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Transcatheter aortic valve replacement outcomes in patients with high gradient versus low ejection fraction low gradient severe aortic stenosis: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: The outcome of Low Flow-Low Gradient (LF-LG) severe aortic stenosis (AS) patients who underwent Transcatheter Aortic Valve Replacement (TAVR) procedure is not well defined. We conducted a systematic review of the literature to compare the outcomes of TAVR in LF-LG AS patients to the more traditional high gradient (HG) aortic stenosis.

Methods: We comprehensively searched for controlled randomized and non-randomized studies from 4 online databases. We are presenting the data using risk ratios (95 % confidence intervals) and measuring heterogeneity using Higgins' I^2 index.

Results: Our analysis included 4380 patients with 3425 HG patients and 955 LF-LG patients from 6 cohort (5 retrospective and 1 prospective) studies. When compared to LFLG; TAVR was associated with significantly lower 30 days mortality in HG patients (5.1 % vs 7.4 %; relative risk [RR]: 0.55; 95 % confidence interval [CI]: 0.35 to 0.86; $p < 0.01$). Similar findings were also observed in 12-month cardiovascular (CV) mortality (5.5 % vs. 10.4 %; RR: 0.47; 95 % CI: 0.38 to 0.60; $p < 0.01$ and 12-month all-cause mortality (15.9 % vs 20.9 %; RR: 0.70; 95 % CI: 0.49 to 1.00; $p < 0.05$). There was no significant difference in myocardial infarction (MI) after TAVR between HG and LF-LG at 30 days (0.16 % vs. 0.95 %; $p < 0.09$) or 12 months (0.43 % vs. 0.95 %; $p = 0.20$). Similarly, there was no difference in stroke rates at 30 days (2.9 % vs. 2.86 %) or at 12 months (3.6 % vs. 3.06 %).

Conclusions and relevance: Patients with LF-LG severe AS who underwent TAVR had worse 1-year all-cause mortality, 30-day all-cause, and 1-year CV mortality when compared to TAVR in HG severe AS. There was no difference in MI or stroke rates. Therefore, with heart team discussion and informed patient decision regarding the risk and benefit, TAVR would still offer better outcomes in LFLG AS compared to conservative medical management.

1. Background

The 2020 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease subcategorized patients with severe symptomatic (Stage D) aortic stenosis (AS) into 3 categories based on aortic valve velocity (Vmax), mean gradient, aortic valve area (AVA), and left ventricular ejection fraction (LVEF). Stage D1 are patients with High Flow-High Gradient (HF-HG). Stage D2 and D3 are characterized by low flow (LF) state (i.e. stroke volume index [SVi] <35 mL/cm^2) and low-gradient state. Stage D2 is a low-flow low-gradient state with reduced left ventricular function (EF <50 %) (Classic LF-LG) and Stage D3 is a low-flow low-gradient state with preserved LVEF (i.e. paradoxical LF-LG) [1]. Although prior studies showed that patients with severe aortic stenosis with a low-flow state (D2 and D3) have higher overall mortality, intervention still carries a better prognosis compared to conservative medical/palliative management, especially in patients with low surgical risk (STS < 2) [2,3].

On the other hand, data for the management of patients with low-flow low-gradient severe aortic stenosis with high or prohibitive surgical risk is controversial and discussions with those patients to reach an informed decision is important as some patients might still benefit from an intervention.

Abbreviations: AS, aortic stenosis; HG, high gradient; LF-LG, low flow low gradient; CI, confidence interval; HR, hazard ratio; LV, left ventricle/ventricular.; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS score, Society of Thoracic Surgery score; TAVR, transcatheter aortic valve replacement; TF, transfemoral; LOS, length of stay; PAD, peripheral artery disease; SVi, stroke volume index; MG, mean gradient.

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Transcatheter aortic valve replacement (TAVR) has emerged as a feasible therapeutic alternative to the conventional surgical management of severe aortic stenosis (AS) in high- and intermediate-risk surgical candidates [4–7]. Moreover, given the high rate of stroke, atrial fibrillation, acute kidney injury, and blood transfusion in surgical valve replacement intervention, TAVR has been an alternative option to SAVR even in intermediate-risk surgical candidates with noninferior results at 2 year follow up after randomization [6]. However, the impact of LF on the outcomes following TAVR yielded conflicting results.

Given the lack of clear consensus, we performed a meta-analysis of studies comparing LF-LG compared to HF-HG. The aim of the study is to examine the impact of TAVR on high-flow high-gradient severe AS compared to low-flow low-gradient severe AS outcomes.

2. Method

2.1. Data sources and search strategy

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception until March 30, 2018, using the keywords ("low flow low gradient" OR "normal flow low gradient" OR "high gradient" OR "severe aortic stenosis" AND "mortality" OR "death" AND "transcatheter aortic replacement"). A manual search of reference lists of appropriate review articles and of the original retrieved studies was also performed to identify studies potentially missed by the database searches. References of selected articles and reviews were manually reviewed for potentially relevant citations. The quality of the identified studies was assessed with respect to control for confounders, measurement of exposure, completeness of follow-up, and blinding. We followed a scoring system based on a checklist derived from a criteria recommended by the QUOROM (The Quality of Reporting of Meta-analyses) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to assess the quality of the trials used in this meta-analysis [8,9].

2.2. Eligibility criteria

To be included in the meta-analysis, studies must make head-to-head comparisons of high gradient (HG or D1), LF-LG or (D2), and paradoxical LF-LG (D3) in TAVR patients; all randomized controlled trials and observational studies that fulfilled the inclusion criteria were included. We included only completed and published trials. The inclusion criteria for the studies to be included are: 1) Involved patients with SAS with preserved

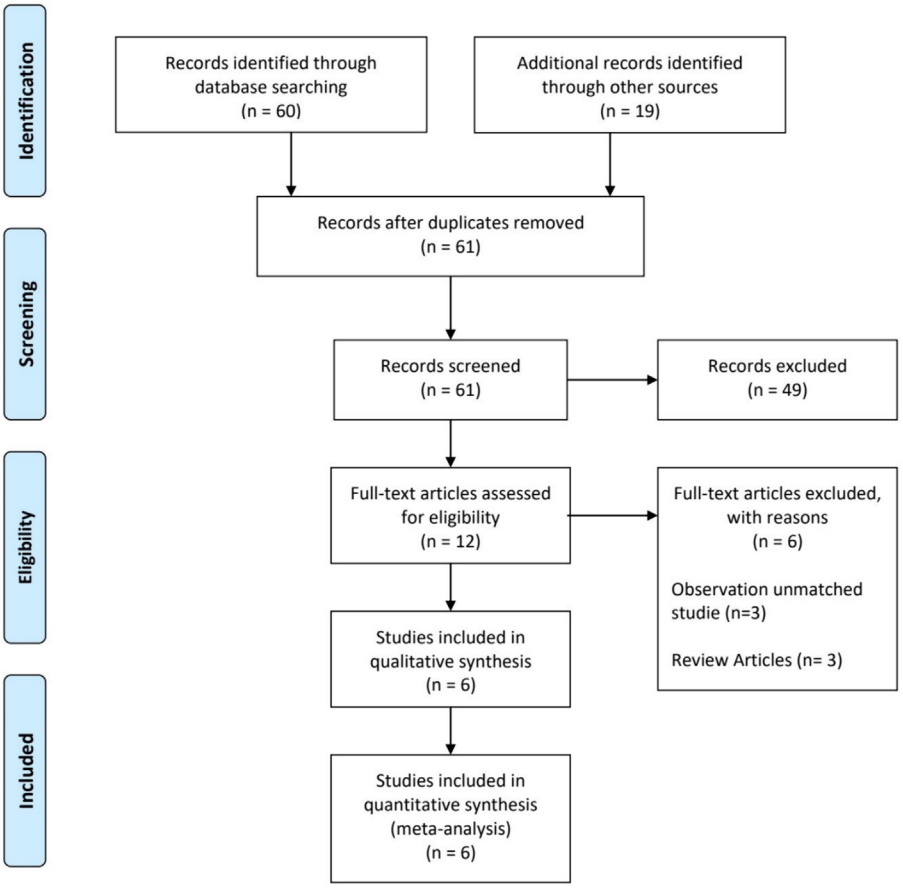

Fig. 1. PRISMA flow diagram.

and low ejection fraction; 2) Compared at least 2 groups of the following SAS categories; high-gradient and low-flow low-gradient (LFLG); 3) Reported any mortality outcome; and 4) Were in English language and published online in a peer-reviewed journal. Exclusion criteria were the following: 1) Studies not reporting mortality outcomes; 2) Studies without a clear definition of flow and gradient patterns, and 3) Studies of post–aortic valve replacement. Only original articles were considered for this meta-analysis; Reviews, letters to editors, case reports, case series, and conference abstracts without peer-reviewed full manuscripts publication were excluded. Regarding multiple studies from the same dataset, only 1 article was included on the basis of relevance, clearly defined endpoints, and larger sample size.

2.3. Data extraction and study quality

Two investigators (AA and FD) independently reviewed the titles/abstracts, assessed study eligibility, and extracted the data. Disagreements were resolved by consensus or resolved by the senior author (ZF). The following data were extracted from each eligible study: name of trial, first author, year of publication, number of patients, characteristics of the population including age, gender, diabetes mellitus, hypertension, smoking, dyslipidemia, coronary artery disease, prior CABG, the society of thoracic surgery (STS) risk, atrial fibrillation, and body mass index (BMI). We also included echocardiogram characteristics including mean gradient (mm Hg), indexed aortic valve area (cm^2/m^2), Aortic annulus area (cm^2), left ventricle ejection fraction (LVEF), stroke volume index (SVi), aortic regurgitation, and mitral regurgitation. The absolute numbers of events were extracted for the measures of risk. The bias risk of randomized controlled trials was assessed by the Jadad scale [10]. The quality of observational studies was assessed by the Newcastle-Ottawa Scale criteria [11].

2.4. Statistical analysis

Results were extracted from intention-to-treat (ITT) data and expressed as a relative risk (RR) with accompanying 95 % confidence intervals. *P*-values of <0.05 were deemed to be indicative of a statistically significant difference. Meta-analyses were then pursued for all outcomes of interest using random-effects modeling. The I^2 index statistic and forest plots were used to assess the degree of heterogeneity. Causes of heterogeneity were subsequently explored via subgroup analyses and meta-regression. Heterogeneity was assessed using Higgins and Thompson's I^2 statistic. I^2 is the proportion of total variation observed between the studies attributable to differences between studies rather than sampling error (chance) with I^2 values of <25 %, 25 % to 75 %, and >75 % corresponding to low, moderate, and high levels of heterogeneity, respectively [12]. Sensitivity analyses were used to assess the impact of excluding studies based on methodological quality as well as assessing the impact of large studies on the outcomes. Funnel plots were used to assess for publication bias. The analysis was performed using R v3.3.1 statistical software (Foundation for Statistical Computing, Vienna, Austria).

3. Results

We identified 61 articles in our literature search (PRISMA flow diagram in Fig. 1) Characteristics of included studies are summarized in (Table 1) [13–18]. The final analysis included 4380 patients from 6 articles who met the inclusion criteria with a total of 3425 patients having HG (D1) and 955 having LF-LG state.

3.1. Patient characteristics (Table 1)

Only a limited number of baseline characteristics were uniformly reported across the included studies. The mean age was similar in both groups. About 41 % of the patients were males in the HG (D1) group vs. 59.2 % in the LF-LG group. There was no major differences in age or major co-morbidities. In Kataoka [18] and Le Ven [14], there were higher rate of previous CABG in D2 group. The majority of the patients were high-risk patients with a mean STS score of >6 in both groups. Table 1 summarizes the baseline characteristics of patients in each of the included studies.

3.2. Echocardiographic findings (Table 2)

No significant difference was noted in aortic valve area (AVA) in both arms, both had severe aortic stenosis with a mean AVA of <0.8 cm^2. The

Table 1
Baseline characteristics.

	1. Kataoka et al. 2017			2. Le Ven et al. 2013			3. Lauten 2014		
	D1 *n* = 501	D2 *n* = 44	p value	D1 *n* = 353	D2 *n* = 90	p value	D1 *n* = 1864	D2 *n* = 359	p value
Age	85 (81–88)	84 (79–88)	0.713	82 ± 8	80 ± 8	0.12	81.4 ± 6.1	79.1 ± 6.1	<0.001
Male	150 (30)	16 (36)	0.11	165 (46.7)	59 (65.6)	0.005	732 (39.2)	238 (66.2)	<0.001
DM	115 (23)	17 (39)	0.077	95 (26.9)	32(35)	0.19	601 (32.2)	143 (39.8)	0.002
CAD	127 (25)	12 (27)	0.03	210 (59.4)	66 (73.3)	<0.001	952 (52.1)	255 (71.0)	<0.001
HTN	388 (77)	26 (59)	0.052	271 (83.9)	73 (81)	0.1			
Afib	83 (17)	11 (25)	0.004	112 (31.7)	42 (46.7)	<0.001			
HLD	213 (43)	21 (48)	0.789	233 (66)	77 (85.6)	0.001			
Smoking	95 (19)	6 (14)	0.068	40 (11.3)	13 (14)	0.34			
STS	6.8 (4.7–9.0)	7.8 (4.9–14.6)	0.255	6.8 (4.4–10.2)	7.95 (5.9–12.2)	0.09			
BMI	21.6 (19.6–24.4)	22.4 (20.8–24.6)	0.301	26.5 (26.6)	26.3 (26.7)	0.25	27.0 ± 4.9	26.5 ± 4.4	<0.001
CABG				107 (30.3)	39 (43.3)	0.007	307 (16.5)	110 (30.6)	<0.001

	4. O'Sullivan 2013			5. Gotzmann 2012			6. Abramowitz 2017		
	D1 *n* = 208	D2 *n* = 61	p value	D1 *n* = 86	D2 n = 44	p value	D1 *n* = 357	D2 *n* = 413	p value
Age	82.9 + 5.2	82.0 + 5.0	0.28	79 + 6	80 + 5	0.981	82.2 ± 9.3	81.9 ± 8.2	0.62
Male	80	34	0.053				179 (50.1)	289 (70.0)	<0.001
DM	55 (26)	19 (31)	0.58				95 (26.6)	154 (37.3)	0.02
CAD	111 (53)	45 (74)	0.013	37 (43)	30 (68)	0.056	203 (56.9)	296 (71.7)	<0.001
HTN	174 (84)	51 (84)	0.89				324 (90.8)	378 (91.5)	0.71
Afib	56 (27)	21 (34)	0.45				96 (26.9)	158 (38.3)	0.001
HLD	126 (61)	41 (67)	0.45				69 (19.3)	130 (31.5)	<0.001
Smoking	23 (11)	6 (10)	0.77						
STS	6.9 + 6.2	8.2 + 5.2	0.16				6.3 (4.6–9.7)	7.0 (4.9–10)	0.08
BMI	26.5 + 5.1	25.5 + 5.4b	0.048	27 + 5	27 + 4	0.725	26.1 ± 5.4	27.3 ± 6.0	0.01
CABG	22 (11)	22 (11)	0.07	6 (7)	15 (34)	0.001			

DM – diabetes mellitus; CAD – coronary artery disease; HTN – hypertension; Afib – atrial fibrilation; HLD – hyperlipidemia; STS – The Society of Thoracic Surgery Risk Score; BMI – body mass index; CABG – coronary artery bypass grafts.

Table 2
Echocardiogram findings.

	1. Kataoka et al. 2017		2. Le Ven et al. 2013		3. Lauten 2014		4. OSullivan 2013		5. Gotzmann 2012		6. Abramowitz 2017	
	D1 n = 501	D2 n = 44	D1 n = 353	D2 n = 90	D1 n = 1864	D2 n = 359	D1 n = 208	D2 n = 61	D1 n = 86	D2 n = 44	D1 n = 357	D2 n = 413
AVA (cm^2)	0.63 ± 0.11	0.52 ± 0.11	0.62 ± 0.14	0.67 ± 0.15	n/a	n/a	0.47 ± 0.21	0.58 ± 0.19	0.7 ± 0.1	0.8 ± 0.1	0.70 ± 0.14	0.58 ± 0.16
Indexed AVA ($cm2/m^2$)	0.44 ± 6	0.36 ± 5	n/a	n/a	n/a	n/a	0.26 ± 0.11	0.33 ± 0.10	n/a	n/a	n/a	n/a
SVI (ml/cm^2)	48.8 ± 7	30.1 ± 4	43 ± 7	27 ± 5	n/a	n/a	28.55 ± 8.47	21.85 ± 5.97	n/a	n/a	43.0 ± 7.1	27.3 ± 5.5
LVEF (%)	64.9 ± 4	38.5 ± 7	61 ± 9	32 ± 10	n/a	n/a	56.48 ± 13.82	29.02 ± 6.73	64 ± 5	39 ± 10	62.9 ± 10.8	51.8 ± 15.9
Mean gradient (mmHg)	50.8 ± 11	39.1 ± 10	56 ± 14	27 8	n/a	n/a	55.62 ± 12.39	25.46 ± 8.58	54 ± 11	32 ± 6	48.8 ± 12.7	42.6 ± 13.4
Mod-Sev AR	46 (9.2)	7 (16)	15 (7.7)	4 (4.4)	n/a	n/a	n/a	n/a	4 (15)	4 (9)	39 (11.0)	38 (9.2)
Mod-Sev MR	36 (7.2)	11 (25)	52 (26.7)	28 (31.1)	n/a	n/a	n/a	n/a	13 (48)	24 (55)	48 (13.4)	116 (28.1)

AVA – aortic valve area; SVI – stroke volume index; LVEF – left ventricle ejection fraction; AR – aortic regurgitation; MR – mitral regurgitation.

mean gradient in the D1 group was >40 mmHg in all trials. In addition to the expected higher gradient, Stroke volume index (SVI) and Ejection Fraction (EF) in D1 group; in Kataoka [18] and Le Ven [14], D1 group had more patients with moderate-severe aortic regurgitation while there was more degree of mitral regurgitation than low-flow group. However, this trend has not been reported in the other articles.

3.3. Patients outcomes

3.3.1. Primary outcomes

When compared to LFLG; TAVR was associated with significantly lower 30 days mortality in HG patients (5.1 % vs 7.4 %; relative risk [RR]: 0.55; 95 % confidence interval [CI]: 0.35 to 0.86; $p < 0.01$; Fig. 2).

Similar findings were also observed in 12-month cardiovascular (CV) mortality (5.5 % vs. 10.4 %; RR: 0.47; 95 % CI: 0.38 to 0.60; p < 0.01; Fig. 3) and 12-month all-cause mortality (15.9 % vs 20.9 %; RR: 0.70; 95 % CI: 0.49 to 1.00; $p < 0.05$; Fig. 4).

3.3.2. Secondary outcomes

There was no significant difference in myocardial infarction (MI) after TAVR between HG and LF-LG at 30 days (0.16 % vs. 0.95 %; RR: 0.21; 95 % CI: 0.03 to 1.26; $p < 0.09$) or 12 months (0.43 % vs. 0.95 %; RR: 0.46; 95 % CI: 0.14 to 1.51; $p = 0.20$). Similarly, there was no difference in stroke rates at 30 days (2.9 % vs. 2.86 %; RR: 1.00; 95 % CI: 0.42 to 2.38; $p < 0.99$) or at 12 months (3.6 % vs. 3.06 %; RR: 1.19; 95 % CI: 0.67 to 2.12; $p = 0.55$). Table 3 summarize the secondary outcomes.

4. Discussion

This meta-analysis shows that while severe LF-LG has a worse cumulative 12 months all-cause and cardiovascular mortality rate as well as 30-day mortality rate compared to severe HG AS; there is no significant difference between severe LF-LG AS and severe HG AS in terms of 12 months myocardial infarction (MI), 12-months stroke, and 30 days MI.

After hypertension and coronary artery disease, aortic stenosis is the most common encountered cardiovascular condition. It is associated with high cardiovascular morbidity and mortality all over the world. In fact, it is the most common valvular disease in developed countries [21]. Based on the valve anatomy, valve hemodynamics, left ventricular function and cardiovascular consequences of aortic valve obstruction, and symptoms, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease classified aortic valve stenosis into 4 different categories [22]. Accurate diagnosis and early staging and classification of the disease significantly affect the medical and interventional approach to the management of those patients.

4.1. Higher mortality in TAVR for LFLG AS

Although medical management of the cardiovascular comorbidities impact the mortality associated with aortic stenosis. Specifically achieving target blood pressure goal, coronary artery disease (CAD) management, and lipid-lowering therapies with statins have been shown through multiple RCTs to be associated with lower mortality and morbidity [23–25]. The benefit is still offset by interventional approach, whether surgical or percutaneous replacement of the severe stenotic aortic valve. Hence, timing of intervention is crucial.

Through many RCTs, the evidence is clear regarding the benefit of SAVR versus TAVR in symptomatic high-velocity severe AS (Stage D1) in patients who can tolerate the procedure with no/low prohibitive surgical risk. However, the data is less robust from observational and registry data regarding the management and type of intervention in patients with low-flow, low-gradient severe AS (Stages D2 and D3) [26]. In patients with high or prohibitive risk for SAVR by tools like Society of Thoracic Surgeons

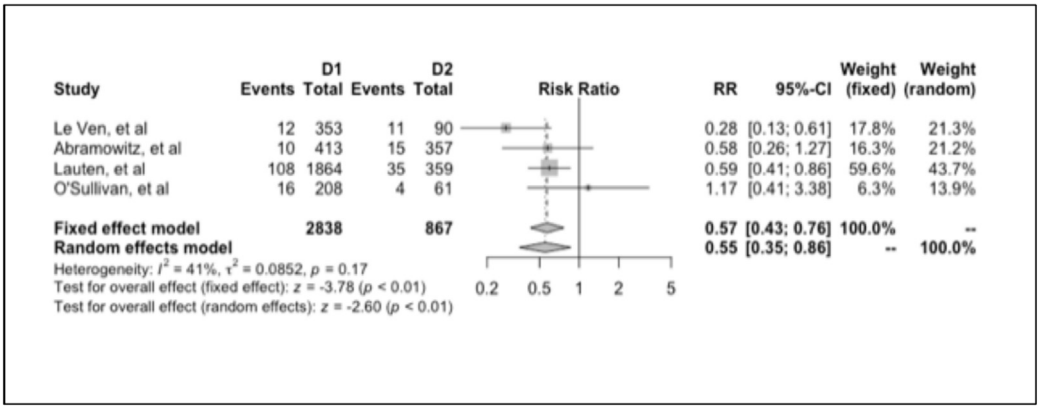

Fig. 2. 30 days mortality in high gradient (HG) versus low flow low gradient (LF-LG).

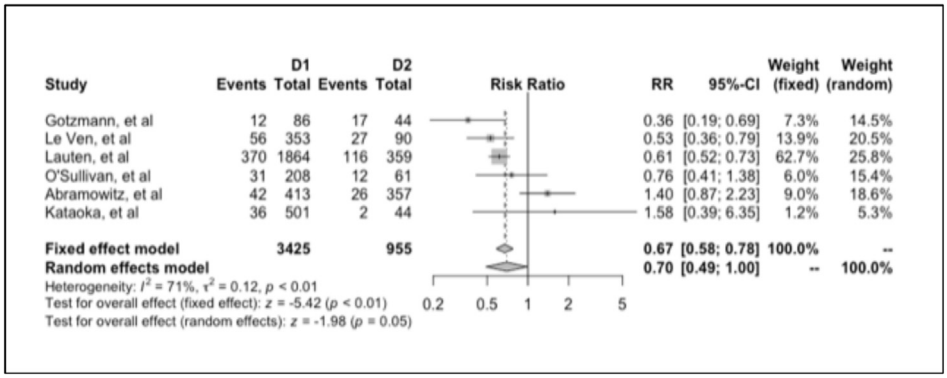

Fig. 3. 12 months mortality in high gradient (HG) versus low flow low gradient (LF-LG).

score (STS), Frailty score, procedural-specific barriers, end-organ dysfunction can guide the decision-making and even help the focuses on TAVI versus palliative care. Understanding the benefit of each decision and the burden of outcome is essential to reach the best outcome and projection of the disease for our patients. Moreover, providing a clear comparison of specific risks associated with each decision can help the patient and the provider reach an informed decision and clear insight on the outcome.

The impact of both low flow (LF) and low gradient (LG) factors on the outcomes following TAVR in patients with SAS is unknown. Multiple observational retrospective studies have been published comparing this impact and have presented conflicting data [20,27–29]. Hence, we performed this meta-analysis study which, due to the lack of RCTs, provides the highest evidence available to date on the outcome of TAVR in severe LF-LG AS patients. This meta-analysis shows that while severe LF-LG has a worse cumulative 12 months all-cause and cardiovascular mortality rate as well as 30-day mortality rate compared to severe HG AS.

These findings are statistically significant and our pooled population shared significant baseline characteristics including the mean age (85 years in HG and 84 years in LF-LG) as well as being high-risk patients (mean STS score > 6 in both groups); at the same time, there was heterogenicity in the gender between both groups (about 41 % of the patients were males in the HG (D1) group vs. 59.2 % in the LF-LG group). Furthermore, in Kataoka et al. and Le Ven et al. [18,30], D1 group had more patients with moderate-severe aortic regurgitation and mitral regurgitation

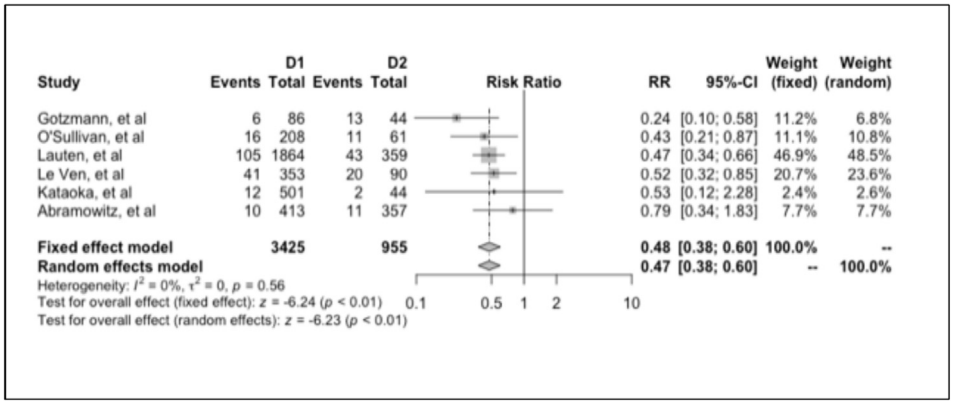

Fig. 4. 12 months cardiovascular mortality in high gradient (HG) versus low flow low gradient (LF-LG).

Table 3
Secondary outcomes:

	High gradient patients	Low flow low gradient patients	Relative risk
			95 % CI
30-day MI	1 (0.16 %)	4 (0.95 %)	0.21 (0.03–1.26)
12-month MI	9 (0.43 %)	4 (0.95 %)	0.46 (0.14–1.51)
30 day stroke	61 (2.9 %)	12 (2.86 %)	1.0 (0.43–2.19)
12-month stroke	75 (3.6 %)	13 (3.09 %)	1.19 (0.67–2.12)

MI – myocardial infarction.

than LFLG group. However, this trend has not been reported in the other articles. In addition to that, although a recent meta-analysis [31] reported a similar outcome in LF LG when compared to HG SAS after SAVR; yet this analysis was affected by high heterogenicity and it was surgical data. Overall, our findings do not contradict with the conclusions of all included studies and are in agreement with the 2020 AHA/ACC valvular disease guidelines which recommend the estimation of SVi as a clinical tool in assessing SAS when low gradient is present and to guide the management using the cut off (SVi <35 ml/m^2) [1]. Finally, we emphasize on including both LF and LG as prognostic factors in the risk stratification for all patients with SAS undergoing TAVR.

A main consideration that may shed a light on why D2 patient do worse with TAVR is the possibility of late recognition of the severity of aortic stenosis in these patients under the presumptions that these patients have moderate aortic stenosis. Early recognition and management in the future may lead to improve outcomes.

4.2. No difference in MI and stroke

Despite the difference in mortality between LFLG and HG groups; there is no significant difference between severe LF-LG AS and severe HG AS in terms of 12 months myocardial infarction (MI), 12-months stroke, and 30 days MI.

This is probably can be explained by the potential absence of the impact of having low EF and/or low flow on either MI or stroke. Most likely the outcomes of MI and stroke may be related to other factor that may be present equally in both patient populations.

5. Future directions

Early recognition of patients with LFLG AS (D2 Group) is extremely important in improving their outcomes and providing them with early access of TAVR. Educating primary care providers and cardiologist in both inpatients and outpatients settings about the different groups of aortic stenosis and about the importance of suspecting aortic stenosis in patients with calcified aortic valve and reduced aortic valve area with reduced SVi in the setting of heart failure as well as seeking additional testing like dobutamine stress echo and/or calcium scoring of the aortic valve for these patient will hopefully improve the diagnosis of these patients and facilitate their access to the appropriate therapeutic options.

6. Limitations and strengths

The main limitation of this study that it relies on data derived from small number of studies that are mainly non-randomized cohorts. Furthermore, the results may be biased by the effect of one of the studies that provided around 50 % of the cohort. It is important to mention that the secondary outcomes analysis was based on 2 trials only [19,20], which reported the secondary outcomes and were missing in the rest of the included articles. The strength of this study on the other hand is that it provides probably the largest pooled data comparing the outcomes of LFLG patients with those of HG. Our hope that this study will increase awareness of the importance of the early prompt diagnosis and management of this sick and potentially under recogniozed population.

7. Conclusion

Patients with LF-LG severe AS who underwent TAVR had worse 1-year mortality, 30-day and 1-year CV mortality when compared to HG severe AS. However, there is no significant difference between severe LF-LG AS and severe HG AS in terms of 12 months myocardial infarction (MI), 12-months stroke, and 30 days MI.

Authorship declaration

All authors listed above meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors and in agreement with the manuscript.

Disclosure statement

None.

CRediT authorship contribution statement

Asseel Al-Bayati: Writing – review & editing, Methodology. **Abdullah Alrifai:** Writing – original draft, Validation, Investigation. **Fahed Darmoch:** Validation, Formal analysis, Data curation. **Haytham Alkhaimy:** Writing – review & editing, Validation. **Zaher Fanari:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

All the authors have no declarations to make.

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None.

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