

André Filipe Jorge Beco

**Reverse left ventricular remodeling after aortic valve replacement
for aortic stenosis: systematic review and meta-analysis**

Remodelação Reversa do Ventrículo Esquerdo pós substituição da
válvula aórtica na estenose aórtica: revisão Sistemática e Metanálise

ABRIL, 2021

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Reverse left ventricular remodeling after aortic valve replacement
for aortic stenosis: systematic review and meta-analysis

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Faculdade de Medicina da Universidade do Porto, 09/04/2021

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DESIGNAÇÃO DA ÁREA DO PROJECTO

3.2. Medicina Clínica

TÍTULO DISSERTAÇÃO

Reverse left ventricular remodeling after aortic valve replacement for aortic stenosis: systematic review and meta-analysis

ORIENTADOR

Luís Filipe Vilela Pereira de Macedo

COORDINADOR (se aplicável)

Fábio Sousa Nunes

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 09/04/2021

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André Beco

Dedicatória

Ao meu avô Adérito, que, não sendo médico, me mostrou que a Medicina é a mais bonita das profissões.

À minha avó Zé, que me ensinou que cuidar dos outros nunca deverá ser um papel secundário.

Reverse left ventricular remodeling after aortic valve replacement for aortic stenosis: systematic review and meta-analysis

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Abstract

Introduction and Objectives: Reverse Left Ventricle (LV) remodeling after Aortic Valve Replacement (AVR), in patients with aortic stenosis, is well documented as an important prognostic factor. However, there are no reference values for the expected reverse remodeling phenomenon. With this systematic review and meta-analysis, we aimed to characterize the response of the unloaded LV after AVR.

Methods: We searched on MEDLINE/PubMed, Web of Science, and Embase for studies reporting echocardiographic findings before and at least 1 month after AVR for the treatment of aortic stenosis. 5626 studies were identified and 4493 were screened for inclusion. Main factors of interest were structural and dynamic measures of the LV and Aortic Valve. We performed a random-effects meta-analysis to compute standardized mean differences (SMD) between follow-up and baseline values for each outcome.

Results: 31 studies met the eligibility criteria, yielding 2206 patients. AVR resulted in reduced Mean Aortic Gradient (SMD: -42.18, 95% CI: -44.39 to -39.96, $I^2 = 95.8\%$), LV Mass (for surgical AVR, SMD: -84.40, CI: -103.24 to -65.57, $I^2 = 78.4\%$), Indexed LV Mass (SMD: -40.31, CI: -47.39 to -33.22, $I^2 = 78.8\%$), End-Diastolic LV Diameter (SMD: -2.06, CI: -3.17 to -0.94, $I^2 = 87.3\%$), End-Diastolic LV Volume (SMD: -13.10, CI: -18.77 to -7.43, $I^2 = 52.4\%$), Posterior Wall Thickness (SMD: -1.89, CI: -2.50 to -1.29, $I^2 = 94.1\%$), Interventricular Septal Thickness (SMD: -1.72, CI: -2.12 to -1.33, $I^2 = 88.1\%$), and increased Effective Aortic Valve Area (SMD: 1.02, CI: 0.86 to 1.18, $I^2 = 96.9\%$), and LV Ejection Fraction (SMD: 3.54, CI 2.22 to 4.86, $I^2 = 90.6\%$).

Conclusions: Reverse remodeling occurs after AVR and it is expressed in all of the main factors of interest of this systematic review and meta-analysis.

Keywords: Aortic Stenosis, Transcatheter aortic valve implantation (TAVI), Surgical Aortic Valve Replacement (SAVR), Reverse Left Ventricle Remodeling

Introduction

Aortic Stenosis (AS) is the most common form of valve disease in the developed world, and its prevalence increases with age. It causes a chronic pressure overload state, increasing ventricular afterload, resulting in left ventricular hypertrophy and myocardial fibrosis, leading to ventricular dysfunction and the development of symptoms.^{1 2} The only effective treatment for severe AS is aortic valve replacement (AVR), either surgical (SAVR) or transcatheter (TAVI). Indication for intervention depends on the presence of symptoms, the severity of AS, left ventricular ejection fraction (LVEF), and whether another cardiac surgery is indicated. Nearly all indications for AVR for AS are for patients with severe AS, which is generally identified by an aortic jet velocity over ≥ 4.0 m/s or mean transvalvular pressure gradient ≥ 40 mmHg (high flow/high grade AS).³

Successful AVR reduces the pressure in the LV and wall stress, resulting in geometric changes, such as mass regression and volume reduction, known as reverse remodeling, which improves LV function.^{4, 5}

It is known that the extent of reverse remodeling is an important prognostic factor in patients who underwent AVR, whether in terms of symptoms, survival, or hospitalizations.⁶⁻⁸ However, because data to predict the response of the LV to AVR are lacking, there are no reference values for the expected reverse remodeling phenomenon, meaning we do not know how much mass regression or LV volume reduction is expected after AVR.

With this work, we conducted a systematic review and meta-analysis to characterize the response of the unloaded LV after AVR.

Methods

Eligibility and Search Strategy

This systematic review and meta-analysis was undertaken according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.⁹ The literature research was done on December 9th, 2020, in three electronic databases: MEDLINE (through PubMed), Web of Science, and Embase. The search was conducted with no restrictions on language or year of publication. Full details of the search are presented in Table 1.

Studies were included if they reported echocardiographic findings before and at least one month after SAVR or TAVI for the treatment of pure and isolated Aortic Stenosis. This time interval was chosen so that there would be time for acute changes to resolve and for reverse remodeling to occur.¹⁰ Studies also needed to report at least one interest variable of outcome for the measurement of the left ventricle reverse remodeling to be included.

We excluded non-human studies, studies that included patients with aortic valvular lesions other than pure isolated AS, more than mild mitral regurgitation, patients submitted to balloon aortic valvuloplasty, valve-in-valve implantation, or reoperations to AS. We also excluded case-control studies, case reports, revisions, articles with unavailable statistical data, unavailable results, or not yet completed. Articles without original data, articles without available full text, and duplicates were also excluded.

Study selection, data collection process, and study outcomes

For each study, the title and abstract screening for relevance was performed by four independent investigators (AB, FN, CM, JRS), meaning that at least two independent investigators screened each study. The full texts of the remaining studies were individually and independently assessed for inclusion based on predefined criteria. All discrepancies were resolved by consensus. Also,

the investigators of primary studies were contacted for clarifications if relevant data was missing.

The data extraction was performed by four investigators (AB, FN, CM, JRS), meaning that the data from each study were extracted by one investigator and verified by at least another one. For each study, we extracted the following information: publication characteristics (authors, publication year, journal), study design (clinical setting, the country where the study was performed, the period of recruitment and evaluation, duration of follow-up, number of patients randomized and analysed for each outcome), baseline characteristics of the population (eligibility criteria, age, gender, BSA, NYHA class, hypertension, diabetes, coronary heart disease, and other comorbidities and relevant baseline data), intervention (SAVR or TAVI, type of valve), and outcome data of interest. Summary of studies and baseline characteristics are presented in Tables 3 and 4.

The main outcomes of interest were Effective Aortic Valve Area (AVA), Mean Aortic Gradient (MAG), End-Diastolic Left Ventricular Diameter (EDLVD), End-Diastolic Left Ventricular Volume (EDLVV), LV mass (LVM), LV mass index (LVMI), LV ejection fraction (LVEF), Posterior Wall Thickness (PWT) and IV septal thickness (IVST).

Risk of bias assessment

we used the Study Quality Assessment for observational cohort and cross-sectional studies tool from the National Institute of Health to categorize several domains for all the eligible studies, The overall risk of bias was independently assigned to each study by four investigators (A.B., F.N., C.M., J.R.) and classified into "good", "fair", and "poor", as detailed in Table 2.

Statistical Analysis

We performed random-effects meta-analysis, using the restricted maximum likelihood approach, to compute pooled mean differences between post-follow-up and baseline values for

each outcome. Heterogeneity was assessed by the Cochran Q statistic p-value and by the I^2 statistic - a p-value<0.10 and an I^2 >50% were considered to represent substantial heterogeneity. Sources of heterogeneity were explored by means of univariable meta-regression models (except for cases in which the number of primary studies did not exceed 10), with tested covariates including the publication year, participants' mean age, percentage of females, average BSA, and percentage of patients in NYHA classes III/IV, with hypertension, with diabetes, and with coronary heart disease. In addition, we performed subgroup analyses for the follow-up period (with the follow-up being categorized in three groups – between one and six months, between six and twelve months, and higher than twelve months), and for the initial LVEF (classes in two groups - lower than 50% and higher than 50%). Finally, sensitivity analyses were performed for studies in which SAVR was undertaken.

All statistical analyses were performed using meta package of software R.

Results

A total of 5626 publications were identified through our search of MEDLINE/Pubmed (2,871 records), Embase (1,709 records), and Web of Science (1,046 records). After removing the duplicates, we remained with 4,493 records. Following the title and abstract screening, we selected 143 articles for full-text review. After excluding articles that did not meet the inclusion criteria, we ended with 31 primary studies, with a total of 45 study cohorts included for meta-analysis¹¹⁻⁴¹ (Fig. 1).

The studies were published between 1994 and 2019, assessing a total of 2,206 patients, who completed echocardiographic pre- and at least 1-month post-AVR. 27 studies exclusively accessed SAVR patients, while three studies exclusively accessed patients who underwent TAVI. One study included patients who underwent SAVR or TAVI but presented the results in two independent cohorts.

Effective Aortic Valve Area

Fourteen cohorts (n=805) reported results for AVA before and at least 1 month after AVR. The pooled SMD was 1.02 cm² (95% CI: 0.86 to 1.18, p<0.001), indicating a significant increase after AVR. However, the results were significantly heterogeneous between cohorts (I²=96.9%, p< 0.001) (Fig. 2). Univariate meta-regression identified average follow-up time as a heterogeneity source (R²=41.04%) and showed significant differences between the follow-up time subgroups (p=0.01), with R² meaning the proportion of the variance in the SMD that is predictable from the independent variable. SMDs within the follow up time subgroups were 1.11 cm² (95% CI: 0.78 to 1.43, three cohorts, I²=91.5%) for the 1 to 6 months subgroup, 1.12 cm² (95% CI: 0.96 to 1.29, eight cohorts, I²=96.0%) for the 6 months to 1 year subgroup and 0.66 cm² (95% CI: 0.41 to 0.92, three cohorts, I²=92.2%) for the after 1 year subgroup. Meta-regression also identified the sex of participants as a source of heterogeneity (R²=17.14%).

Initial LVEF, participants' mean age, publication year, average BSA, percentage of hypertensive patients, and type of procedure were not identified as significant sources of heterogeneity ($R^2 < 10\%$).

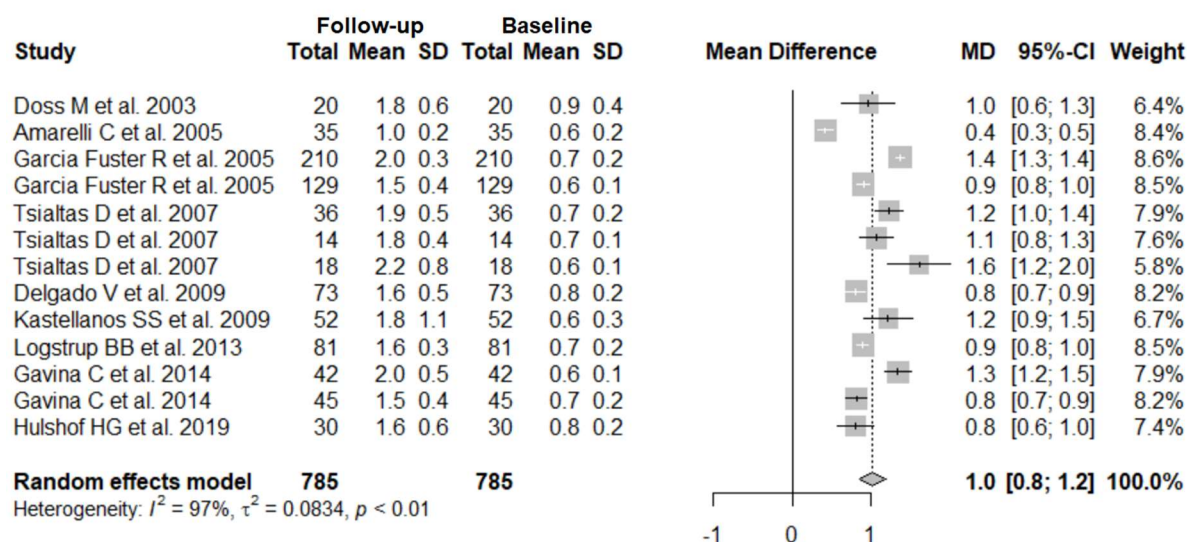


Fig. 2 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for AVA

Mean Aortic Gradient

Twenty-six cohorts ($n=1,293$) reported results for MAG before and at least one month after AVR. The pooled SMD was -42.18 mmHg (95% CI: -44.39 to -39.96 , $p < 0.001$), indicating a significant decrease after AVR. However, the results were significantly heterogeneous between cohorts ($I^2=95.8\%$, $p < 0.001$).

Subgroup analysis using the random-effects model showed a significant difference ($p=0.04$) in MAG results between patients who underwent SAVR and those who underwent TAVI. Three cohorts reported results for MAG difference before and at least one month after TAVI, with a pooled SMD of -45.33 mmHg (95% CI: -47.79 to -42.86), and with no evidence of significant heterogeneity between them ($I^2=0.0\%$). For SAVR, twenty-three cohorts reported MAG results

before and at least one month after the procedure, and the pooled SMD was -41.79 mmHg (95% CI: -44.19 to -39.32), but the results were significantly heterogeneous ($I^2=95.5\%$) (Fig. 3).

Subgroup analysis showed significant differences in MAG between the one cohort that had LVEF<50% and the other seventeen who had LVEF>50% ($p<0.001$). When analysing the patients who underwent SAVR with initial LVEF>50% independently, the pooled SMD is -41.06 mmHg (95% CI: -43.18 to -38.95, $I^2=64.7\%$).

For the cohorts of patients who underwent SAVR with reported MAG results, univariate meta-regression found that the percentage of patients with diabetes (fifteen cohorts), and with coronary heart disease (eight cohorts), could explain the heterogeneity, with R^2 values of 33.95% and 91.17%, respectively, with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable. Follow-up length (twenty-three cohorts), publication year (twenty-four cohorts), participants' mean age (twenty-two cohorts), sex of participants (twenty-three cohorts), average BSA (eighteen cohorts), percentage of patients in NYHA classes III/IV (twelve cohorts), and percentage of hypertensive patients (eighteen cohorts) were not identified as significant sources of heterogeneity ($R^2<10\%$).

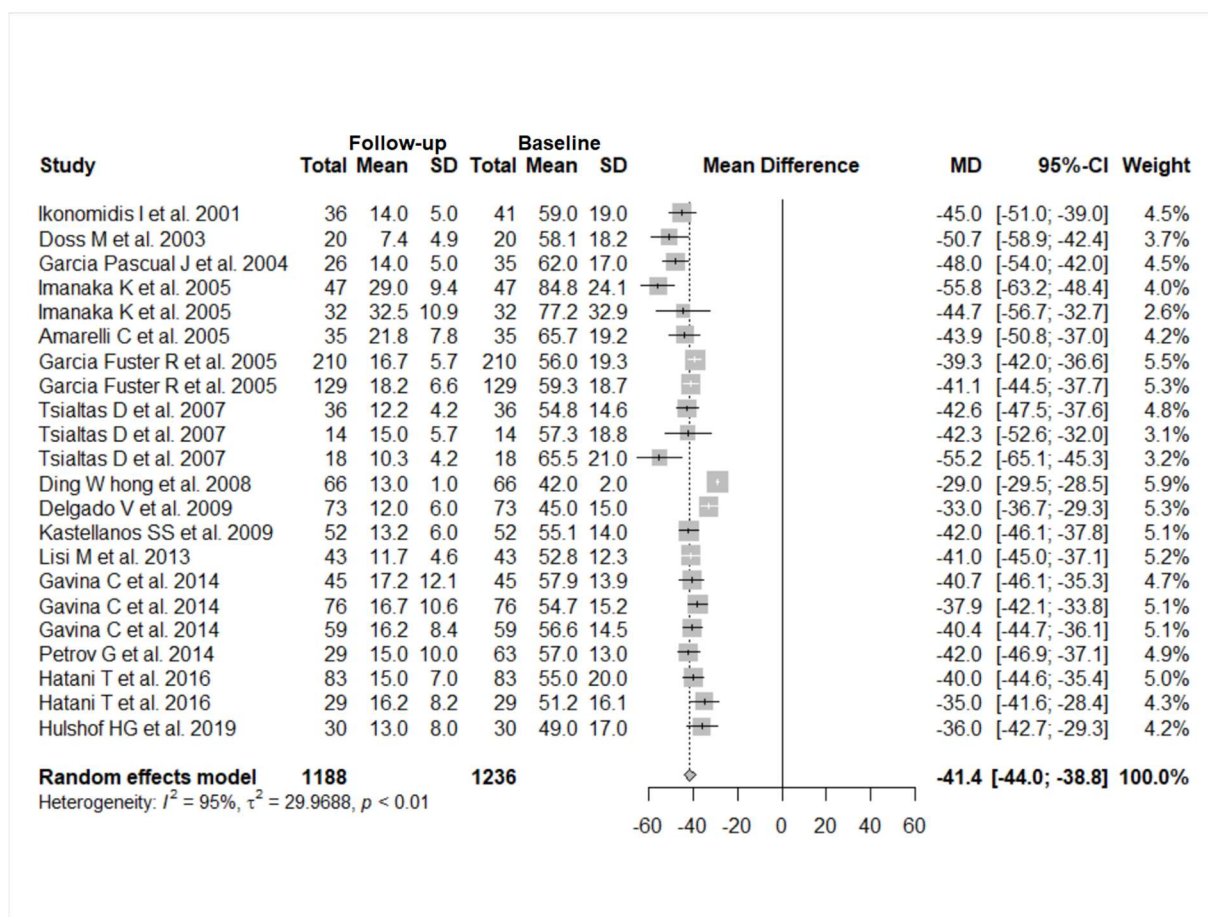


Fig. 3 - Standardized mean difference (SMD) post-SAVR vs. pre-SAVR for MAG

Left Ventricular Mass

From the eighteen cohorts (n=531) that reported results for LVM before and at least one month after AVR, only one refers to the TAVI cohort, which was significantly different from the others ($p < 0.001$), and reported LVM difference of -16.80 g (-42.70 to 9.10).

For the seventeen cohorts that report LVM values for SAVR, the pooled SMD was -84.40 g (95% CI: -103.23 to -65.57), which indicated a significant decrease after SAVR. However, the results were significantly heterogeneous ($I^2 = 78.4\%$) (Fig. 4). For the cohorts of patients who underwent SAVR, a subgroup analysis between patients with initial LVEF > 50% and < 50% showed significant differences between the groups ($p < 0.001$): the pooled SMD for LVM of the subgroup with initial LVEF > 50% (fourteen cohorts) was -70.26 g (95% CI: -84.24 to -56.28,

$I^2=48.6\%$); for the subgroup with initial LVEF<50% (two cohorts) it was -164.60 g (95% CI: -190.69 to -138.50, $I^2=0.0\%$). Another variable that accounted for heterogeneity was the sex of participants (seventeen cohorts, $R^2=28.09\%$), with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable. Publication year (seventeen cohorts), participants' mean age (sixteen cohorts), the mean follow-up length (thirteen cohorts), and average BSA of the patients (ten cohorts) were not identified as significant sources of heterogeneity ($R^2<10\%$).

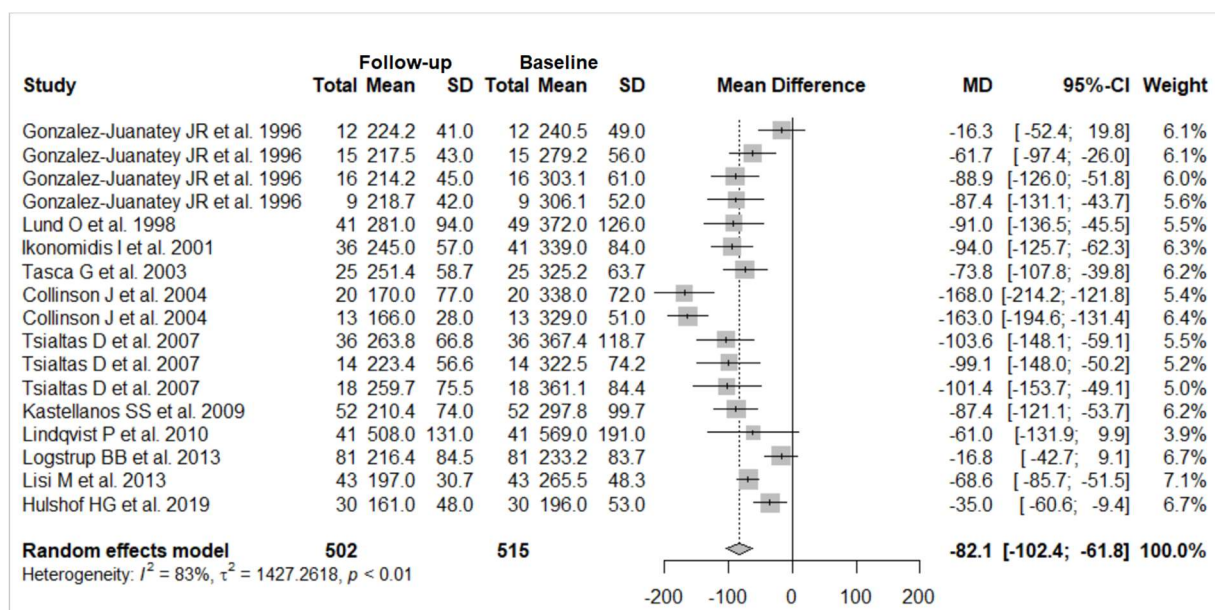


Fig. 4 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for LVM

Left Ventricular Mass Index

Thirty cohorts (n=1,413) reported results for LVMI before and at least one month after AVR. The pooled SMD was -40.31 g/m² (95% CI: -47.39 to -33.22, $p<0.001$), which indicated a significant decrease after AVR. However, the results were significantly heterogeneous ($I^2=78.8\%$, $p<0.001$) (Fig. 5).

Subgroup analysis between patients with initial LVEF>50% and <50% was made, showing significant differences between the groups ($p=0.04$): the pooled SMD for LVMI of the subgroup

with initial LVEF>50% (twenty-four cohorts) was -39.69 g/m² (95% CI: -46.1451 to -33.24, I²=61.7%); for the subgroup with initial LVEF<50% (two cohorts), it was -19.54 g/m² (95% CI: -36.41 to -2.66, I²=84.0%).

Univariate meta-regression found that the percentage of patients with diabetes accounted for some of the heterogeneity (sixteen cohorts, R²=15.05%), with R² meaning the proportion of the variance in the SMD that is predictable from the independent variable. Procedure (thirty cohorts), publication year (thirty cohorts), mean follow-up length (twenty-five cohorts), participants' mean age (twenty-eight cohorts), sex of participants (twenty-nine cohorts), average BSA (twenty-one cohorts), percentage of patients in NYHA classes III/IV (nineteen cohorts), percentage of hypertensive patients (eighteen cohorts), and percentage of patients with coronary heart disease (fifteen cohorts) were not identified as significant sources of heterogeneity (R²<10%).

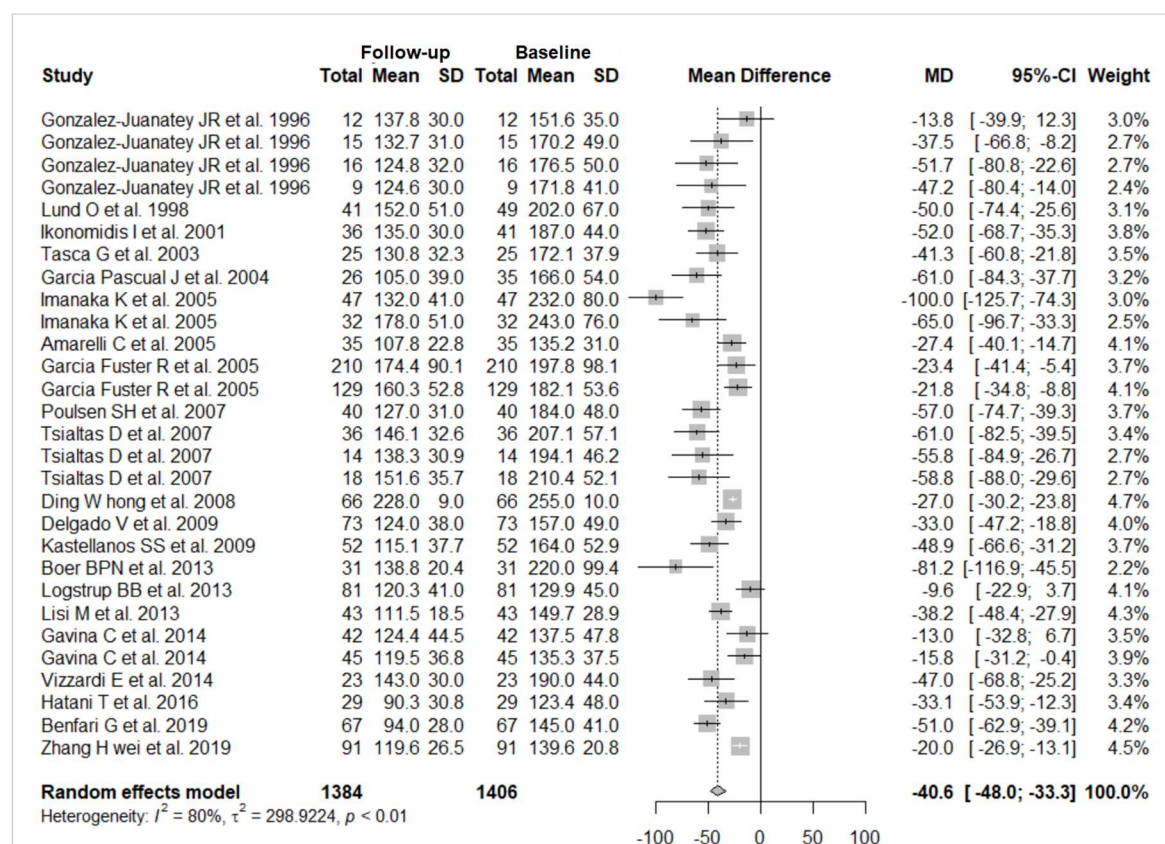


Fig. 5 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for LVMI

Left Ventricular Ejection Fraction

Thirty-nine cohorts (n=1,952) reported results for LVEF before and at least one month after AVR. The pooled SMD was 3.54 % (95% CI: 2.22 to 4.86, $p<0.001$), which indicated a significant increase after AVR. However, the results were significantly heterogeneous ($I^2=90.6\%$, $p<0.001$) (Fig. 6).

Subgroup analysis was made between patients with pre-AVR LVEF $>50\%$ and $<50\%$, showing significant differences between the groups ($p<0.001$): the pooled SMD for LVEF of the subgroup with initial LVEF $>50\%$ (thirty-four cohorts) was 2.35% (95% CI: 1.32 to 3.38, $I^2=53.8\%$); for the subgroup with initial LVEF $<50\%$ (seven cohorts), it was 10.93% (95% CI: 7.66 to 14.21, $I^2=67.7\%$), which shows a greater increase of LVEF in the initial LVEF $<50\%$ subgroup.

Univariate meta-regression was used to show the amount of heterogeneity accounted for sex of participants (thirty-eight cohorts), percentage of hypertensive patients (twenty-seven cohorts), and percentage of patients with coronary heart disease (twenty-one cohorts), which presented R^2 values of 10.21%, 11.93%, and 16.92%, respectively, with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable.

Average follow-up length (thirty-four cohorts), publication year (forty-one cohorts), participants' mean age (forty cohorts), average BSA (twenty-six cohorts), percentage of patients in NYHA classes III/IV (twenty-four cohorts) or with diabetes (twenty-one) were not identified as significant sources of heterogeneity ($R^2<10\%$).

Differences between SAVR (thirty-five cohorts) and TAVI (four cohorts) were not statistically significant ($p=0.08$). When analysing only the patients who underwent SAVR (thirty-one cohorts), there is a significant difference between the follow-up time subgroups ($p=0.0380$). SMDs within the follow-up time subgroups were 1.18% (95% CI: 0.01 to 2.35, six cohorts,

$I^2=0.0\%$) for the 1 to 6 months subgroup, 3.47% (95% CI: 1.40 to 5.54, twelve cohorts, $I^2=76.0\%$) for the 6 months to 1-year subgroup, and 4.66% (95% CI: 1.50 to 7.82, thirteen cohorts, $I^2=91.6\%$) for the after 1-year subgroup.

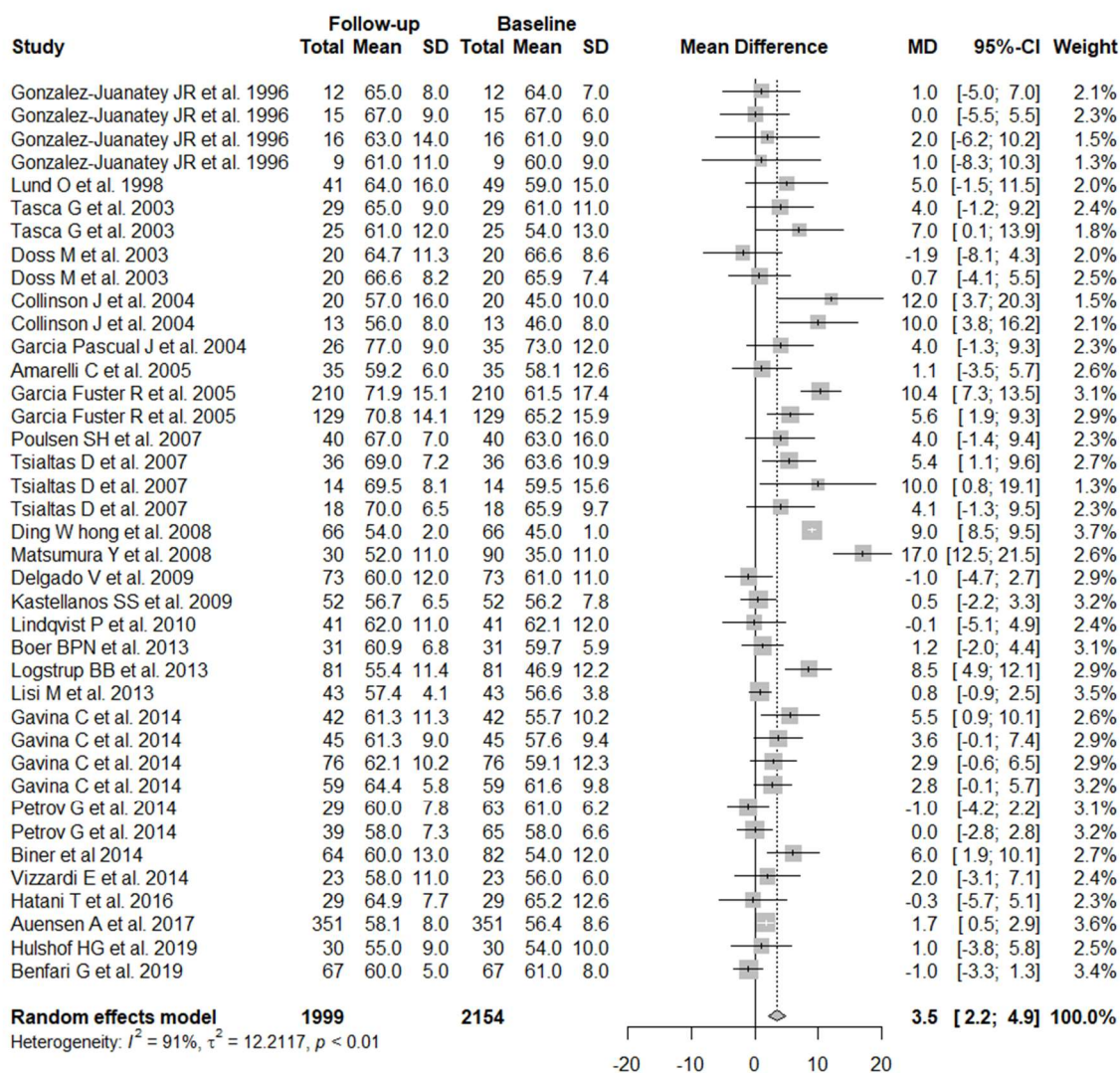


Fig. 6 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for LVEF

End-Diastolic Left Ventricular Diameter

Twenty-four cohorts (n=1,007) reported results for EDLVD before and at least one month after AVR. The pooled SMD was -2.06 mm (95% CI: -3.17 to -0.94, $p < 0.001$), which indicated a significant decrease after AVR. However, the results were significantly heterogeneous ($I^2=87.3\%$, $p < 0.001$) (Fig. 7). Univariate meta-regression was used to show the amount of

heterogeneity accounted for the sex of participants (twenty-four cohorts), average BSA (thirteen cohorts), and percentage of hypertensive patients, which presented R^2 values of 14.43%, 100.00%, and 45.97%, respectively, with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable. Differences between SAVR (twenty-three cohorts) and TAVI (one cohort) were not statistically significant ($p=0.12$). Average follow-up length (nineteen cohorts), publication year (twenty-four cohorts), participants' mean age (twenty-three cohorts), and percentage of patients in NYHA classes III/IV (fourteen cohorts) were not identified as significant sources of heterogeneity ($R^2<10\%$).

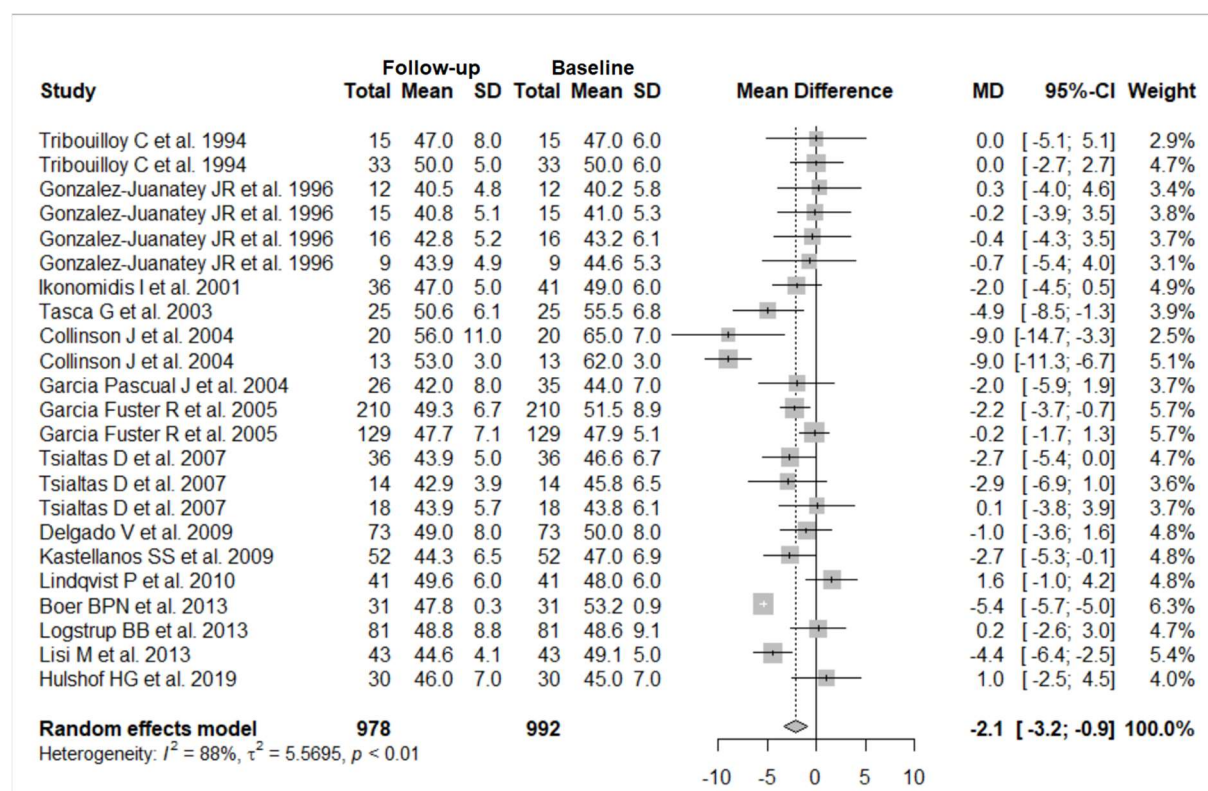


Fig. 7 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for EDLVD

End-Diastolic Left Ventricular Volume

Eleven cohorts ($n=484$) reported results for EDLVV before and at least one month after AVR. The pooled SMD was -13.10 mL (95% CI: -18.77 to -7.43, $p<0.001$), which indicated a significant decrease after AVR. However, the results were significantly heterogeneous

($I^2=52.4\%$, $p=0.0211$). Subgroup analysis found statistical differences in EDLVV between patients who underwent SAVR and TAVI ($p=0.001$). The pooled SMD for EDLVV in SAVR (nine cohorts) was -16.58 mL (95% CI: -21.43 to -11.72 , $I^2=13.1\%$) (Fig. 8), and in TAVI (two cohorts) it was -0.52 mL (95% CI: -8.96 to 7.92 , $I^2=0.0\%$), which shows a more significant decrease of LVEF in the SAVR subgroup. Univariate meta-regression was used to show the amount of heterogeneity accounted for average follow-up length (10 cohorts) and participants' mean age (eleven cohorts), which presented R^2 values of 44.79% and 35.48% , respectively, with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable. Publication year (eleven cohorts) and sex of participants (eleven cohorts) were not identified as significant sources of heterogeneity ($R^2<10\%$).

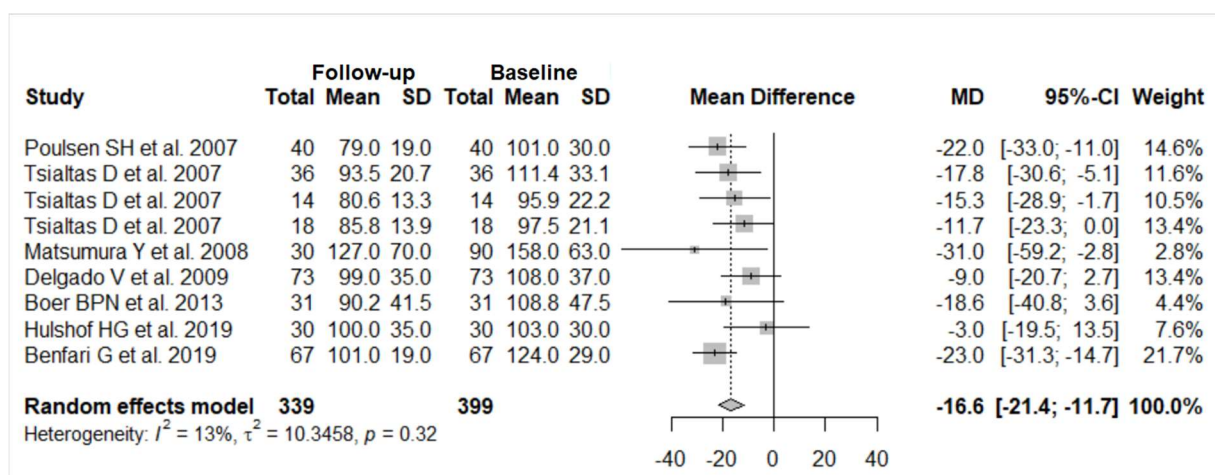


Fig. 8 - Standardized mean difference (SMD) post-SAVR vs. pre-SAVR for EDLVV

Posterior Wall Thickness

Twenty-seven cohorts ($n=1,426$) reported results for PWT before and at least one month after AVR. The pooled SMD was -1.89 mm (95% CI: -2.50 to -1.29 , $p<0.001$), which indicated a significant decrease after AVR. However, the results were significantly heterogeneous ($I^2=94.1\%$, $p<0.001$) (Fig. 9). Subgroup analysis showed significant differences between the follow-up subgroups ($p=0.02$). SMDs within the follow up time subgroups were -2.60 mm

(95% CI: -3.65 to -1.56, five cohorts, $I^2=91.6\%$) for the 1 to 6 months subgroup, -1.95 mm (95% CI: -3.26 to -0.64, eight cohorts, $I^2=90.8\%$) for the 6 months to 1 year subgroup and -1.02 mm (95% CI: -1.58 to -0.46, seven cohorts, $I^2=88.9\%$) for the after 1 year subgroup. Subgroup analysis was also performed between patients with pre-AVR LVEF>50% and <50%, showing significant differences between the groups ($p=0.0071$): the pooled SMD for PWT of the subgroup with initial LVEF>50% (twenty-three cohorts) was -2.05 mm (95% CI: -2.75 to -1.36, $I^2=92.8\%$); for the subgroup with initial LVEF<50% (three cohorts), it was -0.73 mm (95% CI: -1.40 to -0.06, $I^2=84.4\%$). Differences between SAVR (twenty-five cohorts) and TAVI (two cohorts) were not statistically significant ($p=0.39$).

Univariate meta-regression was also used to show the amount of heterogeneity accounted for publication year (twenty-seven cohorts) and percentage of patients with diabetes (thirteen cohorts), which presented R^2 values of 12.21%, and 25.39%, respectively, with R^2 meaning the proportion of the variance in the SMD that is predictable from the independent variable. Participants' mean age (twenty-six cohorts), sex of participants (twenty-seven cohorts), average BSA (nineteen cohorts), percentage of patients in NYHA classes III/IV (sixteen cohorts), with hypertension (seventeen cohorts), and with coronary heart disease (fourteen cohorts) were not identified as significant sources of heterogeneity ($R^2<10\%$).

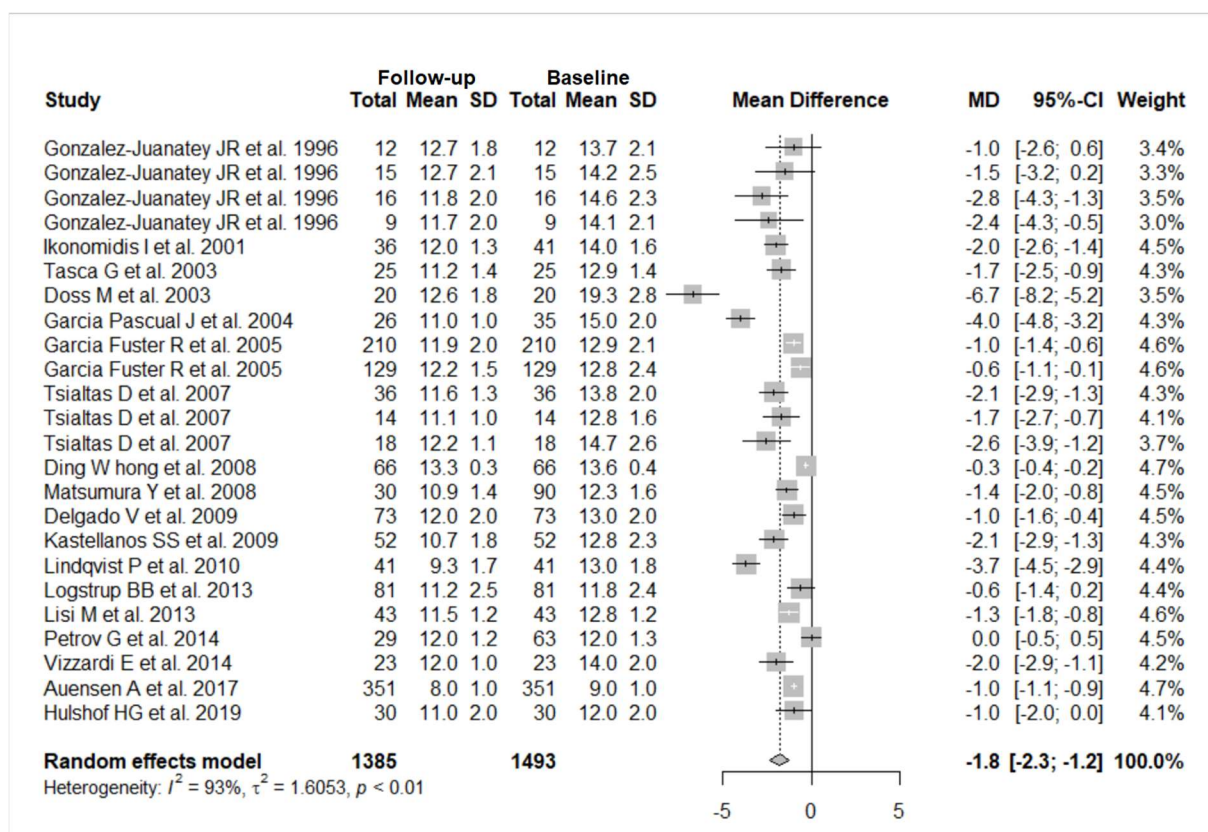


Fig. 9 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for PWT

Interventricular septal thickness

Twenty-seven cohorts ($n=1,426$) reported results for IVST before and at least one month after AVR. The pooled SMD was -1.72 mm (95% IC: -2.12 to -1.33 , $p<0.001$), which indicated a significant decrease after AVR. However, the results were significantly heterogeneous ($I^2=88.1\%$, $p<0.001$) (Fig. 10). Subgroup analysis found no statistically significant differences in IVST difference between patients who underwent SAVR and TAVI ($p=0.56$), nor between patients with initial LVEF $>50\%$ and $<50\%$ ($p=0.051$).

Univariate meta-regression was used to show the amount of heterogeneity accounted for, publication year (twenty-seven cohorts, $R^2=21.10\%$), sex of participants (twenty-seven cohorts, $R^2=25.70\%$), average BSA (nineteen cohorts, $R^2=45.26\%$), percentage of patients with diabetes (thirteen cohorts, $R^2=24.75\%$), and with coronary heart disease (fourteen cohorts, $R^2=17.07\%$), with R^2 meaning the proportion of the variance in the SMD that is predictable from the

independent variable. The follow-up length (twenty-two cohorts), participants' mean age (twenty-six cohorts), percentage of hypertensive patients (seventeen cohorts), percentage of patients in NYHA classes III/IV (sixteen cohorts) were not identified as significant sources of heterogeneity ($R^2 < 10\%$).

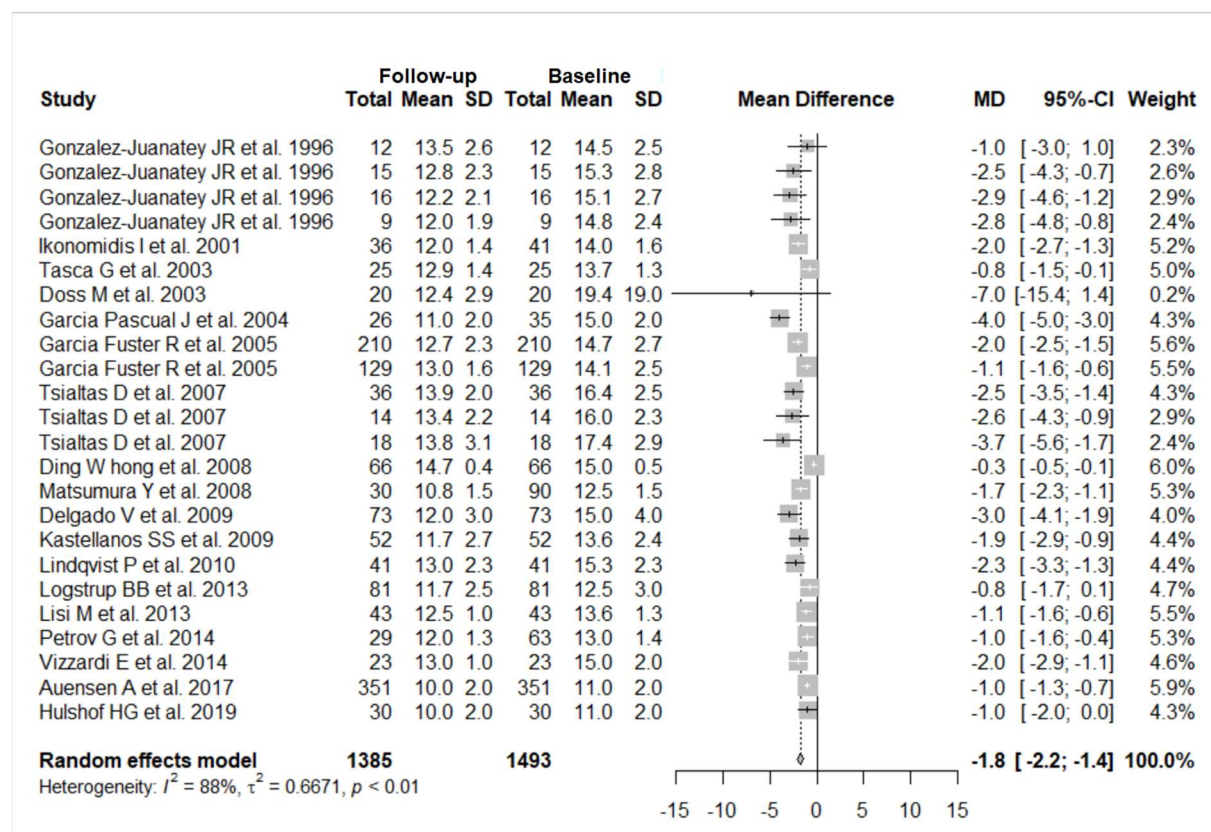


Fig. 10 - Standardized mean difference (SMD) post-AVR vs. pre-AVR for IVST

Discussion

This systematic review and meta-analysis assessed the characterization of the response of the unloaded LV after AVR. As data to predict the response of the LV to aortic stenosis are lacking, there are no reference values for the expected reverse remodeling phenomenon. However, the prognostic impact of the extent of reverse remodeling is well recognized in patients who underwent AVR for the treatment of AS, whether in terms of symptoms, survival, or hospitalization.⁶⁻⁸ This study builds upon previous findings by providing comprehensive estimates of association based on pre-existing data reported from individual studies on the topic.¹¹⁻⁴¹ Random-effects meta-analysis indicates that among patients undergoing AVR who completed echocardiographic follow-up at least 1 month after the procedure, there was evidence for reverse LV remodeling and presents results for the difference observed in some of the main structural and dynamic measures of the LV and Aortic Valve, after AVR. The reduction observed in MAG, LVM, LVMI, EDLVD, EDLVV, PWT, and IVST, and the increased values of and LVEF are consistent with reverse LV remodeling after AVR and reflect the improvement of the preload and afterload. These results are consistent with those from Mehdipoor et al,⁴² who reported LVMI reduction and increased LVEF within 6-15 months after TAVR, on 10 primary studies that involved 305 patients.

In the present meta-analyses, severe heterogeneity was observed. A meta-regression and subgroup analysis was performed to identify possible variables that differed between studies and could explain the differences between primary studies.

For AVA, LVEF, and PWT, subgroup analysis showed a significant difference between the follow-up time subgroups, suggesting an evolution of these measures through time and implying that we may expect different AVA, LVEF, and PWT values when performing

echocardiographic follow-up in patients at one to six months, six to twelve months or after twelve months post-AVR.

For MAG, LVM, and EDLVV, subgroup analysis between SAVR and TAVI also showed significant differences, suggesting that we should not expect the same results for these variables when following a patient that underwent SAVR and a patient that underwent TAVI.

For MAG, LVM (when analysing the SAVR subgroup), LVMI, LVEF, and PWT, subgroup analysis showed a significant difference between the subgroup of patients which had LVEF>50% at baseline and the subgroup with initial LVEF<50%, also suggesting that we should expect different results for these variables when following patients who underwent AVR, depending on baseline LVEF values.

Sex of participants was found to be a significant source of heterogeneity for AVA, LVM, LVEF, EDLVD, and IVST. These possible differences between men and women in terms of remodeling capacity have already been described by Singh et al,⁴³ which further supports that sex is a significant effect modifier of LV reverse remodeling after AVR. We found that several variables are associated with different responses after AVR: Average BSA, percentage of patients with hypertension, diabetes, and coronary heart disease. Future studies on post-AVR reverse remodeling should pay particular attention to the correct characterization of patients in these variables.

These values should be interpreted with caution because some variables were not described in all of the studies. The missing baseline characteristics in some studies is possibly by itself an explanation for some of the observed heterogeneity and implies that these R^2 values (R^2 proportion of the variance in the SMD that is predictable from the independent variable) could be overestimated.

Another possible source of heterogeneity is the use of echocardiography to access the LV after AVR. Although it is the most common technique for routine follow-up in cardiology, echocardiography is subject to image acquisition limitations, alongside inter-observer and intra-observer variability. We believe that by analysing studies that reported Cardiovascular Magnetic Resonance results, the results may be different and the heterogeneity across studies could be diminished, even though arguably less clinically useful.⁴⁴⁻⁴⁶ Another possible source of heterogeneity is a prosthesis-patient mismatch, which is present when the effective orifice area of the inserted prosthetic valve is too small in relation to body size and could alter the results by leading to worse hemodynamic function and less regression of LV hypertrophy.⁴⁷ This variable was not analysed because it was not reported in most of the included studies.

Strengths and Limitations

To our knowledge, this is the most extensive systematic review and meta-analysis conducted to assess the reverse LV remodeling profile in patients who underwent AVR. We excluded studies that included patients with aortic valvular lesions other than pure isolated AS, more than mild mitral regurgitation, patients submitted to balloon aortic valvuloplasty, valve-in-valve implantation, or reoperations to AS, to obtain more reliable results regarding the effect of the unloaded LV after AS. We performed meta-regression and subgroup analyses to explore sources of heterogeneity, identifying variables that explained differences across studies. To minimize publication and information bias, we searched three different electronic bibliographic databases without applying exclusion criteria based on the date or language of publication and contacted authors whenever relevant information was missing. This study could revamp the need for standardization of reference values for the expected reverse remodeling phenomenon after AVR.

Our analysis must be viewed in the context of its limitations. Of the 31 studies included, only one was a prospective randomized trial, while all of the others were observational studies, where there's always a risk of bias due to residual confounding. Data from patients who later died during follow-up is unavailable, meaning that most of the patients undergoing follow-up echocardiography may be survivors with improved heart function.

Also, data regarding valve type was not available for most studies, and baseline characteristics are described heterogeneously across included studies.

The restrictions we made with our inclusion and exclusion criteria, with the intention to have the most uniform population possible, may not reproduce most of the patients with AS.

Conclusion

Echocardiography demonstrates reverse LV remodeling after the first month post-AVR, with reductions in MAG, LVM, LVMI, EDLVD, EDLVV, PWT, and IVST, and improved AVA and LVEF. Because no reference values for the expected reverse remodeling phenomenon currently exist, our study provides a contributing part in the initial steps for the establishment of those standards, which could have clinical follow-up importance in the prognosis prediction. To better enhance the personalized delivery of AVR for AS, further prospective studies are needed, with more extended baseline characterization, predefined follow-up time, and preferably within the same center, with the same operators and echocardiographic technique.

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PRISMA Flow Diagram

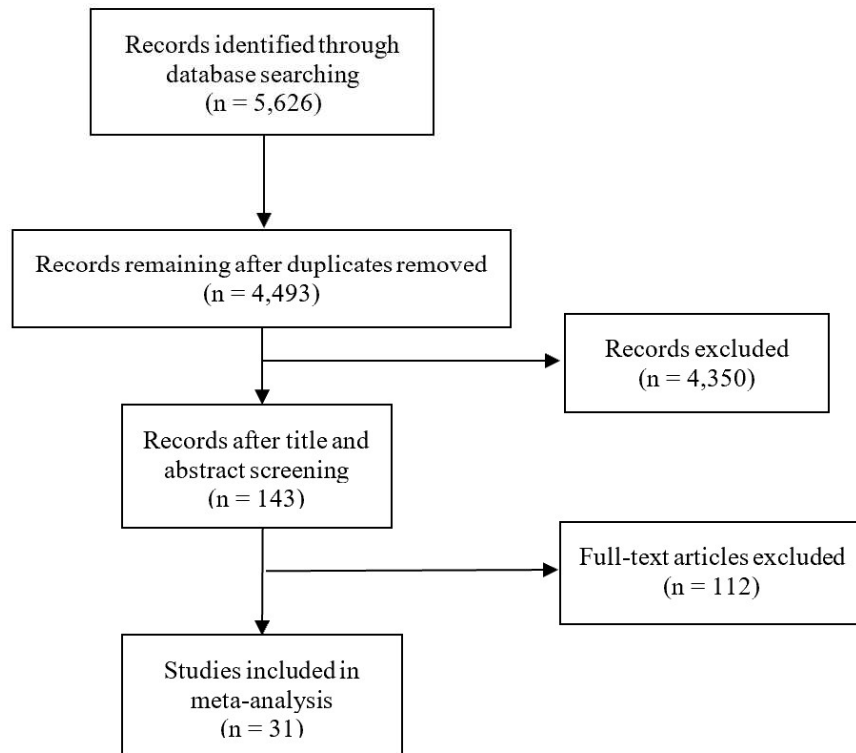


Fig. 1 - Flow diagram of the studies selection according to PRISMA guidelines.

Table 1 - Keywords used to perform the query in the 3 databases used in this study

ISI Web of Knowledge	((aortic stenosis OR (valv* AND (disease OR diseases)))) AND ((TAVI OR PAVR OR TAVR OR ((surgery OR surgical) AND (valv* OR heart OR aortic)) OR ((percutaneous OR transcath*) AND (valv* OR heart OR aortic)) OR ((transap* OR transcentric OR percutan* OR transcath*) AND (deliver* OR access* OR approach* OR minimal*)))) AND ((ventricul* remodel* OR ventricul* mass OR ventricul* volum* OR ventricul* dimension* OR ventricul* diameter*))
MEDLINE/Pubmed	(aortic valve stenosis[MeSH Terms] OR aortic stenosis[Title/Abstract] OR heart valve diseases[MeSH Terms] OR (valv*[Title/Abstract] AND (disease[Title/Abstract] OR diseases)[Title/Abstract])) OR aort* stenosis OR (abnormalities[MeSH Subheading]) AND (aortic valve[MeSH Terms]) OR valv* disease[Title/Abstract]) AND TAVI[Title/Abstract] OR PAVR[Title/Abstract] OR TAVR[Title/Abstract] OR (((surgery[Title/Abstract] OR surgical[Title/Abstract]) AND (valv* [Title/Abstract] OR heart[Title/Abstract] OR aortic[Title/Abstract])))) OR (((percutaneous[Title/Abstract] OR transcath*[Title/Abstract]) AND (valv*[Title/Abstract] OR heart[Title/Abstract] OR aortic[Title/Abstract])))) OR (((transap*[Title/Abstract] OR transcentric[Title/Abstract] OR percutan*[Title/Abstract] OR transcath*[Title/Abstract]) AND (deliver*[Title/Abstract] OR access*[Title/Abstract] OR approach*[Title/Abstract] OR minimal*[Title/Abstract])))) AND (((Validat*[Title/Abstract] OR Predict*[Title/Abstract] OR Rule*[Title/Abstract]) OR (Predict*[Title/Abstract] AND (Outcome*[Title/Abstract] OR Risk*[Title/Abstract] OR Model*[Title/Abstract])) OR ((History[Title/Abstract] OR Variable*[Title/Abstract] OR Criteria[Title/Abstract] OR Scor*[Title/Abstract] OR Characteristic*[Title/Abstract] OR Finding*[Title/Abstract] OR Factor*[Title/Abstract]) AND (Predict*[Title/Abstract] OR Model*[Title/Abstract] OR Decision*[Title/Abstract] OR

	Identif*[Title/Abstract] OR Prognos*[Title/Abstract])) OR (Decision*[Title/Abstract] AND (Model*[Title/Abstract] OR Clinical*[Title/Abstract])) OR (Prognostic[Title/Abstract] AND (History[Title/Abstract] OR Variable*[Title/Abstract] OR Criteria[Title/Abstract] OR Scor*[Title/Abstract] OR Characteristic*[Title/Abstract] OR Finding*[Title/Abstract] OR Factor*[Title/Abstract] OR Model*[Title/Abstract])))) NOT (animals[MeSH Terms]) NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]) NOT (((((((case control study[MeSH Terms]) OR (case*[Text Word] AND control*[Text Word])) OR case study[MeSH Terms]) OR (case*[Text Word] AND series[Text Word])) OR case reports[MeSH Terms]) OR (case*[Text Word] AND report*[Text Word])) OR (case*[Text Word] AND stud*[Text Word])) OR "editorial"[Publication Type] OR "comment"[Publication Type] AND ((ventricul* remodel* OR ventricul* mass OR ventricul* volum* OR ventricul* dimension* OR ventricul* diameter*) OR ("ventricular remodeling"[MeSH Terms]))
EMBASE	((('aortic valve stenosis':ab,ti OR 'aortic stenosis':ab,ti OR 'valvular heart disease':ab,ti) OR (valv*:ab,ti AND (disease:ab,ti OR diseases:ab,ti)) OR (aort* AND stenosis) OR ('valv* disease':ab,ti)) AND (tavi:ab,ti OR pavr:ab,ti OR tavr:ab,ti OR ((surgery:ab,ti OR surgical:ab,ti) AND (valv*:ab,ti OR heart:ab,ti OR aortic:ab,ti)) OR ((percutaneous:ab,ti OR transcath*:ab,ti) AND (valv*:ab,ti OR heart:ab,ti OR aortic:ab,ti)) OR ((transap*:ab,ti OR transcentric:ab,ti OR percutan*:ab,ti OR transcath*:ab,ti) AND (deliver*:ab,ti OR access*:ab,ti OR approach*:ab,ti OR minimal*:ab,ti))) NOT (animal NOT ('human'/exp OR human)) AND (((((ventricul* AND remodel* OR ventricul*) AND mass OR ventricul*) AND volum* OR ventricul*) AND dimension* OR ventricul*) AND diameter* OR 'heart ventricle remodeling')

Table 2 - Quality Assessment Tool

Study Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality rating
11	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
12	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
13	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
14	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
15	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
16	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
17	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
18	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
19	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
20	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
21	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
22	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
23	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
24	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
25	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
26	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
27	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	N	N	Fair
28	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
29	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
30	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
31	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	N	N	Fair
32	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
33	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
34	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
35	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
36	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
37	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
38	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	N	N	Fair
39	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good
40	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	N	N	Fair
41	Y	Y	Y	Y	N	Y	Y	NA	NA	NA	Y	NA	Y	N	Good

Y: yes, N: no, NA: Not applicable

Table 3 – Studies characteristics

Study Reference	Year	Country	Number of patients included	Inclusion Criteria	Exclusion Criteria	Procedure	Outcomes	Type of Study
11	1994	France	48	SAVR for severe AS (AVA<0.75cm ²)	Atrial fibrillation, tachycardia, high-degree atrioventricular block or pacemaker, mitral valve disease, mild aortic valve regurgitation, and perioperative death	SAVR	EDLVD, ESLVD, LVFS	Single-center, prospective cohort
12	2016	Japan	29	SAVR for severe AS	Prior cardiac surgery, concomitant moderate or severe aortic regurgitation, concomitant moderate or severe mitral valve regurgitation or stenosis who underwent mitral valvuloplasty or mitral valve replacement, concomitant hypertrophic obstructive cardiomyopathy who underwent myomectomy, documented atrial fibrillation on electrocardiogram before or after AVR	SAVR	MAG, Vmax, LVMI, LVEF,	Single-center, retrospective cohort
13	2019	Netherlands	30	SAVR for severe AS (AVA<1.0 cm ²)	Greater than mild coexisting aortic regurgitation, mitral, pulmonic, or tricuspid valve disease; atrial fibrillation; signs of any kind of infiltrative cardiomyopathy influencing cardiac function post-surgery (i.e., inflammation, myocardial stunning, or tamponade)	SAVR	AVA, MAG, Vmax, LVM, EDLVD, EDLVV, ESLVV, LVEF, PWT, IVST, LVID, PPM	Single-center, retrospective cohort
14	2013	Brazil	31	SAVR for AS patients with preserved systolic function and NYHA class III or IV	Severe coronary failure, other moderate or severe valvular heart diseases, atrial fibrillation, hypothyroidism, neoplasia, chronic kidney disease, or severe chronic obstructive pulmonary disease	SAVR	LVMI, EDLVD, ESLVD, EDLVV, ESLVV, LVEF,	Single-center, prospective cohort

15	2014	Spain	87	AVR for severe symptomatic AS and LVEF $\geq 40\%$	Significant LV systolic dysfunction, concomitant moderate to severe mitral valve disease or aortic regurgitation, significant CHD	TAVI/ SAVR	AVA, AVAI, MAG, Vmax, LVMI, EDLVVI, ESLVVI, LVEF, PPM	Multicenter, prospective cohort
16	2008	United Kingdom	66	SAVR for isolated aortic stenosis	Sub-optimal echocardiographic windows, pacemakers, prosthetic valves, prior aortic valve surgery, concomitant significant aortic regurgitation, and other hemodynamically significant cardiac diseases	SAVR	AVAI, MAG, PAG, LVMI, EDLVDI, ESLVDI, LVEF, PWT, IVST,	Single-center, retrospective cohort
17	2019	Italy	67	SAVR for severe isolated aortic stenosis	Significant coronary artery disease; history or presence of atrial fibrillation; more than moderate associated valvular disease or valvular prosthesis; congenital cardiac abnormalities; emergency surgery; severe chronic obstructive pulmonary disease; mechanical prosthesis implantation; inadequate acoustic window	SAVR	LVMI, EDLVV, LVEF	Single-center, prospective cohort
18	2014	Italy	23	TAVI with CoreValve prosthesis for “pure” symptomatic severe AS	History of ischemic heart disease, high blood pressure, hypertensive cardiomyopathy, dilated cardiomyopathy, and congenital heart defects.	TAVI	MAG, PAG, LVMI, EDLVDI, LVEF, PWT, IVST	Single-center, retrospective cohort
19	2001	United Kingdom	36	SAVR for isolated AS and normal LV systolic function	Other associated valve diseases, LVEF $< 50\%$, global hypokinesia or regional wall motion abnormalities, atrial fibrillation, need for calcium channel blockers or beta-blockers	SAVR	MAG, PAG, LVM, LVMI, EDLVD, ESLVD, PWT, LVFS, IVST	Single-center, prospective cohort
20	2019	China	91	SAVR for symptomatic AS	Preoperative LVEF $< 50\%$, previous valvular surgery, infective endocarditis, more than mild aortic/mitral	SAVR	LVMI, PPM	Single-center, retrospective cohort

					regurgitation, concomitant coronary disease, and other severe comorbidities.			
21	2005	Japan	79	SAVR for "pure" AS	A coexistent disease that causes LV volume overload such as significant aortic regurgitation, significant mitral valve disease, or patent ductus arteriosus	SAVR	MAG, LVMI	Single-center, retrospective case-series
22	1996	Spain	52	SAVR for "pure" AS with sinus rhythm before the operation and greater stenosis of a native aortic valve than of any other valve,	Previous cardiovascular operation, moderate-severe aortic insufficiency, mitral valve disease, coronary artery disease	SAVR	LVM, LVMI, EDLVD, LVEF, PWT, LVFS, IVST,	Single-center, retrospective cohort
23	2004	United Kingdom	33	SAVR for AS with significant left ventricular systolic dysfunction, LVEDD >60 mm, FS <25%, and in sinus rhythm before surgery	Redo aortic valve surgery or any additional procedure (i.e. coronary artery bypass grafting, other valvular interventions)	SAVR	LVM, EDLVD, ESLVD, LVEF, LVFS	Single-center, retrospective cohort
24	2013	Denmark	81	TAVI for isolated AS, not amenable to surgery because of severe comorbidities	Patients who died during follow-up, patients who underwent echocardiography on an ultrasound machine produced by a different manufacturer, and patients who had poor echocardiographic quality or missing follow-up echocardiograms	TAVI	AVA, PAG, LVM, LVMI, EDLVD, EDLVV, ESLVV, LVEF, PWT, IVST,	Single-center, retrospective cohort
25	2005	Italy	35	SAVR for isolated AS	Associated procedures (other than CABG)	SAVR	AVA, AVAI, MAG, PAG, LVMI, LVEF, PPM	Single-center, retrospective cohort
26	2014	Portugal	135	SAVR for severe symptomatic AS	Patients with aortic regurgitation NII/IV or other significant valve diseases (Nmild), and significant coronary artery disease (lesions N 50% on coronary angiography)	SAVR	AVAI, MAG, Vmax, LVEF,	Single-center, prospective cohort

27	2014	Germany	68	SAVR for isolated AS	Emergency surgery, prior AVR, TAVI, LVEF $\leq$ 40%, coronary artery narrowing $\geq$ 50%, coincident significant congenital or acquired valvular defects other than AS, pre-existing inflammatory heart diseases, cardiomyopathies, uncontrolled hypertension (blood pressure $\geq$ 160/ $\geq$ 100 mm Hg), or other extracardiac comorbidities (i.e., human immunodeficiency virus, metabolic disorders, malignancies, and so on)	SAVR	MAG, PAG, LVEF, PWT, LVFS, IVST, LVID	Single-center, prospective cohort
28	2003	Italy	54	SAVR for “pure” AS	More than mild aortic regurgitation; other heart diseases	SAVR	LVM, LVMI, EDLVD, ESLVD, LVEF, PWT, IVST, PPM	Single-center, retrospective cohort
29	2017	Norway	304	SAVR for severe AS, in patients >18 years and with the ability to read and write Norwegian.	unwilling participants, or patients with previous AVR or percutaneous balloon valvuloplasty, other diagnoses	SAVR	LVEF, PWT, IVST, LVID	Single-center, prospective cohort
30	1998	Denmark	41	SAVR for AS	Declined participation; re-evaluation of the aortic root angiogram showing significant aortic regurgitation; Heart disease other than aortic stenosis with or without concomitant coronary artery disease, and diagnostic investigation, including heart catheterization at other hospitals	SAVR	PAG, LVM, LVMI, EDLVV, LVEF, LVFS	Single-center, prospective cohort
31	2014	Israel	64	TAVI by transfemoral approach for either typical severe AS or LGSAS with preserved LVEF	Any valvular regurgitation greater than moderate by echocardiography, any degree of concomitant valvular stenosis other than AS, unstable patients requiring intravenous vasopressors or diuretics before TAVI, those without interpretable echocardiogram, and	TAVI	MAG, Vmax, EDLVV, ESLVV, LVEF	Single-center, retrospective cohort

					patients with LGSAS and an LVEF <50%. MPG<40 mm Hg, consistent with low gradient AS, and Vmax meeting criteria for typical severe AS (i.e., Vmax>4 m/s).			
32	2005	Spain	339	SAVR for “pure” or predominant AS	Significant aortic valve insufficiency, coronary artery bypass surgery, and other valve or aortic surgical procedures. Emergent operations, infectious endocarditis, and patients without preoperative echocardiographic data or with previous aortic valve replacement were also excluded.	SAVR	AVA, MAG, PAG, LVMI, EDLVD, LVEF, PWT, LVFS, IVST,	Single-center, retrospective cohort
33	2003	Germany	40	SAVR for isolated aortic stenosis (PAG >50 mmHg or AVA <0.8 cm ²) in which preoperative evaluation indicated the need for an isolated AVR; Patients expected to survive the surgery and expected to be available to return to the study site for all follow-up examinations	Patients who specifically chose to have a mechanical valve; Patients that required repair or replacement of an additional heart valve; prior implantation of a valve or annuloplasty device; active endocarditis, emergency operation, history of myocardial infarction; Intraoperatively: if aortic root and surrounding tissues had severe calcifications that could not be completely removed surgically and if their valve anatomy indicated an abnormally dilated aortic root or would require excessive trimming of the bioprosthesis	SAVR	AVA, MAG, LVEF, PWT, IVST	Single-center, prospective randomized trial
34	2007	Denmark	40	SAVR for isolated AS	Previous myocardial infarction or significant coronary artery disease, more than mild aortic or mitral regurgitation, and renal insufficiency	SAVR	LVMI, EDLVV, ESLVV, LVEF, LVFS,	Single-center, prospective cohort
35	2013	Italy	43	SAVR for severe isolated AS	Atrial fibrillation, flutter, or other major arrhythmias; high-degree atrioventricular block, reduced LVEF	SAVR	MAG, PAG, Vmax, LVM, LVMI, EDLVD,	Single-center, prospective cohort

					(<50%); coronary artery disease or previous cardiac surgery; coexisting valve disease or signs of pulmonary hypertension (defined as right ventricular-right atrial peak pressure drop>40 mm Hg).		ESLVD, LVEF, PWT, IVST	
36	2007	Italy	68	SAVR for isolated critical aortic stenosis	Ischemic heart disease, severe hypertension, complex atrial and ventricular arrhythmias, pacemaker, other valvular involvement, endocarditis, and dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) $\leq$ 40%	SAVR	AVA, AVAI, MAG, PAG, LVM, LVMI, EDLVD, ESLVD, EDLVV, ESLVV, LVEF, PWT, IVST,	Single-center, prospective cohort
37	2009	Netherlands	73	SAVR for Severe AS (AVA < 1cm ²)	Concomitant moderate-to-severe aortic regurgitation, subvalvular AS, mitral stenosis or moderate-to-severe mitral regurgitation, depressed LVEF (<50%), and previous valve replacement.	SAVR	AVA, MAG, PAG, LVMI, EDLVD, ESLVD, EDLVV, ESLVV, LVEF, PWT, IVST,	Single-center, retrospective cohort
38	2004	Spain	26	SAVR for isolated severe symptomatic AS in elder (65-82 years old) women	Other significant valve lesions (except mild regurgitation in any cardiac valve), significant CAD, absence of SR, and presence of left to right shunts	SAVR	MAG, PAG, LVMI, EDLVD, ESLVD, LVEF, PWT, LVFS, IVST,	Single-center, prospective cohort
39	2009	Greece	52	SAVR for severe AS	Coronary artery disease, regional LV wall abnormalities, AF, CKD, chronic active inflammatory disease, AR >1, other valvular diseases	SAVR	AVA, AVAI, MAG, PAG, LVM, LVMI, EDLVD, LVEF, PWT, IVST,	Single-center, prospective cohort
40	2008	USA	30	Isolated SAVR without other cardiac operation, for severe AS (AVA<1.0 cm ²)	Known coronary artery disease, significant aortic regurgitation, significant other valve diseases, pacing rhythm at the preoperative examination,	SAVR	EDLVV, ESLVV, LVEF, PWT, IVST	Single-center, retrospective cohort

				with LV systolic dysfunction (EF<50%) SAVR for severe AS (PAG >70 mmHg)	and inadequate image quality of echocardiography Significant (>50% stenosis) CAD; pre-operatively not in sinus rhythm or impaired LV systolic function (EF <50%), signs of raised left atrial pressure (E/A >2 and/or short isovolumic relaxation time, <60 ms), or signs of pulmonary hypertension (peak right ventricular-right atrial pressure drop >35mmHg). Patients with more than mild additional valve disease, chronic obstructive pulmonary disease, or renal failure			
41	2010	Sweden + Italy	41			SAVR	LVM, EDLVD, ESLVD, LVEF, PWT, IVST	Multicenter, prospective cohort

AS, aortic stenosis; AVA, effective aortic valve area; AVAI, effective aortic valve area index; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CHD, coronary heart disease; EDLVD, end-diastolic left ventricle diameter; EDLVV, end-diastolic left ventricle volume; ESVV, end-systolic left ventricle volume; ESLVD, end-systolic left ventricle diameter; IVST, interventricular septum thickness; LGSAS, low-gradient severe aortic stenosis; LV, left ventricle; LVEF, left ventricle ejection fraction; LVID, left ventricle internal diameter; LVFS, left ventricle fraction shortening; LVM, left ventricular mass; LVMI, left ventricular mass index; MAG, mean aortic gradient; PAG, peak aortic gradient; PWT, posterior wall thickness; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; Vmax, Aortic valve peak velocity;

Table 4 - Baseline characteristics

Study Reference	Cohort	Female sex (%)	Age (years)	NYHA III/IV	HTN (%)	Diabetes (%)	CHD (%)	BSA (m ²)	Initial LVEF >50% (Y/N)	Follow-up (months)	Evaluation dates	Valve
11	Group 1 (NYHA I, II)	40	69±7	0	NR	NR	33.3	NR	NR	3	NR	NR
	Group 2 (NYHA III, IV)	66.7	70±8	100	NR	NR	9.1	NR	NR	3	NR	NR
12		56.6	73.2±7.9*	NR	75.9	25.3	NR	1.55±0.17	Y	36	2006-2011	Both
13		37	67±16	NR	50	23	NR	NR	Y	14.355**	2004-2016	Both
14		67.7	61.15±14.72	100	NR	NR	NR	NR	Y	6	NR	NR
15	Group 1 (TAVI)	61.9	83.5 (79-87)	88	83.3	26.2	0	1.75 (1.6-1.8)	Y	6	2009-2010	Biological
	Group 2 (SAVR)	62.2	73 (68-78)	26.7	62.2	28.9	0	1.76 (1.57-1.86)	Y	6	2009-2010	Biological
16		19.7	70±2	63.6	42	38	56	NR	N	13*	1998-2003	Both
17		66	72±8	NR	78	19	NR	1.87±0.21	Y	12	2015-2016	Biological
18		56.5	83±8	65.2	0	NR	0	1.77±0.17	Y	6	2011	Biological
19		31.7	NR	0	NR	NR	NR	NR	NR	48	1991-1992	Both
20		38.5	48.8±9.6	33	33	24.2	0	1.64±0.11	NR	48.6**	2010-2016	Mechanical
21	Group 1 (N)	36	60.7±12.3	NR	17	6	NR	1.51±0.17	NR	31.7±-14.7*	1991-2000	Mechanical
	Group 2 (H)	50	67.4±6.3	NR	28	19	NR	1.52±0.16	NR	31.7±-14.7*	1991-2000	Mechanical
22	Group 1 (19mm)	75	65.1±6.4	83.3	NR	NR	0	1.57±0.12	Y	18*	1989-1994	Both
	Group 2 (21mm)	67	59.7±8.1	80	NR	NR	0	1.64±0.11	Y	29*	1989-1994	Both
	Group 3 (23mm)	50	53.3±11.4	62.5	NR	NR	0	1.71±0.18	Y	16*	1989-1994	Both
	Group 4 (25mm)	44	58.8±12.6	77.8	NR	NR	0	1.78±0.17	Y	18*	1989-1994	Both
23	Group 1 (stentless)	15	64±11	NR	0	NR	NR	NR	N	30**	1992-1997	Both
	Group 2 (stented)	8	67±14	NR	0	NR	NR	NR	N	30**	1992-1997	Both
24		54.32	81±7	51.8	53.1	11.1	64.8	NR	N	12	2006-2010	Biological
25		91.4	63.4±17	68.6	60	11.6	11.6	1.59±0.13	Y	28.2±-22.7*	1997-2003	Mechanical
26	Group 1 (HT±AS)	63.2	69.4±9.1	31.6	100	18.4	0	1.76±0.19	Y	12	2006-2009	Both
	Group 2 (ASwHT)	50.8	63.1±14.2	11.9	0	22	0	1.75±0.18	Y	12	2006-2009	Both

27	Group 1 (women)	100	71±9	NR	86	27	2	1.8±0.2	Y	38.4	2005-2012	Both
	Group 2 (men)	0	70±10	NR	89	31	11	2±0.2	Y	38.4	2005-2012	Both
28	Group 1 (21 mm CEP)	48	75.7±4.6	NR	65	27	59	1.77±0.17	Y	28.8±14.4*	1997-2001	Biological
	Group 2 (23 mm CEP)	0	74.9±6.2	NR	58	8	44	1.9±0.13	Y	20.4±8.4*	1997-2001	Biological
29		42	73±10	44	46	9	30	NR	Y	1	2010-2013	Both
30		39	61±14	73	NR	NR	35	NR	Y	18	1988-1989	Mechanical
31		65	83.3±4.5	100	83	25	53	1.59±0.39	Y	1	2009-2011	Biologicala
32	Group 1 (non significant ppm)	36.2	63±9	70	39.5	16.2	NR	1.7±0.2	Y	10**	1994-2001	Both
	Group 2 (ppm)	57.4	70±5	74.4	53.5	24	NR	2±0.3	Y	10**	1994-2001	Both
33	Group 1 (perimount)	60	79±4.3	90	45	NR	NR	1.85±0.8	Y	12	1999-2001	Biological
	Group 2 (primaplus)	45	78±3.8	85	50	NR	NR	1.79±0.6	Y	12	1999-2001	Biological
34		65	67±10	40	33	13	NR	NR	Y	12	2002-2003	NR
35		38.46	71.5±9.7	20.9	72.9	13.4	NR	NR	Y	3	NR	NR
36	Group 1 (CEP)	52.8	70.9±6.9	NR	NR	NR	NR	1.7±0.2	Y	12	2002-2004	Biological
	Group 2 (Shelhigh)	64.3	77.8±3.2	NR	NR	NR	NR	1.64±0.2	Y	12	2002-2004	Biological
	Group 3 (Toronto)	61.1	74.3±6.6	NR	NR	NR	NR	1.7±0.2	Y	12	2002-2004	Biological
37		43.8	65±13	NR	52	14	NR	1.9±0.2	Y	17**	NR	Both
38		100	73.2±4.7	85	57	NR	NR	NR	Y	6	1997-2002	NR
39		38.5	67.1±10.4	NR	NR	NR	0	1.82±0.17	Y	6	NR	NR
40		26.7	69±11	NR	NR	NR	0	1.96±0.22	N	24±14*	2002-2006	Both
41		36.6	64±13	29	64	12	NR	NR	Y	6	2007-2009	NR

BSA, body surface area; CHD, coronary heart disease; HTN, hypertension; LVEF, left ventricle ejection fraction

For follow-up (months): * mean±SD; ** median



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Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. - MANDATÓRIO	"With this work, we conducted a systematic review and meta-analysis to characterize the response of the unloaded LV after AVR", page 3
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. - SEGUIR RECOMENDAÇÕES DA REVISTA	Abstract, page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. - MANDATÓRIO <i>O rationale corresponde à justificação da importância da revisão sistemática</i>	"It is known that the extent of reverse remodeling is an important prognostic factor in patients who underwent AVR, whether in terms of symptoms, survival, or hospitalization. ⁶⁻⁸ However, because data to predict the response of the LV to aortic stenosis are lacking, there are no reference values for the expected reverse remodeling phenomenon, meaning we do not know how much mass regression or LV volume reduction is expected after AVR.", Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). - MANDATÓRIO	Methods, page 4
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. - FACULTATIVO	
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. - MANDATÓRIO <i>É altamente recomendado, de acordo com as boas</i>	"The literature research was done on December 9 th , 2020, in three electronic databases: MEDLINE (through PubMed), Web of Science, and Embase. The search was conducted with no restrictions on language or year of publication. Full details of the search are presented



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		<i>práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.</i>	in Table 1.", "Studies were included if they reported echocardiographic findings before and at least one month after SAVR or TAVI for the treatment of pure and isolated Aortic Stenosis. This time interval was chosen so that there would be time for acute changes to resolve and for reverse remodeling to occur. ¹⁰ Studies also needed to report at least one interest variable of outcome for the measurement of the left ventricle reverse remodeling to be included.", Page 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. – MANDATÓRIO <i>Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaio clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.</i> <i>Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.</i>	"The literature research was done on December 9 th , 2020, in three electronic databases: MEDLINE (through PubMed), Web of Science, and Embase. The search was conducted with no restrictions on language or year of publication. Full details of the search are presented in Table 1.", Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. – MANDATÓRIO <i>A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)</i>	Table 1
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). – MANDATÓRIO <i>As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de</i>	"For each study, the title and abstract screening for relevance was performed by four independent investigators (AB, FN, CM, JRS), meaning that at least two independent investigators screened each study. The full texts of the remaining studies were individually and



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		<i>selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.</i>	independently assessed for inclusion based on predefined criteria. All discrepancies were resolved by consensus. Also, the investigators of primary studies were contacted for clarifications if relevant data was missing.”, Page 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. – MANDATÓRIO <i>Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.</i>	“The data extraction was performed by four investigators (AB, FN, CM, JRS), meaning that the data from each study were extracted by one investigator and verified by at least another one. For each study, we extracted the following information: publication characteristics (authors, publication year, journal), study design (clinical setting, the country where the study was performed, the period of recruitment and evaluation, duration of follow-up, number of patients randomized and analyzed for each outcome), baseline characteristics of the population (eligibility criteria, age, gender, BSA, NYHA class, Hypertension, Diabetes, coronary heart disease, and other comorbidities and relevant baseline data), intervention (SAVR or TAVI, type of valve), and outcome data of interest. Summary of studies and baseline characteristics are presented in Tables 3 and 4.”, “and contacted authors whenever relevant information was missing.”, Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. – MANDATÓRIO <i>Trata-se de descrever as variáveis para as quais foi obtida informação.</i>	“For each study, we extracted the following information: publication characteristics (authors, publication year, journal), study design (clinical setting, the country where the study was performed, the period of recruitment and evaluation, duration of follow-up, number of patients randomized and analyzed for each outcome), baseline characteristics of the population (eligibility criteria, age, gender, BSA, NYHA class, Hypertension, Diabetes, coronary heart disease, and other comorbidities and relevant baseline data), intervention (SAVR or TAVI, type of valve), and outcome data of interest. Summary of studies and baseline characteristics are presented in Tables 3 and 4. The main outcomes of interest were Effective Aortic Valve Area (AVA),



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			Mean Aortic Gradient (MAG), End-Diastolic Left Ventricular Diameter (EDLVD), End-Diastolic Left Ventricular Volume (EDLVV), LV mass (LVM), LV mass index (LVMI), LV ejection fraction (LVEF), Posterior Wall Thickness (PWT) and IV septal thickness (IVST).”, Page 5
Risk of bias in individual studies / Risk of bias across studies	12/15	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. – MANDATÓRIO <i>Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).</i>	“According to the National Institutes of Health, we used the Study Quality Assessment Tools to categorize several domains for all the eligible studies, using a tool for observational cohort and cross-sectional studies. The overall risk of bias was independently assigned to each study by four investigators (A.B., F.N., C.M., J.R.) and classified into "good", "fair", and "poor", as detailed in Table 2.”, Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	“pooled mean differences between post-follow-up and baseline values for each outcome”, Page 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. – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	“Heterogeneity was assessed by the Cochran Q statistic p-value and by the I^2 statistic - a p-value<0.10 and an I^2 >50% were considered to represent substantial heterogeneity.”, Page 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	“Sources of heterogeneity were explored by means of univariable meta-regression models (except for cases in which the number of primary studies did not exceed 10), with tested covariates including the publication year, participants' mean age, percentage of females, average BSA, and percentage of patients in NYHA classes III/IV, with hypertension, with diabetes mellitus, with coronary heart disease. In addition, we performed subgroup analyses for the follow-up period (with the follow-up being classed in three groups – between one



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			and six months, between six and twelve months, and higher than twelve months), and for the initial LVEF (classes in two groups - lower than 50% and higher than 50%). Finally, sensitivity analyses were performed for studies in which SAVR was undertaken.”, Page 6
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. – MANDATÓRIO	“A total of 5626 publications were identified through our search of MEDLINE/Pubmed (2,871 records), Embase (1,709 records), and Web of Science (1,046 records). After removing the duplicates, we remained with 4,493 records. Following the title and abstract screening, we selected 143 articles for full-text review. After excluding articles that did not meet the inclusion criteria, we ended with 31 primary studies, with a total of 45 study cohorts included for meta-analysis.”, Page 7
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. – MANDATÓRIO	Table 3 and 4
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). – MANDATÓRIO	Table 3 and 4
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. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Table 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. – FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE	“Fourteen cohorts (n=805) reported results for AVA before and at least 1 month after AVR. The pooled SMD was 1.02 cm ² (95% CI: 0.86 to 1.18, p<0.001), indicating a significant increase after AVR. However, the results were significantly heterogeneous (I ² =96.9%, p< 0.001) (Fig. 2). (...)” etc, Pages 7-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	“Univariate meta-regression identified average follow-up time as a heterogeneity source (R ² =41.04%) and showed significant differences between the follow-up time subgroups (p=0.01). SMDs within the follow



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			up time subgroups were 1.11 cm ² (95% CI: 0.78 to 1.43, three cohorts, I ² =91.5%) for the 1 to 6 months subgroup, 1.12 cm ² (95% CI: 0.96 to 1.29, eight cohorts, I ² =96.0%) for the 6 months to 1 year subgroup and 0.66 cm ² (95% CI: 0.41 to 0.92, three cohorts, I ² =92.2%) for the after 1 year subgroup. Meta-regression also identified the sex of participants as a source of heterogeneity (R ² =17.14%). Initial LVEF, participants' mean age, publication year, average BSA, percentage of hypertensive patients, and type of procedure were not identified as significant sources of heterogeneity (R ² <10%).” Etc, Pages 7-19
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). – MANDATÓRIO	“there was evidence for reverse LV remodeling and presents results for the difference observed in some of the main structural and dynamic measures of the LV and Aortic Valve, after AVR. The reduction observed in MAG, LVM, LVMI, EDLVD, EDLVV, PWT, and IVST, and the increased values of AVA and LVEF are consistent with reverse LV remodeling after AVR and reflect the improvement of the preload and afterload.”, Page 20
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). – MANDATÓRIO	“Our analysis must be viewed in the context of its limitations (...)”, Page 23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. – MANDATÓRIO	Conclusion, Page 23
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. – SEGUIR RECOMENDAÇÕES DA REVISTA	

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

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INSTRUCTIONS FOR AUTHORS

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1. Revista Española de Cardiología

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3.1. BEFORE YOU BEGIN

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 4. Key points. Include the following information at the end of the article:
 - What is known about the topic?
Include 3 or 4 sentences that summarize key points on what is known about the research topic (do not exceed 100 words).
 - What does this study add?
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