Survival after aortic valve replacement vs. conservative management in severe low-flow, low-gradient aortic stenosis

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Abstract

Background and aim. Classical and paradoxical low-flow, low-gradient aortic stenosis (LFLGAS) are the most challenging aortic stenosis (AS) subtypes. The current therapeutic options are aortic valve replacement (AVR) and conservative management. The matter is controversial because AVR promotes long-term survival, but it is invasive, while no aortic valve replacement (noAVR) in non-invasive, but it is associated with poor prognosis. This meta-analysis aims to investigate the survival rate in patients with LFLGAS undergoing AVR versus noAVR interventions. Methods. A meta-analysis was conducted comparing the outcomes of AVR and noAVR in terms of survival. A meta-regression was carried out to investigate the impact of preserved and reduced left ventricular ejection fraction (LVEF) on survival in both the AVR and noAVR group. Results. The log IRR of survival between AVR group and noAVR group was 0.58 [0.28, 0.87] (p-value = 0.0001), suggesting that survival is significantly better in the AVR group compared to the noAVR group. The meta-regression revealed that low LVEF is related to higher survival rates in the AVR group (p-value = 0.04) when compared to preserved LVEF. LVEF has no impact on survival in the noAVR group (p-value = 0.18). Conclusions. Patients with LFLGAS have better survival in the AVR group rather than in the noAVR group. Reduced LVEF was related to better survival than preserved LVEF in the AVR, and no difference between low and preserved LVEF was found in the noAVR group.

Introduction

Low-flow, low-gradient aortic stenosis (LFLGAS) is the most challenging aortic stenosis (AS) subtype, regardless of whether it is accompanied by either depressed left ventricular ejection fraction (LVEF) or preserved LVEF[1,2]. The challenge derives from the inconsistency between aortic valve area (AVA) and gradient, which does not allow a realistic evaluation of the entity of the stenosis, fundamental in choosing the right therapeutic approach [3].

Currently, the available therapeutic managements for LFLFAS are aortic valve replacement (AVR) in symptomatic patients with left ventricular (LV) dysfunction, and conservative management [4]. AVR promotes long-term survival and improvement of the functional status of patients in both classical and paradoxical LFLGAS. Still, it is more invasive, and it is associated with high operative mortality risk in patients with reduced LV contractile reserve [4-7]. On the other hand, a noAVR approach mainly via medical management is considered the treatment of choice in elderly patients and subjects with high preoperative risk, as it is not invasive [8]. However, noAVR approaches predispose patients to a poorer prognosis in both classical and paradoxical LFLGAS [8].

Since noAVR approach leads to a poor prognosis and AVR is burdened by a high operative risk, literature reports controversial results about the superiority of one type of management over the other.

Therefore, this meta-analysis aims to investigate the survival rate in patients with LFLGAS undergoing AVR versus noAVR interventions.

Materials and methods

Search strategy

We conducted our study using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) investigation guidelines. We searched for all available articles that reported the survival rate in patients with LF LG AS following either AVR or no AVR[9]. A literature search was conducted in Embase and Medline databases through PubMed, as well as Google Scholar and Cochrane library. Moreover, we checked the relevant articles which are suggested on those databases as well as the references of the selected materials. We used both free text words and MeSH terms.

The search terms were "Therapy/Broad[filter]" AND "Aortic Valve Stenosis" OR "Aortic Valve Stenosis [MeSH Terms]" OR "Aortic Stenosis" OR "Aortic Stenosis [MeSH Terms]" AND "Low Flow" OR "Low-Flow" AND "Low Gradient" OR "Low-Gradient" AND "Aortic Valve Replacement" OR "Aortic Valve Replacement [MeSH Terms]" AND "Conservative Management" OR Conservative Management [MeSH Terms]" OR "Medical Treatment" OR "Medical Treatment [MeSH Terms]" AND "Surgical Intervention" OR "Surgical Intervention [MeSH Terms]" AND "Low-Flow Low-Gradient" OR Low Flow Low Gradient."

Selection criteria

We included articles that met the following criteria: (a) performed on humans, (b) studies with more than 20 patients, (c) articles comparing AVR to noAVR procedures, (d) articles focused on LF LG AS, (e) studies published in English and (f) articles published within the last 15 years (2004 - 2019). On the other hand, we excluded articles with the following conditions: (a) performed on animals, (b) not in English, (c) case reports (d) literature reviews and meta-analyses, (e) population study of 20 or less, (f) articles that are older than 15 years, (g) studies not focusing on LFLGAS (h) studies which did not report a comparison between AVR and no AVR.

Methodological quality assessment

To assess the quality of the included studies, we used a modified tool of Down and Black's Checklist for Measuring Quality[10]. This tool consists of 18 questions evaluating five criteria: (a) the overall quality of the study, (b) the external validity, (c) study bias, (d) confounding and selection bias, and (e) power of the study. Each question is graded on a binary basis (0 or 1) except for two items, ranked out of 2 and out of 5, respectively.

Two researchers (SA And LM) conducted the evaluation. A third researcher was involved in reviewing (OP). The agreement was quantified using Cohen's kappa [11].

Endpoints

The primary endpoint of our study was the survival rate at follow up in patients with LFLG AS, treated with AVR or noAVR. Also, we aimed to investigate the impact of LVEF on survival. In the AVR group, we included both surgical valve replacement (SAVR) and transcatheter valve replacement (TAVR), while in the no AVR group, we included conservative medical management and valvuloplasty[3].

LFLGAS was defined as an aortic valve area (AVA) of [?]1 cm^2 or indexed AVA <0.6 cm^2/m^2, a stroke volume indexed (SVI) [?] 35 mL/m^2 and a transvalvular mean pressure gradient [?] 40 mmHg. Preserved LVEF was identified as > 55% (paradoxical LFLGAS), while reduced LVEF was defined as < 50% (classical LFLGAS) [3].

Statistical analysis

This meta-analysis was conducted using V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). We used Incidence Rate (IR) and proportions as main statistical indexes. Since the follow-up time was different in each article, we employed the IR test to analyze survival rates in both groups. Heterogeneity was evaluated by using the I-square test, and the publication bias was evaluated by using the Egger regression test. Furthermore, meta-regression was performed to evaluate the impact of LVEF on survival in both AVR and the noAVR group. We defined statistical significance for P values < 0.05.

Results

Characteristics of the studies

The steps that we followed in selecting the articles are shown in the PRISMA flow diagram in **Figure 1** . In total, we found 49 articles. After the selection process, we retrieved four papers, and nine articles were added manually from the references of the formers. In the end, the final number of the included in our meta-analysis was 13 articles [14-26].

The overall population size was 2,013 patients, 1,066 (53%), and 947 (47%) in the AVR and noAVR group, respectively. The baseline characteristics of the included patients are shown in **Table 1** . Twelve papers defined whether their cohort of patients presented preserved or reduced LVEF [14-21,23-26]. Out of 1,533 patients, 952 (62.1%) patients had preserved LVEF, and 581 (37.9%) had low LVEF. The mean age of the total population was 74.9 [73.3-76.6] years old [14-18,20-23,25,26], particularly 73.2 [69.7-76.7] years old in the AVR group and 77.7 [74.8-80.7] years old in the noAVR group. Overall AVA was 0.81 [0.77-0.84] cm^2 [14-18,20-23,26]; overall mean gradients was 27.21 [24.43-29.98] mmHg[14-18,20-23,26]; overall SVI was 34.82 [27.61-42.04] mL/m^2 [15-18,20,21,23,26].

The determination of the number of patients undergoing either SAVR or TAVR was conducted on 11 papers [14-21,23,25,26]. The number of patients treated with SAVR was 607 (81.7%), while 136 (18.3%) patients received TAVR (**Table 2**). In the noAVR group, the majority of patients were treated medically rather than with valvuloplasty (99.9% vs. 0.1%).

Methodological quality

The average overall quality rating was 0.81 ± 0.53, with ratings ranging from 0 to 1.81. **Appendix A** illustrates the average scores on the elements of the checklist. The analysis revealed lower scores related to the internal validity for both bias and selection bias, and for power analysis, which is related to the quality of reporting. The low values shown are due to the study type being a retrospective with no randomized samples validity studies. Acceptable interrater agreement was found (ϰ = 0.89; %-agree = 94.9).

Follow up

The mean follow up period, calculated in 9 papers, was 35.66 [27.50- 43.81] months [14-18,20,21,25,26]. The longest follow up period was 55.2 months [17]. Follow up was 100% complete in 9 studies [14-17,19,20,23-25].

Main endpoints

Figure 2A shows that the log IRR of survival between AVR group and noAVR group was 0.58 [0.28, 0.87] (p-value = 0.0001; I-square = 24.16%, p-value = 0.25; Egger's test: 0.18 [-0.18, 0.55], p-value = 0.002). This suggests that the overall survival is significantly better in the AVR group compared to the noAVR group. The funnel plot is shown in **Figure 2B** (funnel plot asymmetry test: p-value = 0.10). Moreover, the meta regression revealed that low LVEF is related to higher survival rates in the AVR group (p-value = 0.04) when compared to preserved LVEF (**Figure 3A**). Conversely, LVEF has no impact on survival in the noAVR group (p-value = 0.18), as shown in **Figure 3B** .

Discussion

Low flow, low gradient aortic stenosis (LFLGAS) is associated with a higher risk of a cardiac event and heart failure, increasing the rate of all-cause mortality, cardiovascular- and valvular-related death[27]. Aortic valve replacement (AVR) is effective in either classical or paradoxical LFLGAS [28]. AVR has shown to be able to reduce the rate of adverse events and improve left ventricle ejection fraction (LVEF), enhancing long-term survival when compared to non-aortic valve replacement (noAVR) approaches. However, in patients with concomitant coronary artery disease (CAD and reduced contractile reserve (CR), the preoperative risk is too high to opt for AVR [29,30]. In these cases, medical management is the recommended alternative approach, despite its reduced long-term survival rates [31]. The aim of techniques alternative to AVR is to treat patients who are inoperable because of concomitant life-threatening comorbidities and the reduced life expectancy[32]. The therapy has more palliative purposes, and it is per se related to complications such as stroke, aortic regurgitation, myocardial infarction [33], restenosis, and deterioration of the aortic valve (AV) [34,35].

The main finding of your meta-analysis is the superiority of AVR over noAVR in enhancing survival in patients with LFLGAS. Our result is consistent with studies reporting improved outcomes following AVR rather than noAVR [36]. AVR bears an elevated preoperative risk, but its benefits still outweigh the disadvantages when compared to noAVR. This is attributable to the fact that in high-risk patients with low life expectancy, medication with or without valvuloplasty represents a mere palliative cure not aimed at achieving therapeutic responses. NoAVR approach is mainly oriented towards the management of the cardiovascular risk factors, which include controlling hypertension and volume status. Furthermore, the low survival rate in the noAVR group could be the result of the increased risk of restenosis after valvuloplasty, which leads to deterioration of the valve already after one year[37,38]. Indeed, if, on the one hand, valvuloplasty reduces the transvalvular pressure gradient and improves symptoms, on the other hand, the post-valvuloplasty AVA does not exceed 1.0 cm^2 [33,39]. Moreover, our result could have been influenced by the employment of the TAVR technique in some of the patients included in our analysis, as TAVR has better survival rates than SAVR as well as better LVEF recovery[3,40,41].

The second finding of our meta-analysis was the increased survival at follow up in patients with reduced LVEF compared to those with preserved LVEF in the AVR group. Despite this could be initially counterintuitive, it is critical to acknowledge that it has been widely proved that LV dysfunction is present even with preserved LVEF. Indeed, studies employing speckle-tracking echocardiography have shown that in patients with LFLGAS and normal LVEF, LV systolic longitudinal dysfunction manifests as a result of the increased afterload [12]. Additionally, in patients with a low LVEF undergoing coronary artery bypass grafting (CABG) concomitantly to AVR, long-term survival appears to be enhanced. CABG makes the myocardium in certain areas viable, increasing LV function, and exerting a protective effect[35,42] leading to an improvement in LVEF that was reduced consequently to CAD.

Being the majority of the patients in our meta-analysis operated on AVR+CABG, we believe that the simultaneous CABG procedure might have been beneficial for patients with low LVEF [2].

Furthermore, we found that LVEF does not impact survival in the noAVR group. We believe that these results are attributable to the fact that conservative management has palliative purposes, thus not improving cardiac function but only dealing with symptoms [31]. This is because both classical and paradoxical LFLGAS can induce heart failure via different mechanisms. Patients with classical LFLGAS have low survival rates as the cardiac function is severely compromised by the small LV cavity size due to LV hypertrophy, severe myocardial fibrosis, and the restrictive pattern of LV filling [2]. On the other hand, some studies suggest that conservative management is not particularly useful in increasing survival in the case of paradoxical LFLGAS as a result of the advanced stage of myocardial fibrosis, the systolic and diastolic dysfunction and the reduced stroke volume index [2]. Moreover, patients with paradoxical aortic stenosis mostly have diffused atherosclerosis and increased stiffness of arterial walls, which decreases arterial compliance[2]. In this situation, medical management is only useful in treating resulting hypertension rather than affecting the aortic valve [3].

Limitation

This meta-analysis has some limitations that need to be addressed. First, the number of patients is not high enough to draw definite conclusions. Second, the majority of papers were retrospective studies, so this might have led to inherent selection bias. Third, one included review was an abstract so that we could retrieve limited data from it. Fourth, the papers about reduced LVEF and preserved LVEF were not evenly distributed.

Conclusion

Patients with LFLGAS have a better survival rate following AVR rather than noAVR. Besides, patients with reduced LVEF seemed to have better survival than patients with preserved LVEF in the AVR group. No difference between low and protected LVEF was found in the noAVR group.

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Table 1 . Patients' characteristics

Author (year)	**Study design**	**No. patients**	**No. patients**	**No. patients**	**No. patients**	**Age**	**Female**	**Symptoms**	**AVA (cm^2)**	**SVi (mL/m^2)**	**Mean gradient (mmHg)**	**LVEF (%)**	**Clas LFL GAS LFL GAS**
			AVR	**AVR**	**noAVR**								
Hachicha et al. (2007)	RCS	171	80	91	91	73±13	92 (51)	-	0.76±0.23	-	32±17	62±8	Para LFL
Clavel et al. (2008)	MPOS	101	44	57	57	71±10	23 (23)	49 (49)	0.92±0.24		21±8	29±9	Class LFL
Pai et al. (2008)	RCS	167	46	121	121	72±13	-	-	-	-	-	-	Class LFL-GAS 115 (68.9 Paradoxical LFL-GAS 52 (31.1

Author (year)	**Study design**	**No. patients**	**No. patients**	**No. patients**	**No. patients**	**Age**	**Female**	**Symptoms**	**AVA (cm^2)**	**SVi (mL/m^2)**	**Mean gradient (mmHg)**	**LVEF (%)**	**Clas LFL GAS LFL GAS**
Tarantini et al. (2011)	RCS	101	72	29	29	78 [72–81]	59 (58)	90 (88)	0.80 [0.70-0.89]	46 ±13	33 [27–38]	0.69 [0.61–0.74]	Para LFL
Clavel et al. (2012)	RCS	187	83	104	104	74 ±12	96 (51)	44 (22)+ 104 (56)++	0.82 ± 0.16	30 ± 4	22±8	62±8	Para LFL
Mohty et al. (2013)	RCS	99	83	16	16	77±6	50 (51)	88 (89)	0.72±0.17	29±5	30±7	70±11	Para LFL
Melis et al. (2013)	RCS	40	18	22	22	78 [73.0-83.0]	25 (59.5)	-	0.77 [0.73-0.81]	31 [30-32]	26 [24-29]	64 [62-67]	Para LFL
Herrmann et al. (2013)	RCS	130	105	25	25	-	-	-	-	-	-	-	Class LFL
Eleid et al. (2013)	RCS	53	27	26	26	77±12	18 (34)	41 (77)	0.87±0.11	31±3	30±6	60±7	Para LFL
Ozkan et al. (2013)	PCS	135	54	81	81	-	-	-	-	-	-	-	Para LFL
Tribouilloy et al. (2015)	RCS	114	57	57	57	78.5 [73.5–86.3]	33 (57.9)	9 (15.8)	0.8 [0.7–0.9]	30.1 [27.2–32.2]	30 [20.5–34.5]	60 [55–67]	Para LFL
Annabi et al. (2019)	PCS	480	269	211	211	75 ± 10	136 (28.3)		0.79±0.15	-	26±7	-	Class LFL-GAS 341 (71) Paradoxical LFL-GAS 139 (29)

Author (year)	Study design	No. patients	No. patients	No. patients	No. patients	Age	Female	Symptoms	AVA (cm^2)	SVi (mL/m^2)	Mean gradient (mmHg)	LVEF (%)	Clas LFL GAS LFL GAS
Sato et al. (2019)	ROS	235	128	107	107	80 [73–85]	61 (26)	-	0.75 [0.65–0.92]	25 [20–33]	22±7	29 [23–37]	Clas LFL

Values are expressed as mean±standard deviation, median [interquartile range] or number (%). Abbreviations: No= Number, AVR= Aortic Valve Replacement, AVA= Aortic Valve Area, SVI= Stroke Volume Index, LVEF= Left Ventricle Ejection Fraction, LFLGAS= Low-Flow, Low-Gradient Aortic Stenosis, CAD= Coronary Artery Disease, MCD= Multivessel Coronary Disease, RCS= Retrospective Cohort Study, MPOS= Multicenter Prospective Observational Study, ROS= Retrospective Observational Study. * maximum follow up, +mild symptoms, ++ moderate/severe symptoms.

Author (year)	AVR	AVR	AVR	
	TAVR/SAVR	Concomitant CABG	Operative mortality	Operative mortality
Hachicha et al. (2007)	SAVR	-	-	-
Clavel et al. (2008)	SAVR	30 (68.2)	-	-
Pai et al. (2008)	SAVR	-	-	-
Tarantini et al. (2011)	SAVR	38 (52)	2 (2.7)	2 (2.7)
Clavel et al. (2012)	SAVR	44 (53)	-	-
Mohty et al. (2013)	SAVR	-	8 (9.8)	8 (9.8)
Melis et al. (2013)	SAVR	-	1 (5.6)	1 (5.6)
Herrmann et al. (2013)	SAVR: 56 (53.3) TAVR: 49 (46.7)	-	-	-
Eleid et al. (2013)	SAVR 26 (98) TAVR 1 (2)	12 (23)	-	-
Ozkan et al. (2013)	SAVR: NS TAVR: NS	-	-	-
Tribouilloy et al. (2015)	SAVR	-	-	-
Annabi et al. (2019)	SAVR: NS TAVR: NS	-	-	-
Sato et al. (2019)	SAVR: 42 (32.8) TAVR: 86 (67.2)	-	-	-

Table 2. Surgical data of AVR

Values are expressed as number (%). Abbreviations: AVR= Aortic Valve Replacement, SAVR = Surgical

Aortic Valve Replacement, TAVR = Transcatheter Aortic Valve Replacement, CABG= Coronary Artery Bypass Grafting.

Figures Legend

Figure 1. PRISMA flowchart of the selection process

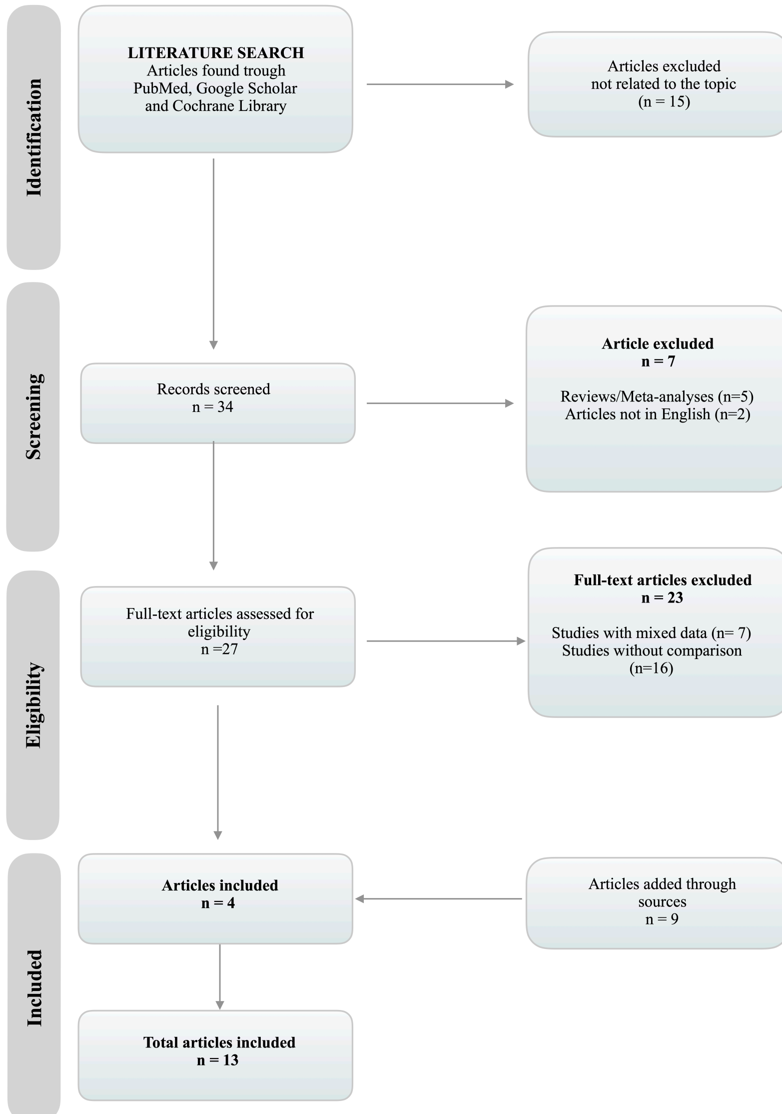
Figure 2. Survival AVR vs noAVR. **A.** Forest plot.**B.** Funnel plot. *LVEF< 35%; **LVEF between 35% and 54%; ***LVEF > 55%.

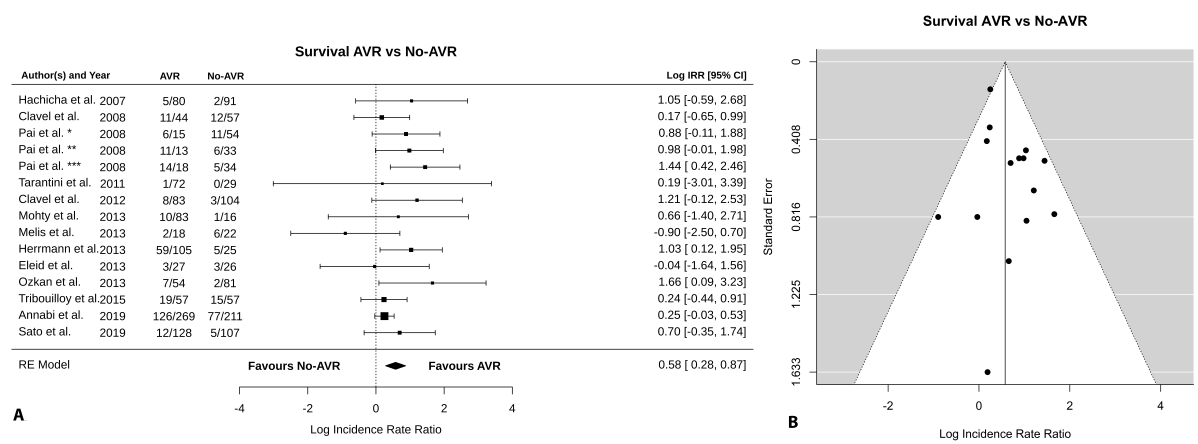
Figure 3 . Meta regression on the impact of LVEF on survival in**A** . AVR and **B.** noAVR

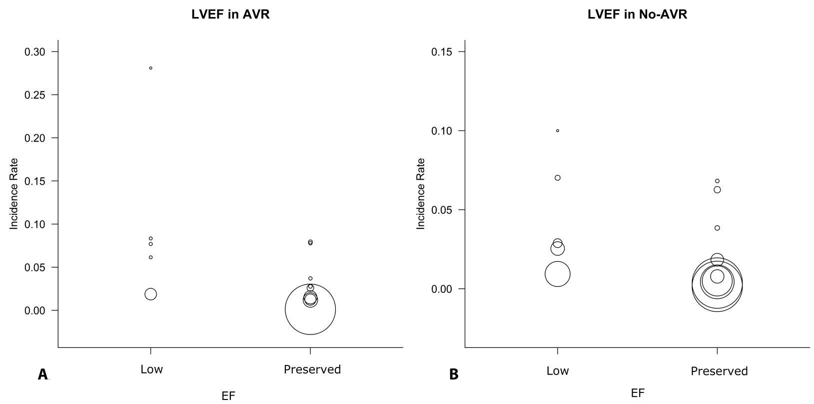
Appendix A. Quality assessment

Item		**Mean**	**SD**
1	Study hypothesis/aim/objective described?	0.92	0.27
2	Main outcomes described in the introduction or methods?	1.00	0.00
3	Participant characteristics described?	1.00	0.00
4	Contacted participants representative?	0.04	0.20
5	Prepared participants representative?	0.08	0.27
6	Participants recruited from the same population?	0.50	0.51
7	Participants recruited over the same time?	0.71	0.46
8	Measures and experimental tasks described?	0.83	0.38
9	Main outcome measures valid and reliable?	1.00	0.00
10	Task engagement assessed?	0.33	0.48
11	Confounders described and controlled for?	1.81	0.57
12	Statistical tests appropriate?	1.00	0.00
13	Main findings described?	1.00	0.00

Item		Mean	SD
14	Estimates of the random variability in data main outcomes?	1.00	0.00
15	Probability values reported?	0.96	0.20
16	Withdrawals and drop-outs reported?	0.27	0.45
17	Data dredging made clear?	0.86	0.35
18	Sufficient power analysis provided?	0.00	0.00


Identification
LITERATURE SEARCH
Articles found trough
PubMed, Google Scholar
and Cochrane Library
Articles excluded
not related to the topic
(n = 15)
Screening
Records screened
n = 34
Article excluded
n = 7
Reviews/Meta-analyses (n=5)
Articles not in English (n=2)
Eligibility
Full-text articles assessed for
eligibility
n =27
Full-text articles excluded
n = 23
Studies with mixed data (n= 7)
Studies without comparison
(n=16)
Included
Articles included
n = 4
Articles added through
sources
n = 9
Total articles included
n = 13


Survival AVR vs No-AVR
Author(s) and Year
AVR
No-AVR
Log IRR [95% CI]
Hachicha et al. 2007 5/80 2/91 1.05 [-0.59, 2.68]
Clavel et al. 2008 11/44 12/57 0.17 [-0.65, 0.99]
Pai et al. * 2008 6/15 11/54 0.88 [-0.11, 1.88]
Pai et al. ** 2008 11/13 6/33 0.98 [-0.01, 1.98]
Pai et al. *** 2008 14/18 5/34 1.44 [0.42, 2.46]
Tarantini et al. 2011 1/72 0/29 0.19 [-3.01, 3.39]
Clavel et al. 2012 8/83 3/104 1.21 [-0.12, 2.53]
Mohty et al. 2013 10/83 1/16 0.66 [-1.40, 2.71]
Melis et al. 2013 2/18 6/22 -0.90 [-2.50, 0.70]
Herrmann et al. 2013 59/105 5/25 1.03 [0.12, 1.95]
Eleid et al. 2013 3/27 3/26 -0.04 [-1.64, 1.56]
Ozkan et al. 2013 7/54 2/81 1.66 [0.09, 3.23]
Tribouilloy et al. 2015 19/57 15/57 0.24 [-0.44, 0.91]
Annabi et al. 2019 126/269 77/211 0.25 [-0.03, 0.53]
Sato et al. 2019 12/128 5/107 0.70 [-0.35, 1.74]
RE Model 0.58 [0.28, 0.87]
Favours No-AVR
Favours AVR
-4
-2
0
2
4
Log Incidence Rate Ratio
A
Survival AVR vs No-AVR
Standard Error
0
0.408
0.816
1.225
1.633
-2
0
2
4
Log Incidence Rate Ratio
B



LVEF in AVR
Incidence Rate
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Low
Preserved
EF
A
LVEF in No-AVR
Incidence Rate
0.15
0.10
0.05
0.00
Low
Preserved
EF
B