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Transcatheter Tricuspid Valve Replacement for Tricuspid Regurgitation: A Systematic Review and Meta-analysis

ABSTRACT

Background: The present data aim to evaluate the feasibility of the orthotopic transcatheter tricuspid valve replacement devices, echocardiographic, functional improvements, and mortality rates following replacement in patients with significant tricuspid valve regurgitation.

Methods: We systematically searched for the studies evaluating the efficacy and safety of transcatheter tricuspid valve replacement for significant tricuspid valve regurgitation. The efficacy and safety outcomes were the improvements in New York Heart Association functional class, 6-minute walking distance, all-cause death, and periprocedural and long-term complications. In addition, a random-effect meta-analysis was performed comparing outcomes before and after transcatheter tricuspid valve replacement.

Results: Nine studies with 321 patients were included. The mean age was 75.8 years, and the mean European System for Cardiac Operative Risk Evaluation II score was 8.2% (95% CI: 6.1 to 10.3). Severe, massive, and torrential tricuspid valve regurgitation was diagnosed in 95% of patients (95% CI: 89% to 98%), and 83% (95% CI: 73% to 90%) of patients were in New York Heart Association functional class III or IV. At a weighted mean follow-up of 122 days, New York Heart Association functional class (risk ratio = 0.20; 95% CI: 0.11 to 0.35; $P < .001$) and 6-minute walking distance (mean difference = 91.1 m; 95% CI: 37.3 to 144.9 m; $P < .001$) significantly improved, and similarly, the prevalence of severe or greater tricuspid valve regurgitation was significantly reduced after transcatheter tricuspid valve replacement (baseline risk ratio = 0.19; 95% CI: 0.10 to 0.36; $P < .001$). In total, 28 patients (10%; 95% CI: 6% to 17%) had died. Pooled analyses demonstrated non-significant differences in hospital and 30-day mortality and >30-day mortality than predicted operative mortality (risk ratio = 1.03; 95% CI: 0.41 to 2.59; $P = .95$, risk ratio = 1.39; 95% CI: 0.69 to 2.81; $P = .35$, respectively).

Conclusion: Transcatheter tricuspid valve replacement could be an emerging treatment option for patients with severe tricuspid regurgitation who are not eligible for transcatheter repair or surgical replacement because of high surgical risk and poor prognosis.

Keywords: Interventional cardiology, transcatheter tricuspid valve replacement, tricuspid regurgitation

META-ANALYSIS

INTRODUCTION

Tricuspid regurgitation (TR) is a common echocardiographic finding observed in 75%-90% of the population and, when severe, is associated with poor clinical outcomes and high mortality rates.[1,2] The etiology of TR can be divided into primary (organic) and secondary (functional), according to the presence of structural abnormalities of the tricuspid valve (TV). While primary TR is associated with the anatomical abnormality of the TV apparatus in merely 8%-10% of patients, secondary TR results from an annular dilation due to right ventricular dilatation and dysfunction by pulmonary hypertension following left-sided heart disease or atrial fibrillation. Additionally, right ventricle (RV) device leads cause evident TR in 20%-30% of patients.[3,4]

According to current guidelines, initial treatment must necessarily be pharmacological treatment. Tricuspid valve surgery for functional TR can be considered

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when performing surgery for concomitant left-sided valve disease; otherwise, if possible, TV repair techniques should be selected for functional disease. The crucial principle for tricuspid intervention, whether valve repair or replacement, should exist before irreversible remodeling of the RV.[1] In the past, minor or moderate functional TR was expected to diminish or disappear after surgical correction of left-sided valve disease. Hence, TR has been excluded for a long time since it is intertwined with primary left heart disease signs and symptoms, leading to the late referral of the patients. Eventually, the fact that many patients with symptomatic severe TR are at high or prohibitive surgical risk with an ineffective pharmacological therapy has forced to use only the palliative management options.

Transcatheter tricuspid valve interventions (TTVI) have emerged in the wake of the successes achieved with aortic and mitral valve interventions as a less-invasive approach to TV diseases and provoked cardiologists to evaluate the efficacy and safety of the novel devices in early feasibility trials and small cohort studies.[5] In this context, the European Society of Cardiology's 2021 Valvular Heart Disease Guideline recommends TTVI for severe symptomatic TR in inoperable patients, emphasizing the importance of early referral as IIb level C category.[1] They can be categorized into leaflet-directed interventions (MitraClip/TriClip, PASCAL), occupying the regurgitant orifice area (PASCAL, FORMA), annulus-reshaping repair-ring annuloplasty (Cardioband), and annulus-reshaping repair-suture annuloplasty (Trialign, TriCinch). Transcatheter tricuspid valve replacement (TTVR) devices are classified into: (a) orthotopic (NaviGate, EVOQUE, Trisol, LUX-Valve, Intrepid, TRICares), where the valve is placed at the TV annulus, and (b) heterotopic, where valves are placed in superior and inferior vena cava aiming to diminish the hemodynamic consequences of TR.[6] Apart from the repair techniques with the advances in transcatheter-based devices and expertise, orthotropic TTVR therapies have shed new light on the treatment of TR. Transcatheter tricuspid valve replacement has better results in extensive damage of TV apparatus, leaflet dislocation (pacemaker lead-induced TR), or secondary TR due to severe annulus dilation and excessive leaflet tethering.[2,7]

HIGHLIGHTS

- Transcatheter tricuspid valve replacement (TTVR) has emerged as a less-invasive approach to tricuspid regurgitation (TR). The present meta-analysis evaluated the efficacy and safety of orthotropic TTVR for moderate-severe native TR.
- Our analysis showed that patients with orthotropic TTVR had low mortality rates, experienced NYHA functional class improvements, and reduced echocardiographic parameters of TR severity.
- Orthotropic TTVR may become the preferred treatment option for surgically ineligible high-risk patients.

Based on the present data, we aimed to evaluate the feasibility of the orthotopic TTVR devices, echocardiographic, functional improvements, and mortality incidence rates following replacement in this pooled analysis.

METHODS

Search Strategy and Study Selection

We systematically searched MEDLINE/PubMed, EBSCO, the Cochrane Library, Web of Science, www.tctmd.com, www.ClinicalTrials.gov, and www.clinicaltrialresults.org for the studies published on or prior to November 10, 2021. The search was limited to English papers. Additionally, references of case series studies, reviews, editorials, and commentaries were manually searched to find relevant studies. Search terms included Cardiovalve (Boston Medical, Shrewsbury, MA, USA), Evoque (Edwards Lifescience, Irvine, CA, USA), LuX-Valve (Jenscare Biotechnology, Ningbo, China), NaviGate (NaviGate Cardiac Structures Inc., Lake Forest, CA, USA), Trisol (Trisol Medical, Yokneam, Israel), Intrepid (Medtronic Plc, Minneapolis, MN, USA), Tricares (TRiCares SAS, Paris, France) or TV regurgitation or insufficiency; and TTVR/TTVI. Both authors manually reviewed all full-text articles to determine eligibility for inclusion in the meta-analysis. EndNote and Rayyan software were used to remove any duplicates and select eligible studies from the database findings and other sources (lists of references in included studies). Two authors (BB and EIC) independently reviewed all retrieved title abstracts to determine the potential for inclusion using Rayyan software.[8] Any discrepancies were resolved after discussion with the senior author (CB). Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines[9,10] were used. Two authors (BB and EIC) independently assessed the quality of studies and risk for bias according to the ROBINS-I tool.[11] The original study protocol was registered on the International Prospective Register of Systematic Review (PROSPERO) platform: registration number, CRD42021291523.[12]

Eligibility Criteria

Studies were considered eligible if they fulfilled all the following criteria: (1) the study population was patients with at least moderate native TR and treated with orthotropic TTVR; (2) the design was a case series study enrolling ≥4 patients; (3) at least 1 of the efficacy outcomes included all-cause mortality (in-hospital and ≥30-day). Patients with TR were excluded due to structural dysfunction of bioprostheses or failed surgical annuloplasty rings, valve-in-valve, valve-in-ring, and heterotopic TTVR. Data of TTVR device type, duration of follow-up, predicted operative mortality (such as European System for Cardiac Operative Risk Evaluation [EuroSCORE]), and 30-day and late (>30-day) all-cause mortality were extracted (if available) from each study.

Study Outcomes

Baseline characteristics include the total number of participants and pooled mean or incidence rate of age, sex, hypertension, diabetes, stroke/transient ischemic attack (TIA), renal impairment, coronary artery disease, previous interventions (coronary artery bypass grafting and/or prior valve

surgery), percutaneous coronary interventions, and permanent pacemaker.

Efficacy outcomes of this analysis were the rate reduction of (1) severe TR; (2) New York Heart Association (NYHA) functional class III or IV at longest follow-up; and (3) The changes in functional and echocardiographic parameters, including 6-min walking distance (6MWD), left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), and right ventricular fractional area change (RV FAC), and RV end-diastolic basal diameter. Procedural success definition included successful device implantation and retrieval of the delivery system, correct and stable positioning of the valve prosthesis, and no severe or life-threatening adverse events during the procedure.

Safety outcomes included periprocedural and long-term complications that included all-cause deaths, stroke, or TIA, myocardial infarction (MI), paravalvular regurgitation, central valve regurgitation, device embolization and/or malpositioning/migration, major bleeding, conversion to surgery, vascular complications, need for support device (extracorporeal membrane oxygenation [ECMO], intra-aortic balloon pump [IABP], or other), and conduction abnormality requiring a permanent pacemaker.

Statistical Analysis

Statistical heterogeneity of exposure was evaluated by I^2 statistics. If I^2 <25%, it suggests that there is negligible statistical heterogeneity. If I^2 >75%, it indicates possible statistical heterogeneity. We calculated pooled risk ratios (RRs) and standardized mean differences (MDs) with 95% CIs to summary statistics for outcomes of interest using a random-effects model according to DerSimonian and Laird,[13] and for the outcomes of interest represent within-group changes. A leave-one-out sensitivity analysis was performed on the efficacy endpoints to evaluate if the results were primarily affected by single studies. We also pooled the baseline characteristics individually and presented them as weighted means and 95% CIs. When data were available only as medians and interquartile ranges, mean ± standard deviation (SD) was calculated according to Wan et al.[14] Inverse variance-weighted average of the logarithm of study-specific RRs was combined in the random-effects model. Statistical significance was set at a 2-sided *P* value <.05. Sensitivity analyses were performed for primary endpoints by assessing removing individual studies on the pooled RR. Egger and Begg tests and visual inspection of funnel plots were used to evaluate publication bias. All analyses were performed using Review Manager version 5.3 (available from http://tech.cochrane.org/revman) and comprehensive meta-analysis software.[15]

RESULTS

Systematic Review of Studies

A total of 9447 published articles were identified from electronic databases and other sources. After removing duplicate studies (n=677), 8770 studies were eligible for an initial screening based on titles and abstracts. Following the initial screening, 8560 records were removed, and the full texts of 210 articles were screened against the defined eligibility criteria. After the full-text screening, 4 published studies,[16-19] 2 case series,[20,21] and 3 conference presentations (A New, Non-Radial Force Transcatheter Tricuspid Valve Replacement (LuX Medical) | tctmd.com; https://www.tctmd.com/slide/navigate-transcatheter-tricuspid-valve-replacement-early-findings-technology-and-clinical; https://www.tctmd.com/slide/triscend-six-month-outcomes-transfemoral-tricuspid-valve-replacement-patients-tricuspid) were included in this meta-analysis with a total of 321 patients with at least moderate TR undergoing TTVR. Figure 1 shows the PRISMA flowchart.

Patients were treated with different orthotropic transcatheter tricuspid valves:

1. NaviGate (n=71) is a radial force-dependent TTVR device, delivered via transatrial or transjugular approach with a 42 Fr system.
2. The EVOQUE system (n=157) is another radial force-dependent TTVR device, delivered via transatrial approach with the 28 F transfemoral system.
3. LuX-Valve (n=93) is a self-expanding tissue valve delivered via a 32-F catheter through a minimally invasive right thoracotomy and transatrial approach.

Additional information on individual studies' case reports is shown in Table 1.

Baseline Characteristics

This present meta-analysis involves 9 studies with 321 high-risk patients.[16-22] Patients had a mean age of 75.8 years (95% CI: 72.3 to 79.3 years), including 67% (59%-74%) female, and were at high surgical risk, with a mean EuroSCORE II score of 8.2 (95% CI: 6.1 to 10.3). Severe, massive, and torrential TR was diagnosed in 95% of patients (95% CI: 89% to 98%), and 83% (95% CI: 73% to 90%) of patients were in NYHA functional class III or IV (Supplementary Figure 1). Other baseline characteristics are reported in Table 1.

Efficacy Outcomes

Procedure time was on average 122.3 minutes (95% CI: 82.1 to 162.5). Many of the procedures 74% (95% CI: 36% to 93%) were performed via a trans atrial approach with a minimally invasive right thoracotomy in the right fourth intercostal space. The pooled analysis showed the procedural success of TTVR was achieved in 92% of patients (95% CI: 87% to 96%). The prevalence of technical success was 90% (95% CI: 78 to 95%) in NaviGate system, 95% (95% CI: 90 to 97%) in the EVOQUE system, and 98% (95% CI: 91 to 99%) in the LuX-Valve.

A statistical comparison of baseline characteristics, procedural safety, and efficacy outcomes is shown in Tables 2 and 3. New York Heart Association functional class (RR=0.20; 95% CI: 0.11 to 0.35; *P* < .001) and 6MWD (MD=91.1 m; 95% CI: 37.3 to 144.9 m; *P* < .001) significantly improved following TTVR, and similarly, the prevalence of severe or greater TR was significantly reduced after TTVR baseline (RR=0.19; 95% CI: 0.10 to 0.36; *P* < .001).

Other echocardiographic findings after TTVR showed noticeable reductions in RV end-diastolic basal diameter (MD=−0.51 cm; 95% CI: −0.83 to −0.20 cm; *P* < .001).

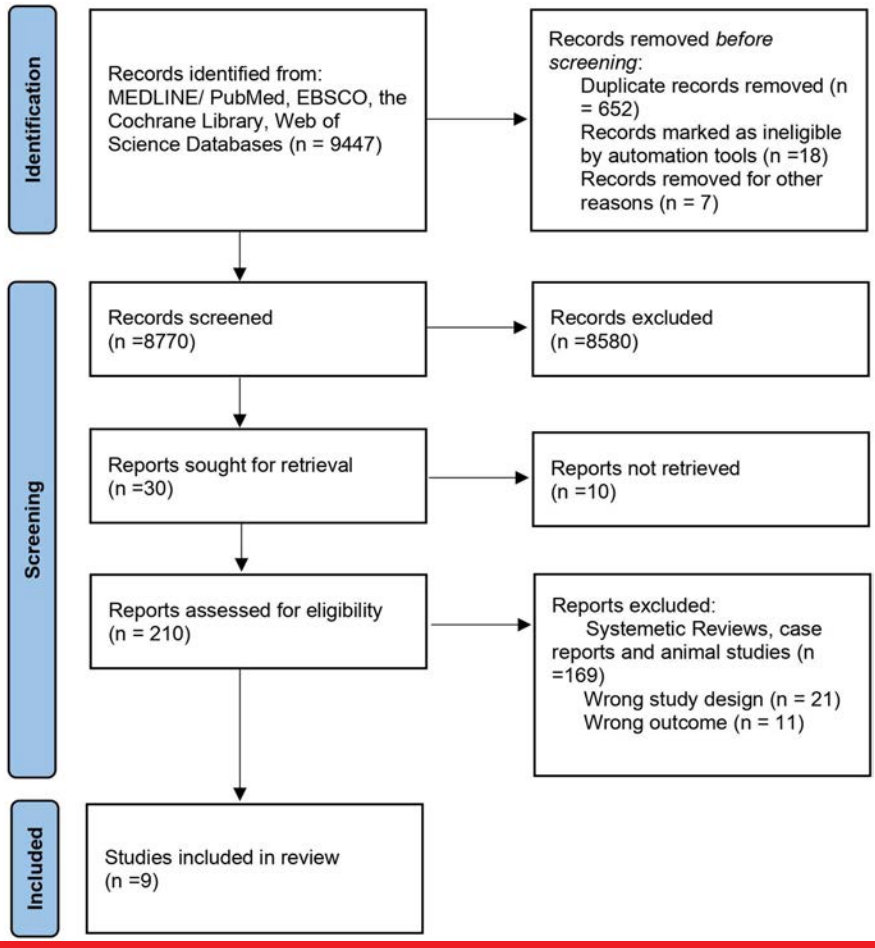


Figure 1. Diagram of the studies' search and selection.

Negligible differences were found regarding LVEF, TAPSE, and RV FAC before and after TTVR (MD = –1.42 mm; 95% CI: –3.08 to 0.24 mm; *P* = .09, MD = –3.18; 95% CI: –9.75 to –3.38%; *P* = .34). Functional and echocardiographic parameters at baseline and after TTVR are reported in Table 3. Forest plots describing the mean difference and RR of the study's primary outcomes before and after TTVR are represented in Figure 2. Funnel plots and Egger's regression test results are reported in Supplementary Figure 2. The exclusion of any single trial from the analysis did not substantively alter the overall results of our analysis.

Safety Outcomes

The meta-analysis revealed an incidence of periprocedural and non-periprocedural stroke of 0%, while the incidence of paravalvular and central TR was 31% (95% CI: 15% to 53%) and 15% (95% CI: 6% to 34%), respectively. In addition, the incidence rate of MI, renal dysfunction, major bleeding, major vascular complications, device embolization, and/or malpositioning/migration, conversion to surgery, need for support device (ECMO, IABP, or other), and conduction abnormality requiring permanent pacemaker were shown in Table 3 and supplemental Table 1.

According to the pooled analysis of all devices, the prevalence of atrioventricular block and paravalvular leakage was 6% (95% CI: 2% to 15%), 50% (95% CI: 12% to 87%) in NaviGate system; 7% (95% CI: 3% to 12%), 52% (95% CI: 33% to 70%) in EVOQUE system; and 1% (95% CI: 0.4% to 8%), 9% (95% CI: 4% to 20%) in the LuX-Valve, respectively.

Patients were discharged on average of 10.7 days (95% CI: 4.5 to 16.9) after the procedure. At last available follow-up after TTVR, 28 patients (10%; 95% CI: 6% to 17%) had died (Figure 3, Supplementary Figure 3). Pooled analyses demonstrated nonsignificant differences in hospital and 30-day mortality than predicted operative mortality (RR = 1.03; 95% CI: 0.41 to 2.59; *P* for effect = .95; *P* for heterogeneity = .29, I^2 = 19), while nonsignificantly higher >30-day mortality (RR = 1.39; 95% CI: 0.69 to 2.81; *P* for effect = .35; *P* for heterogeneity = .46, I^2 = 0) (Table 4, Supplementary Figure 4).

DISCUSSION

The present analysis evaluated the efficacy and safety of orthotropic TTVR for significant TR. The main findings of this pooled analysis can be summarized as follows: patients undergoing TTVR showed low mortality rates, experienced significant improvements in functional status, and a significant reduction in TR severity; moreover, echocardiographic parameters of TR consistently improved following TTVR.

The TV was virtually ignored for a long time; however, it is frequently related to the poor prognosis, and it may affect as much as 65%-85% of the population.[23] In addition, approximately 80% of significant TR is functional and associated

Table 1. Study Design and Patient Characteristics

		Criteria								
First Author Year	**Device**	**Access Site Minimally invasive Right Thoracotomy and Trans Atrial Approach**	**Access Site Trans Femoral Approach**	**Delivery Sheat Size**	**Inclusion**	**Exclusion**	**Patient Number**	**Age (Years)**	**Female**	**Functional TR**
Pooled estimates: mean/ incidence (95% CI)		0.74 (0.36 to 0.93)						75.8 (72.3 to 79.3)	0.67 (0.59 to 0.74)	
Kodali 2021	EVOQUE		132	28 F	Patients with symptomatic ≥ moderate tricuspid regurgitation, functional or degenerative TR, signs and/or symptoms, or prior heart failure hospitalizations from TR despite optimal medical therapy	Tricuspid valve anatomic contraindications Need for emergent or urgent surgery or any planned cardiac surgery within the next 12 months Hemodynamic instability Refractory heart failure requires advanced intervention Currently participating in another investigational study in which the patient has not reached a primary endpoint	132	79.2 ± 7.39	97 (74%)	93 (70.5%)
Lu 2021	LuX-Valve	46	32 F		Patients were inoperable or at excessive risk for surgical intervention after being carefully assessed by the multidisciplinary heart team	Patients with poor left or right ventricular function, severe pulmonary arterial hypertension and untreated severe coronary artery disease were excluded	46	68.0 (59.8, 74.0)	34 (73.9)	28 (60.9)

(*Continued*)

Table 1. Study Design and Patient Characteristics (*Continued*)

					Criteria					
First Author Year	**Device**	**Access Site Minimally invasive Right Thoracotomy and Trans Atrial Approach**	**Access Site Trans Femoral Approach**	**Delivery Sheat Size**	**Inclusion**	**Exclusion**	**Patient Number**	**Age (Years)**	**Female**	**Functional TR**
Fam 2021	EVOQUE		25	28 F	Patients had right-sided HF (NYHA functional class II to IV) despite medical therapy and were decided to be at high surgical risk or inoperable by the local heart team. The heart team judged that transcatheter leaflet repair would not be feasible (i.e., large [>10 mm] coaptation gaps, severe leaflet tethering, and/or pacemaker-induced TR), with suitable anatomy for EVOQUE implantation. Patients were considered anatomically suitable for EVOQUE TTVR if they had adequate screening transesophageal echocardiographic imaging of the tricuspid valve leaflets for procedural guidance and computed tomography-derived tricuspid valve annular dimensions compatible with 44- or 48-mm valves.	There were no specific anatomic exclusions. Patients with severe RV dysfunction or significant pulmonary arterial hypertension (pulmonary artery systolic pressure >60 mm Hg) were excluded.	25	76 ± 3	22 (88)	19 (76)
Hahn 2020	NaviGate	25		42 F	All patients were considered inoperable or at high risk for surgery.		30	78 (70, 80)	17 (56)	

(*Continued*)

Table 1. Study Design and Patient Characteristics (*Continued*)

		Criteria								
First Author Year	**Device**	**Access Site Minimally invasive Right Thoracotomy and Trans Atrial Approach**	**Access Site Trans Femoral Approach**	**Delivery Sheat Size**	**Inclusion**	**Exclusion**	**Patient Number**	**Age (Years)**	**Female**	**Functional TR**
Lu 2020	LuX-Valve	12		32 F	Patients in this study were assessed by the multidisciplinary heart team and were deemed to be inoperable or at excessive risk for surgical intervention.	Left ventricular ejection fraction <35%, untreated severe coronary artery disease, tricuspid annular plane systolic excursion <10 mm, right ventricular fractional area change <20%, and systolic pulmonary artery pressure >60 mm Hg	12	69 (66, 74)	7 (58.3)	
Hahn 2019	NaviGate	5		42 F	All patients had symptomatic, massive, and/or torrential TR at baseline.		5	84.4±7.02	2 (40)	
Cao 2019	LuX-Valve	35		32 F			35	69.1±7.0	24 (63.3)	
Elgharably 2019	NaviGate	3			Severe symptomatic TR, prohibitive risk for conventional surgery (significant comorbidities, hazardous redo-sternotomy, severe RV dysfunction), pulmonary artery pressure ≤90 mmHg (by echocardiography and right heart catheterization), and favorable anatomy.		4	74.5±7.0	3 (75)	
Hahn 2018	NaviGate	26		35 F			32	73.5±12.9	17 (53)	

HF, heart failure; NYHA, New York Heart Association; RV, right ventricle; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement.

Table 1. Study Design and Patient Characteristics (*Continued*)

	Comorbidities n, %						Previous Interventions			NYHA Class	
First Author Year	**DM**	**HT**	**CAD**	**Renal Impairment**	**Stroke**	**AF**	**CABG and/or Prior Valve Surgery**	**PCI**	**Permanent Pacemaker**	**NYHA III**	**NYHA IV**
Pooled estimates: mean/ incidence (95 % CI)	0.31 (0.21-0.44)	0.39 (0.21-0.60)	0.32 (0.17-0.52)	0.52 (0.41-0.63)	0.12 (0.08-0.16)	0.88 (0.83-0.91)	0.67 (0.53-0.79)	0.07 (0.03-0.14)	0.31 (0.26-0.36)	0.83 (0.73-0.90)	
Kodali 2021	25 (19)	NA	NA	73 (55)	16 (12)	119 (90)	26 (20), 50 (38)	NA	46 (35)	100 (76)	
Lu 2021	13 (28.3)	NA	8 (17.4)	28 (60.9)	5 (10.9)	41 (93.5)	3 (6.5) 28 (60.9)	NA	12 (26.1)	13 (28.3)	33 (71.7)
Fam 2021	8 (32)	17 (68)	7 (28)	15 (60)	6 (24)	21 (84)	5(20), 11(44)	2 (8)	9 (36)	19 (76)	3 (12)
Hahn 2020	11 (37)	21 (70)	8 (27)	19 (63)	2 (7)	27 (30)	10 (33), 12 (30)	5 (17)	9 (30)	16 (57)	8 (29)
Lu 2020	NA	NA	NA	7 (58.3)	NA	10 (83.3)	9 (75)	NA	5 (41.7)	7 (58.3)	5 (41.7)
Cao 2019	9 (25.7)	16 (45.7)	5 (14.3)	5 (14.3)	NA	30 (85.7)	24 (68.6)	1 (2.9)	10 (28.6)	35 (100)	
Hahn 2019	3 (60)	4 (80)	4 (80)	3 (60)	1 (20)	5 (100)	5 (100)	NA	1 (20)	4 (80)	0
Elgharably 2019	1 (20)	2 (40)	3 (60)	NA	NA	4 (80)	4 (80)	NA	1 (20)	NA	NA
Hahn 2018	19 (59)	13 (41)	20 (63)	19 (59)	3 (9)	27 (84)	10 (41), 21 (66)	NA	6 (19)	20 (63)	

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; NA, not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Table 2. Procedural and 30-Day Outcomes

First Author Year	Procedural Success	Operation Time (min)	Length of Stay (Aays)	Complications
Pooled estimates: mean/incidence (95% CI)	0.92 (0.87 to 0.96)	122.3 (82.1 to 162.5)	10.7 (4.5 to 16.9)	
Kodali 2021	128 (96.2%)	72.8 ± 28.15 (130)	3 (0.35)	Reintervention (n = 2, 1.6%), renal dysfunction (n = 1, 0.8%), major bleeding (n = 22, 17.7%), renal complications requiring unplanned dialysis or renal replacement therapy (n = 1, 0.8%), major access site and vascular complications (n = 2, 1.6%), major cardiac structural complications (n = 1, 0.8%), conduction disturbances requiring permanent pacemaker (n = 8, 10.5%).
Lu 2021	45 (97.8)	150.0 (118.8, 180)	12.0 (9.0, 20.0)	Central valve regurgitation (n = 2, 4.4%), paravalvular regurgitation (n = 5, 10.9%), perforation of right ventricle wall (n = 1, 2.2%), reoperation for bleeding (n = 4, 8.7%), renal failure requiring dialysis (n = 6,13.0%), gastrointestinal hemorrhage (n = 6,13.0%), device migration (n = 1, 2.5%), MI (n = 2, 4.4%).
Fam 2021	23 (92)	140 ± 79	NA	Central valve regurgitation (n = 10, 56%), paravalvular regurgitation (n = 13, 44%), reintervention (n = 1, 4%), major bleeding (n = 3.12%; 1 gastrointestinal bleed, 1 spontaneous thigh intramuscular hematoma, and 1 retroperitoneal bleed from the nonaccess site), renal failure requiring dialysis (n = 1, 4%), conduction disturbances requiring permanent pacemaker (n = 2, 8%).
Hahn 2020	26 (87)	102 ± 51	NA	Central valve regurgitation (n = 9, 32%), paravalvular regurgitation (n = 13, 54%), conversion OHS (n = 2, 7%; 1 of whom had an RV perforation and the second with the valve implanted into the ventricle), MI (n = 1, 3%), device malpositioning (n = 4, 13%), bleeding/access-site complications (n = 4, 13%), conduction abnormality (n = 2, 10%).
Cao 2019	35 (100)	150.2 ± 48.1	NA	Reintervention for bleeding (n = 1, 2.9%), MI (n = 1, 2.9%), gastrointestinal bleeding (n = 1, 2.9%), hydrothorax need drainage (n = 5, 14.3%), IABP implantation (n = 1, 2.9%)
Hahn 2019	5 (100)	NA	19.4 ± 15.9	Central valve regurgitation (n = 2, 40%), paravalvular regurgitation (n = 2, 40%), conversion OHS (n = 1, 20%), temporary pacer for bradycardia (n = 1, 20%), major bleeding (n = 3, 60%), continuous veno-venous hemofiltration (n = 1, 20%).
Lu 2020	12 (100)	NA	16.5 (5, 94)	Central valve regurgitation (n = 1, 8.3%), reintervention for bleeding (n = 1, 8.3%), post-operative acute kidney injury (n = 2, 16.7%), temporary dialysis (n = 1, 8.3%), MI (n = 1, 8.3%)
Elgharably 2019	4 (100)	NA	14.5 ± 10.3	Central valve regurgitation (n = 2, 50%), paravalvular regurgitation (n = 2, 50%)
Hahn 2018	32 (100)	NA	NA	Conversion OHS (n = 5, 15.6%).

IABP, intra-aortic balloon pump; MI, myocardial infarction; NA, not available; OHS, open heart surgery; RV, right ventricle

with the increased RV afterload due to left heart disease and subsequent postcapillary pulmonary hypertension. Although the primary approach is conventional pharmacological therapy, an interventional strategy to treat severe TR has gained expanded clinical consideration because it has been shown to reduce mortality and hospitalization rates.

From a surgical perspective, whether to repair or replace the TV is based on disease severity, amount of salvageable leaflet tissue, concomitant procedures on other heart valves, and patient's comorbidities. Previous studies revealed a high perioperative mortality rate associated with TV replacement in the range of 20%.[24,25] Tricuspid valve repair is generally performed in patients with tricuspid annular dilatation during concomitant left-sided heart surgery. In contrast, isolated TV repair is not preferred because it continues to have the highest surgical risk and increases in-hospital mortality (up to 10%).[26] Although surgically TV repair is associated with a better perioperative survival rate, it has relatively high recurrent and residual TR, leading to biventricular heart failure, death, or reintervention. The latter is related to high mortality rates in the range of 40%.[25,27,28]

Our pooled analysis demonstrated the feasibility and highly successful implantation rates of TTVR with a low mortality rate at follow-up independent from the advanced clinical status. Besides, there was a significant improvement of functional status alongside a noticeable reduction in TR severity

Table 3. Functional and Echocardiographic Parameters at Baseline and After Transcatheter Tricuspid Valve Replacement

	Baseline			Follow-Up				
		Pooled Mean or Incidence (95% CI)	Number of Studies Included		Mean Difference or Relative Risk (95% CI)	*P*	I^2 (%)	*P* for Heterogeneity
Functional status								
NYHA functional class III or IV	Incidence	83% (73% to 90%)	7	Relative risk	0.20 (0.11 to 0.35)	<.001	63	.01
6MWD (m)	Mean	217.9 (190.1 to 245.8)	3	Mean difference	91.1 (37.3 to 144.9)	<.001	50	0.14
Echocardiographic data								
TR severe or greater	Incidence	95% (89% to 98%)	9	Relative risk	0.19 (0.10 to 0.36)	<.001	66	.005
TAPSE (mm)	Mean	13.8 (0.7 to 0.59)	4	Mean difference	−1.42 (−3.08 to −0.24)	.09	54	.09
RV basal diameter	Mean	5.2 (4.9 to 5.5)	3	Mean difference	−0.51 (−0.83 to −0.20)	.002	14	.31
RV FAC (%)	Mean	37% (36% to 38%)	3	Mean difference	−3.18 (−9.75 to −3.38)	.34	75	.02
LVEF (%)	Mean	57% (55% to 59%)	3	Mean difference	0.02 (−3.23 to −3.28)	.99	0	.81

6MWD, 6-minutes walking distance; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricle; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

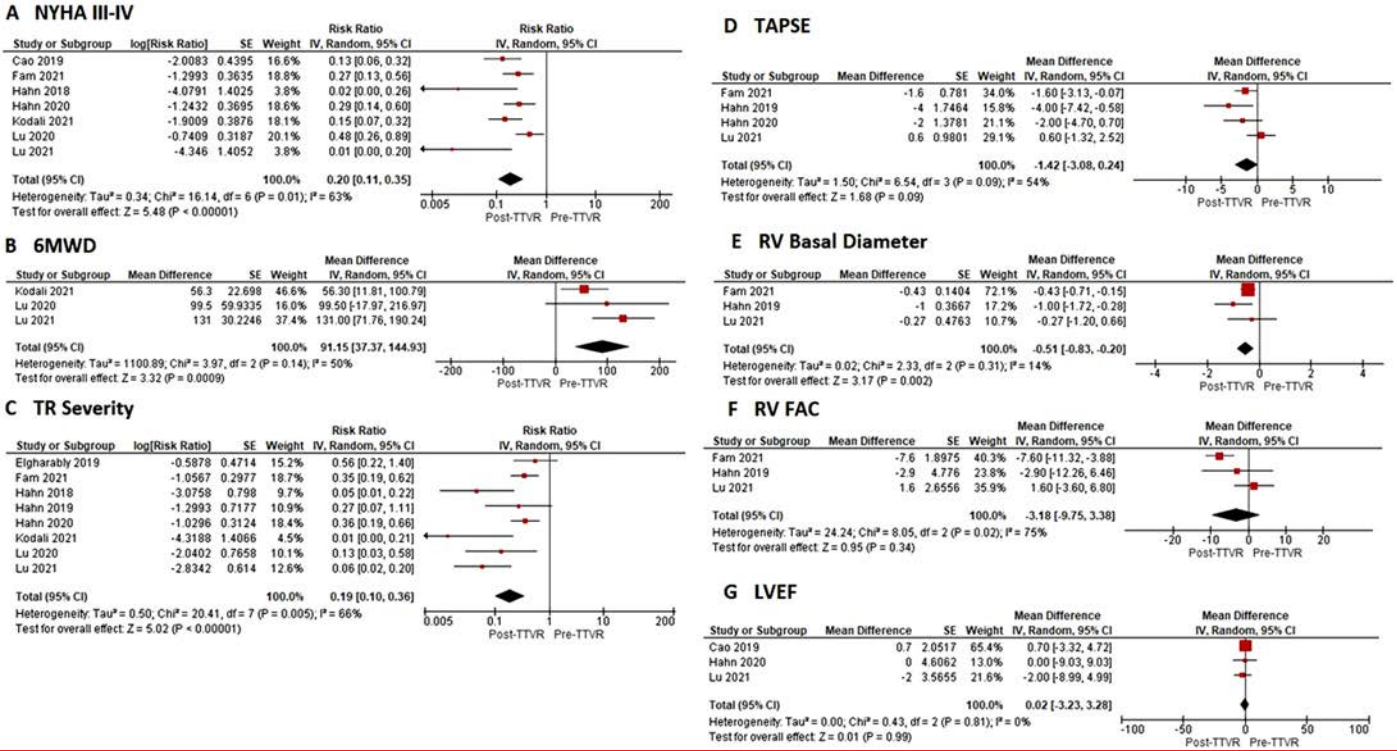
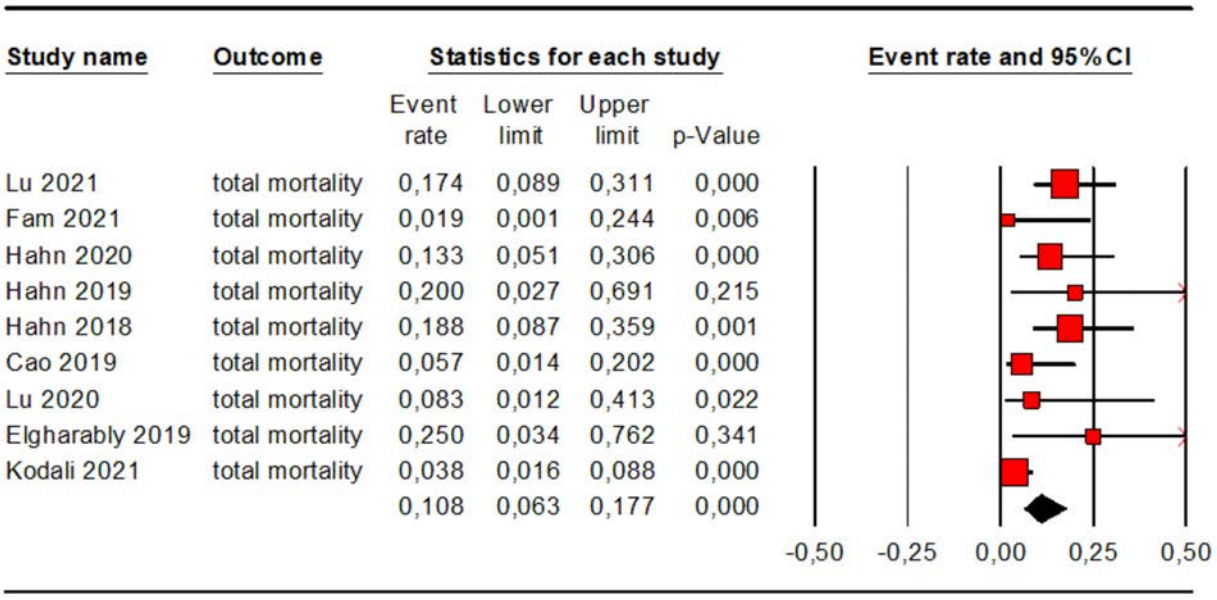


Figure 2. Forest plots describe the mean difference and risk ratio of the primary outcomes of the study before and after TTVR: NYHA III-IV (A), 6MWD (B), TR severity (C), TAPSE (mm) (D), RV basal diameter (mm) (E), RV FAC (%) (F), LVEF (%) (G). 6MWD, 6-minutes walking distance; IV, inverse variance; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricle; RV FAC, right ventricular fractional area change; SE, standard error; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement.



Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	9	0,112	0,079	0,158	-10,250	0,000	14,064	8	0,080	43,118	0,300	0,367	0,135	0,548
Random	9	0,108	0,063	0,177	-7,159	0,000								

Figure 3. Forest plots describe pooled incidence rate of mortality.

following TTVR. Tricuspid valve replacement may terminate the problem of residual regurgitation; however, it can result in an acute increase of the RV afterload.[29] Although a significant reduction in RV end-diastolic basal diameter was a favorable anatomical change as shown in this analysis, it might not be accompanied by concomitant improvements in echocardiographic parameters of RV systolic function such as TAPSE and RV FAC. It is assumed that early and abrupt elimination of the TR may be associated with a significant increase of the RV afterload leading to RV dysfunction.[30] Moreover, the studies included in this analysis have varieties of pulmonary arterial pressure (PAP) definitions for the inclusion and exclusion criteria. In the studies with LuX-Valve and EVOQUE,[16,19] patients with severe pulmonary arterial hypertension, PAP >60 mm Hg, were excluded, while PAP ≤ 90 mm Hg was defined as inclusion criteria by echocardiography and right heart catheterization in a study with NaviGate system.[20] Furthermore, there were no such definitions in the other studies mentioned in this analysis.[17,18,21] However, RV dysfunction and pulmonary hypertension reflect a more advanced stage of the disease and may determine a high rate of periprocedural and long-term complications, including RV dysfunction and death.[31,32] This may arise potential concerns about treatment effectiveness in such cases.

Even if the clinical outcome was influenced by the beginning of the training process with novel TTVR, in-hospital and 30-day all-cause mortality was 7% and 10% at follow-up (weighted mean 122 days) in the present analysis. Since isolated TV surgical repair has an 8.8% in-hospital mortality and surgical replacement carries nearly twice the repair risk, TTVR provided lower mortality rates than surgical repair and replacement.[33] Transcatheter TV repair devices have been studied more than replacement devices; however, Bocchino et al[34] showed mortality rates are about 11% at the last available follow-up after isolated TV replacement; their meta-analysis included 14 trials. Although the risk of death was substantial, it should be remembered that these patients were already receiving optimal medical therapy and were not deemed candidates for surgery, primarily because of high surgical risk with a mean EuroSCORE II score of 8.2%.

This pooled analysis included a range of devices that treat severe TR using different types of orthotropic valves: the NaviGate, LuX-Valve, and EVOQUE. Although clinical and anatomic characteristics influence the most suitable device to treat TR in each patient, high procedural success, clinical and functional improvement, low complication, and mortality rates were observed across all device subgroups in our analysis. Nevertheless, the long-term durability of these transcatheter devices remains unknown. Since tricuspid devices will be exposed to lower pressures within the right heart, it is expected to have a longer lifetime than the devices on the left. However, the durability of tricuspid devices remains unclear, especially when TTVR expands to younger and lower-risk patients with organic or functional TR until more information is gathered.[35]

Table 4. Predicted Operative Mortality, Observed in Hospital/30-Day Mortality, >30-Day Mortality and Overall Rate

First Author Year	Predicted Operative Mortality	In Hospital/30-day Mortality			>30-Day Mortality			Overall Rate (%)
Pooled estimates: mean/incidence (95% CI)	8.2 (6.1 to 10.3)	0.07 (0.04-0.12)			0.04 (0.02-0.07)			0.10 (0.06-0.17)
	EuroSCORE	Number	Rate (%)	Causes	Number	Rate (%)	Causes	Number, %
Kodali 2021	5.3 ± 4.3%	4	3.03%		1	0.78		5, 3.78%
Lu 2021	10.0% (8.2, 12.7)	6	13%		2		One patient died of subarachnoid hemorrhage, pneumonia-caused respiratory failure, gastrointestinal bleeding, and hepatic encephalopathy. Another patient had severe liver disease before operation and died of hepatic failure.	8, 17.4%
Fam 2021	7.7 ± 2.2%	0	0		0	0		0
Hahn 2020	11.1% (7.16-14.11)	3	10%	Patient with uncontrolled bleeding due to an acquired coagulopathy, 1 with progressive multi-organ failure (with baseline cirrhosis and chronic kidney disease), and the third after surgical conversion performed following malpositioning of the valve	1	0		4, 13%
Cao 2019	7.4 ± 4.8%	0	0		2	5.7%		2, 5.7%
Hahn 2019	NA	1	20 %	This patient experienced prolonged mechanical ventilation, re-intubation, and renal failure that required continuous veno-venous hemofiltration	0			1, 20%
Lu 2020	NA	1	8.3 %	Vasospastic myocardial infarction	0	0	NA	1, 8.3%
Elgharably 2019	NA	0	0		1	25%	Ischemic colitis and sepsis	1, 25%
Hahn 2018	NA	3	9.3 %	Procedure-related	3	10.3%		6, 18.7%

NA: not available.

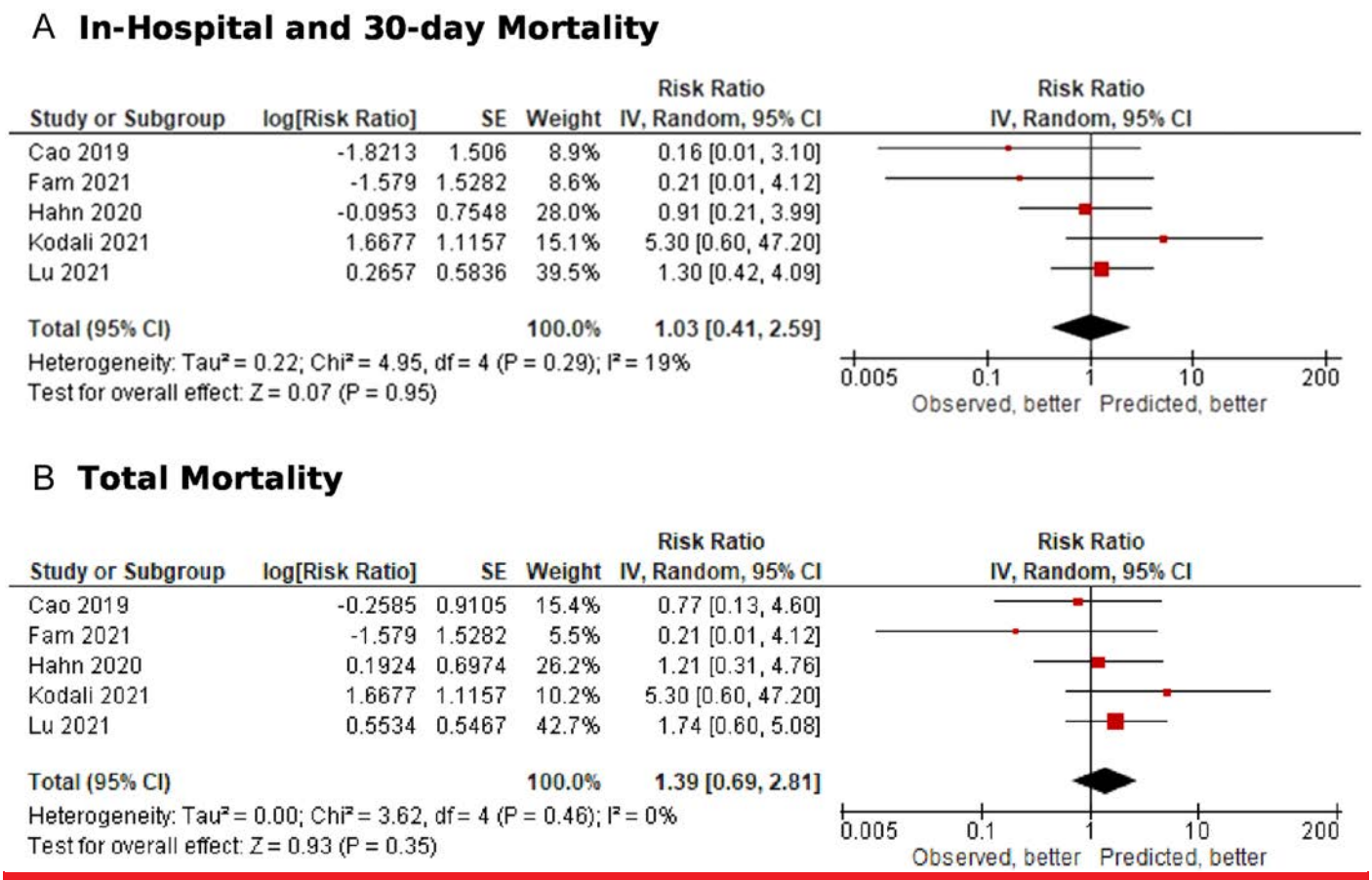


Figure 4. Forest plots describe observed and predicted in-hospital/30-day and total mortality based on European System for Cardiac Operative Risk Evaluation (EuroSCORE). IV, inverse variance; SE, standard error.

Concerns regarding access selection, residual paravalvular and central regurgitation, interaction with conduction system, pacing devices, and antithrombotic treatment remain a vital drawback of TTVR. Since saddle-shaped and enlarged TV annulus after dilating the right heart, prosthetic TV valves are designed with a large profile requiring large-caliber sheaths (up to 45 Fr). Trans-jugular access provides an excellent angle to approach TV, while the steep angle between the inferior vena cava and TV may be challenging for the femoral vein access. Furthermore, the surgical transatrial approach via anterior right thoracotomy allows to reach TV directly but more invasively. Hence, there is no evident answer on which access routes and devices are the best. However, our analysis revealed that the LuX-Valve showed higher technical success with lower atrioventricular block and paravalvular leakage, which create crucial differences comparing NaviGate and EVOQUE valve systems. This may be attributed to its self-expanding tissue valve design, which does not rely on radial forces but instead utilizes a septal anchoring mechanism and its adaptive skirt to prevent the paravalvular leak.

Study Limitations

This present analysis included only single-arm interventional studies case series, and no randomized controlled trials were available for inclusion at the time of the study. It should be noted that the studies have more potential for bias regarding excellent treatment effects and significant heterogeneity when they are not randomized or controlled.[13] As a result of this fact, this analysis comprehended specific devices with different mechanisms of TV replacement alongside favorable outcomes inducing a potential selection bias regarding patient and anatomic features.

Moderate heterogeneity was found concerning the included studies' results. Because there were changing degrees of reductions in NYHA functional class and baseline TR severity expanded from moderate to torrential even though leave-one-out analysis affirmed the consistency of the results.

As there are currently no specific guideline recommendations for patient selection for TTVR, the studies included in this meta-analysis are also limited by the lack of uniformity in the definition of procedural success. However, as seen with the transcatheter aortic valve replacement, outcomes will be reported according to the valve academic research consortium, which clarified specific definitions and expanded the understanding of patient risk stratification and case selection.[36] Furthermore, outcomes will improve as each generation of the device can address imperfections in its forerunner and as operators complete their learning curve performing the procedure.

CONCLUSION

Transcatheter TV repair techniques had been on the agenda for some time and presented as a valuable alternative to surgery to correct at least moderate TR. Our pooled analysis has demonstrated, for the first time in the literature, that orthotropic TTVR devices have benefited in numerous ways over surgical replacement and TV repair. The most characteristic feature distinguishes these TTVR devices from repair methods, primarily because they are independent of leaflet morphology and etiology and have a lower mortality risk. Hence, TTVR is an arising treatment for patients with severe TR who are not eligible for transcatheter repair or surgical replacement because of high surgical risk and poor prognosis. Nevertheless, the findings reported from well-conducted randomized controlled trials with "real-world evidence" addressing optimal device and patient selection are warranted.

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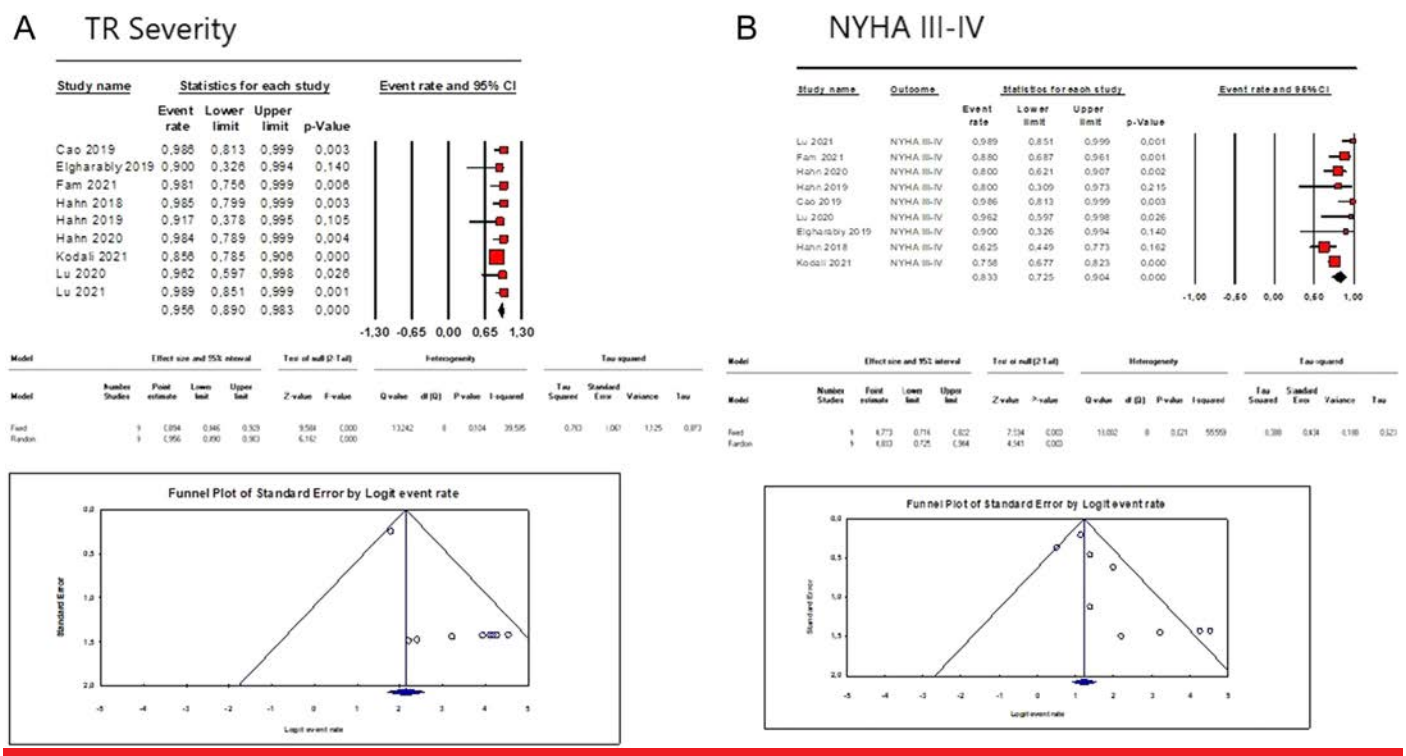
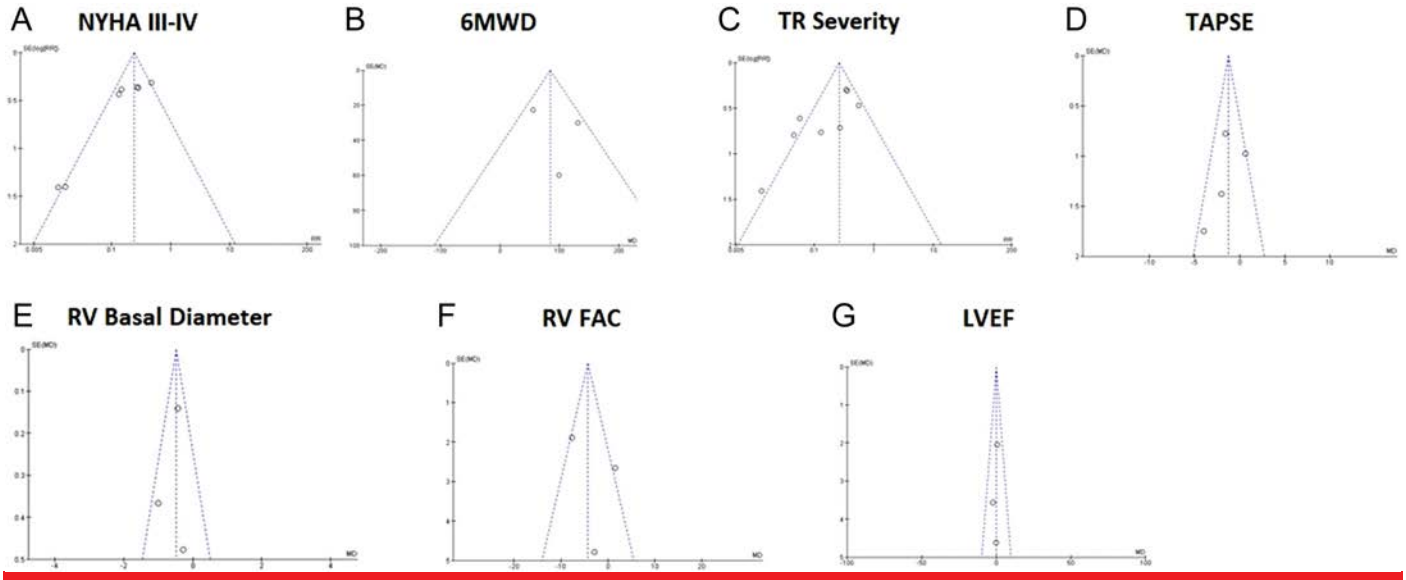
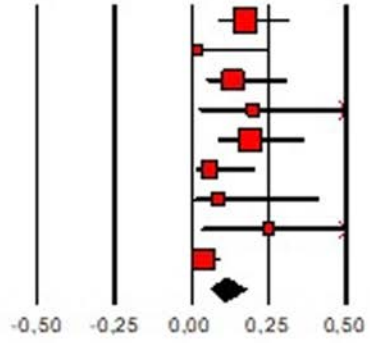


Supplementary Figure 1. Forest and Funnel plots describe pooled incidence rate of TR severity and NYHA III-IV: TR severity (A), NYHA III-IV (B). NYHA: New York Heart Association; TR, tricuspid regurgitation.



Supplementary Figure 2. Funnel plot and Egger's test explore assessing the publication bias of the outcomes of interest: NYHA III-IV (A), 6MWD (B), TR severe or greater (C), TAPSE (mm) (D), RV basal diameter (mm) (E), RV FAC (%) (F), LVEF (%) (G). 6MWD, 6-minutes walking distance; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricle; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Study name	Outcome	Statistics for each study				Event rate and 95% CI
		Event rate	Lower limit	Upper limit	p-Value	
Lu 2021	total mortality	0,174	0,089	0,311	0,000	
Fam 2021	total mortality	0,019	0,001	0,244	0,006	
Hahn 2020	total mortality	0,133	0,051	0,306	0,000	
Hahn 2019	total mortality	0,200	0,027	0,691	0,215	
Hahn 2018	total mortality	0,188	0,087	0,359	0,001	
Cao 2019	total mortality	0,057	0,014	0,202	0,000	
Lu 2020	total mortality	0,083	0,012	0,413	0,022	
Elghamrawy 2019	total mortality	0,250	0,034	0,762	0,341	
Kodali 2021	total mortality	0,038	0,016	0,088	0,000	
		0,108	0,063	0,177	0,000	



Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
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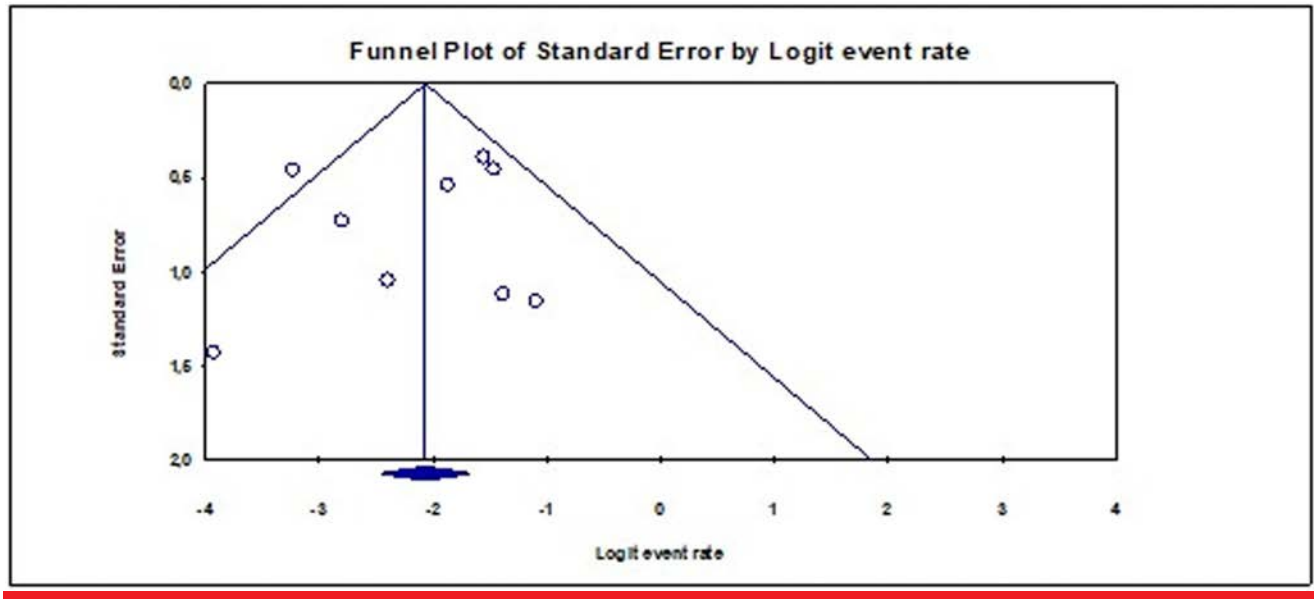
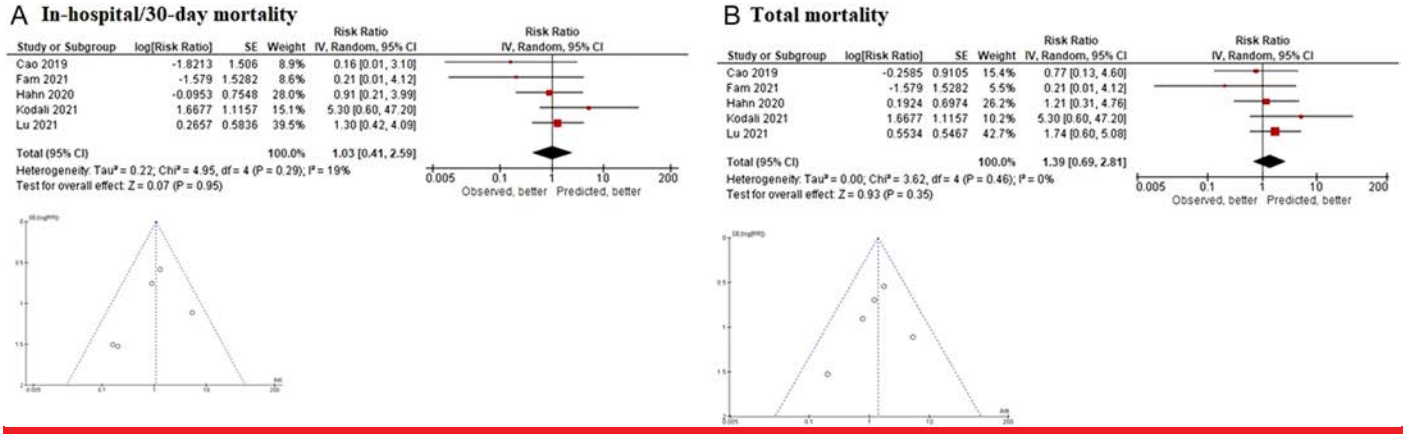
Random	9	0,108	0,063	0,177	-7,159	0,000								



Supplementary Figure 3. Forest and Funnel plots describe pooled incidence rate of mortality.



Supplementary Figure 4. Forest and Funnel plots describe observed and predicted in-hospital/30-day and total mortality based on EuroSCORE: in-hospital/30-day mortality (A), total mortality (B). IV, inverse variance; SE, standard error.