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Effect of Transcatheter Aortic Valve Replacement on Right Ventricular Systolic Function: Systematic Review and Meta-analyses

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Abstract

Objectives: We ought to compare the effect of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) on right ventricular systolic function (RVSF) in high risk patients with severe aortic stenosis (AS).

Methodology:

Data source: PubMed, EMBASE, Cochrane library, and references of selected articles.

Study endpoints: Transthoracic echocardiography was utilized to assess the change in RVSF post TAVR versus SAVR using tricuspid annular plane systolic excursion (TAPSE), and fractional area change (RVFAC).

Statistical analyses: Random effect model on standardized mean difference (Hedges; g) were used together with heterogeneity assessment.

Result: We included 485 patients from five single-center observational studies. TAVR had no effect while SAVR had negative effect on RVSF, and the effect was in favor of TAVR when TAVR compared to SAVR [TAPSE (g=2.88, SE=0.63, P<0.001, Q=73.18, I^2=94.53, r=0.65), and RVFAC (g=0.91, SE=0.16, P<0.001, Q=2.39, I^2=16.61), r=0.65].

Conclusion: Compared with SAVR, TAVR is preferred aortic intervention for patients with severe symptomatic AS and RV systolic dysfunction.

Keywords: Transcatheter Aortic Valve Replacement (TAVR); Surgical Aortic Valve Replacement (SAVR); Aortic stenosis (AS); Right ventricle; Outcome; Intervention; Echocardiography; Meta analyses

Introduction

Right ventricular systolic function (RVSF) is risk predictor for transcatheter aortic valve replacement (TAVR) outcome [1], the procedure done when patients with severe symptomatic aortic stenosis (AS) are deemed unfit for surgical aortic valve replacement (SAVR) [2,3]. Both TAVR and SAVR collectively are known as aortic valve intervention (AVI). Among the determinants of RV dysfunction in AS and its response to AVI are pulmonary hypertension [4] and left ventricular (LV) dysfunction [5]. Once RV systolic dysfunction is established, it is considered an independent contributor to heart failure mortality [6]. New echocardiographic (echo) guidelines have been established with regard to recommendations for techniques and tools used to evaluate and quantify RVSF in adult [7]. Despite the current echo recommendation, there is substantial clinical and methodological diversity within the available few studies reporting the change in RVSF intra and post AVI precluding postoperative validation of echo parameters used to assess RVSF [7,8].

For these reasons, we undertook the present systematic review of available published studies to summarize the current data measuring the change in RVSF post AVI, to demonstrate the reasons of in between studies' heterogeneities, and to make recommendation to improve future conduct and reporting in this regard. The future consistency in reporting might validate echo parameters used to assess RVSF post AVI, thus identifying patients benefit most from the less-invasive TAVR.

Methodology

Study selection and data source

Two reviewers (M.Z. and S.G.) conducted search in PubMed, EMBASE, Cochrane library Ovid Medline, Cochrane Central Register of Controlled Trials (CCTR), and Cochrane Database of Systematic Reviews (CDSR). We used the keywords (transcatheter, or percutaneous, or transcutaneous; aortic; valve; implantation, or replacement; and right ventricle, or right ventricular, or right-sided heart) in our literature search. Citations were screened twice (M.Z.) at the title and abstract level and were retrieved as full text if they reported RVSF pre and post AVI. The references of the full text of all potential articles were further reviewed twice in detail (M.Z.) to obtain additional relevant studies. Thereafter, the full text of the chosen articles were reviewed by a level III expert echocardiographer and an expert interventional cardiologist, both well versed with TAVR procedure, for assessment of study quality using quality of reporting in systematic reviews from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [9], MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [10], and Quality of Reporting in Systematic Reviews of Implantable Medical Devices [11]. Any disagreement was solved by consensus.

Study inclusion criteria

Comparative clinical studies where patients with AS had transthoracic echocardiography (TTE) evaluating RVSF pre and post TAVR and or SAVR, head to head or separately, were included. The search was up to July 2014 and was restricted to only published full text English articles on human adult with no attempt to get missing data from authors. When centers have published duplicate studies with accumulating numbers of patients or increased period of follow-up, the most comprehensive studies were selected [12,13].

Study exclusion criteria

Studies were excluded if they were abstracts, case reports, editorials, expert opinions, and conference presentations. Also excluded were studies unpublished or indexed on the search engine after the last search date, and studies with unclear or lacking data concerning the change in RVSF post AVI.

Description of intervention and its comparator

The intervention was TAVR two commercial devices, including the self-expandable Medtronic CoreValve (MC) porcine pericardial device (Medtronic, Inc., Minneapolis, Minnesota) and the balloon expandable Edwards SAPIEN (ES) bovine pericardial device (Edwards Life Sciences, Irvine, California) [14]. Trans-femoral (TF) rout is used for MC and ES delivery while trans-apical (TA) is used only for ES delivery. In our systematic review, TAVR has been compared to SAVR. Intraoperatively, SAVR requires sternotomy, pericardiotomy [15], cardiomyotomy, and utilized cardiopulmonary bypass and hypothermia [16]. While TA-TAVR is performed through mini-thoracotomy, mini-pericardiotomy, and cardiomyotomy incisions in sequence [17]. All those intra-operative procedures were presumed to affect RVSF.

Definition of echocardiographic parameters for RVSF evaluation

We used the recently published echocardiography guidelines from 2010 with regard to parameters used to assess RVSF in adult [7]. RVSF was measured by tow dimensional (2-D) transthoracic echocardiography (TTE). RV systolic dysfunction was defined quantitatively by the presence of at least one of the following: Tricuspid annular plane systolic excursion (TAPSE) <16 mm, Fractional Area Change (RVFAC) <35%, and tissue Doppler imaging derived systolic velocities of the annulus (RV-TDIS') <10 cm/s; with or without RV index of myocardial performance (RIMP)>0.40 by pulsed Doppler and >0.55 by tissue Doppler, and 2D RV ejection fraction (RVEF) <44%. Of note, RVFAC, a measure of global RVSF, is independent risk predictor for sudden death and heart failure, and is obtained by tracing the RV endocardium both in systole and diastole. TAPSE is used to measure regional longitudinal shortening of RVSF through measuring the distance of systolic excursion of tricuspid annular segment along its longitudinal plane.

Data extraction and synthesis

All data were extracted by M.Z. from article texts, tables and figures. These data were transferred into an excel sheet to build up tables and figures for our systematic review. Data were collected with regard to, but not limited to, study selection process, study characteristics (first author, publication year, sample size, type of AVI used and its delivery approach, study design, preoperative patients' surgical risk scores, follow up period, inclusion and exclusion criteria, study limitations), health status of study population at baseline, and echo evaluation of RVSF pre and post AVI. Due to inconsistent follow up period of reporting the progressive changes in RVSF related to AVI, we have chosen the latest reported follow up, and that might have been before hospital discharge, after one month, or after 6 month post AVI.

Study endpoints

The primary endpoints were early and midterm change in RVSF after: 1) TAVR and SAVR; 2) TF-TAVR and TA-TAVR delivery approach; and 3) MC and ES TAVR' devices. The secondary endpoints were to assess early and midterm change in RVSF for their validation post AVI, and overall RVSF and biventricular systolic function composite endpoints.

Statistical analyses

Random-effects (RE) model on continuous variables was used to obtain a single summary effect size (standardized mean difference; Hedges' *g*, and 95% confidence interval; 95% CI) from the primary studies. Because the cutoff points of the change in RVSF parameters were not defined to convey clinical importance of treatment effect, we added standard error (SE), and so Hedges' g can be transformed back into original scale to judge the clinical significance [18,19]. Any *p* value less than 0.05 was considered statistically significant. To assess heterogeneity, we used Cronbach's Q statistic to assess heterogeneity of the means across studies, and I^2 statistic to estimate the percentage of total variation across studies due to true heterogeneity rather than random error. I^2 value of greater than 75% and p value >0.1 were considered to represent high heterogeneity [18]. If there was high heterogeneity, the possible clinical and methodological reasons for this variation were explored. The overall RVSF and biventricular composite endpoints were planned to be calculated. Analyses were performed using comprehensive Meta Analyses (CMA) software, version 2.

Results

Study selection

The study selection process in Figure 1 was according to PRISMA and MOOSE statements. About 2153 records were identified using key words in our search engine PubMed and EMBASE. Out of those, 119 were screened at the title level and ultimately 73 records for exact and close duplicates were excluded. From the remaining 46 records, 13 full text articles were excluded because they were either non-relevant or containing non extractable data or unclear reporting of RVSF noticeably in those articles concerning the prognostic utility of RV post TAVR.

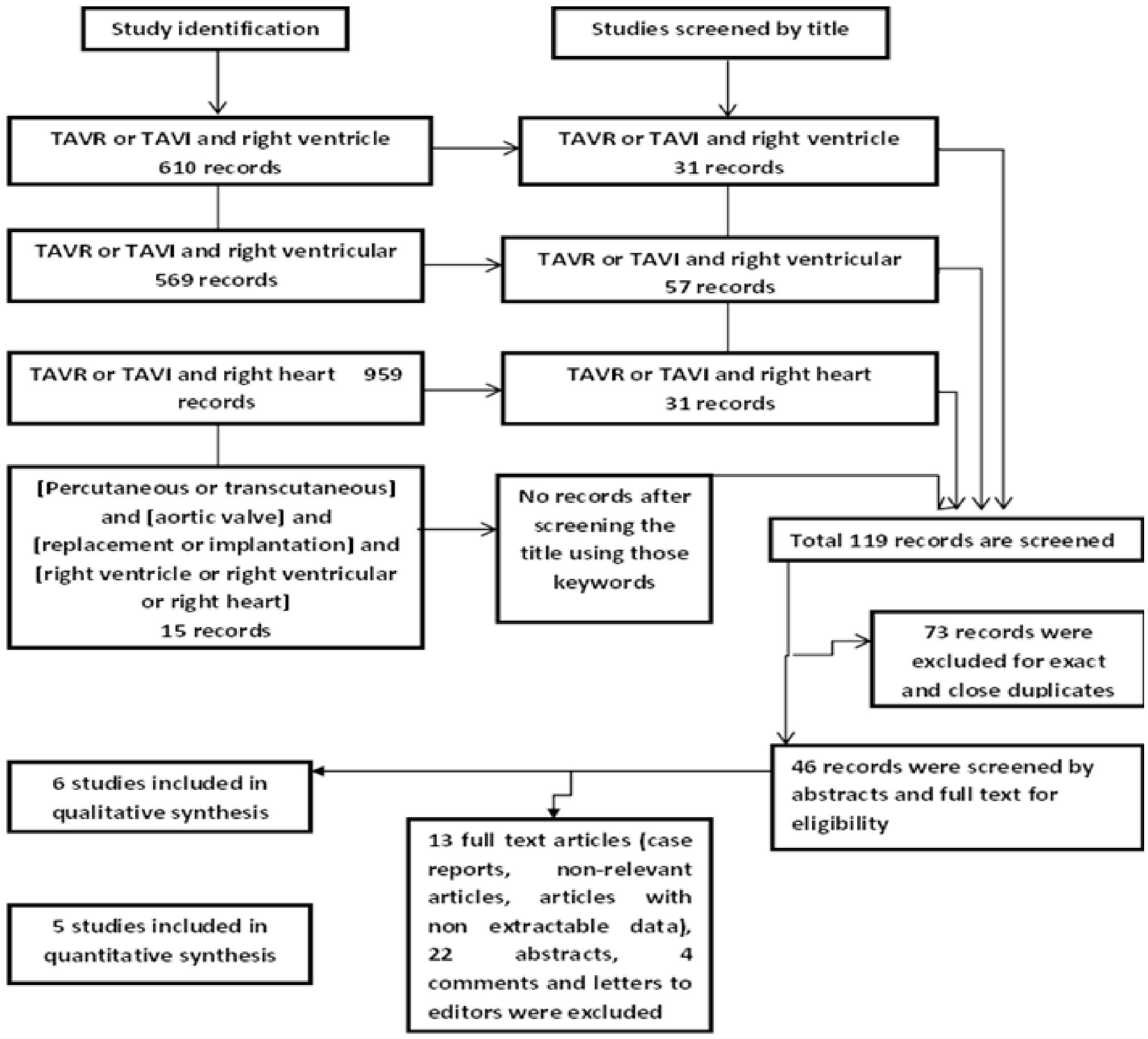

Figure 1: PRISMA diagram showing selection of studies process.

Author, year	Procedure	Sample size per approach	Device	Total Sample size	Mean STS	Study Design	Country	Study duration
Ayhan et al.	TAVR	2subclav, 48TF	ES-XT	50	6.8 ± 5.0	SC, OS	Ankara, Turkey	7 months
Okada et al.	TAVR, SAVR	TF, TA, sternotomy	ES, NR	37/52	NR	SC, OS, R from RCT (PART-NER)	Pennsyl-vania, USA	21 months
Forsberg et al.	All TAVR	TF, TA	ES	60	4.4 ± 2.3	SC, P, OS (cross sectio-nal)	Linkoping, Sweden	34 months
	TA-TAVR	TA	ES	25	5 ± 2.1			
	TF-TAVR	TF	ES	35	3.9 ± 2.3			
	mTAVR	TF, TA	ES	27	3.0 ± 1.9			
	mSAVR	sternotomy	Mechanical	27	2.3 ± 1.3			
Quick, et al.	TF-TAVR	TF	MC	74	8.6 ± 4.9	SC	Dresden, Germany	44 months

	TA-TAVR	TA	ES	88	8.4 ± 5.2			
	All TAVR	TF, TA	MC, ES	162	8.5 ± 5			
	SAVR	sternotomy	Mechanical	63	2.2 ± 1.8			
Kempny et al.	TAVR	60 TF, 41 TA	ES	101	NA	SC, OS, P	Muenster, Germany	27 months
	SAVR	sternotomy	Mechanical	22	NA			
Zhao et al.	TAVR	NR	NR	20	17.1 ± 5.6	SC, OS, P	Umea, Sweden	NR
	SAVR	sternotomy	NR	30	NR			

CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Graft; ES: Edwards SAPIEN; f/u: Follow up; LVF: LV Function; MC: Medtronic CoreValve; mTAVR: Matched TAVR; NR: Not Reported; OS: Observational Study; P: Prospective; RCT: Randomized Clinical Trial; R: Retrospective; SC: Single Center; Subclav: Subclavian; TF: Transfemoral; TA: Trans-Apical

Table 1: Characteristics of Studies Comparing Transcatheter Aortic Valve Replacement with Surgical Aortic Valve Replacement.

Qualitative analyses

A total of 572 patients from 6 single-center studies met our inclusion criteria and were included in our qualitative analyses, 5 studies were head to head comparing 365 TAVR and 157 SAVR patients [12,17,20-22] and one included only 50 TAVR patients [23]. All studies have been approved by their institutional ethics committees, but the approval was not reported in one [20]. All the included studies were published after the publication of echocardiography guidelines for RV evaluation in adult [7], but only three studies [20,21,23] followed TAVR related VARC-2 criteria [24] in their study methodology. A summary of study characteristics was presented in Table 1. The follow up period was various ranged from 7 days post SAVR, and from 7 days to 6 months post TAVR. At the latest follow up period, the outcome was improved RVSF post TF-TAVR in tow studies [22,23], and four reported unchanged RVSF post TAVR [17,20,21].

Studies reported improvement in early and midterm RVSF postoperatively [22,23] have used TAPSE and RVEF to conclude, and they have used TF approach for TAVR delivery regardless of TAVR device used. Their male gender and age were around 40%, and 80 years old respectively. Among those, 30% had Coronary intervention in form of PCI or CABG, and other cardiac surgeries. Those also had reasonable pre-operative kidney function; borderline STS scores; mean aortic pressure gradient (PG) ranged from 47.3 ± 15 to 53.6 ± 15.9 of which the higher values was for TF-TAVR; LVEF ≥ 38%; and 50% to 60% were in NYHA class III (Table 2A and 2B).

Studies reported unchanged RVSF post TF-TAVR and TA-TAVR [12,20,21] had heterogeneous LV function and patient's characteristics, and had higher incidence of CAD and previous or concomitant cardiac surgeries. The mean aortic PG for TAVR group ranged from 54.5 ± 18.4 to 58 ± 19 with no preference to any delivery approach, and for SAVR group ranged from 51 ± 16 to 65.2 ± 18.9. In their RVSF assessment post TAVR, mostly have used TAPSE, one recommended RVFAC instead o TAPSE of which the result was equivalent to TAPSE in TAVR group, and one has used exclusively RV-TDIS' [12].

Echocardiography evaluation and intended measure. Four studies reported offline image acquisition limiting RVSF data gathering. Three studies stated American society of Echocardiography and European Association of Echocardiography guidelines in their references. No data available to correct for measurement errors in this meta analyses, and that might confound the results. The recorded RVSF parameters, measured by various TTE machines, and their change post AVI were shown in Table 3.

	Intervention	Sample size (n)	Male [n (%)]	Age [m ± SD]	CAD [n (%)]	CHF [n (%)]	PCI [n (%)]	CABG [n (%)]	Previous cardiac surgery[n (%)]	Kidney function [n (%) or m ± SD]
Ayhan et al.	TAVR	50	21 (42%)	78.1 ± 8.5	38 (76%)	RVF 20-28 (40-56%)	NR	15 (30%)		NR
Forsberg et al.	All TAVR	60	26 (43%)	8 ± 67	27 (45%)	21 (35%)	15 (25%)	13 (22%)	20 (33%)	107 ± 46 (1.2)
	TA-TAVR	25	14 (56%)	83 ± 5	15 (60%)	10 (40%)	6 (24%)	7 (28%)	10 (40%)	123 ± 61 (1.39)
	TF-TAVR	35	12 (34%)	79 ± 7	12 (34%)	11 (31%)	9 (26%)	6 (17%)	10 (29%)	95 ± 27 (1.07)
	mTAVR	27	15 (56%)	76 ± 7	18 (67%)	8 (30%)	8 (30%)	9 (33%)	13 (48%)	94 ± 27 (1.06)
	mSAVR	27	15 (56%)	74 ± 6	15 (56%)	3 (11%)	10 (37%)	0	0	90 ± 22 (1.01)
Okada et al.	SAVR	15	9 (60%)	79.6 ± 5.9	10 (66.7%)	5 (33.3%)	2 (13.3%)	9 (60.0%)	NR	0

Citation: Zahaf M, Basu S, Bokowski J, Gasil S, Palacios I (2016) Effect of Transcatheter Aortic Valve Replacement on Right Ventricular Systolic Function: Systematic Review and Meta-analyses. J Clin Exp Cardiolog 7: 447. doi:10.4172/2155-9880.1000447

	TA-TAVR	9	9 (60%)	82.3 ± 5.1	4 (44.4%)	8 (88.9%)	2 (22.2%)	4 (44.4%)	NR	0
	TF-TAVR	13	6 (46.2%)	82.4 ± 4.3	9 (69.2%)	13 (100.0%)	3 (23.1%)	5 (38.5%)	NR	2 (15.4%)
Quick et al.	TF-TAVR	74	27 (36.5%)	80.5 ± 4.9	NA	NR	20 (27%)		NR	128 ± 45.7 (1.4)
	TA-TAVR	88	34 (38.6%)	81.1 ± 4.1	NA	NR	26 (29.5%)	NR	122 ± 50.8 (1.3)	
	All TAVR	162	61 (37.6%)	80.8 ± 4.3	NA	NR	46 (28.4%)	NR	124.7 ± 47.2 (1.4)	
	SAVR	63	22 (34.9%)	73.8 ± 8.1	NA	NR	0	NR	99 ± 23	
Kempny et al.	TAVR	101	33 (32.7%)	81 ± 11	51 (50%)	NR	NR	NR	25 (25%)	31 (31%)
	SAVR	22	8 (36.4%)	71 ± 12	9 (41%)	NR	NR	NR	1 (5%)	2 (9%)
Zhaoa et al.	TAVR	20	14 (46.7%)	79 ± 6	11 (55%)	NR	NR	NR	NR	104 ± 48 (1.1)
	SAVR	30	19 (63.3%)	62 ± 11	2 (7%)	NR	NR	NR	NR	79 ± 21 (0.89)
CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction; M: Mean; MSAVR: Matched SAVR; MTAVR: Matched TAVR; NYHA: New York heart Association; PCI: Percutaneous Coronary Intervention; PH: Pulmonary Hypertension; RVF: RV Failure; SD: Standard Deviation										

Table 2A: Impact of Baseline Population Characteristics on RV Systolic Function Outcome Post Aortic Intervention.

Study	COPD [n (%)]	PH [n(%), or m ± SD]	LVEF (m ± SD)	NYHA class [n(%)]			
				NYHA I	NYHA II	NYHA III	NYHA IV
Ayhan et al.	50 (100%)		53.6 ± 15.5	NR	2 (4%)	31 (62%)	17 (34%)
Forsberg et al.	6 (10%)	11 (18%)	NR	1 (2%)	3 (5%)	49 (82%)	7 (11%)
	1 (4%)	4 (16%)	NR	0	1 (4%)	20 (80%)	4 (16%)
	5 (14%)	7 (20%)	NR	1 (3%)	2 (6%)	29 (83%)	3 (8%)
	2 (7%)	5 (19%)	NR	0	3 (11%)	29 (83%)	3 (11%)
	1 (4%)	1 (4%)	NR	0	11 (41%)	16 (59%)	0
Okada et al.	NR	9 (60.0%)	52.7 ± 14.7	NR	NR	NR	NR
	NR	6 (66.7%)	63.0 ± 11.1	NR	NR	NR	NR
	NR	8 (61.5%)	47.7 ± 23.6	NR	NR	NR	NR
Quick et al.	16 (21.6%)	NR	53.2 ± 9.5	35 (47.3%)		39 (52.7%)	
	18 (20.5%)	NR	50.5 ± 11.1	40 (45.5%)	48 (54.5%)		
	34 (21%)	NR	NA	75 (46.3%)	87 (53.7%)		
	4 (6.1%)	NR	57.2 ± 9.6	40 (63.5%)	23 (36.5%)		
Kempny et al.	26 (26%)	28.0 ± 11.5	56.7 ± 17.3	0	19 (18.8%)	65 (64.3%)	17 (16.8%)
	4 (18%)	24.4 ± 9.5	67.7 ± 7.7	1 (4.5%)	4 (18.1%)	17 (77.3%)	0
Zhaoa et al.	NR	NR	54 ± 8.3	0	0	13 (65%)	7 (35%)
	NR	NR	65 ± 6.7	1 (3.3%)	17 (56.7%)	12 (40%)	0

CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction; M: Mean; MSAVR: Matched SAVR; MTAVR: Matched TAVR; NYHA: New York heart Association; PCI: Percutaneuos Coronary Intervention; PH: Pulmonary Hypertension; RVF: RV Failure; SD: Standard Deviation

Table 2B: Impact of Baseline Population Characteristics on RV Systolic Function Outcome Post Aortic Intervention (continued).

Quantitative analyses

We included 485 patients of 5 observational studies which had comparative RV echo systolic parameters pre and post AVI, 355 patients in TAVR group, and 130 patients in SAVR group.

RVSF post AVI. All five studies reported TAPSE, three reported RVFAC, and four reported LV ejection fraction (LVEF). Our expert level III echocardiographer speculated the suitable correlation coefficient (r) that has been uniformly applied to all the included studies and that might bias the results (TAPSE [r=0.65], RVFAC [r=0.65], LVEF [r=0.7]). However, we could not calculate the overall RVSF and biventricular composite endpoints due to data unavailability. The pooled analyses of the change in TAPSE, RVFAC, and LVEF post AVI were shown in Figure 2.

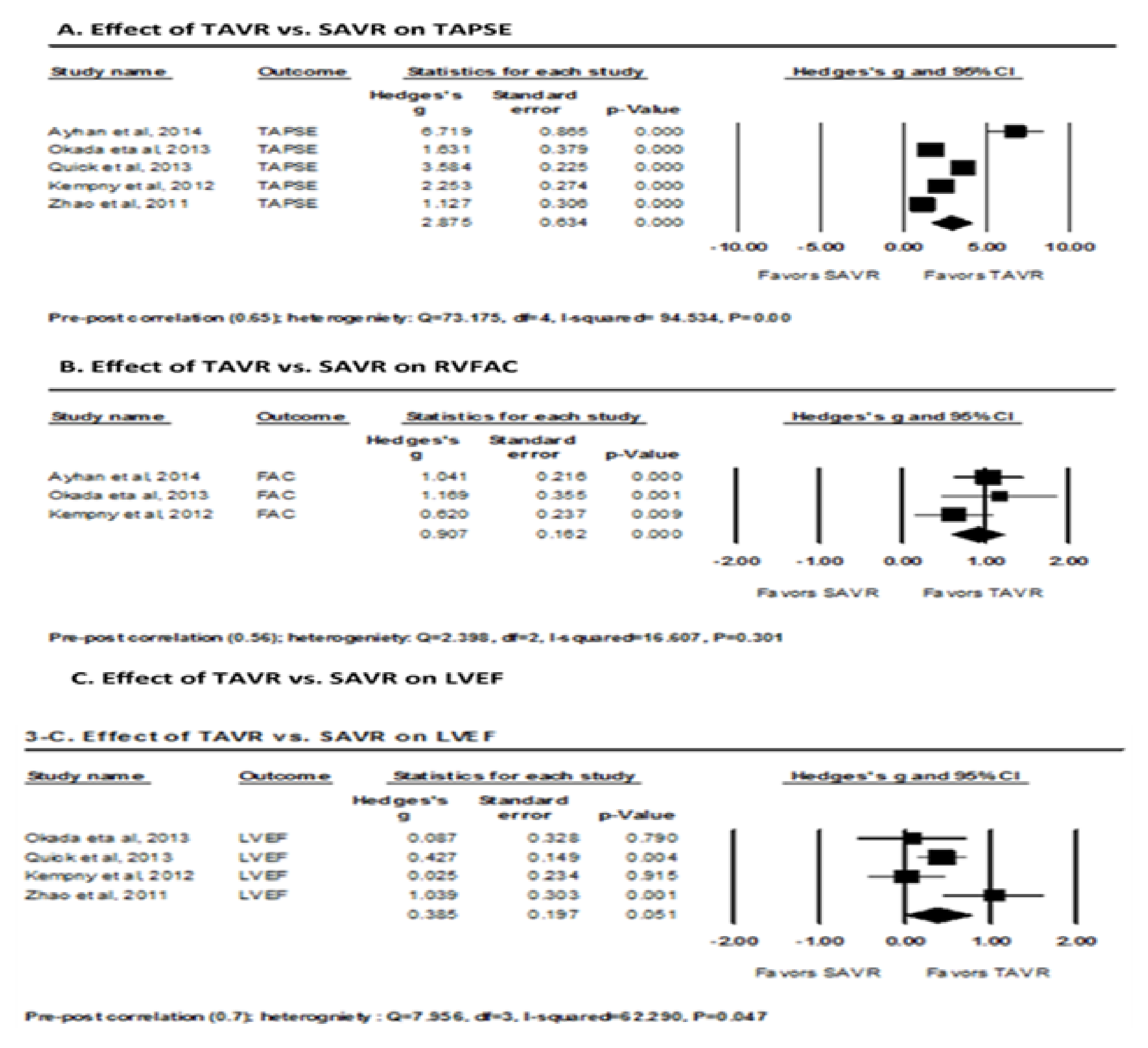

Figure 2: Forest plot comparing the effect of aortic intervention on right ventricular systolic function measured by TAPSE and RVFAC.

Both TAPSE and RVFAC were deteriorated post SAVR but showed no change post TAVR. However, when TAVR compared with SAVR, the outcome was in favor of TAVR [TAPSE (g=2.88, SE=0.63, P<0.001, Q=73.18, I^2=94.53, r=0.65), RVFAC (g=0.91, SE=0.16, P<0.001, Q=2.39, I^2=16.61), r=0.65]. TAPSE had greater reduction post SAVR and thus greater effect size than RVFAC post AVI suggesting altered RV geometry but not function. RVFAC showed less in between studies' heterogeneity in comparison to TAPSE and no publication bias, thus

RVFAC was chosen among the two to better assess RVSF post AVI. Overall, we could not validate RVSF parameters post AVI due to high within and in between studies' heterogeneity.

LV post aortic intervention. SAVR had no effect on LVEF, while TAVR had positive effect on LVEF, but the effect was similar when TAVR compared to SAVR (g=0.38, SE=0.19, P=0.05, Q=7.96, I2=62.29, r=0.7), in favor of TAVR. There was also high heterogeneity, but no publication bias.

Subgroup analyses of RVSF per TAVR devices and delivery approaches. Due to insufficient number of our single-center studies required for random effect model, we were unable to perform quantitative subgroup comparison of the pooled estimate of the overall change in early and midterm RV echo systolic parameters in between TAVR' delivery approaches TA and TF, or in between TAVR' commercial devices MC and ES. Particularly, the variation in postoperative reporting periods in those subgroups and SAVR might bias the outcome.

Author	Name of Echo machine	Echo timing	Echo Type / Technique / Views	Echo RV parameters	RV parameters used to conclude	RV parameters' status post intervention
Ayhan	Philips iE33	pre TAVR, 24hrs, 1mo, 6 mo post TAVR	TTE/2D, Doppler/PLAX, PSAX, A4C, S4C	TAPSE, RVFAC, RVTDIS', RVEF, RVSP	TAPSE, RVFAC, RVTDIS'	all parameters improved at 6 mo and were statistically significant
Forsberg et al.	Vivid 7 ultrasound system, GE Vingmed Ultrasound	1 day pre and 7 wks, and 6 mo post TAVR and SAVR	TTE/pulsed TDI, M-mode/NR	PSVRV, AVPDRV	PSVRV, AVPDRV	AVPDRV unchanged post TA-TAVR and TF-TAVR, but PSVRV improved early post TF-TAVR and markedly decreased post SAVR
Okada	Philips Sonos or a GE Vivid 7 Dimension	Median 32 days preop, and 7 days postop AVR	TTE/M-mode, 2D, CF, and Doppler/ standard views; A4C	TAPSE, RVFAC, RV dimensions (RVD1, RVD2, RVD3), RVEF	RVFAC preferred, TAPSE	RVF unchanged with TA-, TF-TAVR, but TAPSE deteriorated and RV FAC unchanged post SAVR
Quick	iE33 echo-cardiogra-phy System (Philips, NL)	<2 months pre and 7day post intervention	TTE/NR/standard views; 2 chambers and 4 chambers views	TAPSE, RV dimension, RVEF(4 grades), RVSP	TAPSE and RVEF	TAPSE, RVEF deteriorated post TA-TAVR and SAVR, but unchanged post TF-TAVR
Kempny et al.	Vivid 7 Dimension system	median 19, 18 Ds pre and 70, 100 Ds post TAVR and SAVR	TTE/conventional and STE; M-mode, 2D/PLAX, PSAX, A4C	TAPSE, RVFAC, RVEF, RVSP, RVEDD, RVEDA, RV-LS	TAPSE, RVFAC, RV-LS	RVFAC, TAPSE, RV-LS deteriorated post SAVR and unchanged post TAVR
Zhao et al.	Vivid 7 ultrasound system	1 D pre, 1 wk, 6 wks post intervention	TTE/ Doppler, M-mode/ standard views	TAPSE, septal radial motion	TAPSE, septal radial motion	TAPSE and septal radial motion reduced post TAVR and SAVR but they were unchanged at 6 wks post TAVR

A4C: Apical 4- Chamber; AVPD: Atrioventricular Plane Displacement; CF: Continuous Flaw; D: Day; Ds: Days; 2D: Two-Dimensional; Echo: Echocardiography; Mo: Month; PLAX: Parasternal Long-Axis; PSAX: Parasternal Short-Axis; RVF: Right Ventricle Function; PSVRV: RV Peak Systolic Velocity; RVSP: RV Systolic Pressure; RV-LS: RV Longitudinal Strain; S4C: Subcostal 4-Chamber; STE: Speckle Tracking Echocardiography; TDI: Tissue Doppler Imaging (S'); Wk: Week

Table 3: Echocardiography Imaging Acquisition and Analyses of Right Ventricular Systolic Function.

Discussion

Among parameters used in assessment of RVSF; only RVEF was clinically and instrumentally validated, TAPSE and RVFAC were well correlated with each other [25] and with RVEF [26,27], and RV velocity was a reliable index of contractility [28]. In this modern era, AVI approaches are various and have led to different patterns of RV contractions, and thus the need for approach-nonbiased parameters to assess accurately RVSF becomes paramount. Unfortunately, because of our included inconsistent primary studies, we were only able to include RVFAC and TAPSE in our analyses which were the most commonly used indices for RVSF [7]. TAPSE is an echo measure of longitudinal RVSF and can be reduced even in absence of RV dysfunction suggesting change in geometry rather than function postoperatively [29]. Our meta analyses revealed that TAVR was the preferred AVI to SAVR in patients with RV systolic dysfunction and that goes in line with the VARC-2 recommendation [24]. TAVR effect on TAPSE and RVFAC was regardless of TAVR delivery approach or its commercial device used. In our meta analyses, RVFAC as a measure of global RVSF was the recommended parameter to use post AVI since it did not show high in between studies heterogeneity compared to TAPSE.

The variability among studies could be due to unadjusted moderators related to patients' baseline characteristics including age, gender, body mass index, preoperative surgical risk scoring, biventricular functional status, kidney function, pulmonary hypertension, past or concomitant cardiac surgeries; variations in echo machines and its imaging acquisition and analyses, and parameters used to assessing RVSF pre and post AVI; variations in TAVR delivery approaches; variations in post procedure follow up periods and reporting; and to variations in those small sized- single center study designs and that collectively preclude validity generalization. Of course, that is in addition to poor reporting of data relevant to device-specific and operator-specific characteristics.

TAVR group was older, and with higher preoperative risk scores than SAVR and that would impact RV status post operatively. Interestingly, populations of those ecological studies were different and thus their genetic propensity for RV remodeling [30] and reverse remodeling post AVI was suspected. Particularly, the degree of AS and the resultant pressure overload was the major determinant of the extent of biventricular compliant and adaptive negative remodeling, and thus their extent of recovery thereafter. The thin walled and the highly compliant right ventricle cannot maintain its contractility in the face of increased pulmonary resistance due to left heart pressure overload. Unfortunately, the direct relationships of increased pulmonary pressure, as a consequence of severe AS, and the resultant RV systolic dysfunction could not be assessed in this meta analyses. Intuitively, to certain mean aortic PG limit, RV systolic dysfunction is reversible since RV is more tolerant to volume than pressure overload. This was reflected in our qualitative analyses of the relation of mean aortic PG pre-TAVR and the improvement in RV systolic parameters post-TAVR.

RV systolic dysfunction is also directly associated with LV systolic dysfunction (interventricular dependence) [28,31,32]. RV dysfunction once occurs as a consequence of left heart pressure-overload leads to trans-septal gradient reversing the diastolic interaction and that adds to LV dysfunction. In our meta analyses, we were unable to correlate the changes in RV dimensions and function with those of LV post AVI, but we were able to demonstrate that TAVR group had LVEF>38% and were class III NYHA suggesting LV diastolic rather than systolic dysfunction. This suggested that reversal of diastolic ventricular interaction play a role following severe AS and thus RVSF improvement postoperatively. Smulyan et al. also concluded that RV filling pressures in patients with AS are often elevated without presence of LV systolic failure [33].

Intra-operatively, Lindqvist et al. [34] reported altered pattern of RV contraction and selective fall in RV longitudinal function induced by SAVR, possibly due to open sternotomy, pericardiotomy, cardiomyotomy, intra operative cannulation, hypothermia, cardioplegia, and cardiopulmonary bypass machines. Those procedures, beside their potential myocardial damaging effect, might lead to septal wall motion reversed toward RV cavity, and that was correlated with depressed TAPSE [17]. TAPSE might be recovered six months post SAVR due to reversed RV remodeling, or in other retrospective study, RV changes might be permanent [35]. Unfortunately in our meta analyses, intraoperative RVSF was lacking, and the nature of concomitant or previous cardiac surgeries associated with AVI were not consistently or sufficiently defined in our studies. While TF-TAVR, the default approach, did not alter the integrity of thorax-pericardium-myocardium complex-interactive structures, the less commonly used TA-TAVR involves direct access to the aortic valve via the left ventricular apex and pericardiotomy, and that might impair LV function. In contrary, Zhao et al., Kempny et al., and Quick et al. disclosed that TAPSE and visually estimated RVEF decreased slightly after TA-TAVR and they related that to probable pericardial disruption and postoperative pericardial adhesion, the same mechanisms were applied to SAVR. However, Okada et al. reported improved RVFAC post TF-TAVR that was not statistically significant (p=0.07), preserved RVFAC post TA-TAVR and SAVR, preserved TAPSE post TA-TAVR and TF-TAVR but decreased post SAVR, and concluded that the global RVFAC is the preferred method for RV systolic assessment postoperatively. He also concluded that the selective change in RVFAC was not a result of change in LVEF.

Wilbring et al. reported that AS patients with concomitant mitral and tricuspid valve regurgitation had reduction in their grade of regurgitation and their concomitant pulmonary hypertension and RV systolic pressure post-TAVR. The intuitively improved RVSF paradoxically did not show improvement when measured by TAPSE and the authors attributed that to the organized RV remodeling due to long standing AS [36]. Moreover, AVI alters the configuration of mitral valve and thus lead to improving the back pressure on RV, and that leads to further improvement of LV hemodynamic function [37]. However, whether the altered valve configuration itself leads to alteration in RV dimensions remained to be explored.

The improvement of RVSF post AVI [22,23] was also related to improved coronary flow resulted, firstly, from decreased back pressure on the thin-walled RV due to TAVR- corrected AS lesion, secondly, from improving the pressure gradient between the aorta and RV, and thirdly, from concomitant correction of coronary lesions [38]. Interestingly, there was no change in RVSF post TAVR when our included patients had past or concomitant coronary intervention with TAVR, and that included PCI, CABG, or other undefined cardiac surgeries [12,20,21]. The reasons might be related to CAD related myocardial injury and scarring, no intervention to coronary lesions crucial for RV blood supply, RV hypoperfusion after cardioplegia [39], hypothermia [40], bypass machine and the concomitant inflammatory changes [41], pericardiotomy [42], RA dysfunction post venous cannulation [43], RV adhesion, and post coronary intervention-induced lesions and restenosis. Again, Quick et al. univariate regression analyses showed no difference between TA-TAVR patients with CAD/PCI/CABG, and those without CAD/PCI/CABG with regard to baseline and post-procedural TAPSE and RVEF, and in other study, the changes in RV function were similar in both off-bump and on-bump CABG [44].

When TAVR compared with SAVR effect on LVEF in our meta analyses, their effect was similar in favor of TAVR. Crouch et al. [45] reported similar results on LVEF with LVEF preservation post SAVR, but there was LVEF deterioration post TAVR due to paravalvular aortic regurgitation. The variation in the observed reverse LV remodeling post operatively depends on type of AVI, in favor of non-myocardial damaging TF-TAVR' approach, pre-operative reduced LVEF [17,22], time point after AVI [46], and techniques that can accurately measure that change, beside other factors.

Study limitation. The observed high heterogeneity in TAPSE might be related to its reliability as measurement parameter within and a cross studies, beside variation in those small size single-center observational studies' methodology and clinical diversity. We could not assess both echocardiographers and operators of cohorts' AVI, and their centers' experiences. Variations in Echo machines used to assess RVSF cause measurement errors contributing to heterogeneity and yield an erroneous effect size estimate. Especially poor echo windows at early postoperative period following SAVR made the comparison arbitrary. Due to insufficient data, we were unable to do subgroup and meta regression analyses with regards to moderators contributed to high heterogeneity. Particularly, the speculated correlation coefficients of RVSF echo parameters might bias the estimate of the summary effect size.

Conclusion

When compared to SAVR, TAVR was the preferred AVI for patients with AS and RV systolic dysfunction. RVFAC is the recommended parameter for assessment of RVSF post AVI. However, because our cohort studies were various in important issues, our conclusion was not robust, but instead the reasons of their variation sought. We are planning to follow this meta analyses with future well controlled multicenter randomized clinical trial adjusting for clinical and methodological variations and taking into account full assessment of RV function including its influential covariates and RV clinical outcome status compared to LV post AVI, in addition to developing standard protocol for reporting after AVI which would further identify the robustness of using TAVR in comparison to SAVR. Alternative and more accurate technique used to measure RVSF as 3-D TTE, or cardiac magnetic resonance imaging [47,48] is recommended in the future studies for RVSF validation post AVI.

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