conducted but modestly sized open-label trial. Participants and investigators not blinded, which is typical for a randomized trial of surgery vs no surgery.

CT.gov, clinicaltrials.gov.

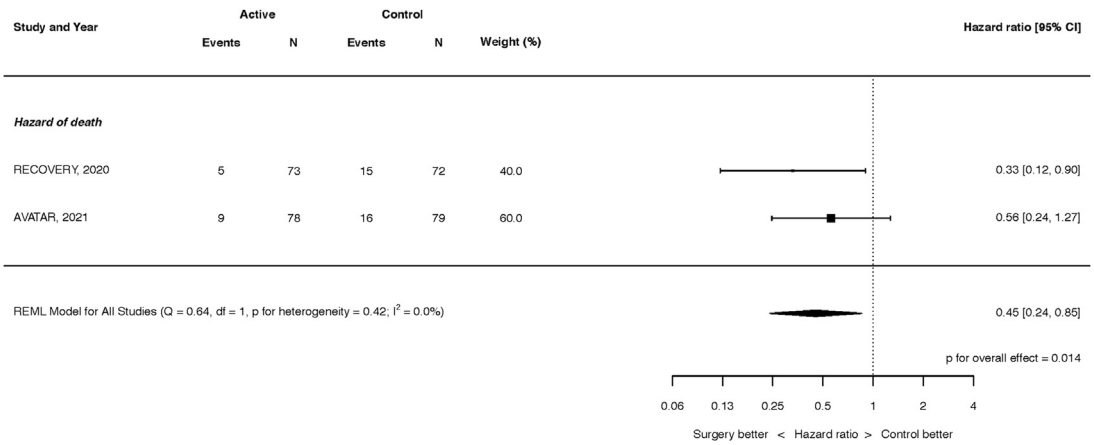


Figure 2. All-cause mortality after randomization to either early surgery or watchful waiting.

environment R[9] with the metafor package[10] was used for all statistical analyses.

Results

Two suitable trials were eligible,[11,12] with a total of 302 randomized patients (151 to SAVR and 151 to watchful waiting). The source of included studies is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart in Figure 1.

The characteristics of the included trials are shown in Table 1. The risk of bias assessment is shown in Table 2. In Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY),[11] the mean age was 64.2 ± 9.4 years and the European System for Cardiac Operative Risk Evaluation was 0.9%; in Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR),[12] the average was 67 years and the median Society of Thoracic Surgeons–predicted risk of mortality score was 1.7%.

In RECOVERY, the median follow-up was 6.2 years (interquartile range [IQR], 5.0-7.4), whereas in AVATAR, the median follow-up duration was 32 months. In the present analysis, the overall weighted mean follow-up duration of both trials combined was 52.2 months.

The etiology of the AS was most commonly a bicuspid aortic valve in 61% of patients in RECOVERY, with 33% suffering from degenerative disease and 6% from rheumatic disease. In AVATAR, the etiology of the AS was most commonly degenerative disease in 85% of patients, whereas 14% had a bicuspid aortic valve and 1.3% had rheumatic disease. The mean peak aortic jet velocity was 5.1 ± 0.5 m per second in RECOVERY, with a mean aortic valve area of 0.63 ± 0.09 cm^2; in AVATAR, this was 4.5 m per second and 0.73 cm^2.

In RECOVERY, all 72 patients randomized to early SAVR successfully underwent surgery; half of these patients received a mechanical valve, and half received a bioprosthetic valve. In AVATAR, 92.3% of patients randomized to early SAVR underwent surgery; 53% of these patients received a mechanical valve, and 47% received a bioprosthetic valve. The median time from randomization to surgery in the early SAVR group was 23 days (IQR, 10-36) in RECOVERY and 55 days (IQR, 36-79) in AVATAR.

For patients randomized to watchful waiting, 74% ultimately underwent aortic valve intervention in RECOVERY (1 patient underwent transcatheter aortic valve replacement [TAVR], and all others underwent SAVR). The median time from randomization to aortic valve replacement in these patients was 700 days (IQR, 277-1469). In AVATAR, 32% of patients randomized to watchful waiting ultimately underwent surgery. The median time from randomization to aortic valve replacement in these patients was 400 days (IQR, 191-619).

Early SAVR was associated with a 55% reduction in all-cause mortality (Figure 2, HR, 0.45; 95% CI, 0.24-0.85; $P = .014$). There was no heterogeneity ($I^2 = 0.0\%$). Early SAVR was also associated with a 79% reduction in HF hospitalization (Figure 3, HR, 0.21; 95% CI, 0.05-0.96; $P = .044$). There was mild heterogeneity ($I^2 = 16.9\%$). There was no significant difference between the 2 groups for the end point of cardiovascular mortality (Figure 4, HR, 0.36; 95% CI, 0.03-3.79; $P = .394$). There was significant heterogeneity ($I^2 = 78.4\%$). There was no significant difference between the 2 groups for the end point of thromboembolism (Figure 5, HR, 0.56; 95% CI, 0.13-2.35; $P = .429$). There was no heterogeneity ($I^2 = 0.0\%$). All results were

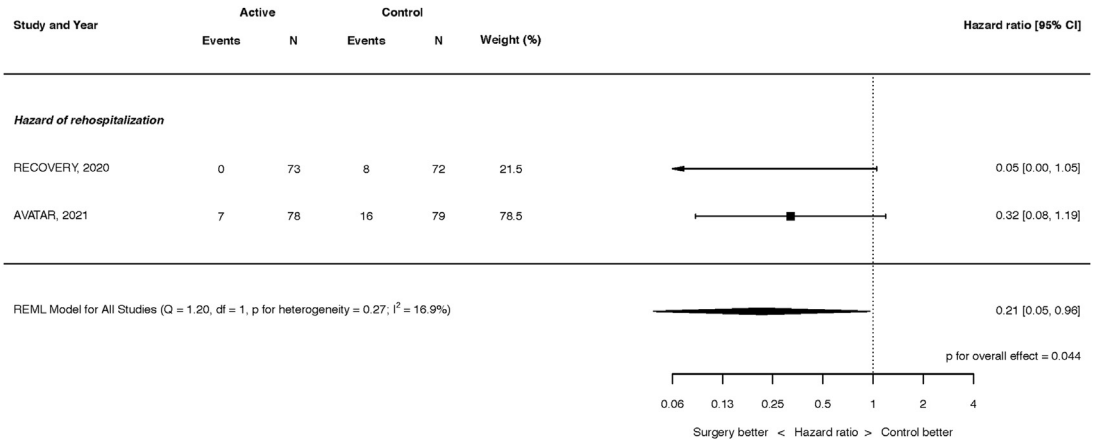


Figure 3. Heart failure hospitalization after randomization to either early surgery or watchful waiting.

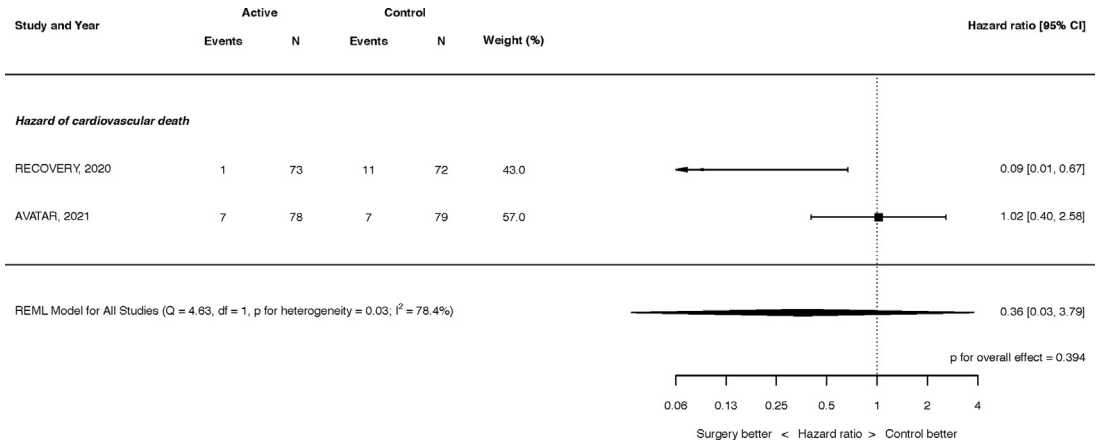


Figure 4. Cardiovascular mortality after randomization to either early surgery or watchful waiting.

consistent when assessed by fixed effect (see Supplemental Figures S1-S4).

For the outcome of all-cause mortality, we digitized the published survival curves from both trials and utilized these to perform a reconstructed individual patient data analysis. The Kaplan-Meier plot for all-cause mortality for the pooled trials is shown in Figure 6. The results of this analysis were highly concordant with our primary meta-analysis (HR, 0.44; 95% CI, 0.23-0.83; $P = .011$).

Discussion

This meta-analysis finds that early SAVR reduces all-cause mortality and HF hospitalization when compared to watchful waiting (Central Illustration). The results are consistent across the 2 included trials, with no or low heterogeneity. This challenges the traditional approach of waiting for symptoms or a decline in ventricular function before offering intervention for severe AS and has implications for the clinical care of these patients and for guidelines. There were no significant differences in the occurrence of cardiovascular death or of clinical thromboembolism between the 2 groups.

The conventional treatment paradigm for patients with severe AS has been watchful waiting with surveillance echocardiography, looking either for progression of stenotic disease or a decline in left ventricular function. This approach has been in large part based on historical post-mortem data[3] and other small observational data sets.[13] Conversely, the risk of sudden cardiac death has been observed to be greater in asymptomatic patients with severe AS than that in the general population.[14] Furthermore, this was also true of patients with milder forms of AS: patients with mild and moderate AS also had excess mortality when compared to the general population without AS.[15] More recent observational data have suggested a 25% mortality at 2 years for patients with asymptomatic severe AS.[16] A potential clinical advantage for early surgery over watchful waiting had been raised by prior observational analyses, but these analyses were all necessarily confounded by selection bias and bias by indication.[17,18] We now, however, have the results of 2 randomized trials to inform therapeutic decision-making for these patients.

It should be noted that the results of these trials apply only to patients at a low surgical risk: in RECOVERY, the mean age was 64.2 ± 9.4 years and the European System for Cardiac Operative Risk Evaluation was 0.9%; in AVATAR, the average was 67 years and the median Society of Thoracic Surgeons–predicted risk of mortality score was 1.7%. Accordingly, the operative mortality was 0% in RECOVERY and 1.4% in AVATAR. This is particularly important when contemplating intervention for asymptomatic patients; the operative morbidity and mortality needs to be necessarily low for the balance of risk and benefit to be in favor of early intervention. These results do not therefore apply to older and more comorbid patients or those at a higher surgical risk. For those patients, a less invasive approach with TAVR may represent an attractive option with reduced procedural risk. Such an approach would need to be evaluated in RCTs before being recommended, and these trials are underway. The 900-patient Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis trial (NCT03042104) has now completed enrollment. There are also several other large, ongoing trials of transcatheter aortic valve intervention outside of the traditional indication of severe symptomatic AS. This

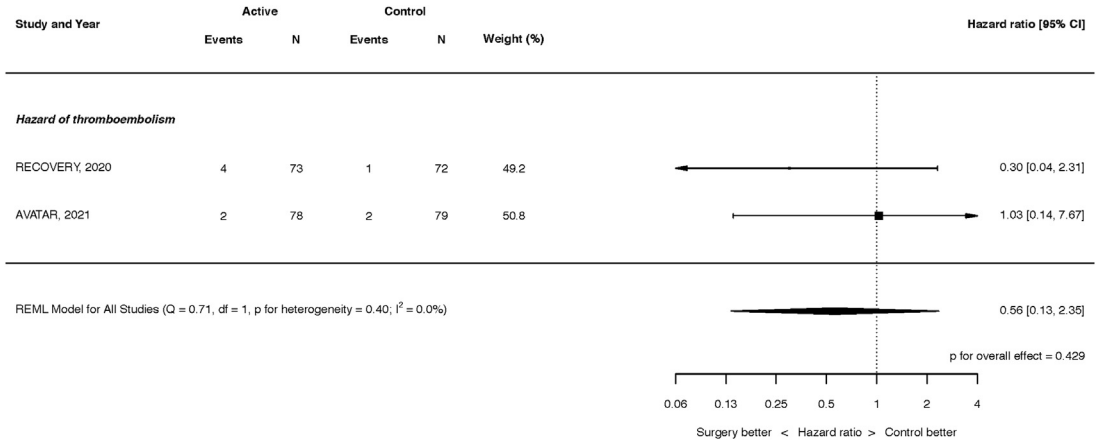


Figure 5. Thromboembolic complications after randomization to either early surgery or watchful waiting.

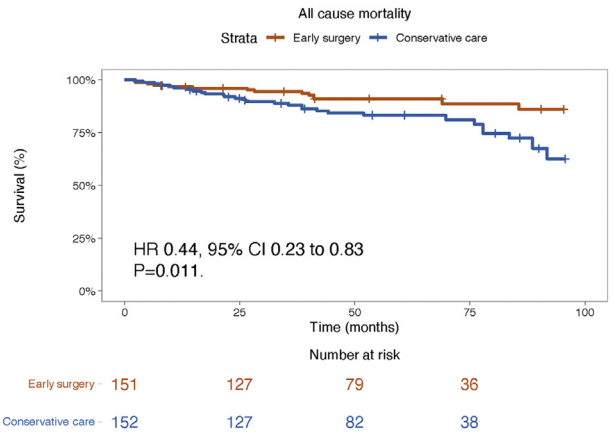
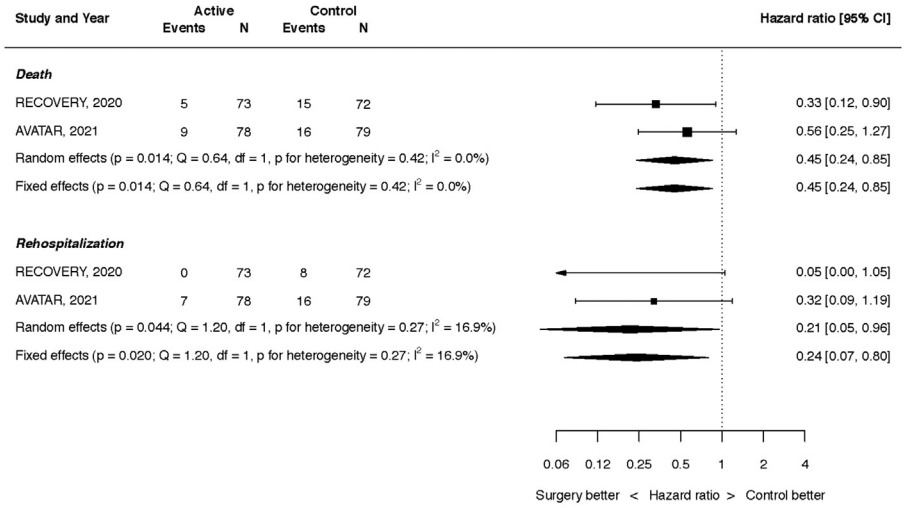


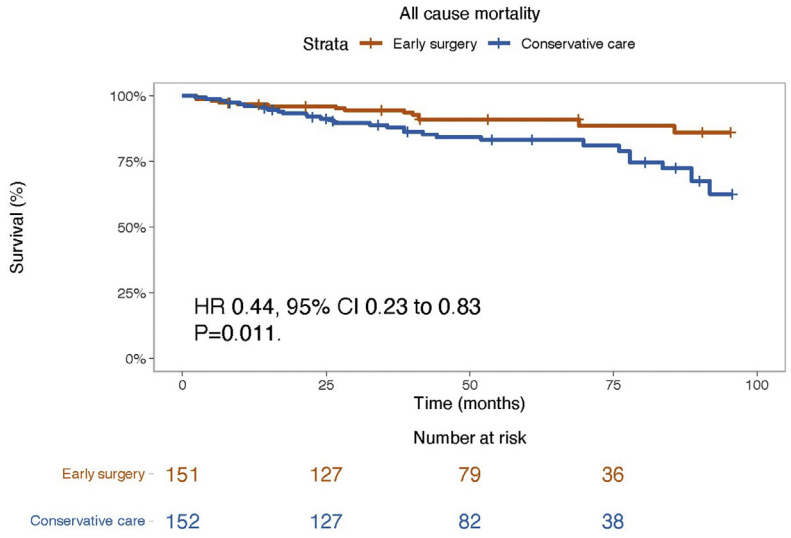
Figure 6. Kaplan-Meier plot for all-cause mortality pooled across the included trials, using reconstructed individual patient data (hazard ratio, 0.44; 95% confidence interval, 0.23-0.83; $P = .011$).

includes asymptomatic severe AS with evidence of midwall late gadolinium enhancement on cardiac magnetic resonance imaging (NCT03094143)[19] and 2 trials of patients with moderate AS and either clinical evidence of HF (NCT02661451) or other forms of cardiac dysfunction (NCT04889872). As well as these ongoing trials specifically studying the role of transcatheter approaches, there are also ongoing trials of both an early surgical approach vs a delayed surgical approach (NCT02627391) and also a large-scale international pragmatic trial where asymptomatic patients with normal left ventricular systolic function will be randomized either to expectant management or to aortic valve intervention which can be either with SAVR or TAVR.

There are important differences in eligibility criteria between the 2 trials: AVATAR mandated exercise testing and recruited fewer bicuspid patients (14% vs 61%) and less critical AS than RECOVERY. Despite these differences, there was no or low heterogeneity for most of our assessed end points. The median time from randomization to surgery for patients in the watchful waiting groups was 400 days in AVATAR and 700 days in RECOVERY, which may have exaggerated differences between SAVR and watchful waiting.

Exercise testing is recommended by international guidelines for the evaluation of patients with severe AS who report no symptoms.[1,2] As mentioned, the AVATAR trial mandated exercise testing prior to recruitment, whereas this was not the case in RECOVERY. Fourteen patients in AVATAR (~7% of patients screened for eligibility) were ultimately excluded on the basis of a positive exercise test. It is unknown whether the reduction in all-cause mortality seen





Central Illustration. (Top panel) Summary of main clinical outcomes (all-cause mortality and heart failure hospitalization). (Bottom panel) Kaplan-Meier plot for pooled effect of early surgery on all-cause mortality across the included trials.

in RECOVERY could partially be explained by the inadvertent inclusion of patients who were not truly asymptomatic. Future trials of therapeutic strategies in asymptomatic severe AS should consider mandating exercise testing as part of the trial protocol prior to randomization to ensure that only a truly asymptomatic patient cohort is recruited.

Our analysis differs from previously published meta-analysis in several ways.[20-22] First, we include only data from randomized trials. We are unable to provide insights from observational studies regarding comparative effectiveness of competing therapies due to inherent bias from measured and unmeasured confounders; therefore, pooling their results with randomized trials is not appropriate. No statistical matching methodology can overcome this; the only reliable method to account for measured and unmeasured confounders is randomization, and it is for this reason that we include only randomized trials in our analysis so that we can provide a true estimate of the impact of SAVR on outcomes when compared to watchful waiting. Secondly, we perform a reconstructed individual patient data analysis for the outcome of all-cause mortality. This allows us to generate a pooled Kaplan-Meier survival plot, allowing us to assess temporality of events and visually assess the proportional hazards assumption had not been violated. Such an approach has not been previously utilized.

Limitations

Firstly, we could only report the available data, and important data elements were not uniformly reported in both trials. Secondly, there are important differences in inclusion criteria and study populations between the included trials. Follow-up duration differed between the 2 trials; we used HRs to account for this varying follow-up duration. AVATAR mandated exercise testing for all patients, whereas in the RECOVERY trial, it was utilized based on clinical decision-making. Bicuspid aortic valve disease represented the majority of patients in RECOVERY, whereas in AVATAR, the majority had degenerative disease. Finally, the severity of the AS was greater in RECOVERY than that in AVATAR. Despite this, heterogeneity was low or absent for most of our outcomes of interest. We chose all-cause mortality as our primary end point as it is the most bias-resistant and clinically-important end point. The included trials are limited by their relatively small sample size and number of events and the absence of centralized core laboratory analyses. We did not have access to individual patient data, and therefore, detailed subgroup analyses could not be performed. These results do not apply to patients at a higher baseline surgical risk or those being considered for TAVR. The COVID-19 pandemic may have impacted the results of the AVATAR trial, with challenges to recruitment and delays in surgery for patients randomized to early SAVR; moreover, COVID-related pneumonia was present in 3 patients who had died in the watchful waiting arm, compared to none in the early surgery arm. There was no difference in cardiovascular mortality overall, which would be the presumed mechanism of benefit for a reduction in all-cause mortality from SAVR over watchful waiting. This may reflect the previously mentioned confounding effect of COVID-19 in the AVATAR trial or may in fact represent difficulties in adjudicating causes of death. The surgical outcomes in both the included trials were uniformly excellent with little or no operative mortality across both trials. This is not necessarily generalizable to routine clinical practice worldwide, where surgical outcomes may be more variable. Finally, we included only RCTs which only assess the effect of therapy on patients who meet the strict inclusion criteria. This can lead to claims of lack of generalizability, but randomization remains the only reliable method of avoiding bias from measured or unmeasured confounders.

Conclusions

This analysis finds that in patients with severe asymptomatic AS and normal ejection fraction, early SAVR reduces death and HF hospitalization compared to initial conservative management. This challenges current treatment standards and has implications for the clinical care of these patients and for guidelines.

Declaration of competing interest

Dr Arnold reports honoraria and sponsorship from Medtronic and Bayer. Dr Madhavan was supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr Forrest is a consultant for Edwards Lifesciences and Medtronic and receives grant support from Edwards Lifesciences and Medtronic; Dr Mack has served as a co-principal investigator for Edwards Lifesciences and Abbott and as a study chair for Medtronic. Dr Lansky reports research grants from Sinomed, MicroPort, Abiomed, and Boston Scientific and speaker/consulting fees from Sinomed, MicroPort, AstraZeneca, and Medtronic. Dr Leon has received research support to his institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott; has served on advisory boards for Medtronic, Boston Scientific, Gore, Meril Lifescience, and Abbott; and has served as the co-principal investigator of the PARTNER 3 trial (Edwards Lifesciences, no direct compensation).

Ethics statement

This research is a study-level meta-analysis of published data; therefore, ethical approval was not required. The research adhered to ethical guidelines.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at https://doi.org/10.1016/j.jscai.2022.100383.

Peer review statement

Given her role as Editor in Chief, Alexandra Lansky had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Andrew M. Goldsweig.

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