Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

# Optimal Threshold of Left Ventricular Ejection Fraction for Aortic Valve Replacement in Asymptomatic Severe Aortic Stenosis: A Systematic Review and Meta-Analysis

Andrew S. Perry, MD; Song Li, MD

**BACKGROUND:** The optimal threshold of left ventricular ejection fraction (LVEF) that should prompt aortic valve replacement (AVR) in asymptomatic patients with high-gradient severe aortic stenosis (AS) is controversial. The aim of this study was to assess the relationship between LVEF and mortality benefit in comparing early AVR versus watchful waiting in asymptomatic patients with severe AS.

**METHODS AND RESULTS:** MEDLINE, Embase, Web of Science, and Google Scholar were searched for observational studies and randomized controlled trials on adults with asymptomatic severe AS. Severe AS was defined by a peak aortic velocity ≥4 m/s and/or mean aortic valve gradient ≥40 mm Hg and/or calculated aortic valve area <1.0 $cm^2$ or an indexed valve area <0.6 $cm^2$. Studies comparing AVR with conservative management were included and meta-analysis on all-cause mortality was performed. Ten eligible studies were identified with a total of 3332 patients. In 5 observational studies comparing early AVR versus watchful waiting, our meta-analysis showed early AVR was associated with lower mortality with a hazard ratio (HR) of 0.41 (CI, 0.23–0.71; $P<0.01$). In 4 observational studies comparing AVR versus no AVR, our meta-analysis showed AVR was associated with lower mortality with a HR of 0.31 (CI, 0.17–0.58; $P<0.001$). In a meta-regression analysis pooling all 10 studies, there was no statistically significant correlation between study mean LVEF and the size of mortality benefit of AVR ($P=0.83$).

**CONCLUSIONS:** Among asymptomatic patients with high-gradient severe AS, AVR was associated with a mortality benefit across the spectrum of LVEF. Our study calls into question the need of an LVEF threshold for recommending AVR in this patient population.

**Key Words:** aortic stenosis ■ aortic valve replacement ■ heart failure ■ left ventricular dysfunction

Aortic stenosis (AS) is a common condition with an estimated prevalence of 12.4% across all ages and a prevalence of 3.4% for severe AS among those 75 years or older.[1] Although the presence of any degree of AS is associated with an increased risk of mortality, the risk of sudden cardiac death is considered relatively low until the onset of symptoms from severe AS.[2,3] The treatment option for AS, aortic valve replacement (AVR), has inherent risks with both surgical and transcatheter approaches. Thus, the American College of Cardiology, American Heart Association and European Society of Cardiology guidelines generally recommend that asymptomatic patients with high-gradient severe AS be managed conservatively, reserving AVR for those patients who become symptomatic.[4-6] Nevertheless, both guidelines give a Class

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020252

For Sources of Funding and Disclosures, see page 10.



*JAHA* is available at: www.ahajournals.org/journal/jaha

## CLINICAL PERSPECTIVE

### What Is New?

- Current clinical guidelines recommend aortic valve replacement (AVR) in asymptomatic patients with severe, high-gradient, aortic stenosis when the left ventricular ejection fraction (LVEF) is <50%. It is controversial whether an LVEF of 50% is the optimal threshold to guide decisions around AVR.
- This systematic review and meta-analysis showed that AVR is associated with a mortality benefit in asymptomatic severe aortic stenosis across the spectrum of LVEF.
- There was no statistically significant correlation between LVEF and the size of mortality benefit associated with AVR in this patient population.

### What Are the Clinical Implications?

- This study calls into question the need for an LVEF cutoff in deciding whether to recommend AVR in asymptomatic patients with high-gradient severe aortic stenosis and adds to the evidence that AVR may have a mortality benefit in asymptomatic patients with severe aortic stenosis and preserved LVEF as well.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AS** | aortic stenosis |
| **AVR** | aortic valve replacement |

I recommendation for AVR in asymptomatic patients with severe AS when the left ventricular ejection fraction (LVEF) is <50%. These recommendations primarily are based on clinical experience and expert opinion. The American College of Cardiology/American Heart Association guidelines cite only 2 observational studies, one showing acceptable surgical risk in patients with AS and severely reduced LVEF <35% and the other suggesting that AVR was beneficial in patients with low-flow, low-gradient severe AS.[7,8] although the recommendation applies to patients with high-gradient severe AS. The European Society of Cardiology guidelines does not reference any specific studies evaluating AVR outcomes in patients with severe high-gradient AS and a low LVEF.

The appropriate management strategy for asymptomatic patients with high-gradient, severe AS has been a controversial subject for many years. Although it is increasingly evident that reduced LVEF in this patient population is associated with increased mortality and incidence of heart failure (HF), there is a lack of high-quality evidence to support that early valve replacement significantly improves outcomes compared with watchful waiting. On the other hand, given recent evidence that even preclinical left ventricle dysfunction as measured by global longitudinal strain is associated with worse outcomes in severe AS, it is unclear whether the LVEF cutoff of 50% used in the guidelines is the optimal threshold.

The published literature on asymptomatic severe AS has mostly been scattered observational studies over the past 15 years and no study to our knowledge has systematically assessed the benefit of early AVR in relation to left ventricle function in this patient population. Thus, we decided to perform a systematic review and meta-analysis on the mortality outcome of early AVR versus watchful waiting in asymptomatic patients with severe AS, aiming to determine whether there is a significant correlation between LVEF and the benefit of AVR. In this study, we focused on severe AS defined by elevated velocities and gradients and not on low-flow, low-gradient severe AS.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for this review. This review was registered at www.researchregistry.com (registration number: reviewregistry1005) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is provided in Table S1.

### Criteria for Considering Studies for This Review

Published observational studies and randomized controlled trials (RCTs) were included. We included studies on adults (18 years of age or older) of both sexes with asymptomatic severe AS. Severe AS was defined according to both American and European guidelines (peak aortic velocity ≥4 m/s and/or mean aortic valve gradient ≥40 mm Hg and/or calculated aortic valve area <1.0 $cm^2$ or an indexed valve area <0.6 $cm^2$).[4,6] Asymptomatic status was defined per individual studies' definitions and exercise testing was not required to confirm asymptomatic status. Studies that included patients with asymptomatic *very severe* AS (typically defined as aortic valve area <0.75 $cm^2$ and peak velocity >4.5 m/s or mean gradient >50 mm Hg) were included and the difference in effect size between severe and very severe AS was analyzed as described later.

We included studies that compared either surgical or transcatheter AVR with conservative management. We preferentially included studies that compared an

early AVR strategy (typically defined as within 3 months of diagnosis) versus a watchful waiting strategy (AVR upon development of symptoms). We also included studies that compared AVR at any time versus no AVR. Given the substantial difference in study design between these 2 types of comparisons, the pooled effect size was separately calculated and represented in the forest plot for our main meta-analysis.

The primary outcome analyzed all-cause mortality. Secondary outcomes included cardiovascular mortality, sudden cardiac death, and HF. Included studies were required to report the primary outcome but not the secondary outcomes.

## Search Methods for Identification of Studies

We searched MEDLINE, Embase, Web of Science, and Google Scholar on June 11, 2020 using the search strategies listed in Table 1 from inception to present and imposed no restriction on language of publication. We also reviewed reference lists of included studies for additional studies not previously captured.

Records returned by our search were first screened by both authors independently based on the title and abstract. Disagreements were handled by discussion and reaching a consensus. Studies passing screening underwent full-text review for inclusion/exclusion and reasons for exclusion of the ineligible studies were recorded. For articles based on the same registry or patient cohort, only the article with the most complete cohort data was included.

## Assessment of Risk of Bias

The risk of bias of the included nonrandomized studies was assessed using the Newcastle-Ottawa scale, which includes the following domains: patient selection, comparability of groups, and assessment of outcomes. A score of 9 (out of 9) stars was judged to be at low risk of bias, a score of 7 or 8 stars medium risk, and a score of 6 or less high risk. The risk of bias of the 1 included RCT was assessed using the Cochrane Risk of Bias Tool.[9] The risk of reporting bias of the primary outcome was assessed by funnel plot.

**Table 1. Search Strategy by Database**

| Database | Keywords |
|---|---|
| Embase | ('aortic valve stenosis'/exp OR 'aortic valve stenosis') AND ('asymptomatic disease'/exp OR 'asymptomatic disease') |
| MEDLINE | (aortic valve stenosis[MeSH Terms]) AND (asymptomatic disease[MeSH Terms]) |
| Web of Science | TS=(asymptomatic) AND TS=(severe aortic stenosis) Indexes=SCI-EXPANDED Timespan=All years |
| Google Scholar (first 200 references) | asymptomatic severe aortic stenosis |

## Statistical Analysis

A data collection form was used to extract study characteristics and outcome data for all included studies (see Table 2 for information extracted). We performed a meta-analysis for all-cause mortality and divided the included observational studies into 2 subgroups: those comparing early AVR versus watchful waiting and those comparing AVR at any time versus no AVR. There was also 1 RCT comparing early AVR versus watchful waiting identified which was included on the forest plot as a separate group. We compared effect size across the 2 observational study groups and the RCT but did not pool the effect sizes together because of the markedly different study designs. We tested for differences in the mean effects in the different subgroups by using a standard test for heterogeneity across subgroup results rather than across individual study results. A random effects model was used to pool the studies within the same subgroup.[10,11] Heterogeneity among studies was assessed by visually inspecting the effect sizes and overlaps between CIs and statistically using $Tau^2$, $I^2$, and the $\chi^2$ statistic. Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020) was used for meta-analysis in this study.

Most included studies reported effect sizes using hazard ratios (HR) or a combination of HRs and risk ratios (RR), although a few early and small studies reported only RRs. Given that HRs and RRs cannot be pooled together on the same forest plot and that HRs are methodologically more valid for survival analysis, we included only studies reporting HRs in our meta-analysis. One study reported survival outcome of early AVR versus watchful waiting in Kaplan-Meier curve format but did not report HR so we calculated the HR from the Kaplan-Meier curves using a previously published method.[18,22] In addition to the primary meta-analysis described here, a prespecified subgroup analysis was done comparing patients with *severe* AS versus *very severe* AS.

To elucidate the association between LVEF and the effect size of AVR for asymptomatic severe AS, a meta-regression analysis was performed with the effect size of the included studies as the outcome variable and the mean LVEF of each study as the response variable. A $P$ value of $<0.05$ for the regression coefficient was considered statistically significant. As only 1 study intentionally enrolled patients with reduced LVEF <50%, a sensitivity analysis was also performed for the meta-regression analysis after removing this particular study.

The study complies with the Declaration of Helsinki. Ethics committee approval was not required because

**Table 2. Included Studies With Number of Subjects, Inclusion Criteria and Reported Outcomes**

| First Author | Year Published | Design | N, AVR | N, Conservative | Mean LVEF, % (SD) | AS Defined | (SD) | SAVR or TAVR | Mean Follow-Up (y) | All Cause Death | Cardiovascular Death | Sudden Cardiac Death | Heart Failure | Outcomes Assessed | Newcastle-Ottawa Scale |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pai RG[12] | 2006 | Retrospective. AVR vs no AVR | 99 | 239 | 59 (17) | AVA <0.8 $cm^2$ (mean gradient=43±15) | 71 (15) | SAVR | 3.5 | 10/99 vs 129/239 HR 0.17 (0.10–0.29) | NR | NR | NR | All-cause mortality | 6 stars |
| Kang DH[13] | 2010 | Prospective. Early AVR vs watchful waiting | 102 | 95 | 63 (7) | AVA <0.75 $cm^2$ AND peak velocity >4.5 m/s OR mean gradient >50 mm Hg | 63 (12) | SAVR | 4.1 | 3/102 vs 28/95 HR 0.14 (0.03–0.60) | 0/102 vs 18/95 | 0/102 vs 9/95 | NR | All-cause mortality, cardiac death, heart failure death | 7 stars |
| Henkel DM[14] | 2012 | Retrospective. AVR vs no AVR | 7 | 34 | 43 (6) | Peak velocity ≥4 m/s, mean gradient >40 mm Hg, AVA <1.0 $cm^2$ or AVAi <0.6 $cm^2$ | 73 (14) | SAVR | 7.5 (6.7) | 4/7 vs 27/34 HR 0.77 (0.36–1.67) | NR | NR | NR | All-cause mortality | 7 stars |
| Taniguchi T[15] | 2015 | Prospective. Early AVR vs watchful waiting | 291 | 291 | 68 (8) | Peak velocity ≥4 m/s, mean gradient >40 mm Hg, AVA <1.0 $cm^2$ | 75 (9) | SAVR | 3.3 | 40/291 vs 69/291 HR 0.64 (0.42–0.94) | 25/291 vs 46/291 HR 0.59 (0.35–0.96) | 8/291 vs 5/291 HR 0.43 (0.17–0.99) | 10/291 vs 50/291 HR 0.19 (0.09–0.36) | All-cause mortality, cardiac death, heart failure hospitalization | 7 stars |
| Masri A[16] | 2016 | Prospective. AVR vs no AVR | 341 | 192 | 58 (4) | AVAi <0.6 $cm^2/m^2$ (peak velocity=3.8±2) | 66 (13) | SAVR | 6.9 (3.3) | 44/341 vs 60/192 HR 0.26 (0.16–0.42) | NR | NR | NR | All-cause mortality | 7 stars |
| Bohbot Y[17] | 2018 | Prospective. Early AVR vs watchful waiting | 192 | 247 | 64 (5) | Mean gradient ≥40 mm Hg | NR | SAVR | 3.5 (2.5–6.7) | 89/192 vs 63/247 HR 3.85 (2.1–7.08) | HR 3.7 (1.6–5.82) | NR | NR | All-cause mortality and cardiovascular mortality | 7 stars |
| Campo J[18] | 2019 | Prospective. Early AVR vs watchful waiting | 104 | 161 | 61 (8) | Peak velocity ≥4 m/s, mean gradient >40 mm Hg, AVA <1.0 $cm^2$ | 71 (12) | SAVR | NR | HR 0.58 (0.30–1.11) | NR | NR | NR | All-cause mortality | 7 stars |
| George SA[19] | 2019 | Retrospective. AVR vs no AVR | 147 | 177 | 57 (7) | Peak velocity ≥4 m/s, mean gradient >40 mm Hg, AVA <1.0 $cm^2$ | 78 (10) | SAVR or TAVR | 8 (7–10) | HR 0.15 (0.09–0.28) | 41% of deaths | NR | NR | All-cause mortality | 7 stars |
| Kim HJ | 2019 | Retrospective. AVR vs no AVR | 221 | 247 | 63 (5) | Peak velocity ≥4 m/s, mean gradient >40 mm Hg, AVA <1.0 $cm^2$ | 64 (13) | SAVR | 5.1 (2.5–8.9) | 37/221 vs 109/247 HR 0.62 (0.40–0.97) | 26/221 vs 74/247 HR 0.59 (0.35–0.99) | NR | 7/221 vs 3/247 | All-cause death, cardiac death, major adverse cardiovascular events, non-fatal myocardial infarction, stroke, infective endocarditis, heart failure hospitalization, AV re-op | 7 stars |
| Kang DH[21] | 2020 | RCT. Early AVR vs watchful waiting | 73 | 72 | 65 (5) | AVA <0.75 $cm^2$ AND peak vel >4.5 m/s OR mean gradient >50 mm Hg | 64 (9) | SAVR | 6.2 (5.0–7.4) | 5/73 vs 15/72 HR 0.33 (0.12–0.90) | NR | NR | 0/73 vs 8/72 HR 0.05 (0.00–1.05) | All-cause mortality, cardiovascular death, heart failure hospitalization | Low risk (Cochrane Risk of Bias tool for RCT) |

AS indicates aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; HR, hazard ratio; NR, not reported; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

this was a meta-analysis. Patients and/or the public were not involved in the design, conduct, or reporting of this research.

# RESULTS

## Study Characteristics

Our search resulted in 882 records identified through database searches on June 11, 2020. After removal of duplicates and initial screening, we found 25 records for retrieval and assessment of full text for eligibility. After full-text review, 15 records were removed for the following reasons: duplicate cohorts, patients studied were symptomatic, and no AVR comparison group (Figure 1). A total of 10 studies were included in the meta-analysis, which includes 3332 patients of whom 1577 underwent AVR.[12-21] Characteristics of included studies are reported in Table 2. Overall, the population studied is mostly male in the 7th decade of life with a mean LVEF of 62±8%. One study included patients with LVEF <50%; 3 studies had patients with LVEF 50% to 60% and 6 studies with LVEF >60%. Five studies compared early AVR versus watchful waiting and

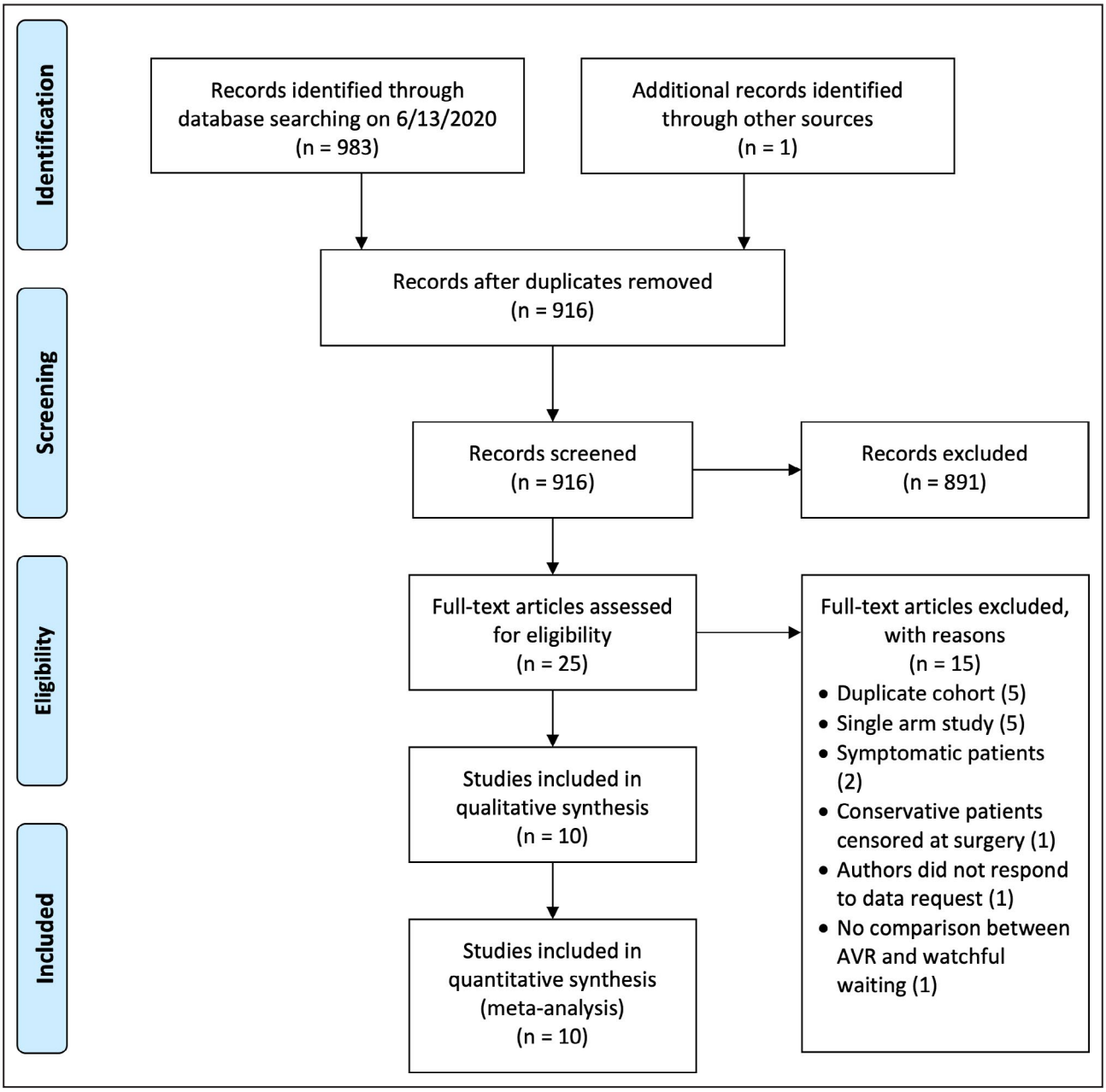


**Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating our search and selection strategy.**
AVR indicates aortic valve replacement.

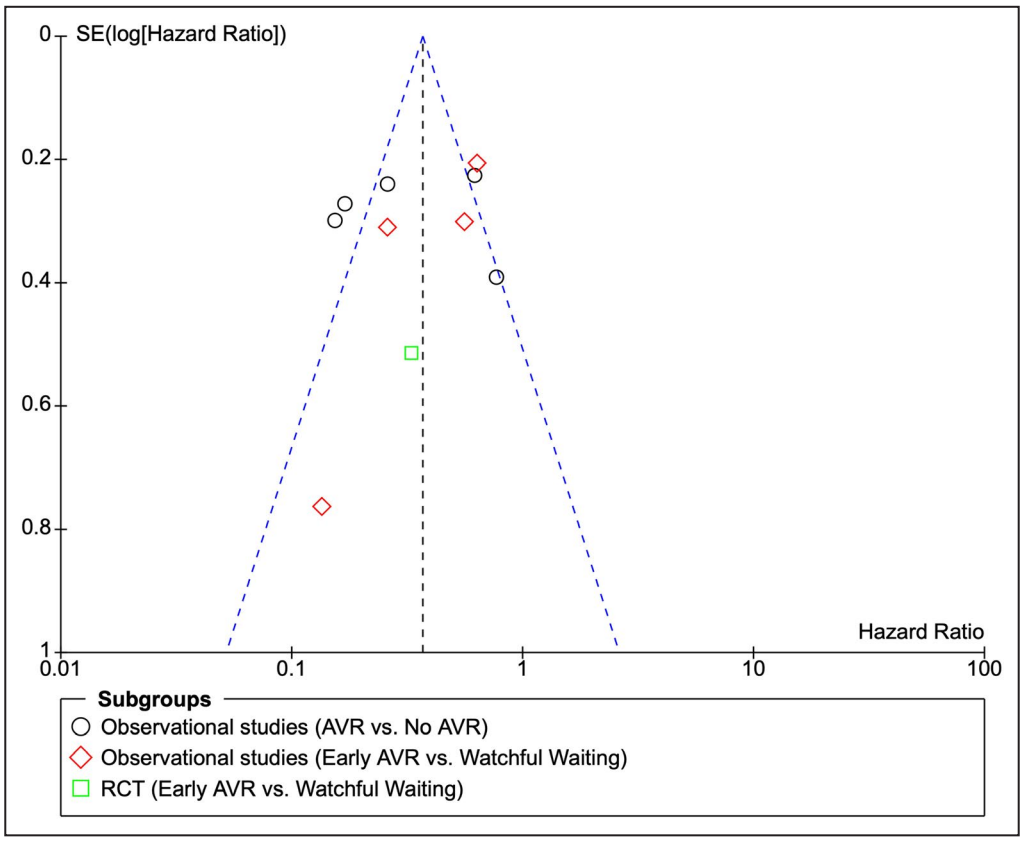


**Figure 2. Funnel plot for assessment of publication bias.**
AVR indicates aortic valve replacement; and RCT, randomized control trial.

5 compared AVR at any time versus no AVR. Seven studies included patients with severe AS whereas 3 included patients with very severe AS. Only 1 study included patients who had transcatheter aortic valve replacement.[19] Six studies were from the United States, 3 studies were from South Korea, 2 studies were from Japan, and 1 study was from France.

## Risk of Bias in Included Studies and Risk of Reporting Bias

Based on the Newcastle-Ottawa scale, none of the included studies was low risk for bias. Most studies were medium risk, with scores of 7 or 8 and 1 study was high risk for bias (Table 2). The single RCT was low risk based on the Cochrane Risk of Bias tool. Funnel plot analysis demonstrated some asymmetry in the lower right quadrant indicating possible publication bias missing small studies reporting null or near-null effect (Figure 2).

## Effects of Interventions

The primary meta-analysis on all-cause mortality demonstrated consistent benefit with AVR across study type subgroups (Figure 3).[12-21] The pooled HR for studies that analyzed patients by early AVR versus watchful waiting is 0.41 (CI, 0.23–0.71; $P$<0.01). The pooled HR for studies that analyzed patients by AVR versus no AVR is 0.31 (CI, 0.17–0.58; $P$<0.001). These are similar to that reported by the single RCT of early AVR versus watchful waiting (HR, 0.33; CI, 0.12–0.90; $P$=0.03).[21] There is no statistically significant difference in the effect size among the 3 subgroups ($\chi^2$=0.42; $P$=0.81).

There is statistically significant heterogeneity among pooled studies in both the early AVR versus watchful waiting group and the AVR versus no AVR group ($\chi^2$=25.72 and 8.79, $P$<0.05 for both). Judging by the Tau$^2$ and I$^2$ statistics, there is substantial heterogeneity in both groups. However, it is important to note that the direction of effects is consistent for all 10 studies in the meta-analysis and favors AVR.

## Association Between LVEF and Effect Size

The mean LVEF of included studies ranged from 43% to 66% (Table 2). Meta-regression analysis demonstrated that LVEF did not have a significant association with the effect size of AVR in terms of all-cause mortality ($P$=0.83, Figure 4). Additionally, the fitted regression line did not cross null effect (HR of 1) for any LVEF, suggesting a benefit for AVR in all asymptomatic

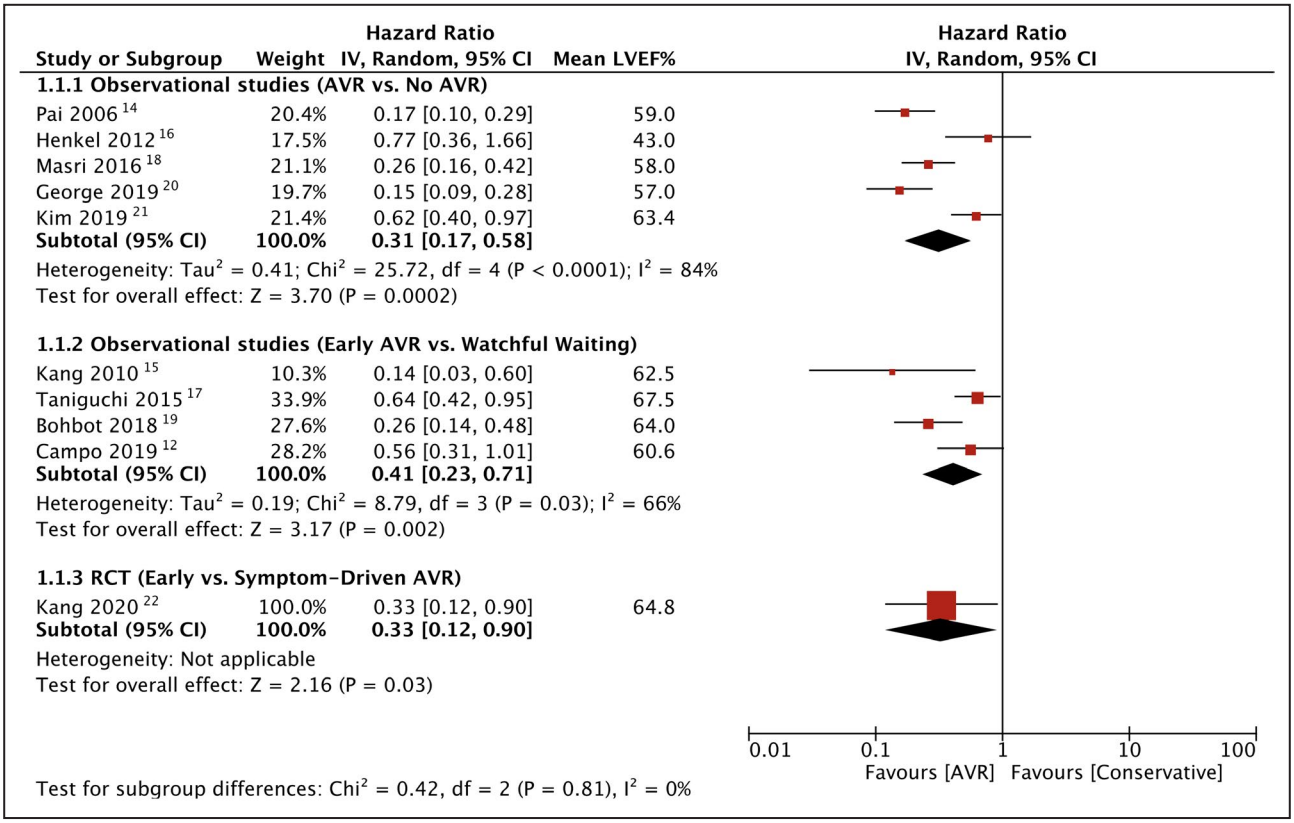


**Figure 3. Forest plot, divided by comparison type, assessing the effect of AVR on all-cause mortality.**
AVR indicates aortic valve replacement; IV, inverse variance; LVEF, left ventricular ejection fraction; and RCT, randomized control trial.

patients with severe AS regardless of LVEF. As only 1 study had a mean LVEF <50% and may have unduly influenced the results, a sensitivity analysis was done after removing this study. Using the remaining 9 studies with mean LVEF ranging from 57% to 67.5%, there was a significant association between lower mean LVEF and higher magnitude of benefit from AVR (*P*=0.013, Figure S1). However, it is notable that the fitted regression line crosses null effect at a LVEF of 72.0%, which is rarely encountered clinically.

## Subgroup Analysis

Given that 3 out of the 10 included studies enrolled patients with very severe AS, a subgroup analysis was performed to confirm the effect of AVR in both severe and very severe asymptomatic AS groups. The pooled HR for studies that enrolled patients with severe AS was 0.40 (CI, 0.26–0.62; *P*<0.001) favoring AVR. The pooled HR for studies that enrolled patients with very severe AS was 0.19 (CI, 0.12–0.30; *P*<0.001) favoring AVR. The subgroup analysis demonstrated benefit of AVR in both groups with severe and very severe AS (Figure 5).[12-21]

## Additional Outcomes

Few studies reported outcomes on sudden cardiac death. Only 1 study performed a proportional hazards analysis showing reduced risk of sudden cardiac death in the early AVR group (HR, 0.43; CI, 0.17–0.99).[15] Other studies reported reduced numbers of sudden cardiac death events in the AVR group, but no statistical tests were performed (Table 2).

HF hospitalization rates were compared in 3 studies. One study that compared AVR versus no AVR found similar HF hospitalization rates (0.4% versus 0.3% per person-year), with a decrease in HF hospitalization rates in the group with AVR after the AVR operation (1.7%–0.2% per person-year).[20] One observational study and the only RCT, both comparing early AVR versus watchful waiting, showed lower HF hospitalizations in the group with early AVR (HR, 0.19; CI, 0.09–0.36; and HR, 0.05; CI, 0.00–1.05, respectively).[15,21]

# DISCUSSION

In this systematic review and meta-analysis, we found that AVR was significantly associated with decreased mortality in asymptomatic patients with high-gradient severe AS. We further demonstrated that AVR was associated with decreased mortality not only in patients with reduced LVEF but also in patients with preserved or even supranormal LVEF.

Current society guidelines recommend watchful waiting in most patients with asymptomatic severe AS

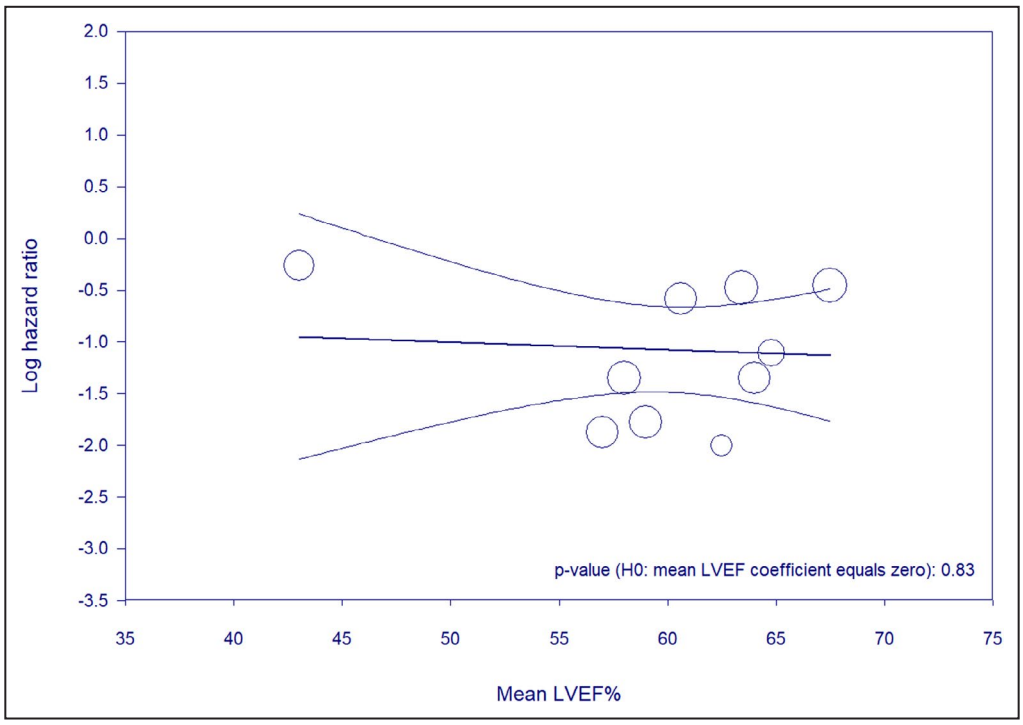


**Figure 4. Meta-regression analysis of the association of study mean LVEF with the size of mortality benefit of AVR.**
AVR indicates aortic valve replacement; and LVEF, left ventricular ejection fraction.

until symptom onset. This recommendation stems from previous literature demonstrating relatively low risks for mortality and sudden cardiac death among this population.[23] However, this reasoning is only part of the equation as patients might suffer other harms while waiting, and procedural outcomes might be worse when patients are older or develop left ventricular dysfunction. As described previously, watchful waiting

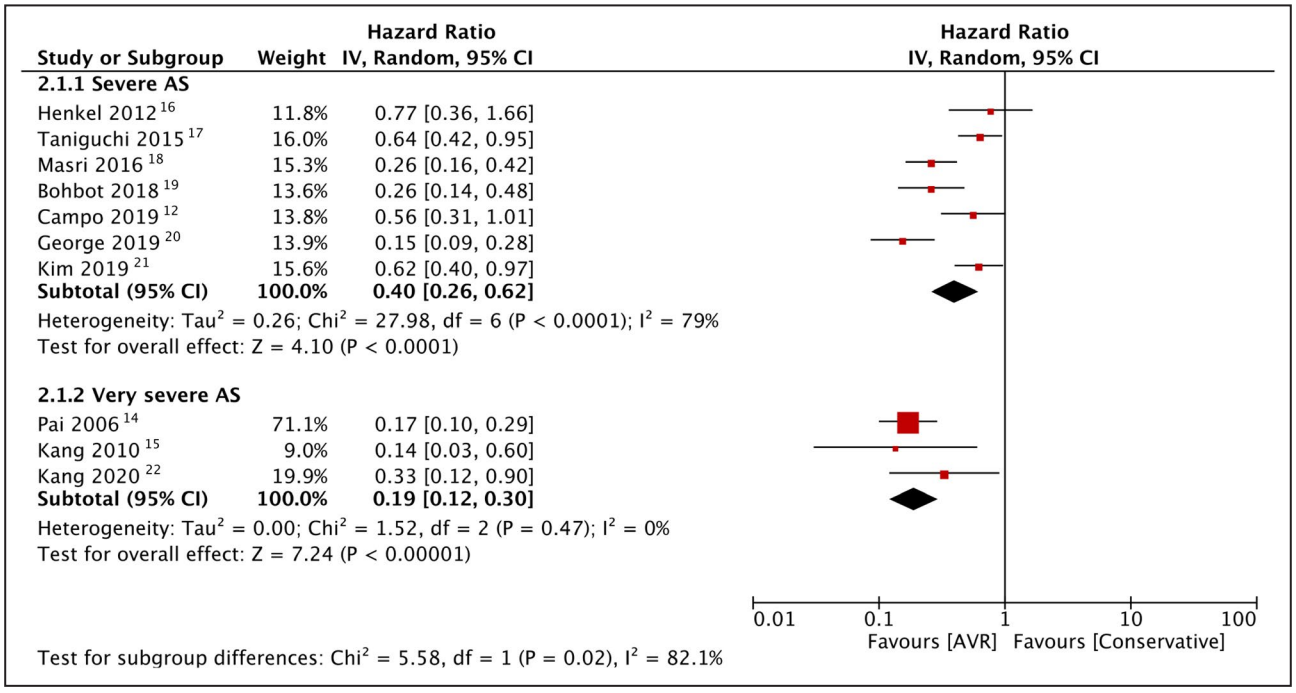


**Figure 5. Forest plot, divided by severity of AS, confirming the effect of AVR on all-cause mortality in both groups.**
AS indicates aortic stenosis; AVR, aortic valve replacement; and IV, inverse variance.

patients likely have much higher incidence of HF than patients receiving early AVR. In terms of periprocedural outcomes, in the CURRENT-AS (Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis) registry, asymptomatic patients referred to early surgery had significantly lower operative mortality than those who had AVR after developing symptoms (1.2% versus 3.7%, $P$=0.03).[15] Therefore, the risk/benefit balance may tip toward benefit in asymptomatic severe AS and explain the findings of our meta-analysis.

Among patients with asymptomatic severe AS, current guidelines also recommend the use of stress tests to risk stratify asymptomatic patients, which is an effective strategy.[24,25] It may be thought, therefore, that the benefit seen in AVR among asymptomatic patients is simply the same benefit seen by performing AVR in the patients who would have had an abnormal exercise stress test. This hypothesis was evaluated by Masri et al, and they demonstrated a significant benefit to AVR in asymptomatic patients with a normal exercise stress test.[16] Our data also support that stress testing is not necessary to risk stratify patients with severe, asymptomatic AS because of the consistent benefit from AVR.

Current guidelines recommend AVR in a subgroup of patients with asymptomatic severe AS and LVEF <50% based on increased risk of mortality. The increased risk of mortality in this subgroup has been supported by many observational studies.[15,26-28] However, from our review of the literature, there has not been any RCT or observational study directly evaluating the appropriateness of the specific LVEF threshold of 50%. Our meta-regression analysis shows that there is a mortality benefit to AVR across the spectrum of LVEF. In fact, all 10 studies in our meta-analysis favored AVR and 6 out of the 10 studies including the 1 RCT had mean LVEF >60%. Our finding that patients with normal LVEF have improved mortality with early AVR is supported by evidence that most patients with severe AS and normal LVEF actually have subtle left ventricular dysfunction by global longitudinal strain and elevated mortality risk. In this population, global longitudinal strain is independently predictive of mortality despite preserved LVEF.[29,30] Thus, it is likely that LVEF is simply not sensitive enough to detect early left ventricular dysfunction that is present in most patients with severe AS and even if asymptomatic these patients with subtle left ventricle dysfunction benefit from early AVR. Although our meta-regression analysis (Figure 4) showed no relationship between LVEF and the degree of mortality benefit, our sensitivity analysis of the meta-regression (Figure S1) demonstrated lower LVEF was associated with greater benefits with early AVR. This may be explained by the fact that the single, small study of patients with LVEF <50% (n=34) excluded from the sensitivity analysis is an outlier.

There are several ongoing clinical trials evaluating the efficacy of AVR in patients with asymptomatic severe AS:

1. EARLY-TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis; NCT03042104).
2. EVOLVED (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143)
3. AVATAR (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; NCT02436655).
4. EASY-AS (Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study; NCT04204915).
5. DANAVAR (Danish National Randomized Study on Early Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis; NCT03972644).

We anticipate these trials will provide much needed additional evidence on the benefit of early AVR in patients with asymptomatic severe AS.

## Limitations

We performed a study-level meta-analysis so only the mean LVEF of each study is used in the meta-analysis. Information about postoperative LVEF was not available so we were unable to evaluate for changes in LVEF with AVR. Most of the studies included are observational studies with significant heterogeneity and most were rated as medium risk of bias including an unavoidable selection bias when selecting patients for AVR. Finally, there is a possible risk for publication bias as some small studies reporting null or near-null effect may not have been published.

# CONCLUSIONS

Our systematic review and meta-analysis support a mortality benefit of AVR in asymptomatic patients with high-gradient severe AS regardless of LVEF. Our findings call into question the need of a LVEF threshold for recommending AVR in this patient population.

## ARTICLE INFORMATION

Received November 21, 2020; accepted March 1, 2021.

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### Acknowledgments

The authors would like to acknowledge Catherine Otto, MD for her assistance in reviewing the manuscript.

Both authors contributed equally to the planning, conduct, and reporting of the present work.

## Sources of Funding

None.

## Disclosures

None.

## Supplementary Material

**Table S1**
**Figure S1**

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# SUPPLEMENTAL MATERIAL

Table S1.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3-4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 11 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4-5 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 5 |

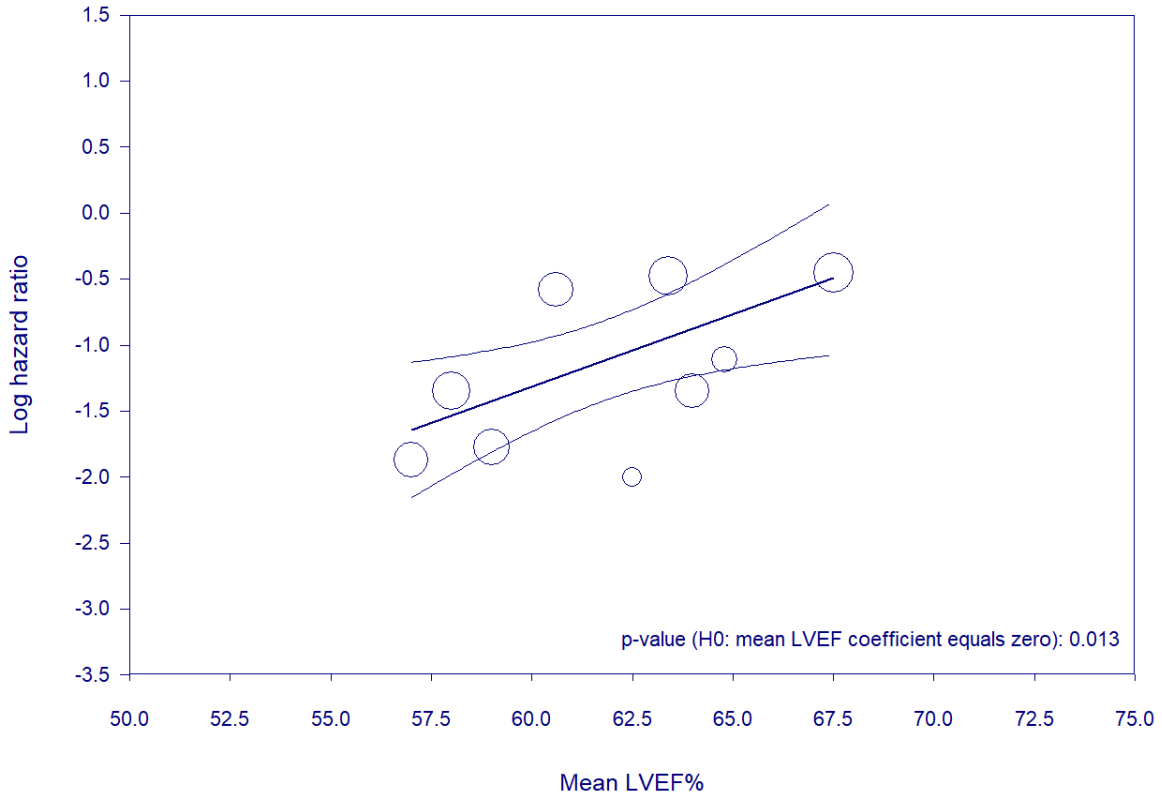
# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Fig 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 2 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Fig 3 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Fig 3 & 5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Fig 2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Fig 4, S1 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 7 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 7-8 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 5 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

**Figure S1. Meta-regression sensitivity analysis showing the association of study mean LVEF with the size of mortality benefit of AVR after removing the lone study with LVEF < 50%.**




LVEF = left ventricular ejection fraction.