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ORIGINAL RESEARCH

Comparative Outcomes of TAVR in Mixed Aortic Valve Disease and Aortic Stenosis: A Meta-analysis

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ABSTRACT

Introduction: Transcatheter aortic valve replacement (TAVR) has become a suitable alternative to surgical aortic valve replacement (SAVR) for the treatment of symptomatic severe aortic stenosis (AS). A high proportion of patients with AS have mixed aortic valve disease (MAVD) with mild or more concurrent aortic regurgitation (AR). Differential outcomes of TAVR among patients with AS and MAVD have not been well characterized. We compared 1-year mortalities following TAVR among patients with MAVD and AS.

Methods: We conducted a meta-analysis of studies published in PubMed/Medline. The primary outcome was 1-year all-cause mortality following TAVR among patients with MAVD vs. AS. Secondary endpoints were: (1) incidence of AR within 30 days following TAVR (post TAVR AR); and (2) 1-year all-cause mortality within each group stratified according to severity of post TAVR AR.

Results: Nine studies involving 9505 participants were included in the analysis. At 1 year following TAVR, mortality was lower in MAVD than in AS; HR 0.89, 95% CI 0.81–0.98. The mortality advantage increased when pre-TAVR AR was moderate or more; HR 0.84, 95% CI 0.72–0.99. The mortality advantage was attenuated after correction for publication bias. There was a higher risk of post TAVR AR in the MAVD group; OR 1.51, 95% CI 1.20–1.90 but the impact on mortality of moderate vs. mild post TAVR AR was greater among patients with AS than in patients with MAVD HR 1.67 95% CI 0.89–3.14 vs. 0.93 95% CI 0.47–1.85.

Conclusions: Patients with MAVD have similar or improved survival 1 year after TAVR compared to those with AS.

Keywords: Mixed aortic valve disease; Pure aortic stenosis; Aortic regurgitation; Transcatheter aortic valve replacement

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Key Summary Points

Whereas pre-existing mitral and tricuspid regurgitation increase mortality after TAVR, pre-existing aortic regurgitation does not increase post TAVR mortality.

Pre-existing aortic regurgitation increases the risk of post TAVR aortic regurgitation.

The adverse impact of post TAVR aortic regurgitation is higher in individuals with aortic stenosis.

Patients without pre-existing AR will benefit most from measures to reduce the incidence of aortic regurgitation after TAVR.

INTRODUCTION

Mixed aortic valve disease (MAVD) occurs when aortic stenosis (AS) co-exists with varying degrees of aortic regurgitation (AR). In the Society of Thoracic Surgeons-American College of Cardiology Transcatheter Valve Therapy (STS-ACC TVT) registry, 78% of patients with severe AS undergoing transcatheter aortic valve replacement (TAVR) had mild or more AR [1]. Whereas the hemodynamic effects, natural history, and management strategies in AS and AR are well known, equivalent data for MAVD are less well established. Untreated, MAVD has a worse prognosis than either AS or AR [2, 3]. Current guidelines advocate that in patients with mixed valvular lesions, efforts should be made to identify the physiologically dominant lesion to guide further management [4], and that symptomatic moderate MAVD be treated as severe AS if any of the three echocardiographic criteria for severe AS (transaortic peak velocity $\geq$ 4 m/s, transaortic mean gradient $\geq$ 40 mmHg, or aortic valve area $\leq$ 1.0 cm^2) are satisfied [4]. In patients with symptomatic severe AS, TAVR improves both quality of life and life expectancy compared to medical management [5, 6] and is a suitable alternative to surgical aortic valve replacement (SAVR) [7]. Many pivotal TAVR clinical trials have excluded patients with severe AR and reports on outcomes in the MAVD population are limited [8–10]. The data available is inconclusive in that some studies have shown improved survival among MAVD patients after TAVR [11–13], while others have not [14–16]. We performed a meta-analysis to compare the 1-year mortality outcomes of TAVR among patients with MAVD and AS.

METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [17], is based on previously conducted studies, and does not contain any new studies with human participants or animals performed by any of the authors. PubMed/Medline database was queried for relevant abstracts and published studies with the search terms "(((transcatheter aortic valve replacement[Title/Abstract]) AND (aortic stenosis[Title/Abstract]) AND (aortic regurgitation[Title/Abstract]) OR (mixed aortic valve disease[Title/Abstract])". Additional studies were identified through an independent internet search and by review of references included in the initially retrieved manuscripts. After removing duplicates, two independent reviewers screened the abstracts of identified papers for relevant content, with disagreements resolved by group consensus. When a decision could not be made on the relevance of a study by reviewing the abstract only, the entire paper was reviewed. In addition to restrictions imposed during the initial search, studies with relevant content were excluded for the following reasons: effect measure of interest could not be abstracted or estimated; less than 6 months of follow-up data was provided; studies restricted to valve-in-valve procedures; case reports. When more than one study reported on the same cohort, only the study that contributed to more endpoints was selected. Figure 1 shows details of study screening.

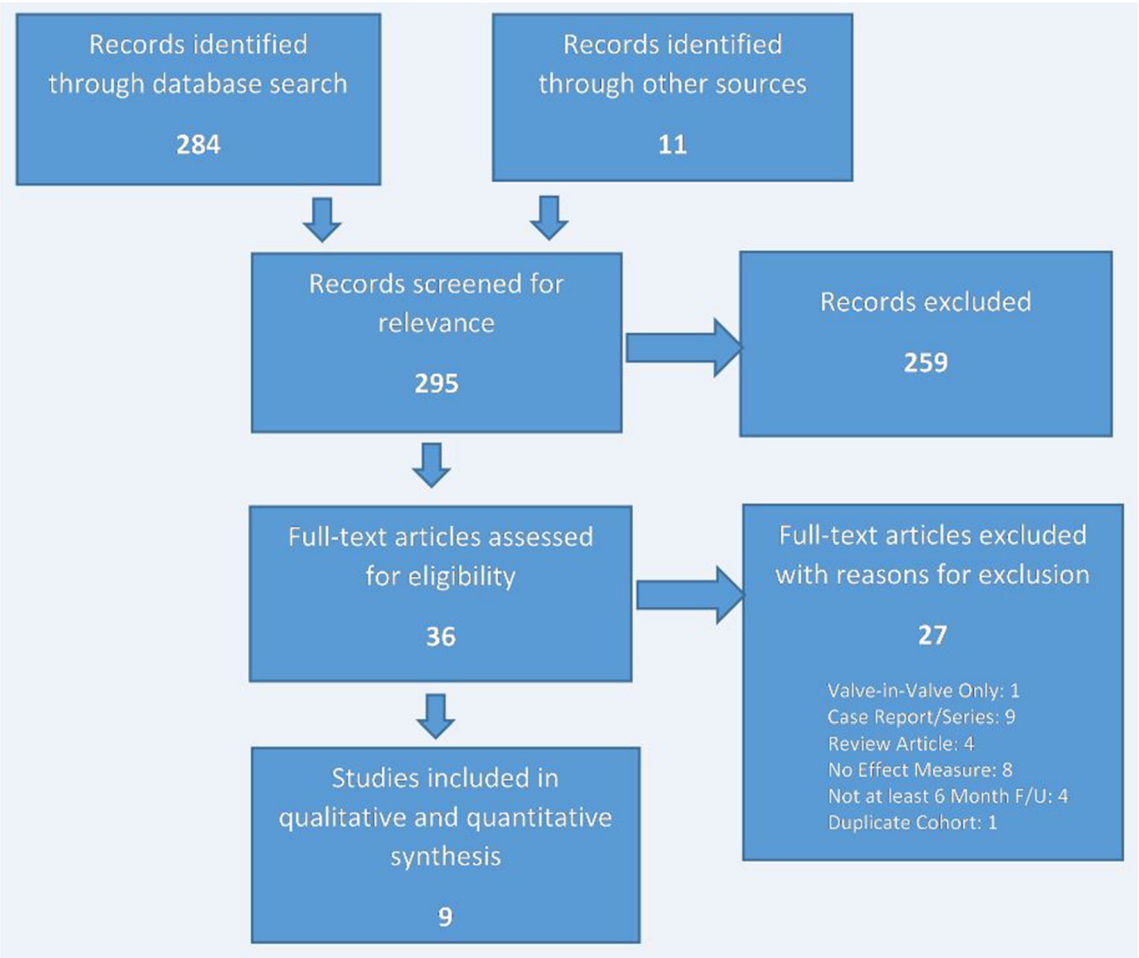

Fig. 1 Study screening flow diagram

Data abstraction was performed by two independent reviewers with disagreements resolved by group consensus. Hazard ratio (HR) was used to compare the primary endpoint of all-cause mortality at 1 year between MAVD and AS. Secondary endpoints were analyzed as follows (1) odds ratio (OR) was used to compare incident post-TAVR (within 30 days) AR in MAVD vs. AS; (2) HR was used to compare 1-year all-cause mortality within each group stratified by severity of post TAVR AR. Definitions of MAVD, AR, and post TAVR AR were as categorized in the original studies. Effect measures were abstracted directly if reported. Where HR was either not reported, reported for a duration greater than 1 year, or reported HR did not fit the pre-specified AR and post TAVR AR categories for secondary endpoints, HR and associated 95% confidence intervals (CIs) were estimated by the methods suggested by Tierney et al. if sufficient summary data were included to enable such estimations [18]. If HR was reported for a duration greater than 1 year and summary data were not included to enable estimation of 1 year HR, we used the reported HR if proportional hazard assumption was satisfied in the original study analysis. Similarly, OR was estimated when appropriate according to the formula presented by Szumilas if not reported [19].

A meta-analysis of the log of HR or log of OR was performed using a random-effects model. Final effect measures were converted back to HR and OR for reporting with 95% CI. We

determined the presence and magnitude of between study heterogeneity using I^2 statistic and the corresponding p value. Individual studies were assessed for non-publication related bias by considering five relevant domains in Cochrane's Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [20]. We considered the overall risk of bias for each study serious if three or more domains showed evidence of serious risk of bias. Publication bias was assessed with a funnel plot, followed by Egger's test, which has a high sensitivity and therefore a low threshold for detecting bias. Publication bias was only assessed with respect to the primary outcome. It was pre-specified that if publication bias was suggested for the primary endpoint, a random-effects non-parametric trim-and-fill analysis with a rightmost-run estimator would be conducted to assess the impact of potentially missing data. For all analyses, the significance level for a two-tailed hypothesis was set at $p < 0.05$. All statistical analyses were performed with StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. Our study did not involve individual patient data so a waiver of informed consent criteria was satisfied per MercyOne IRB policy.

RESULTS

A total of nine studies, comprising 9505 participants were identified that fulfilled the requirements for inclusion in the analysis (Table 1). All nine studies were observational studies, although two studies were sub-studies on participants enrolled in randomized clinical trials [12, 21]. The mean age of participants was 81.6 years. The severity of the regurgitant component of MAVD was mild or more in three studies [12, 13, 22], moderate or more in five studies [11, 14–16, 23], and was not specified in the remaining study [21]. The location of post TAVR AR was paravalvular in seven studies [11, 12, 15, 16, 21–23], total in one study [13] and unspecified in one study [14]. Details of the methods of quantitation of AR and post TAVR AR are provided in Table 1. One of the two sub-studies on clinical trial participants used balloon-expandable (BE) valves [21], while the other implanted only self-expandable (SE) valves [12]. Both SE and BE devices were employed in the remaining studies. All patients included in the sub-studies of clinical trials were at high surgical risk based on Society for Thoracic Surgery (STS) mortality risk predictor (risk score > 8%), whereas the average surgical risk of the cohorts in the other studies was moderate (risk score 4–8%). Access was transfemoral only in two studies [13, 15] while the remaining studies utilized both transfemoral and non-transfemoral access, with a majority utilizing transfemoral access. In all three studies that reported on the prevalence of mitral regurgitation (MR), moderate MR at baseline was more common among the MAVD cohorts [14, 22, 23]. Additional relevant study characteristics are also provided in Table 1 for individual studies. We found evidence for low risk of bias in one study [21] and moderate risk of bias in the remaining eight studies [11–26] (Supplementary Table 1).

Crude mortality ranged from 9.4 to 26.3% over a median follow-up time of 10–27 months. The pooled HR for 1-year all-cause mortality of MAVD versus AS was 0.89, 95% CI 0.81–0.98, (Fig. 2). A funnel plot of studies contributing to the primary endpoint suggested significant publication bias. This was confirmed by the Eggers test with a beta1 value of − 2.27, $p = 0.01$. After a trim-and-fill analysis with imputation of putative effect from missing studies (Fig. 3), the mortality advantage of the MAVD group was attenuated. The revised HR for 1-year all-cause mortality comparing all MAVD to all AS was 0.95, 95% CI 0.88–1.02.

When MAVD with moderate or more, AR was compared to AS among the five studies with available effect measures, the mortality advantage of the MAVD group increased with a HR for 1-year all-cause mortality of 0.84, 95% CI 0.72–0.99 (Fig. 4). There was insufficient data to ascertain the HR for all-cause mortality of MAVD with mild AR compared with AS. Of the eight studies that provided the requisite data, the incidence of post TAVR AR was significantly higher in the MAVD group (OR 1.51, 95% CI 1.20–1.90, Fig. 5). Analysis stratified according to severity of post TAVR AR from five studies

Table 1 Selected individual study characteristics

First author, year [ref #]	Participants in clinical trial	Summarized study goal	MAVD *n* (%female)	AS *n* (%female)	MAVD def and distribution by baseline AR severity (*n*)	Details of AR (quantitation) and PTAR (location and quantitation)	Median follow-up time (months)	Valve implanted (proportion %)	Source of 1-year HR pooled	Mortality reduced in MVAD at 1 year
Hahn 2013 [20]	Yes	Compare echocardiographic findings in patients with critical AS following SAVR or TAVR	*n* = 278 (NA)	*n* = 34 (NA)	NA	AR: by echocardiography, details unspecified Post TAVR AR: paravalvular, by TTE, assessed in the PLAX (none = no regurgitant color flow, trace = pinpoint jet in the aortic valve, mild = jet arc length < 10% of annulus circumference, mod = jet arc length is 10% to 30% of the annulus circumference, severe = jet arc length is > 30% of the annulus circumference)	NA	BE (100)	Reported	No
Van Belle 2014 [11]	No	Identify the predictors of total and paravalvular aortic regurgitation after TAVR and determine the impact of AR on long term clinical outcomes	*n* = 467 (NA)	*n* = 2302 (NA)	Severe AS + ≥ mod AR	AR: by echocardiography, details unspecified Post TAVR AR: paravalvular, by TTE, assessed in the short axis view by measuring the circumferential extent of the regurgitant jet(s) just below the bioprosthesis	Median: 10	BE (NA) & SE (NA)	Reported	Yes

Table 1 continued

First author, year [ref #]	Participants in clinical trial	Summarized study goal	MAVD *n* (%female)	AS *n* (%female)	MAVD def and distribution by baseline AR severity (*n*)	Details of AR (quantitation) and PTAR (location and quantitation)	Median follow-up time (months)	Valve implanted (proportion %)	Source of 1-year HR pooled	Mortality reduced in MVAD at 1 year
Chieffo 2015 [21]	No	Estimate the prevalence of MAVD in patient undergoing TAVR and assess its impact on post procedural AR, short term and long-term outcomes	*n* = 419 (51.6)	*n* = 643 (44.6)	Severe AS + ≥ mild AR mild AR = 302 mod AR = 94 Severe AR = 23	AR: by TTE and TEE, details unspecified Post TAVR AR: paravalvular, by TTE and TEE, details unspecified	NA	BE (NA) & SE (NA)	Estimated	No
Colli 2017 [16]	No	Investigate the effect of preoperative AR and LV volumes on long term outcomes in patients with paravalvular leak after TAVR	*n* = 312 (NA)	*n* = 1383 (NA)	Severe AS + ≥ mod AR	AR: by TTE, details unspecified Post TAVR AR: paravalvular, by TTE, details unspecified	Median: 29	BE (100)	Reported	No
Abdelghani 2017 [14]	No	Compare the outcomes of TAVR in patients with MAVD versus AS	*n* = 106 (NA)	*n* = 687 (NA)	Severe AS + ≥ mod AR	AR: by echocardiography, details unspecified Post TAVR AR: unspecified if paravalvular, transvalvular or total, by echocardiography, details unspecified	Median: 12.9	BE (NA) & SE (NA)	Estimated	No

Table 1 continued

First author, year [ref #]	Participants in clinical trial	Summarized study goal	MAVD *n* (%female)	AS *n* (%female)	MAVD def and distribution by baseline AR severity (*n*)	Details of AR (quantitation) and PTAR (location and quantitation)	Median follow-up time (months)	Valve implanted (proportion %)	Source of 1-year HR pooled	Mortality reduced in MVAD at 1 year
Grayburn 2018 [12]	Yes	Examine the relationship of baseline AR to mortality and quality of life after TAVR	*n* = 182 (NA)	*n* = 204 (NA)	Severe AS + ≥ mild AR	AR: by echocardiography, details unspecified Post TAVR AR: paravalvular, by echocardiography, details unspecified	NA	SE (100)	Estimated	No
Seeger, 2017 [15]	No	Evaluate outcomes in patients undergoing TAVR for MAVD compared to AS	*n* = 69 (NA)	*n* = 665 (NA)	Severe AS + ≥ mod AR	AR: by echocardiography, mod AR (JW 25–64% of LVOT, VC of 0.3–0.6 cm, ERO of 0.10–0.29 cm^2 and PHT of < 500 and > 200 ms), Severe AR (JW > 65% of LVOT, VC > 0.6 cm, ERO ≥ 0.3cm^2 and PHT < 200 ms) on TTE Post TAVR AR: paravalvular, by TTE, details unspecified	NA	BE (NA) & SE (NA)	Estimated	No
Chahine 2019 [13]	No	Compare outcomes of patient with MVAD vs. AS after TAVR, determine impact of pre-existing AR	*n* = 688 (44.5)	*n* = 445 (40.4)	Severe AS + ≥ mild AR mild AR = 378 ≥ mod AR = 310	AR: by echocardiography, details unspecified Post TAVR AR: total, by echocardiography, details unspecified	Median:27	BE (NA) & SE (NA)	Estimated	No

Table 1 continued

First author, year [ref #]	Participants in clinical trial	Summarized study goal	MAVD *n* (%female)	AS *n* (%female)	MAVD def and distribution by baseline AR severity (*n*)	Details of AR (quantitation) and PTAR (location and quantitation)	Median follow-up time (months)	Valve implanted (proportion %)	Source of 1-year HR pooled	Mortality reduced in MVAD at 1 year
Haidari 2020 [22]	No	Evaluate the outcomes of TAVR in MAVD and compare it to AS	*n* = 116 (43.1)	*n* = 506 (42.1)	Severe AS + ≥ mod AR	AR: by echocardiography, details unspecified Post TAVR AR: paravalvular, by echocardiography, details unspecifies	Median: 18	BE (70.6) & SE (29.4)	Estimated	Yes

Ref # reference number, *n* total number of participants, *MAVD* mixed aortic valve disease, *AR* aortic regurgitation, *AS* aortic stenosis, *BE* balloon expandable valve, *SE* self expandable valve, *JW* jet width, *LVOT* left ventricular outflow tract, *VC* vena contracta, *ERO* effective regurgitant orifice, *PHT* pressure half time, *TTE* transthoracic echocardiogram, *TEE* transesophageal echocardiogram, *PLAX* parasternal long axis view, *NA* not available, *def* definition, *HR* hazard ratio, *LV* left ventricular

showed that whereas MAVD with moderate or more post TAVR AR had similar 1-year all-cause mortality as MAVD with mild post TAVR AR (HR 0.93, 95% CI 0.47–1.85, Fig. 6), there was a trend towards increased mortality in the subgroup of AS patients with moderate or more post TAVR AR compared to AS with mild post TAVR AR (HR 1.67, 95% CI 0.89–3.14, Fig. 7).

DISCUSSION

We performed a meta-analysis of the outcomes of TAVR in MAVD vs. AS. Key findings were: (1) reduced mortality 1 year following TAVR in the MAVD group; (2) attenuation of the mortality advantage after correction for publication bias; (3) increased mortality advantage in the subset of MAVD patients with ≥ moderate AR; (4) higher risk of post TAVR AR in the MVAD group; (5) trend towards increased mortality with moderate versus mild post TAVR AR among patients with AS but not among those with MAVD.

Mixed aortic valve disease presents a diagnostic and therapeutic challenge and guidelines regarding appropriate management of MAVD are somewhat ambiguous. The current recommendation is that management of MAVD should follow the guidelines for the predominant lesion (AS or AR) but that in patients with symptomatic moderate MAVD with only one of the three hemodynamic criteria for severe AS (transaortic peak velocity ≥ 4 m/s, transaortic mean gradient ≥ 40 mmHg, or aortic valve area ≤ 1.0 cm^2), management should be as for severe AS, including consideration for TAVR. There is consensus that diagnostic classification and management of MAVD requires further investigation [4].

TAVR improves survival of patients with severe symptomatic AS [5]. One-year mortality following TAVR has decreased dramatically from 24% in 2013 to 13% in 2018 per STS transcatheter valve therapies (STS-TVT) registry with improvement in technology and increasing operator experience [24]. Whereas mitral and tricuspid regurgitation have been associated with increased long-term mortality after TAVR [25–28], this analysis reveals that pre-

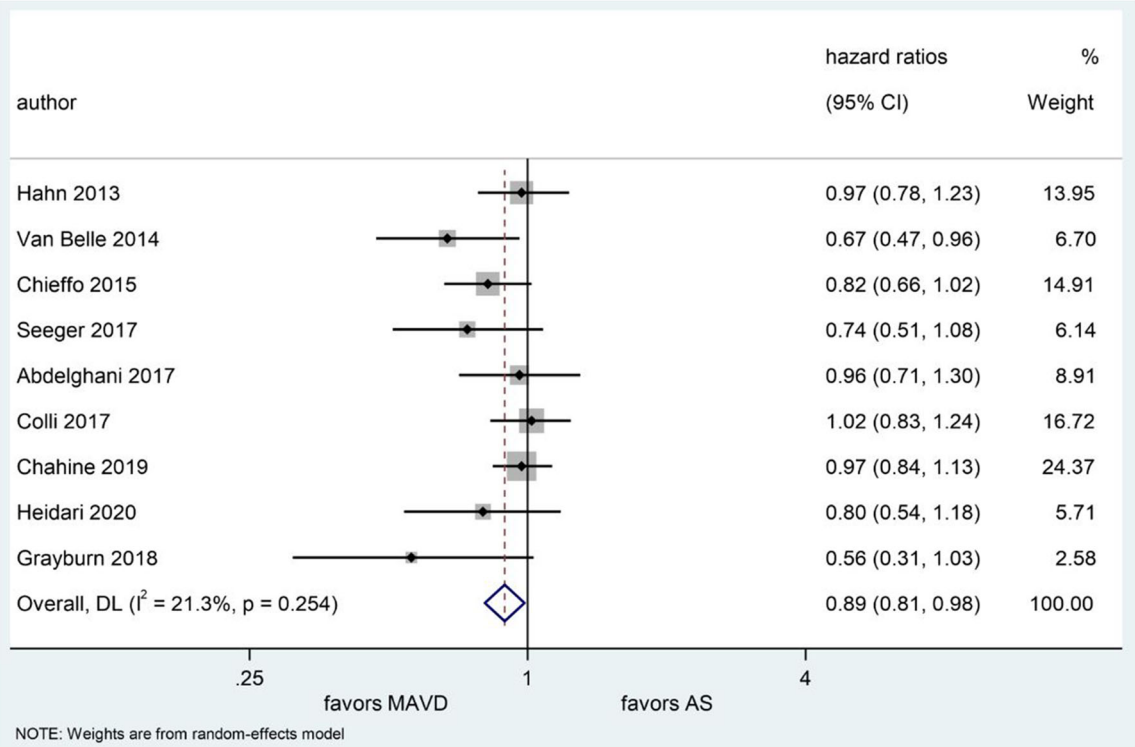

Fig. 2 One-year all-cause mortality in all MAVD vs. all AS

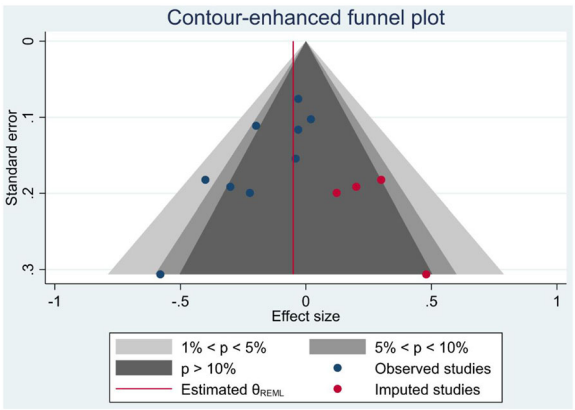

Fig. 3 Funnel plot with original studies (*blue dots*) and imputed studies (*red dots*)

existing AR does not increase mortality and may confer a survival benefit at 1 year among patients with MAVD relative to patients with AS. The mortality advantage increased when comparing MAVD with ≥ moderate AR to AS. Using data from the STS-TVT TAVR registry acquired between 2011 and 2016, Bhardwaj et al. also showed that pre-existing AR was associated with lower 1 year mortality after TAVR [1]. Our analysis, which includes study populations beyond the United States (mainly from Europe) [11, 14, 15, 22], confirms that the mortality benefit is region-independent. A separate recent analysis of post TAVR patients in the STS-TVT registry showed a reduced 30-day mortality among those with pre-existing AR versus AS [29], suggesting that the mortality benefit occurs early and persists through the first year following TAVR among patients with MAVD. The beneficial effect of pre-existing AR on mortality has also been reported in patients undergoing SAVR for AS [12, 30, 31]. The longevity of the survival benefit conferred by MAVD over AS following TAVR remains undefined; conflicting data exist on the differential 3-year survival between the two groups [12, 13]

Since its inception, TAVR has been associated with a relatively high prevalence of post TAVR AR that is predominantly paravalvular [32]. While development of second and third generation prostheses has reduced the

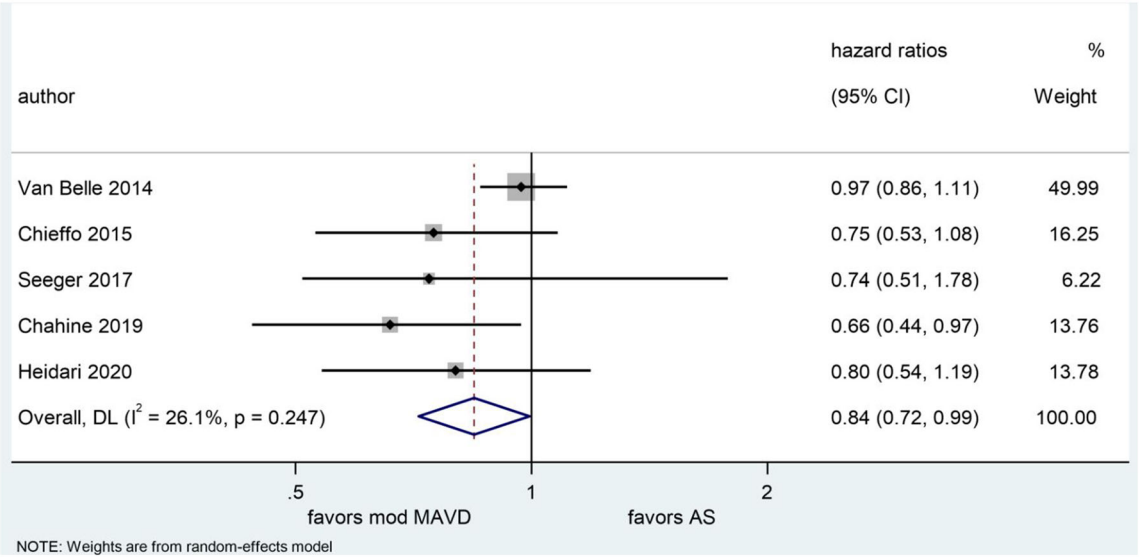

Fig. 4 One-year all-cause mortality in MAVD with baseline moderate AR vs. AS

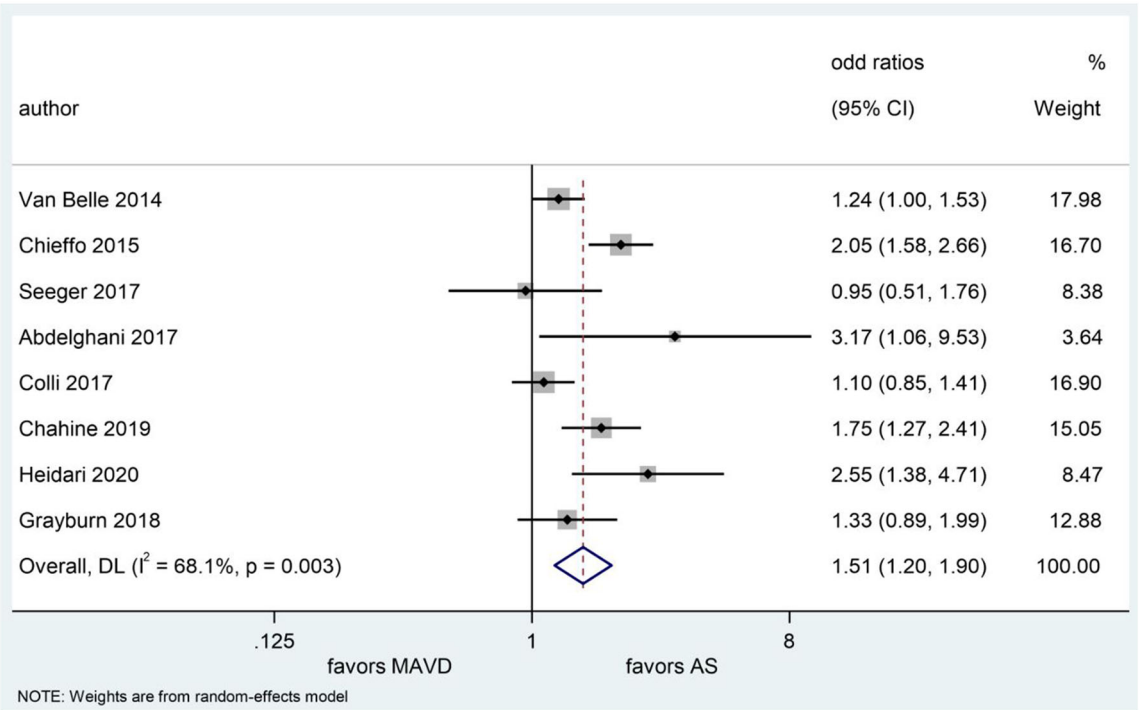

Fig. 5 Risk of post TAVR AR in MAVD vs. AS

incidence of moderate and severe post TAVR AR, mild post TAVR AR continues to be reported in up to 20% of recent TAVR clinical trial participants [33, 34] and even mild post TAVR AR is associated with increased mortality after TAVR [35, 36]. Factors that have been implicated in increased risk of post TAVR AR include extent and patterns of valve leaflet, annular and left

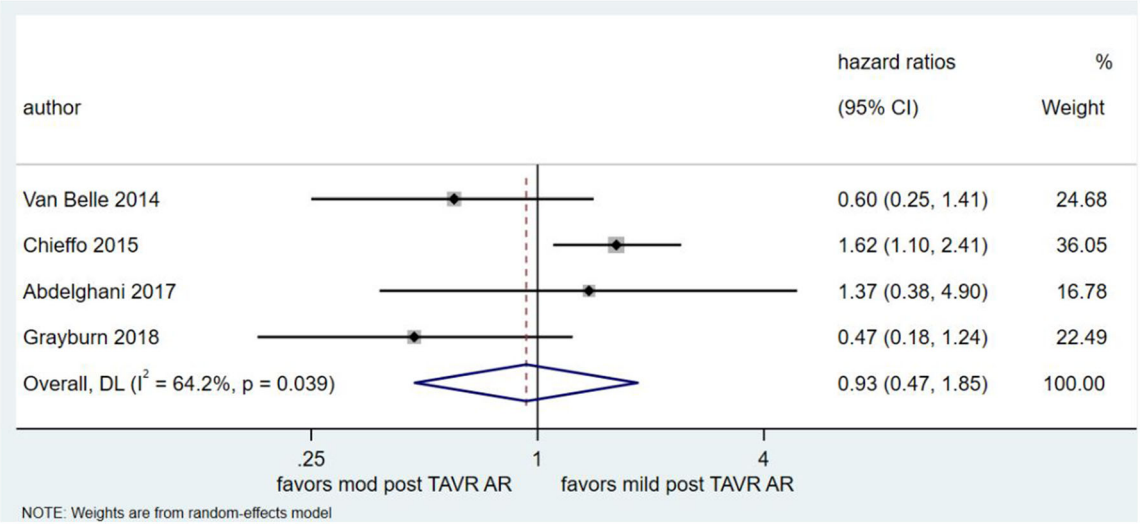

Fig. 6 One-year all-cause mortality in MAVD with moderate vs. mild post TAVR AR

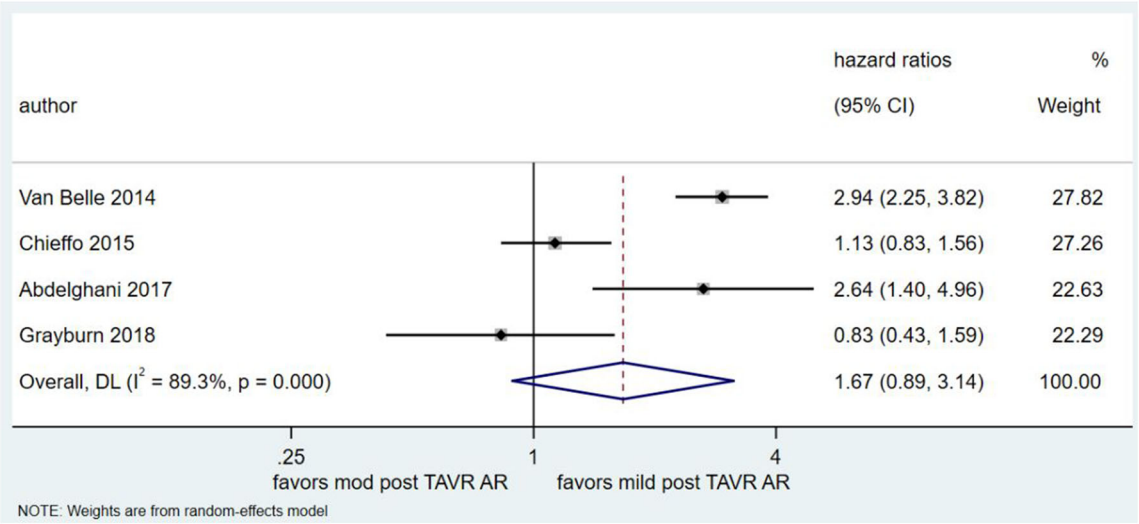

Fig. 7 One-year all-cause mortality in AS with moderate vs. mild post TAVR AR

ventricular outflow tract calcification, use of self-expandable valves, valve implantation depth, valve under-sizing and pre-existing AR [36–38]. Our analysis confirms prior evidence that pre-existing AR is an important risk factor for post TAVR AR.

However, it has been reported that the adverse consequences of post TAVR AR may be mitigated by the presence of pre-existing AR [39]. Our data, which shows a trend towards increased mortality among patients with moderate versus mild post TAVR AR in AS but not in MAVD support these findings. It has been postulated that this mortality benefit that appears to be conferred by MAVD over AS among patients with moderate or more post TAVR AR may be related to differences in ventricular remodeling among the two patient groups. Severe AS might promote more concentric left ventricular hypertrophy resulting in a stiffer, less compliant left ventricular chamber, while MAVD might be associated with more

eccentric left ventricular hypertrophy and a more compliant, dilated left ventricular chamber [13]. Indeed, Colli et al. reported that post-TAVR left ventricular dilatation was associated with increased mortality in AS but not in MAVD [16].

While it does seem plausible that ventricles remodeled by pre-existing AR might better tolerate the volume load imposed by post TAVR AR, the differential hemodynamic impact of post TAVR AR in AS vs. MAVD would then be expected to translate into more recurrent heart failure events in AS. However, in the two studies included in this analysis in which heart failure events were tracked, readmission for heart failure was not significantly different between the two groups [13, 15]. On the other hand, Bhardwaj et al., did show that post-TAVR hospitalization for heart failure decreased with increasing severity of pre-existing AR [1], raising the possibility that the two studies in our analysis may have been underpowered to detect differences with respect to heart failure events. Importantly though, even among patients with pre-existing AR, optimal long-term survival after TAVR is achieved when there is no residual AR post-procedure [12]. It is also conceivable that patients with MAVD manifest higher mean gradients and peak velocities for the same valve area due to increased forward left ventricular outflow volume when compared to patients with AS. Therefore, patients with MAVD may be receiving earlier interventions for less severe stenosis compared to the AS group. Interestingly, of five studies reporting on Valve Academic Research Consortium-2 (VARC-2) composite endpoints [13–15, 22, 23], three studies reported better device success rate (defined as absence of procedural mortality and correct positioning of a single normal functioning prosthetic heart valve into the proper anatomic location) in the AS group [14, 22, 23]. This was partly attributed to increase in flow due to AR potentially resulting in increased turbulence at the site of valve implantation with higher risk of bioprosthesis embolization and malpositioning [22]. One study each reported increased need for pacemaker implantation [13] as well as major and minor bleeding [22] in the MAVD group. There were no reported significant differences in the rates of other major complications including stroke, vascular complications, and acute kidney injury between the MAVD group and PAS groups.

Study limitations: (1) heterogeneity in the definition of MAVD could not be avoided without restricting the analysis to a study sample too small to derive sufficient inferential power for meaningful conclusion. (2) Details of the qualitative and quantitative parameters used to assess and grade the severity of pre-existing AR, MAVD and post TAVR AR in the various studies are limited. (3) Pathologic anatomy of aortic regurgitation was not accurately characterized; specifically, paravalvular and transvalvular regurgitation were not differentiated in a few studies. (4) We did not have access to individual-level data, which limited our ability to make an independent assessment of potential confounding effects of different anatomical and functional parameters relevant to the state of valvular heart disease. (5) Significant publication bias was identified; this was addressed by trim-fill analysis with imputation of missing studies leading to attenuation of the survival advantage for the MAVD group. (6) Substantial between study heterogeneity was noted in the pooled estimates for our secondary endpoints as evidenced by high I^2 statistic. As a result, we opted to present the random effect estimates since this is more robust to the effect of heterogeneity.

CONCLUSIONS

Whereas pre-existing AR is a risk factor for post TAVR AR, it also appears to offer protection against the adverse sequelae of post TAVR AR, as evidenced by improved 1-year survival of patients with MAVD who developed post TAVR AR compared with AS patients with post TAVR AR.

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Author contributions. Justin Ugwu, Daniel Kandah, and Richard Marcus contributed to study conception and design, Okechukwu Ebiem and Judith Ugwu Erugo performed literature search, Justin Ugwu, Daniel Kandah, Judith Ugwu Erugo performed data extraction, Justin Ugwu and Daniel Kandah performed data analysis, all authors performed data interpretation and preparation of manuscript.

Data availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosures. Justin K Ugwu, Daniel R Kandah, Jideofor K Ndulue, Okechukwu P Ebiem, Judith N Ugwu-Erugo, Russell Hamilton, Kofi Osei, Tuncay Taskesen, Daniel M Shivapour, Atul Chawla and Richard H Marcus have nothing to disclose.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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