Meta-Analysis of Outcomes of Transcatheter Aortic Valve Implantation Among Patients With Low Gradient Severe Aortic Stenosis

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Transcatheter aortic valve implantation (TAVI) has emerged as an effective therapy for patients with severe aortic stenosis (AS). However, data on TAVI outcomes in patients with low gradient (LG) AS are limited. We performed a meta-analysis of studies comparing TAVI outcomes between patients with classic high gradient (HG) and LG AS through November 2018. The 30-day mortality, mid-term all-cause, and cardiovascular mortality at maximum follow-up were compared between patients with HG and LG AS (Pairwise meta-analysis), and between the three distinct groups of AS including HG, paradoxical low-flow low-gradient and low gradient with reduced ejection fraction (rEF-LG) (Network meta-analysis). Nineteen studies (n = 27,204 patients) met the inclusion criteria. The HG group had less 30-day, mid-term all-cause and cardiovascular mortality compared with the low-gradient AS group overall, (6% vs 7.5%, OR 0.76, 95% CI 0.66 to 0.87, $I^2 = 18\%$), (21% vs 29%, OR 0.59, 95% CI 0.52 to 0.67, $I^2 = 62\%$), and (12.6% vs 18.7%, OR 0.61, 95% CI 0.49 to 0.76, $I^2 = 62\%$), respectively, p <0.0001. These outcomes were confirmed in a trial sequential analysis in which the cumulative Z-curve crossed the conventional test boundary as well as the trial sequential monitoring boundary for all outcomes. The network meta-analysis revealed that patients with rEF-LG had similar outcomes to those with pLFLG, and both had worse outcomes than patients with classic HG AS. In conclusion patients with classic HG have better 30-day mortality, mid-term all-cause and cardiovascular mortality compared with LG patients following TAVI. Among patients with LG severe AS, TAVI outcomes were similar in patients with rEF-LG and pLFLG. **(Am J Cardiol 2019;124:423−429)**

Transcatheter aortic valve implantation (TAVI) is now the procedure of choice for the majority of patients with severe symptomatic aortic stenosis (AS) in the United States and Europe.[1,2] Nonetheless, outcomes data in patients with low gradient AS (LG) (including both low gradient severe AS with reduced ejection fraction and paradoxical low flow low gradient AS) are conflicting. Several studies have shown that LG is a strong predictor of post-TAVI mortality while others showed no impact of the gradient on post-TAVI outcomes.[3,4] Hence, we used the advanced meta-analysis techniques to synthesize the best evidence on the impact of low gradient on short- and mid-term outcomes following TAVI.

Methods

We conducted a literature search of PubMed, EMBASE, and Cochrane library from inception through November 01, 2018. Our search strategy is presented in eTable-1. We utilized the "related articles" function in PubMed to find relevant articles which were missed by the initial search. Our search and meta-analysis were conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement.[5]

Titles and abstracts of studies retrieved by the initial search were screened by two authors (YA and TF). Consequently, the full texts of the potentially relevant articles were reviewed to determine if the study fulfill the inclusions criteria. Any discrepancies or disagreements were resolved by a third author (MO). The initial database search retrieved 6,835 articles. After excluding duplicates, a total of 6,187 were screened for eligibility by reading the title and abstract of the study. A total of 52 studies were then screened using the predetermined inclusions criteria to assess eligibility. Details of the study selection process are reported following the PRISMA guidelines in (Figure 1).

Studies that reported mid-term (≥12 months) all-cause mortality in patients with high gradient severe AS (HG) and LG with a cut-off mean transaortic gradient (MG) of 40 mm Hg were included. Studies using different cutoff points were excluded. In case of multiple publications from the same cohort, we only included the most recent published data. In the network meta-analysis, we only included studies defining pLFLG and rEF-LG as per the American Heart Association/American College of Cardiology.[6] The prespecified primary outcome of interest was all-cause mortality at maximum follow up. Secondary outcomes included

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See page 428 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.05.006

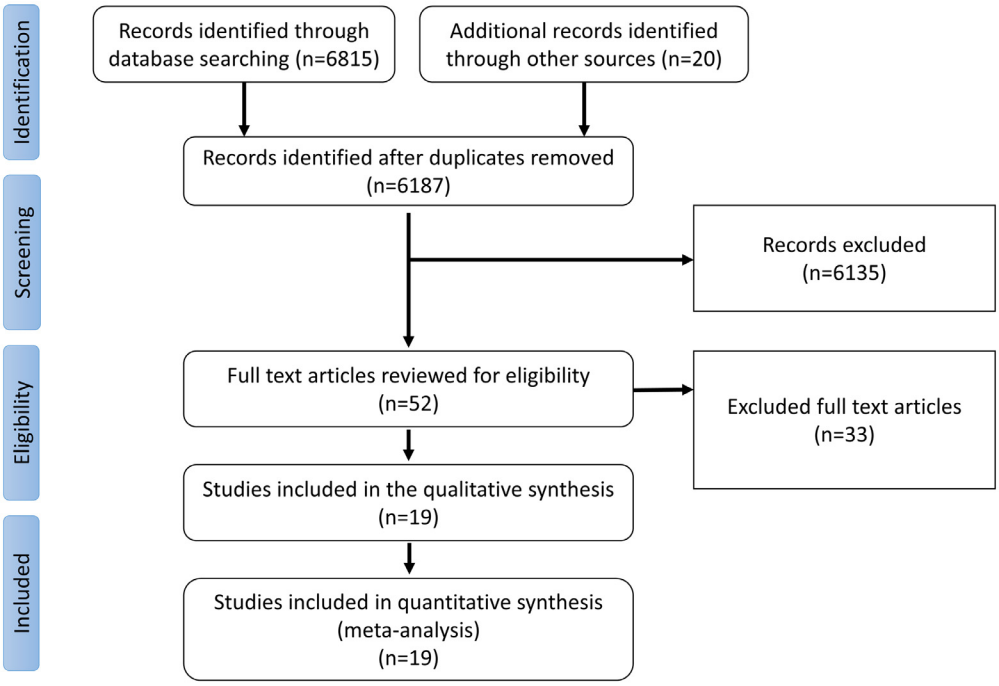

Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

30-day and cardiovascular mortality. We assessed the methodological quality of the studies independently by two authors (KO and BK) using the Modified Newcastle-Ottawa Scale. Disagreements were solved by a third author (MO), as recommended by PRISMA.[5]

For the pairwise meta-analysis, effect estimates were extracted from each study in the form of events in dichotomous data and mean or medians for continuous data. The effect measurements were pooled together using the random effect model to account for between-study variation. Heterogeneity between studies was explored by Cochran Q statistic ($p < 0.05$) and I-squared (I^2) statistic. All statistical tests were two-sided and p values <0.05 were considered significant. Funnel plots were examined for publication bias (eFigure-1) and potential sources of heterogeneity were investigated using subgroup analysis and meta-regression. Sensitivity analysis was performed by removing one study at a time to assess the effect of each study on the overall effect size (leave-one-out analysis). All statistical analyses were conducted with RevMan version 5.3 Windows and Comprehensive Meta-analysis software professional version 3.3.070.

For the network meta-analysis, we followed a Bayesian framework using the Markov Chain Monte Carlo simulation to derive the posterior distribution of the parameter estimates. Convergence was assessed using the Brooks-Gelman-Rubin method. We utilized random effect model on data presentation and interpretation due to the high heterogeneity. Data were reported as odd ratios (ORs) and Bayesian 95% credible intervals (Cr.I). Analysis was performed using NetMetaXL version 1.6.1 and WinBUGS version 1.4.3.

We used trial sequential analysis (TSA) by applying monitoring boundaries to our meta-analysis in order to avoid false statistical inference. By this method, if the cumulative Z curve crossed the TSA boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further studies are needed. However, if the Z curve failed to cross the TSA boundaries and the required information size has not been reached, evidence to reach a conclusion is insufficient and more studies are needed.[7] We performed our analysis to maintain an overall two-sided type-I error rate at 5%, and we calculated the required information (sample) size with a 10% risk of type-II error and 90% power to detect statistically significant intervention effects. Analysis was conducted using TSA software, Copenhagen Trial Unit, version 0.9.5.10 Beta.

Results

A total of 19 studies; with 27,204 patients, 52% women, mean age 81± 2 years, mean Society of Thoracic Surgeons score (STS) 8.2 ± 2 and mean follow-up of 2 ± 1.7 years; were included in the pairwise meta-analysis.[3,4,8–24] The HG group had 18,809 patients with mean gradient of 54 ±12 mm Hg, and an aortic valve area of 0.6 ± 0.1 cm^2. The LG cohort included 8,395 patients with mean gradient of 31 ± 4 mm Hg, aortic valve area of 0.7 ± 0.05 cm^2. Detailed study-level characteristics are shown in (eTable 2). The classic HG group had less 30-day, mid-term all-cause, and cardiovascular mortality compared with the LG group, (6% vs 8%, OR 0.76, 95% CI 0.66 to 0.87, $I^2 = 18\%$), (21% vs 29%, OR 0.59, 95% CI 0.52 to 0.67, $I^2 = 62\%$), (13% vs 19 %, OR 0.61, 95% CI 0.49 to 0.76, $I^2 = 62\%$), p <0.0001 for all, respectively (Figure 2). There was moderate heterogeneity among the studies included for the mid-term all-cause and cardiovascular mortality ($I^2 = 62\%$, p for heterogeneity = 0.0001 and 0.003, respectively). Consequently, we performed a meta-regression to

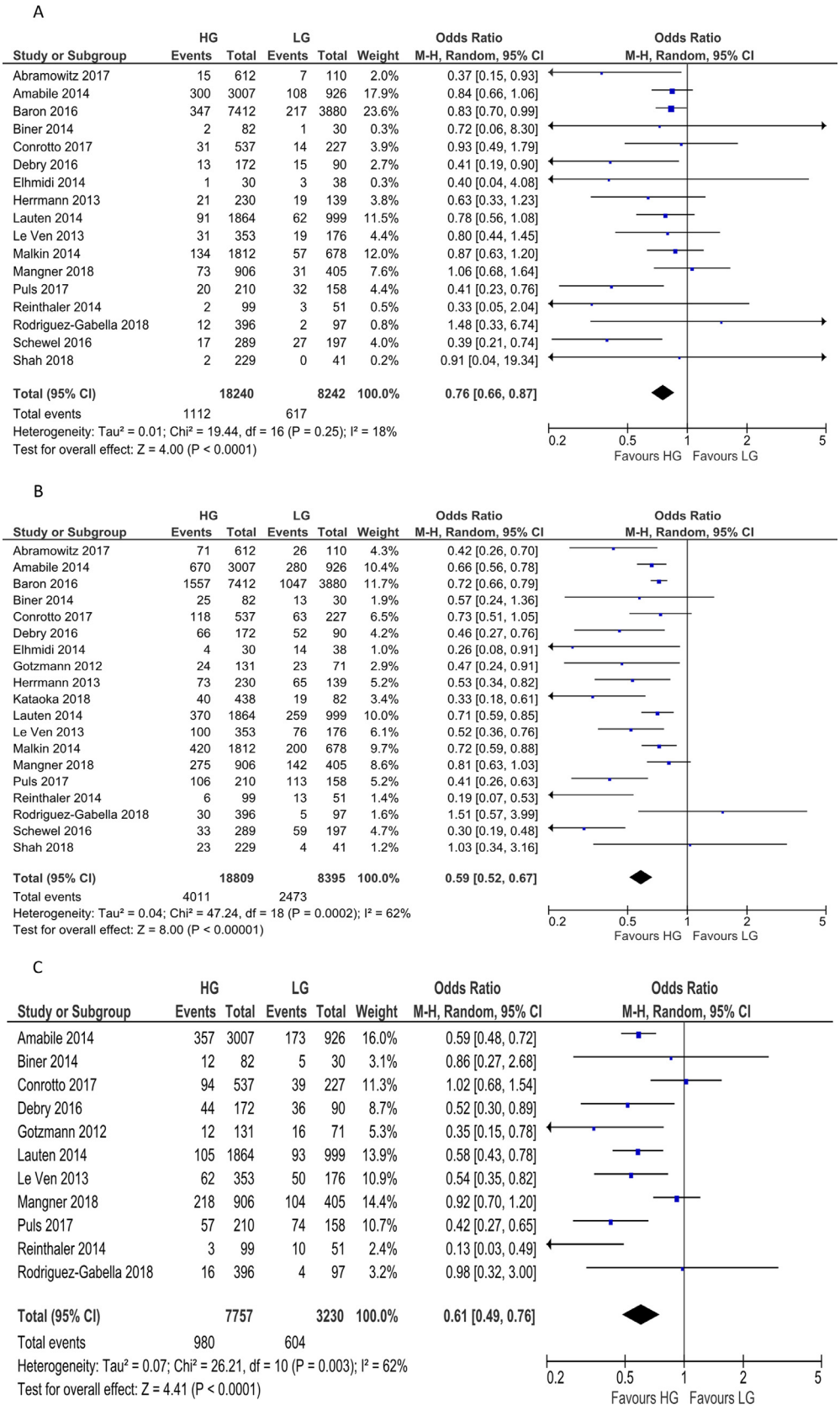

Figure 2. Forest Plots comparing classic sever aortic stenosis with high gradient (HG) and low gradient (LG) groups outcomes. *(A)* 30-day mortality; *(B)* Mid-term all-cause mortality; *(C)* Mid-term cardiovascular mortality.

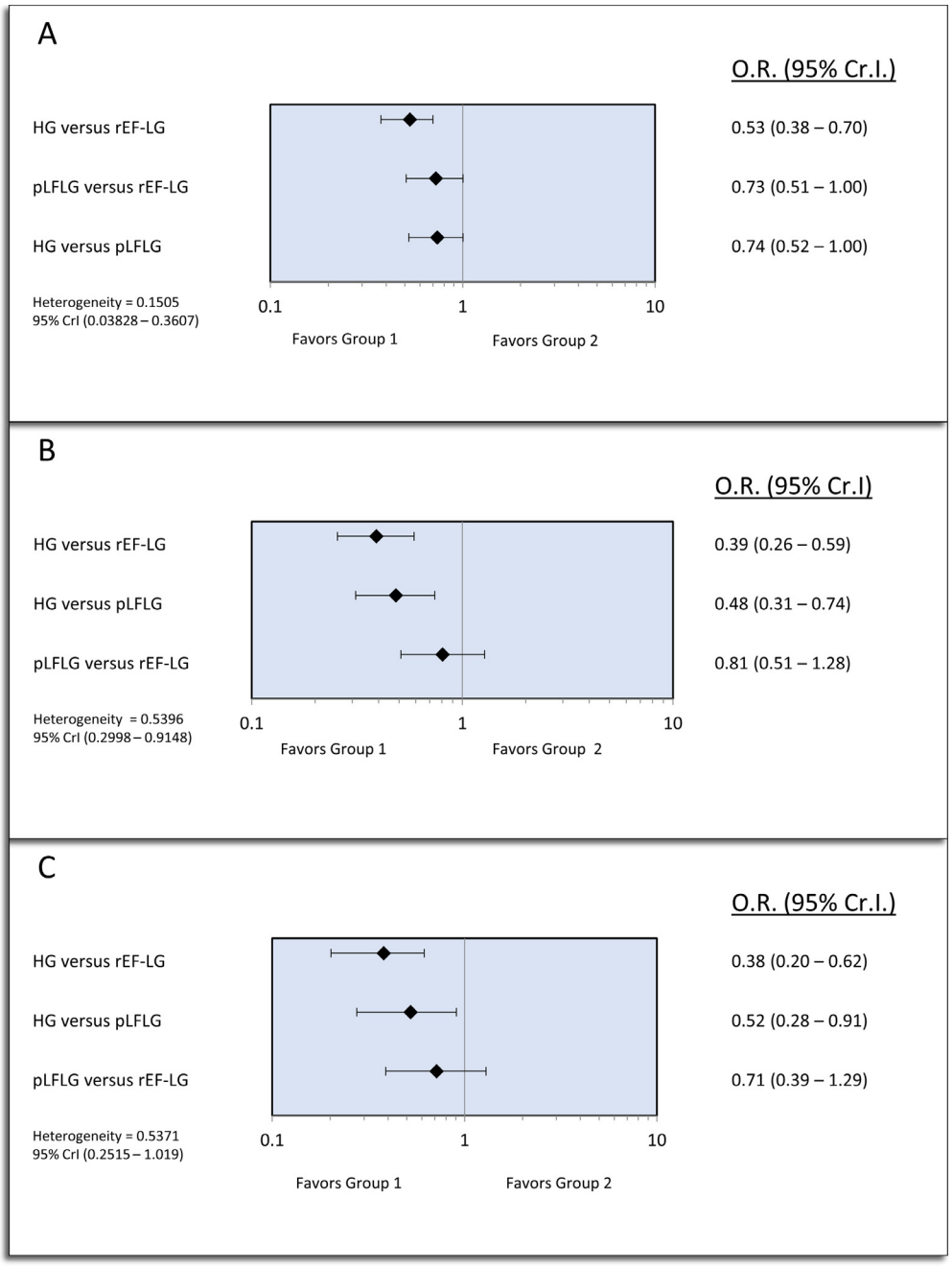

Figure 3. Network meta-analysis forest plots summarizing the outcomes between the competing groups. *(A)* 30-day mortality; *(B)* mid-term all-cause mortality; *(C)* mid-term cardiovascular mortality. Abbreviations: HG = classic sever aortic stenosis with high gradient; pLFLG = paradoxical low flow low gradient severe aortic stenosis; rEF-LG = low gradient severe aortic stenosis with reduced ejection fraction.

explore possible causes of heterogeneity. Studies covariates included in the meta-regression were: Year of publication, duration of follow-up, age, country of publication, Surgical risk scores (Society of Thoracic Surgery risk score and European System for Cardiac Operative Risk Evaluation), Ejection fraction, mean transvalvular gradient, and mean aortic valve area. In the meta-regression, none of the study covariates explained the heterogeneity among the studies. In subgroup analysis, studies were divided into two groups, the first group had registries and multicenter studies and the second group had single center studies, thus eliminating any possibility of overlap. The subgroup analysis did not show any difference between the groups (eFigure-2). Moreover, sensitivity analysis by removing one study at a time had no effect on the result.

The network geometry of the included studies is shown in eFigure-3. Among the total network population, the prevalence of HG, rEF-LG, and pLFLG was 70%, 16%, and 14%, respectively. The rEF-LG ranked as the worst group in term of 30-day mortality outcomes compared with the HG and pLFLG groups, although the latest comparison did not achieve statistical significance (12% vs 6%, OR 0.53, 95% Cr.I 0.38 to 0.70 and 9%, OR 0.73, 95% Cr.I 0.51 to 1.00), respectively. (Figure 3, eFigure-4). The HG group

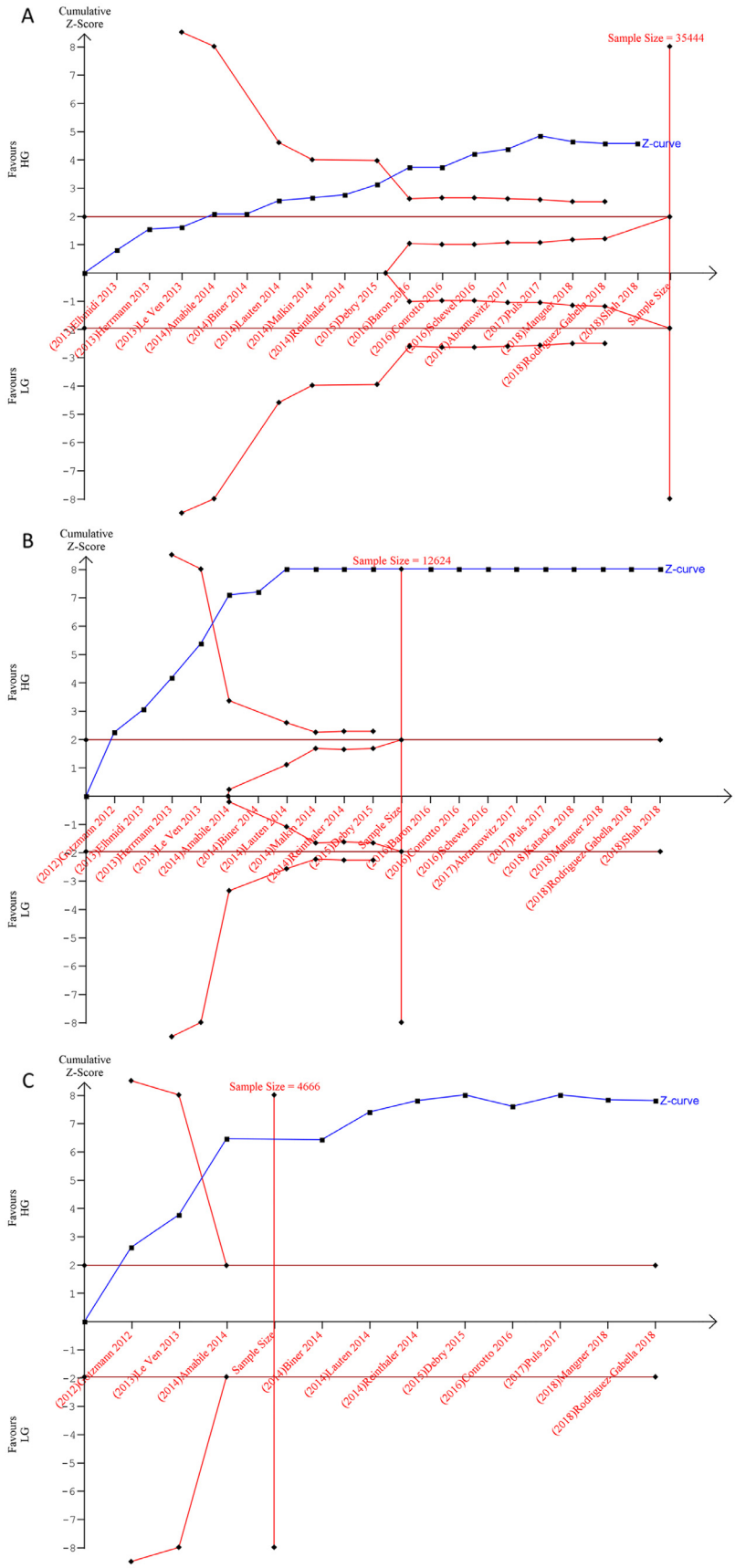

Figure 4. Trial sequential analysis for *(A)* 30-day mortality; *(B)* mid-term all-cause mortality; *(C)* mid-term cardiovascular mortality. The diversity-adjusted information size equal to 35,444; 12,624 and 4,666, respectively *(vertical red lines)*. The cumulative Z-curve *(blue line with small black squares representing each trial)* crosses both the traditional *(horizontal red line)* and the trial sequential monitoring boundary *(concave red line)*, indicating firm evidence of better outcomes in the High gradient (HG) group compared with the low gradient (LG). (Color version of figure is available online.).

had the lowest mid-term all-cause mortality outcomes compared with the rEF-LG and pLFLG groups: (23% vs 43%, OR 0.39, 95% Cr.I 0.26 to 0.59) and (38%, OR 0.48, 95% Cr.I 0.31 to 0.74), respectively. There was no difference in mid-term all-cause mortality between the pLFLG and rEF-LG groups, (38% vs 43%, OR 0.81, 95% Cr.I 0.51 to 1.28) (Figure 3, eFigure 4). The rEF-LG group had higher mid-term cardiovascular mortality outcomes compared with the HG group and the pLFLG groups, but the latest did not achieve statistical significance (20% vs 11%, OR 0.38, 95%Cr.I 0.20 to 0.62 and 17%, OR 0.71, 95% Cr.I 0.39 to 1.29), respectively. The HG group had less cardiovascular mortality compared with the pLFLG group (11% vs 17% OR 0.52, 95% Cr.I 0.28 to 0.91) (Figure 3, eFigure-4).

For the TSA, we based our calculation on 30-day, mid-term all-cause and cardiovascular mortality rates of (6% vs 5%), (27% vs 22%), (19% vs 12%) in the LG versus HG, respectively, as shown from previous large studies and registries.[9,24] Our calculations showed a diversity (D^2)-adjusted information size of 35,444; 12,624 and 4,666 patients required to achieve a statistically significant conclusion for 30-day, mid-term all-cause and cardiovascular mortality, respectively (vs 27,553 patients included in the current meta-analysis). The cumulative Z-curve successfully crossed the conventional test boundary as well as the trial sequential monitoring boundary for all the outcomes, indicating firm evidence for better outcomes in the HG group compared with the LG group (Figure 4).

Discussion

This combined pairwise and network meta-analysis documents that patients with HG AS have better outcomes compared with patients with LG AS. Moreover, the network meta-analysis showed that patients with rEF-LG AS have similar 30-day, long-term and cardiovascular mortality to patients with pLFLG AS, and that both groups have worse mid-term all-cause and cardiovascular mortality compared with patients with classic HG severe AS.

Patients with LG AS pose a unique challenge to the managing physicians, data from the surgical literature suggested worse outcomes after surgical aortic valve implantation in these patients compared with patients with HG AS.[25–27] Furthermore, the outcomes of patients with LG AS (both rEF-LG AS, and pLFLG) following TAVI continue to be a matter of debate.[4,18,21,22] Prior studies have shown worse 30-day mortality in patients with rEF-LG versus those with HG.[28] The 30-day dismal outcomes of the rEF-LG group have been linked to the higher perioperative risk of cardiogenic shock and need of device support, and the inconsistent recovery of left ventricular systolic and diastolic function following valve implantation.[28] Moreover, patients with rEF-LG are known to have high burden of concomitant coronary artery disease as well as other valvular pathologies (e.g., mitral regurgitation) which contribute to the worse 30-day outcomes.[29]

Although our analysis showed a trend of better 30-day mortality, mid-term all-cause, and cardiovascular mortality in patients with pLFLG compared with the rEF-LG group, this did not achieve statistical significance. It has been suggested previously that the main drive of different outcomes between these two groups is the higher cardiovascular mortality in the rEF-LG group, which drive the overall worse all-cause mortality in this group compared with the other phenotypes.[28] While our analysis confirms the trend of better outcomes for the comparison of HG versus LG group, it did not support that for the pLFLG versus rEF-LG.

In patients with pLFLG the low gradient low flow status is secondary to the low stroke volume with normal ejection fraction.[27] The left ventricle in these patients is contracting against a higher afterload due to reduction in the systemic vascular compliance with consequent severe concentric hypertrophy of the left ventricle.[27] In contrast, patients with rEF-LG have dysfunctional ventricles with dilated cavity and inability to generate enough stroke volume to maintain the flow. The finding from our analysis of worse outcomes in both the pLFLG and rEF-LG groups compared with the HG group support the notion of low gradient as predictor of worse outcomes.[9,14]

Our study has several limitations that need to be addressed. First, all studies; with the exception of the subgroup analysis of the PARTNER trial; included in our meta-analysis were observational studies and are therefore subject to all limitations associated with such studies. Second, there was high level of heterogeneity between the included studies, this was addressed by conducting sensitivity analysis, meta-regression analysis, and subgroup analysis. Third, although we achieved enough power as per the TSA analysis to draw a firm conclusion in the pairwise meta-analysis regarding HG versus LG groups, our network meta-analysis lacked the same power and consequently the result should be used to direct future research rather than drawing full conclusion.

In conclusion, the current meta-analysis demonstrated lower 30-day mortality, mid-term all-cause, and cardiovascular mortality in patients with HG AS compared with LG patients post TAVI. Furthermore, among patients with LG AS, outcomes were similar in patients with rEF-LG and pLFLG.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.006.

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