SYSTEMATIC REVIEW AND META-ANALYSIS

Tricuspid Valve Intervention at the Time of Pulmonary Valve Replacement in Adults With Congenital Heart Disease: A Systematic Review and Meta-Analysis

Jef Van den Eynde , BSc; Connor P. Callahan, MD; Mauro Lo Rito , MD; Nabil Hussein , MBChB (Hons); Horacio Carvajal , MD; Alvise Guariento , MD; Arjang Ruhparwar, MD, PhD; Alexander Weymann, MD, PhD; Werner Budts , MD, PhD; Marc Gewillig , MD, PhD; Michel Pompeu Sá , MD, PhD; Shelby Kutty , MD, PhD

BACKGROUND: Tricuspid regurgitation (TR) is a common finding in adults with congenital heart disease referred for pulmonary valve replacement (PVR). However, indications for combined valve surgery remain controversial. This study aimed to evaluate early results of concomitant tricuspid valve intervention (TVI) at the time of PVR.

METHODS AND RESULTS: Observational studies comparing TVI+PVR and isolated PVR were identified by a systematic search of published research. Random-effects meta-analysis was performed, comparing outcomes between the 2 groups. Six studies involving 749 patients (TVI+PVR, 278 patients; PVR, 471 patients) met the eligibility criteria. In the pooled analysis, both TVI+PVR and PVR reduced TR grade, pulmonary regurgitation grade, right ventricular end-diastolic volume, and right ventricular end-systolic volumes. TVI+PVR, but not PVR, was associated with a decrease in tricuspid valve annulus size (mean difference, -6.43 mm, 95% CI, -10.59 to -2.27; P=0.010). Furthermore, TVI+PVR was associated with a larger reduction in TR grade compared with PVR (mean difference, -0.40; 95% CI, -0.75 to -0.05; P=0.031). No evidence could be established for an effect of either treatment on right ventricular ejection fraction or echocardiographic assessment of right ventricular dilatation and dysfunction. There was no evidence for a difference in hospital mortality or reoperation for TR.

CONCLUSIONS: While both strategies are effective in reducing TR and right ventricular volumes, routine TVI+PVR can reduce TR grade to a larger extent than isolated PVR. Further studies are needed to identify the subgroups of patients who might benefit most from combined valve surgery.

Key Words: congenital heart disease
meta-analysis
pulmonary valve insufficiency
pulmonary valve replacement
tricuspid valve

ricuspid regurgitation (TR) is a common finding in adults with congenital heart disease (ACHD) referred for pulmonary valve replacement (PVR), including those with tetralogy of Fallot (TOF), pulmonary stenosis, and pulmonary atresia.¹ Notably, as many as three-quarters of these patients have at least mild TR, and one-third present with at least moderate TR. Despite clearly demonstrated benefits of PVR on right ventricular (RV) volumes and function and the observation that isolated PVR also reduces TR, indications for combined valve surgery remain controversial.^{2,3} Current guidelines do not suggest when concomitant tricuspid valve intervention (TVI) should be recommended.^{4,5} Nonetheless, severe TR is strongly associated with an increased risk of adverse outcomes in ACHD.⁶ Therefore, we aimed to evaluate early results of concomitant TVI at the time of PVR.

Correspondence to: Jef Van den Eynde, BSc, Department of Cardiovascular Diseases, University Hospitals Leuven, KU Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: jef.vandeneynde@student.kuleuven.be

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022909

For Sources of Funding and Disclosures, see page 12.

^{© 2021} The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

 In this systematic review and meta-analysis of 749 adults with congenital heart disease, we demonstrated that concomitant tricuspid valve intervention (TVI) at the time of pulmonary valve replacement (PVR) helped reduce tricuspid regurgitation (TR) grade to a larger extent than isolated PVR, while both strategies were otherwise equally effective.

What Are the Clinical Implications?

- Patients with severe preoperative TR would probably derive the greatest benefit from concomitant TVI in terms of improvement in NYHA class and TR grade; however, concomitant TVI does not seem to be effective in reducing the risk of adverse events such as death, arrhythmias, and heart failure.
- Current data therefore do not support the universal application of this approach for severe TR.
- Further well-designed studies focusing on specific underlying mechanisms of TR and evaluating the effect on adverse events on long-term follow-up may elucidate which patients stand to benefit the most from this approach.

Nonstandard Abbreviations and Acronyms

ACHD	adults with congenital heart disease
MD	mean difference
NYHA	New York Heart Association
PR	pulmonary regurgitation
PVR	pulmonary valve replacement
RVEDV	right ventricular end-diastolic volume
RVESV	right ventricular end-systolic volume
TOF	tetralogy of Fallot
TR	tricuspid regurgitation
Т٧	tricuspid valve
τνι	tricuspid valve intervention

METHODS

Eligibility Criteria, Databases, and Search Strategy

The data that support the findings of this study are available from the corresponding author upon reasonable request. We followed 2 internationally recognized protocols: Preferred Reporting Items for Systematic Reviews Meta-analyses⁷ and Meta-analysis of

Observational Studies in Epidemiology.⁸ Using the Population, Interventions, Comparison, Outcome, and Study Design strategy, studies were included if the following criteria were fulfilled:

- 1. The population comprised ACHD (including TOF, pulmonary stenosis, and pulmonary atresia) who developed at least moderate pulmonary valve insufficiency;
- 2. The intervention group included patients who underwent combined TVI and PVR;
- 3. The control group included patients who underwent isolated PVR;
- 4. Outcomes of the studies included any of the following: tricuspid regurgitation (TR) grade, pulmonary regurgitation (PR) grade, tricuspid valve (TV) annulus size, RV dilatation, RV dysfunction, RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV ejection fraction (RVEF), RV end-diastolic area, RV endsystolic area, New York Heart Association (NYHA) class, reoperation for TR, or 30-day mortality; and
- 5. Studies were prospective or retrospective observational studies or randomized controlled trials.

Databases were searched for articles meeting our inclusion criteria and published by December 29, 2020: PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles. The detailed search terms that were used for this search are given in Data S1. The following steps were taken: (1) identification of titles of records through database searching, (2) removal of duplicates, (3) screening and selection of abstracts, (4) assessment for eligibility through full-text articles, and (5) final inclusion in study. Studies were selected by 2 independent reviewers (C.C. and M.L.R.). When concordance was absent, a third reviewer (J.V.D.E.) made the decision to include or exclude the study.

End Points, Risk of Bias, and Statistical Analysis

The primary end point of the study was TR grade. The secondary end points were PR grade, TV annulus size (mm), RV dilatation, RV dysfunction, RVEDV (mL), RVESV (mL), RVEF (%), RV end-diastolic area (cm²), RV end-systolic area (cm²), NYHA class, reoperation for TR, or 30-day mortality. The grades of TR, PR, RV dilatation, and RV dysfunction were quantitatively assessed on echocardiography and scored on a scale from 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe). Postoperative measurements were defined as the first observation within 12 months after surgery. For studies reporting interquartile ranges, the mean was estimated according to a validated formula.⁹ Two independent reviewers (N.H. and A.G.) extracted the data. When concordance was absent, a third reviewer (J.V.D.E.)

checked the data and made the final decision. From each study, we extracted patient characteristics, study design, and outcomes.

The Risk of Bias in Nonrandomized Studies of Interventions tool was systematically used to assess the included studies for risk of bias.¹⁰ The articles and their characteristics were classified into A (low risk of bias), B (moderate risk of bias), C (serious risk of bias), D (critical risk of bias), or E (no information/unclear). Using the RoB 2 tool,¹¹ the included randomized controlled trials were assessed for biases. Two independent reviewers (C.C. and M.L.R.) assessed the risk of bias. When concordance was absent, a third reviewer (J.V.D.E.) checked the data and made the final decision.

Mean differences (MD) with 95% CI and P values were calculated for continuous variables. For binary variables, odds ratios (ORs) with 95% CI and P values were considered. Forest plots were created to represent the clinical outcomes. The chi-square test and l² test were performed for assessment of statistical heterogeneity.¹² The MD and OR were combined across the studies using a random-effects method (DerSimonian and Laird inverse variance).¹³ The choice for random-effects models was made on the basis of the assumption that the effect sizes in the individual studies represented samples from a mixing distribution. In addition, the results were reanalyzed using fixed-effects models to explore whether this yielded differences regarding the summary inferences. The risk of publication bias could not be assessed because none of the comparisons included >10 studies.^{14,15} All analyses were completed with R Statistical Software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria).

Institutional Review Board Approval

Institutional review board is not applicable for systematic reviews and meta-analyses.

RESULTS

Study Selection and Characteristics

A total of 2031 citations were identified, of which 46 studies were potentially relevant and retrieved as full text. Six publications^{16–21} fulfilled our eligibility criteria (Figure 1). Characteristics of each study and their patients are shown in Tables 1 through 3. A total of 749 patients (TVI+PVR, 278 patients; PVR, 471 patients) were included from studies published from 2015 to 2020. All studies were nonrandomized observational studies. Of all patients, 60.8% were male (450/740), and 65.8% (487/740) had a transannular patch. TOF constituted 84.6% (656/775), while 15.2% (118/775) of patients had pulmonary stenosis. The pooled age at initial repair was 4.96 years (4 studies, 688 patients),

and the pooled age at PVR was 34.3 years (6 studies, 775 patients). Outcomes were reported for a mean follow-up of 10.2 months (5 studies, 721 patients). The overall internal validity was considered low risk of bias (Figure S1).

Synthesis of Results Echocardiographic Parameters

Results from the meta-analyses of echocardiographic and magnetic resonance imaging (MRI) parameters are presented in Table 4; forest plots are given in Figures S2 through S9. Preoperative values were comparable between TVI+PVR and PVR for all parameters considered, although patients in the TVI+PVR tended to have a higher TR grade (MD, 0.64; 95% CI, -0.18 to 1.45; P=0.090; l²=85%). A decrease from preoperative to postoperative TR grade was evident in both TVI+PVR (MD, -1.53; 95% CI, -2.28 to -0.79; P=0.002; l²=94%) and PVR (MD, -0.99; 95% CI, -1.81 to -0.16; P=0.026; I²=91%). However, there was evidence for a larger decrease in TR grade in the TVI+PVR group compared with the PVR group (MD, -0.40; 95% Cl, -0.75 to -0.05, P=0.031; l²=75%). As a result, postoperative TR grade was comparable between both groups (MD, 0.08; 95% Cl, -0.14 to 0.29; P=0.342; /2=0%). A clinically relevant reduction in PR grade was also evident in both TVI+PVR (MD, -2.53; 95% CI, -3.98 to -1.07; P=0.029; l²=36%) and PVR (MD, -2.52; 95% Cl, -3.03 to -2.02, P=0.010; $I^2=0\%$), although no evidence was found to state that TVI+PVR was associated with a larger decrease in PR (MD, 0.03; 95% CI, -0.86 to 0.92; P=0.711; l²=75%).

With regard to TV annulus size, a clear decrease from preoperative to postoperative was observed in TVI+PVR (MD, -6.43 mm; 95% CI, -10.59 to -2.27; P=0.032), whereas it was not evident whether a similar effect was present in the PVR group (MD, -4.20; 95% CI, -10.42 to 2.02; P=0.074; I²=0%) (Table 4). Although no evidence was found for an effect of either TVI+PVR or PVR on qualitative score for RV dilatation, TVI+PVR tended to be associated with a greater increase in gualitative score for RV dilatation compared with PVR (MD, 0.14; 95% CI, 0.08 to 0.19; P=0.020; I²=0%); however, this result should be interpreted cautiously given that Lueck et al¹⁸ reported a tendency toward an increase in RV dilatation, whereas Kogon et al²¹ reported a decrease in RV dilatation with both procedures. No evidence of effects of either treatment or differences between the effects could be observed with regard to RV dysfunction as qualitatively assessed by echocardiography (Table 4).

RV end-diastolic area and RV end-systolic area were reported by only one study. Cramer et al²⁰ reported a decrease from preoperative to postoperative RV end-diastolic area in both TVI+PVR (39.6±12.0 cm²

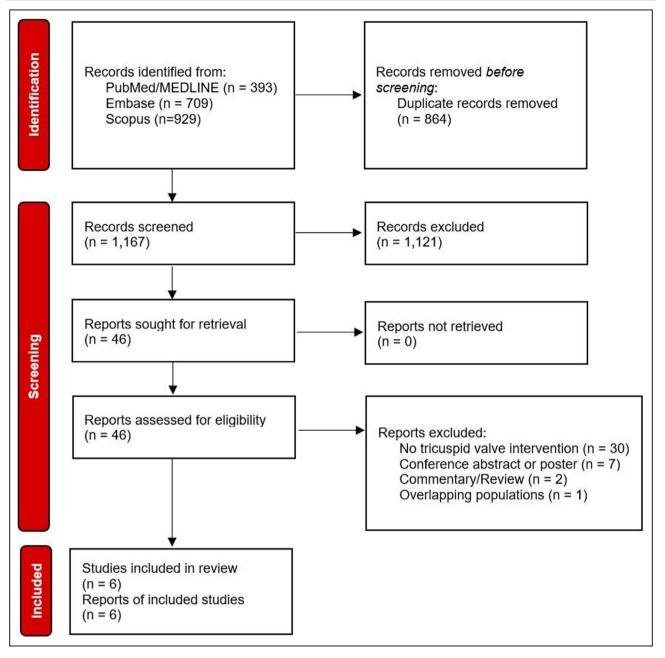


Figure 1. Flow diagram of studies included in data search.

to 28.6 ± 5.7 cm²; *P*=0.001) and PVR (36.2 ± 12.0 cm² to 28.7 ± 8.8 cm²; *P*=0.040). In contrast, they found no evidence of an effect of RV end-systolic area with either TVI+PVR (28.4 ± 8.5 cm² to 23.1 ± 13.1 cm², *P*=0.16) or PVR (25.1 ± 8.6 cm² to 20.1 ± 7.2 cm², *P*=0.07).

MRI Parameters

A clinically relevant decrease from preoperative to postoperative RVEDV was observed in both TVI+PVR (MD, -84.5 mL; 95% CI, -107 to -61.6; P=0.004) and PVR (MD, -76.7 mL; 95% CI, -114 to -39.1; P=0.013).

Similarly, a clinically relevant decrease was observed for RVESV in both TVI+PVR (MD, -28.5 mL; 95% CI, -37.7 to -19.3; P=0.006) and PVR (MD, -25.8 mL; 95% CI, -39.2 to -12.5; P=0.014). However, no evidence could be found for any differences between both treatments with regard to the decreases in RVEDV (MD, -0.74; 95% CI, -24.90 to 23.43; P=0.908; I^2 =62%) and RVESV (MD, -0.37; 95% CI, -11.84 to 11.09; P=0.901; I^2 =12%). No evidence of effects of either treatment nor differences between the effects could be observed with regard to RVEF (Table 4).

NYHA Class

randomized; TR, tricuspid regurgitation;

pulmonary valve replacement; R,

nonrandomized; P, prospective; PVR,

nonmulticenter; NP, nonprospective; NR,

FU indicates follow-up; M, multicenter; ND, not determined; NM,

and TVI, tricuspid valve intervention

7.0±2.8

35 (16 TVI+PVR, 19 PVR) 36 (18 TVI+PVR, 18 PVR)

ΣZ Σ

NP, NR,

NP, NR, I

USA

2002-2008

USA

1999-2012

2015 2015

Cramer²⁰

Kogon²¹

6 mo

TR grade: 2.63±0.43 in TVI+PVR, 2.08±0.26 in PVR

grade: 2.7±0.5 in TVI+PVR, 2.2±0.4 in PVR

Ë

Moderate TR in 24 (8 TVI+PVR, 16 PVR), severe TR in 17 (8 TVI+PVR, 9 PVR)

54.6±36.6 mo

TR grade: 2.79±0.95 in TVI+PVR, 1.45±0.56 in PVR

om

5.5±2.7

67 (38 TVI+PVR, 29 PVR) 28 (10 TVI+PVR, 18 PVR) 41 (16 TVI+PVR, 25 PVR)

ZZ ΣZ ΣZ

NP, NR, ЪЪ, NP, NR,

South Korea

2000-2016

2019 2018

Taejung Kim¹⁷

ď,

Germany

2009-2017 2002-2014

France

2017

Roubertie¹⁹

Lueck¹⁸

Q

TR grade: 2.0±0.77 in TVI+PVR, 1.94±0.62 in PVR

Mild TR in 254 (19 TVI+PVR, 235 PVR), moderate TR

TR grade

=U time

3 mo

362 PVR)

542 (180 TVI+PVR,

ΣZ

NP, NR,

Patient no.

Design

Country Canada

Study period

Year

First author

Study Characteristics

Table 1.

2000-2016

2020

Deshaies¹⁶

in 192 (90 TVI+PVR, 102 PVR), severe TR in 72 (68

TVI+PVR, 4 PVR)

NYHA class was only reported by a single study. Roubertie et al¹⁹ demonstrated that postoperative NYHA class was better in TVI+PVR compared with PVR in patients who had preoperative severe TR (postoperative NYHA class I in 8/8 [100%] with TVI+PVR versus 2/9 [22.2%] with PVR, respectively; P=0.004), whereas they could find no evidence for a benefit of concomitant TVI in patients with preoperative moderate TR (7/8 [87.5%] versus 16/16 [100%], respectively; P=0.333).

Short-Term Outcomes

The overall OR for 30-day mortality showed no evidence of a difference between TVI+PVR and PVR (OR, 1.86; 95% CI, 0.24 to 14.61; P=0.324) (Figure S10). Reoperation for TR was only reported by Roubertie et al¹⁹ and they could establish no evidence for a different between both groups. In this study, 2 of 9 (22%) of patients with severe TR who had undergone isolated PVR required reoperations, compared with 0 of 8 (0%) in the TVI+PVR arm (P=0.47).

Sensitivity Analysis

The treatment effect estimates from fixed-effects models were largely comparable to those from randomeffects models (Figures S2-S10). In contrast to the random-effects models, the fixed-effects models suggested some evidence for a greater decrease in TV annulus size (MD, -2.47; 95% Cl, -2.91 to -2.03; P<0.001), a greater increase in RV dysfunction as qualitatively assessed by echocardiography (MD, 0.29; 95% CI, 0.12 to 0.46; P<0.001), and a smaller increase in RVEF (MD, -6.41; 95% CI, -7.80 to -5.02; P<0.001) with TVI+PVR compared with PVR; however, all of these results should be interpreted with caution given the important statistical heterogeneity in these analyses (/2 of 93%, 25%, and 99%, respectively). Furthermore, the greater increase in qualitative score for RV dilatation with TVI+PVR compared with PVR was no longer evident in fixed-effects analyses (OR, 0.14; 95% CI, -0.01 to 0.29; P=0.077); no evidence for heterogeneity was evident in this analysis ($I^2=0\%$).

DISCUSSION

Summary of Evidence

This meta-analysis investigated the effect of concomitant TVI at the time of PVR in ACHD. The key findings are summarized in Figure 2. Our results demonstrated that both TVI+PVR and PVR reduced TR grade, PR grade, RVEDV, and RVESV. TVI+PVR, but not PVR alone, was associated with a decrease in TV annulus

Procedure Characteristics

Table 2.

Van den Eynde et al

	Tricuspic	l valve an	Tricuspid valve annuloplasty type		Pulmonary valve replacement type	placement type		
Author	Suture	Ring	Commissuroplasty	Other/combination	Bioprosthetic valve	Bioprosthetic valved conduit	Mechanical valve	Concomitant procedures other than TVI
Deshaies 2020 ¹⁶	34	33	8	15 replacements (1 mechanical valve, 14 bioprostheses)	QN	QN	Q	328 (branch pulmonary arterioplasty in 109, residual VSD closure in 38, atrial ablation in 68, ventricular ablation in 70, CABG in 18, mitral valve procedure in 8, aortic valve procedure in 7, thoracic aorta±aortic valve in 5, other in 5)
Taejung Kim 2019 ¹⁷	26	1	26	4 leaflet extension, 1 cleft repair, 2 valve replacement	QN	QN	Q	Q
Lueck 2018 ¹⁸	0	10	0	0	28	0	0	ND
Roubertie 2017 ¹⁹	0	16	7	0	104		0	28
Cramer 2015 ²⁰	4	÷	0	8	57	5	0	12 (Maze procedure)
Kogon 2015 ²¹	13	e	0	0	28	9	۲	9 (pulmonary arterioplasty in 2, VSD closure in 2, Maze procedure in 2, CABG in 1)
CABG indicates coro	nary artery l	bypass gr	afting; ND, not determined	CABG indicates coronary artery bypass grafting; ND, not determined; TVI, tricuspid valve intervention; and VSD, ventricular septal defect.	n; and VSD, ventricula	ır septal defect.		

size after the procedure. Furthermore, TVI+PVR was associated with a larger decrease in TR grade compared with PVR. No evidence could be established for an effect of either treatment on RVEF or echocardiographic assessment of RV dilatation and dysfunction. There was no evidence for a difference in hospital mortality or reoperation for TR. These results suggest that TVI might have a favorable effect on TR grade, although specific indications for combined valve surgery remain unclear.

Comments

Dilatation of the RV is a common complication following repair of TOF, pulmonary stenosis, and pulmonary atresia, primarily attributable to chronic PR.¹ This, in turn, leads to dilatation of the TV annulus, resulting in varying degrees of TR and further RV dilatation. Although the transannular patch repair approach causes PR, many additional factors can contribute to TR in these patients.²² These include damage to the TV leaflets or chordae tendineae during initial surgery, as well as the presence of additional valve abnormalities. Regardless of the causative mechanism, moderate to severe preoperative TR is a well-described risk factor for adverse outcomes in ACHD, leading to heart failure, arrhythmia, and death.⁶ Although concomitant TVI has been shown to reduce TR in these patients, there has been considerable debate regarding this approach.

Several studies have recommended PVR alone to address both PR and TR following TOF repair, arguing that the reduction in RV volume overload resulting from PVR is enough to ameliorate the observed TR. In a comparison between patients undergoing PVR alone versus those with TVI+PVR, Kogon et al²¹ found that patients in the latter group experienced a greater increase in TR at medium follow-up (7.0±2.8 years). These results led them to recommend PVR alone in patients with moderate or greater TR. Similarly, Kurkluoglu et al²³ found that dilatation of the TV annulus improved after PVR alone, suggesting that additional parameters should be taken into account when evaluating patients for TVI+PVR. Results from a single-center study by Lueck et al¹⁸ found longer intensive care unit stays for the TVI+PVR group, as well as greater rates of arrhythmia, renal insufficiency, sternal wound infection, and delirium. Notably, all of these findings were drawn from single-center studies composed of relatively small populations. Conversely, results from a multicenter study performed by Deshaies et al¹⁶ found that TVI+PVR results in a greater reduction in TR. With the exception of a slightly higher incidence of major infections, there was no evidence for differences in adverse outcomes between TVI+PVR and PVR alone.

Another area of debate that our study could not address is the optimal treatment strategy for patients

Downloaded from
В
http:/
/ahajc
ournals
org
by
on
on December 9
, 2021

		Baseline characteristics	racteristics					Original co diagnosis	Original congenital diagnosis	nital		Operative characteristics	ristics
Author	Group	Patient no.	Male sex	Trans-annular patch	Age at initial repair, y	Age at PVR, y	Interval time, y	TOF	PS	PA	Other	Cardiopulmonary bypass time, min	Aortic cross- clamp time, min
Deshaies 2020 ¹⁶	All patients	542	293	314	4.8±0.91	35.6±3.4	DN	433	109	0	0	102.0±11.0	60.0±6.7
	TVI+PVR	180	89	89	6.4±1.4	39.8±4.1	DN	129	51	0	0	128.5±9.6	53.8±5.5
	PVR	362	204	225	4.2±0.78	34.0±3.2	ND	304	58	0	0	88.5±8.6	69.8±7.5
Taejung Kim 2019 ¹⁷	All patients	67	40	40	DN	ND	ND	99	0	0	0	QN	ND
	PVR	29	16	18	DN	21.7±12.3	DN	28	0	0	0	QN	ND
	TVI+PVR	38	24	22	ND	31.2±15.2	ND	œ	0	0	0	QN	ND
Lueck 2018 ¹⁸	All patients	28	17	21	ND	41.1±12.5	32.0±9.5	28	0	0	0	QN	ND
	TVI+PVR	10	DN	QN	DN	QN	ND	10	0	0	0	164	71.0
	PVR	18	ND	DN	ND	DN	ND	18	0	0	0	153	63.5
Roubertie 2017 ¹⁹	All patients	104	64	62	1.7±1.4	26.3±9.50	24.8±9.3	90	N		5 DORV with VSD and PS	94.3±48.1	68.1±23.0
	TVI+PVR (moderate TR)	ω	QN	QN	1.7±0.6	24.6±12.0	23.0±12.0	ω	0	0	0	QN	QN
	TVI+PVR (severe TR)	ω	QN	QN	1.4±1.7	26.1±9.0	24.9±9.0	ω	0	0	0	QN	QN
	PVR (moderate TR)	16	QN	QN	2.3±3.4	25.6±8.0	24.8±8.0	16	0	0	0	QN	DN
	PVR (severe TR)	Ø	QN	QN	1.7±0.75	27.8±10.0	26.2±9.0	0	0	0	0	QN	DN
Cramer 2015 ²⁰	All patients	62	36	50	6.9±3.6	35.2±8.5	29.5±6.2	62	0	0	0	DN	ND
Kogon 2015 ²¹	All patients	35	ND	DN	7.8±11.1	31.3±16.7	23.5±11.5	26	6	0	0	DN	ND
	TVI+PVR	16	DN	QN	10.7±13	31.9±16.3	18.1±11.5	11	D.	0	0	DN	ND
	PVR	19	QN	ND	6.1±9.9	32.3±14.6	26.7±10.6	15	4	0	0	QN	ND

Downloaded fror
п
http://ahajournals.org by
on
December 9,
2021

Outcom
of
Summary
4
e
Tab

J Am Heart Assoc. 2021;10:e022909. DOI: 10.1161/JAHA.121.022909

Table 4. Summary o	Summary of Outcomes					
Variable (unit)	Comparison	No. of (sub)studies (No. of patients)	MD (95% CI)	P value	12 (%)	P value
TR grade (0–3)	Preoperative TVI+PVR vs PVR	4 (82 TVI+PVR/84 PVR)	0.64 (-0.18 to 1.45)	060.0	85	<0.001
	Postoperative TVI+PVR vs PVR	4 (82 TVI+PVR/84 PVR)	0.08 (-0.14 to 0.29)	0.342	0	0.670
	Change from preoperative to postoperative in TVI+PVR	7 (249 TVI+PVR)	-1.53 (-2.28 to -0.79)	0.002	94	<0.001
	Change from preoperative to postoperative in PVR	7 (415 PVR)	-0.99 (-1.81 to -0.16)	0.026	91	<0.001
	Difference in change with TVI+PVR vs PVR*	7 (249 TVI+PVR/415 PVR)	-0.40 (-0.75 to -0.05)	0.031	75	<0.001
PR grade (0-3)	Preoperative TVI+PVR vs PVR	2 (34 TVI+PVR/37 PVR)	-0.03 (-0.59 to 0.53)	0.657	30	0.234
	Postoperative TVI+PVR vs PVR	2 (34 TVI+PVR/37 PVR)	-0.01 (-0.25 to 0.23)	0.603	0	0.889
	Change from preoperative to postoperative in TVI+PVR	2 (34 TVI+PVR)	-2.53 (-3.98 to -1.07)	0.029	36	0.210
	Change from preoperative to postoperative in PVR	2 (37 PVR)	-2.52 (-3.03 to -2.02)	0.010	0	0.701
	Difference in change with TVI+PVR vs PVR*	2 (34 TVI+PVR/37 PVR)	0.03 (-0.85;0.0.92)	0.711	75	0.045
TV annulus (mm)	Preoperative TVI+PVR vs PVR	2 (56 TVI+PVR/47 PVR)	1.10 mm (-7.44 to 9.09)	0.350	0	0.425
	Postoperative TVI+PVR vs PVR	2 (56 TVI+PVR/47 PVR)	-1.50 mm (-21.18 to 18.19)	0.511	82	0.020
	Change from preoperative to postoperative in TVI+PVR	2 (56 TVI+PVR)	-6.43 mm (-10.59 to -2.27)	0.032	0	0.550
	Change from preoperative to postoperative in PVR	2 (47 PVR)	-4.20 mm (-10.42 to 2.02)	0.074	0	0.592
	Difference in change with TVI+PVR vs PVR*	2 (56 TVI+PVR/47 PVR)	-2.45 mm (-13.25 to 8.35)	0.212	93	<0.001
RV dilatation (0–3)	Preoperative TVI+PVR vs PVR	2 (26 TVI+PVR/37 PVR)	0.08 (-0.90 to 1.06)	0.490	0	0.713
	Postoperative TVI+PVR vs PVR	2 (26 TVI+PVR/37 PVR)	0.22 (-0.73 to 1.18)	0.207	0	0.732
	Change from preoperative to postoperative in TVI+PVR	2 (26 TVI+PVR)	-0.14 (-6.32 to 6.04)	0.823	71	0.065
	Change from preoperative to postoperative in PVR	2 (37 PVR)	-0.24 (-6.52 to 6.04)	0.714	85	0.011
	Difference in change with TVI+PVR vs PVR*	2 (26 TVI+PVR//37 PVR)	0.14 (0.08 to 0.19)	0.020	0	0.956
RV dysfunction (0–3)	Preoperative TVI+PVR vs PVR	2 (26 TVI+PVR/37 PVR)	0.39 (-1.32 to 2.10)	0.212	0	0.574
	Postoperative TVI+PVR vs PVR	2 (26 TVI+PVR/37 PVR)	0.71 (-2.21 to 3.63)	0.199	0	0.334
	Change from preoperative to postoperative in TVI+PVR	2 (26 TVI+PVR)	0.25 (-3.94 to 4.43)	0.592	33	0.222
	Change from preoperative to postoperative in PVR	2 (37 PVR)	0.04 (–5.61 to 5.69)	0.948	76	0.040
	Difference in change with TVI+PVR vs PVR*	2 (26 TVI+PVR/37 PVR)	0.28 (–1.05 to 1.62)	0.277	25	0.247
RVEDV (mL)	Preoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	1.07 mL (-32.04 to 34.18)	0.902	0	0.416
	Postoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	-2.87 mL (-23.83 to 18.09)	0.615	0	0.502
	Change from preoperative to postoperative in TVI+PVR	3 (34 TVI+PVR)	-84.46 mL (-107.36 to -61.57)	0.004	0	0.405
	Change from preoperative to postoperative in PVR	3 (43 PVR)	-76.66 mL (-114.22 to -39.11)	0.013	25	0.264
	Difference in change with TVI+PVR vs PVR*	3 (34 TVI+PVR/43 PVR)	-0.74 mL (-24.90 to 23.43)	0.908	62	0.072

(Continued)

Variable (unit)	Comparison	No. of (sub)studies (No. of patients)	MD (95% CI)	P value	12 (%)	P value
RVESV (mL)	Preoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	1.32 mL (-26.18 to 28.82)	0.855	0	0.388
	Postoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	-0.39 mL (-18.28 to 17.51)	0.934	0	0.934
	Change from preoperative to postoperative in TVI+PVR	3 (34 TVI+PVR)	-28.45 mL (-37.65 to -19.25)	0.006	0	0.863
	Change from preoperative to postoperative in PVR	3 (43 PVR)	-25.83 mL (-39.20 to -12.46)	0.014	0	0.704
	Difference in change with TVI+PVR vs PVR*	3 (34 TVI+PVR/43 PVR)	-0.37 mL (-11.84 to 11.09)	0.901	12	0.320
RVEF (%)	Preoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	12.77% (-41.75 to 67.30)	0.420	97	<0.001
	Postoperative TVI+PVR vs PVR	3 (34 TVI+PVR/43 PVR)	6.96% (-18.98 to 32.89)	0.368	06	<0.001
	Change from preoperative to postoperative in TVI+PVR	3 (34 TVI+PVR)	8.38% (-9.77 to 26.54)	0.185	79	0.008
	Change from preoperative to postoperative in PVR	3 (43 PVR)	14.35% (-31.49 to 60.19)	0.310	97	<0.001
	Difference in change with TVI+PVR vs PVR*	3 (34 TVI+PVR/43 PVR)	-6.00% (-34.44 to 22.45)	0.460	66	<0.001
MD indicates mean diffi right ventricular end-systol	MD indicates mean difference; PR, pulmonary regurgitation; PVR, pulmonary valve regurgitation; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection; RVESV, right ventricular end-systelic volume; RVEF, right ventricular ejection; RVESV, right ventricular end-systelic volume; RVEF, right ventricular e	urgitation; RV, right ventricular; RVED VI, tricuspid valve intervention.		RVEF, right ver	ntricular eject	ion fraction; RVESV,

(Difference in change with TVI+PVR vs PVR)=(Change from preoperative to postoperative in TVI+PVR)–(Change from preoperative to postoperative in PVR) בטעו טוו ventricular

who undergo TVI. With the exception of Lueck et al.¹⁸ where the TV was replaced in all 10 of their patients with TVI+PVR, TV repair was the most common TVI in the studies we analyzed. This is similar to other studies of ACHD patients undergoing TVI. A recent singlecenter study from Australia analyzing TVI in adults with Ebstein anomaly and other ACHD found that TV repair was performed in 61% (22/36) of their cohort, while the remaining 39% (14/36) underwent TV replacement.²⁴ In this cohort, 4 patients required reintervention (with 1 death 9 days after reintervention), of which 2 had initial TV replacement and 2 underwent TV repair. Of the 30 patients with available echocardiographic data, all 5 with moderate or greater TR underwent TV repair.²⁴ In an analysis of 109 TV repairs and 19 replacements in 128 patients with ACHD other than Ebstein anomaly. Lo Rito et al²⁵ found that those who underwent suture annuloplasty had a higher rate of moderate or greater TR at latest follow-up (4.95 years; 7.7 interguartile range) compared with those with ring annuloplasty. The only patient who required TV reintervention had an initial biological valve replacement. Importantly, both studies describe a high incidence of atrial arrhythmias following TVI, regardless of surgical approach.^{25,26}

Currently, there are not enough data to identify which patients may benefit the most from concomitant TVI. Our study, however, highlights several salient features that warrant further exploration. In the only included study to report NYHA class, Roubertie et al¹⁹ found that patients with severe preoperative TR experienced an improvement in NYHA class and TR grade following TVI+PVR. This study similarly found no patients with residual moderate or greater TR in the TVI+PVR group, compared with 78% (7/9) of those with PVR alone when analyzing patients with severe TR before surgery. In accordance with this, Deshaies et al¹⁶ found that severe preoperative TR was associated with a higher risk of residual postoperative TR (OR, 9.43; 95% Cl, 4.20–21.33; P<0.001), while TVI+PVR reduced this risk (OR, 0.44; 95% CI, 0.25-0.77; P=0.004). Importantly, only 5.6% (4/72) of patients with severe preoperative TR underwent isolated PVR in this study. In the Cramer et al²⁰ series, 75% (12/16) of patients with severe TR had TVI+PVR, with both approaches resulting in mild residual TR at 6-month follow-up.

Although TR grade and measurements of cardiac volumes and function are valuable indices of the efficacy of TVI, the actual goal of such intervention in ACHD should be the prevention of adverse events such as arrhythmias and heart failure. In this regard, the results of a study by Bokma et al⁶ are concerning. In their cohort of 129 patients with TOF undergoing isolated PVR, those with severe preoperative TR remained at increased risk for adverse events (including death, sustained ventricular tachycardia, heart failure, or supraventricular tachycardia), regardless of

Downloaded from http://ahajournals.org by on December 9, 2021

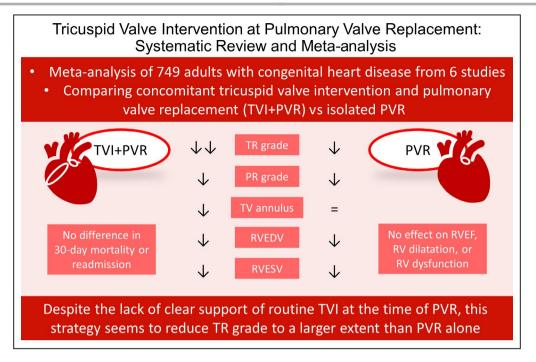


Figure 2. Summary of the key findings of the meta-analysis.

Both TVI+PVR and PVR reduced TR grade, PR grade, RVEDV, and RVESV. TVI+PVR, but not PVR, was associated with a decrease in TV annulus. Furthermore, TVI+PVR was associated with a larger decrease in TR grade compared with PVR. No evidence could be established for an effect of either treatment on RVEF or RV dilatation and RV dysfunction as qualitatively assessed by echocardiography of either treatment. There was no evidence for a difference in hospital mortality or reoperation for TR. PR indicates pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; TR, tricuspid regurgitation; TV, tricuspid valve; and TVI, tricuspid valve intervention.

their postoperative TR grade. The authors suggested that both long-standing volume overload attributable to PR and long-standing right atrial volume and pressure overload attributable to TR might contribute to this risk, leading to RV dysfunction and arrhythmias, respectively. While our findings suggest that patients with severe preoperative TR benefit most from TVI+PVR in terms of improvement of TR grade, a benefit in terms of "hard" outcomes can thus not be directly inferred. These data therefore do not support the universal application of this approach for severe TR. Further well-designed studies focusing on specific underlying mechanisms of TR and evaluating the effect on adverse events on long-term follow-up may elucidate which patients stand to benefit the most from this approach.

Sources of Heterogeneity

Given the nonrandomized nature of the existing studies comparing TVI+PVR against PVR, underlying center- and surgeon-specific bias with regard to treatment allocation was likely. Kogon et al²¹ intervened on 46% (16/35) of patients with moderate or greater TR, stating bias toward a conservative approach based on their prior work²⁶ showing improvement in TV function without concomitant TVI, a view shared by Cramer et al.²⁰ In contrast, Taejung Kim et al¹⁷ performed concomitant TVI in 56.7% (38/67) of patients in their cohort, with no significant difference in baseline TV annulus diameter but larger RV volumes in their TVI+PVR group, reflecting a more aggressive approach to TR at their center. In Deshaies et al.¹⁶ almost 59.8% (158/264) of patients with moderate or greater TR had TVI+PVR, as opposed to only 7.9% (22/278) of those with mild TR. Taken together, these data suggest that considerable heterogeneity may have been present with regard to indications for concomitant TVI. Such indication bias would be expected to result in a greater prevalence of higher-risk patients in the TVI+PVR group, as observed in the studies by Taejung Kim et al,¹⁷ Cramer et al,²⁰ and Kogon et al.²¹ In every study reviewed for this meta-analysis, the addition of TVI was performed on the basis of surgeon and cardiologist preference, which further adds patient-specific heterogeneity regardless of the degree of preoperative TR.

The use of echocardiography and/or MRI also varied among studies. While the use of cardiac MRI has evolved in recent years, only Roubertie et al¹⁹ and

Downloaded from http://ahajournals.org by on December 9, 202

Taejung Kim et al¹⁷ incorporated MRI data into their analyses out of the 6 included studies. Expanded use of cardiac MRI can further quantify TV function and help better understand the role of concomitant TVI in patients with TOF and PR.

Limitations

While the use of meta-analysis enabled us to pool studies and increase our sample size, we were ultimately limited to 6 studies that met the inclusion criteria of comparing PVR with and without concomitant TVI. Accordingly, some of the analyses were based on a low number of subjects. As described earlier, our results may have been susceptible to selection bias. Another limitation is the lack of data regarding patient anatomy and underlying causes of TR, which can be critical in determining when TVI+PVR offers the greatest benefit. Since all included studies focused on adults with childhood TOF repair, the operative technique and age at repair reflect treatment strategies from earlier decades, which have since evolved.^{27,28} Furthermore, long-term follow-up studies of patients with TVI+PVR remains scarce, which precludes the ability to draw definitive conclusions on durability of the results.

CONCLUSIONS

While both TVI+PVR and PVR alone are effective in the reduction of TR and RV volumes, routine TVI at the time of PVR can reduce TR grade to a larger extent than isolated PVR. Further studies are needed to identify the subgroups of patients who might benefit most from combined valve surgery, as current data do not support the universal application of this approach.

ARTICLE INFORMATION

Received June 26, 2021; accepted October 19, 2021.

Affiliations

Helen B. Taussig Heart Center, The Johns Hopkins Hospital and School of Medicine, Baltimore, MD (J.V.d., S.K.); Department of Cardiovascular Sciences, Department of Cardiovascular Diseases, KU Leuven, University Hospitals Leuven, Leuven, Belgium (J.V.d.); Division of Cardiovascular Surgery, The Hospital for Sick Children, Toronto, Canada (C.P.C., A.G.); Department of Congenital Cardiac Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Italy (M.L.R.); Department of Congenital Cardiac Surgery, Yorkshire Heart Centre, Leeds General Infirmary, England, United Kingdom (N.H.); Section of Pediatric Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine in St. Louis/St. Louis Children's Hospital, Saint Louis, MO (H.C.); Department of Thoracic and Cardiovascular Surgery, West German Heart and Vascular Center Essen, University Hospital of Essen, University Duisburg-Essen, Essen, Germany (A.R., A.W.); Department of Cardiovascular Sciences, Congenital and Structural Cardiology, Catholic University Leuven, University Hospitals Leuven, Leuven, Belgium (W.B.); Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium (M.G.); Department of Cardiac Surgery, Lankenau Heart Institute, Main Line Health, Wynnewood, PA (M.P.S.); and Department of Cardiac Surgery Research, Lankenau Institute for Medical Research, Main Line Health, Wynnewood, PA (M.P.S.).

Acknowledgments

J.V.D.E.: concept/design, data collection, data interpretation, drafting article, critical revision of article, approval of article, C.C.: data collection, data interpretation, critical revision of article, approval of article; M.L.R.: data collection, data interpretation, critical revision of article, approval of article, N.H.: data collection, data interpretation, critical revision of article, approval of article; H.C.: data collection, data interpretation, critical revision of article, approval of article; A.G.: data collection, data interpretation, critical revision of article, approval of article; A.G.: data collection, data interpretation, critical revision of article, approval of article; A.G.: data collection, cata interpretation, critical revision of article, approval of article; A.W.: data interpretation, critical revision of article, approval of article; W.B.: data interpretation, critical revision of article, approval of article; M.G.: data analysis/interpretation, statistics, drafting article, critical revision of article, approval of article; M.G.: data analysis/interpretation, statistics, drafting article, critical revision of article, approval of arti

Sources of Funding

None.

Disclosures

J. Van den Eynde was supported by the Belgian American Educational Foundation. Dr Budts is proctor for Abbott and Occlutech. Dr Gewillig is proctor for Edwards and Medtronic. Dr Kutty is consultant for GE Healthcare. The remaining authors have no disclosures to report.

Supplementary Material

Data S1 Figures S1–S10

REFERENCES

- Mahle WT, Parks WJ, Fyfe DA, Sallee D. Tricuspid regurgitation in patients with repaired tetralogy of Fallot and its relation to right ventricular dilatation. *Am J Cardiol.* 2003;92:643–645. doi: 10.1016/S0002 -9149(03)00746-X
- Van den Eynde J, Sá MPBO, Vervoort D, Roever L, Meyns B, Budts W, Gewillig M, Ruhparwar A, Zhigalov K, Weymann A. Pulmonary valve replacement in tetralogy of Fallot: an updated meta-analysis. *Ann Thorac Surg.* 2020;S0003-4975(20)32173-1. doi: 10.1016/j.athor acsur.2020.11.040
- Jones TK, Rome JJ, Armstrong AK, Berger F, Hellenbrand WE, Cabalka AK, Benson LN, Balzer DT, Cheatham JP, Eicken A, et al. Transcatheter pulmonary valve replacement reduces tricuspid regurgitation in patients with right ventricular volume/pressure overload. J Am Coll Cardiol. 2016;68:1525–1535. doi: 10.1016/j.jacc.2016.07.734
- Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller G-P, lung B, Kluin J, Lang IM, Meijboom F, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563–645. doi: 10.1093/eurheartj/ehaa554
- Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e698–e800.
- Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, Koolbergen DR, Groenink M, Mulder BJ, Bouma BJ. Severe tricuspid regurgitation is predictive for adverse events in tetralogy of Fallot. *Heart*. 2015;101:794–799. doi: 10.1136/heartjnl-2014-306919
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *J Am Med Assoc.* 2000;283:2008–2012.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13. doi: 10.1186/1471-2288-5-13

- Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi: 10.1136/bmj.i4919
- Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:I4898. doi: 10.1136/bmj.I4898
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J.* 2003;327:557–560. doi: 10.1136/ bmj.327.7414.557
- DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28:105–114. doi: 10.1016/j.cct.2006.04.004
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088. doi: 10.2307/2533446
- Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634. doi: 10.1136/bmj.315.7109.629
- Deshaies C, Trottier H, Khairy P, Al-Aklabi M, Beauchesne L, Bernier PL, Dhillon S, Gandhi SK, Haller C, Hancock Friesen CL, et al. Tricuspid intervention following pulmonary valve replacement in adults with congenital heart disease. *J Am Coll Cardiol.* 2020;75:1033–1043. doi: 10.1016/j.jacc.2019.12.053
- Taejung Kim S, Song J, Kim YS, Huh J, Kang IS, Yang JH, Jun TG. Repair of tricuspid valve with pulmonary valve replacement in repaired tetralogy of Fallot. *Scand Cardiovasc J*. 2019;53:148–152. doi: 10.1080/14017431.2019.1610572
- Lueck S, Bormann E, Rellensmann K, Martens S, Rukosujew A. Impact of additional tricuspid valve annuloplasty in TOF patients undergoing pulmonary valve replacement. *J Cardiovasc Surg.* 2019;60:268–273. doi: 10.23736/S0021-9509.18.10385-5
- Roubertie F, Séguéla PEP-E, Jalal Z, Iriart X, Roques X, Kreitmann B, Al-Yamani M, Pillois X, Thambo JB. Tricuspid valve repair and pulmonary valve replacement in adults with repaired tetralogy of Fallot. *J Thorac Cardiovasc Surg.* 2017;154:214–223. doi: 10.1016/j.jtcvs.2016.12.062

- Cramer JW, Ginde S, Hill GD, Cohen SB, Bartz PJ, Tweddell JS, Earing MG. Tricuspid repair at pulmonary valve replacement does not alter outcomes in tetralogy of Fallot. *Ann Thorac Surg.* 2015;99:899–904. doi: 10.1016/j.athoracsur.2014.09.086
- Kogon B, Mori M, Alsoufi B, Kanter K, Oster M. Leaving moderate tricuspid valve regurgitation alone at the time of pulmonary valve replacement: a worthwhile approach. *Ann Thorac Surg.* 2015;99:2117–2123. doi: 10.1016/j.athoracsur.2015.01.062
- Cheng JW, Russell H, Stewart RD, Thomas J, Backer CL, Mavroudis C. The role of tricuspid valve surgery in the late management of tetralogy of Fallot: collective review. *World J Pediatr Congenit Hear Surg.* 2012;3:492–498. doi: 10.1177/2150135112450037
- Kurkluoglu M, John AS, Cross R, Chung D, Yerebakan C, Zurakowski D, Jonas RA, Sinha P. Should tricuspid annuloplasty be performed with pulmonary valve replacement for pulmonary regurgitation in repaired tetralogy of Fallot? *Semin Thorac Cardiovasc Surg.* 2015;27:159–165. doi: 10.1053/j.semtcvs.2015.07.003
- Offen S, Cham J, Tan C, Chard RB, Cordina R, Celermajer DS. Tricuspid valve surgery in adults with congenital heart disease: indications, techniques and outcomes. *Int J Cardiol Congenit Heart Dis.* 2021;4:100159. doi: 10.1016/j.ijcchd.2021.100159
- Lo Rito M, Grandinetti M, Muzio G, Varrica A, Frigiola A, Micheletti A, Chessa M, Giamberti A. Results for tricuspid valve surgery in adults with congenital heart disease other than Ebstein's anomaly. *Eur J Cardiothorac Surg.* 2019;56:706–713. doi: 10.1093/ejcts/ ezz093
- Kogon B, Patel M, Leong T, McConnell M, Book W. Management of moderate functional tricuspid valve regurgitation at the time of pulmonary valve replacement: is concomitant tricuspid valve repair necessary? *Pediatr Cardiol.* 2010;31:843–848. doi: 10.1007/s0024 6-010-9717-6
- 27. Starr JP. Tetralogy of Fallot: yesterday and today. *World J Surg.* 2010;34:658–668. doi: 10.1007/s00268-009-0296-8
- Cunningham ME, Donofrio MT, Peer SM, Zurakowski D, Jonas RA, Sinha P. Optimal timing for elective early primary repair of tetralogy of Fallot: analysis of intermediate term outcomes. *Ann Thorac Surg.* 2017;103:845–852. doi: 10.1016/j.athoracsur.2016.07.020

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search strategy.

<u>PubMed</u> (n=393 on 29/12/2020)

("Pulmonary Valve"[Mesh] OR "Pulmonary valve*" OR "Valves, Pulmonary" OR "Valve, Pulmonary") AND ("Replacement*" OR "Replantation*" OR "Surgical Replantation*" OR "Replantation, Surgical" OR "Reimplantation*") AND ("Tricuspid Valve"[Mesh] OR "Tricuspid valve*" OR "Valve, Tricuspid" OR "Valves, Tricuspid" OR "Tricuspid")

Embase (n=709 on 29/12/2020)

(('pulmonary valve'/exp AND ('replacement' OR 'replantation' OR 'reimplantation')) OR 'pulmonary valve replacement'/exp OR 'pulmonary valve replacement') AND ('tricuspid valve'/exp OR 'tricuspid valve' OR 'tricuspid')

<u>Scopus</u> (n=929 on 29/12/2020)

(TITLE-ABS-KEY ("Pulmonary valve*" OR "Valves, Pulmonary" OR "Valve, Pulmonary"
) AND TITLE-ABS-KEY ("Replacement*" OR "Replantation*" OR "Surgical Replantation*" OR "Replantation, Surgical" OR "Reimplantation*") AND TITLE-ABS-KEY ("Tricuspid valve*" OR "Valve, Tricuspid" OR "Valves, Tricuspid" OR "Tricuspid")

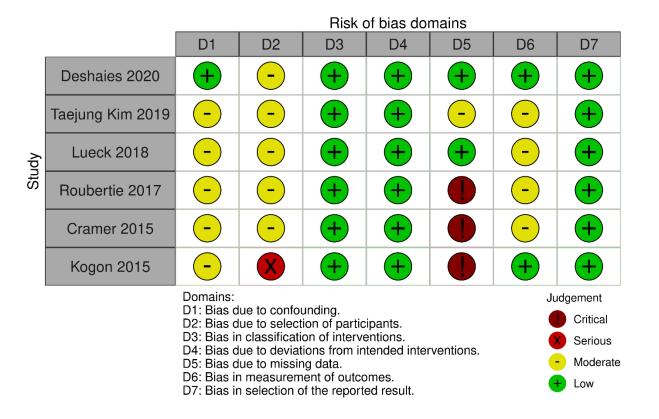


Figure S1. Bias assessment of observational studies (ROBINS-1 tool).

Figure S2. Forest plots for TR grade (0-3). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; SD, standard deviation; TR, tricuspid regurgitation; TVI, tricuspid valve intervention.

A. Difference in pre-op TR grade (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Taejung Kim 2019	38	2.79	0.95	29	1.45	0.56	i	1.34	[0.98; 1.70]	19,1%	25.1%
Lueck 2018	10	2.00	0.77	18	1.94	0.62	i	0.06	[-0.50; 0.62]	8.2%	20.3%
Cramer 2015	18	2.70	0.50	18	2.20	0.40		0.50	[0.20; 0.80]	29.0%	26.7%
Kogon 2015	16	2.63	0.43	19	2.08	0.26	- 	0.55	[0.31; 0.79]	43.7%	27.9%
Fixed effect model	82			84			\$	0.65	[0.49; 0.81]	100.0%	
Random effects model								0.64	[-0.18; 1.45]		100.0%
Heterogeneity: $I^2 = 85\%$, p	< 0.00	1									
Test for overall effect (fixed			95 (p	< 0.001)		.5 -1 -0.5 0 0.5 1 1.5				
Test for overall effect (rand	dom effe	ects): ta	= 2.4	7(p = 0)	0.090)						

B. Difference in post-op TR grade (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Taejung Kim 2019	38	1.42	0.63	29	1.28	0.45	- <u> im</u>	0.14	[-0.12; 0.40]	49.4%	49.4%
Lueck 2018	10	1.60	0.49	18	1.72	0.56		-0.12	[-0.52; 0.28]	20.8%	20.8%
Cramer 2015	18	0.94	0.90	18	0.71	0.70		0.23	[-0.30: 0.76]	11.9%	11.9%
Kogon 2015	16	1.31	0.75	19	1.29	0.50		0.02	[-0.41; 0.45]	17.8%	17.8%
Fixed effect model	82			84				0.08	[-0.11; 0.26]	100.0%	
Random effects mode	el							0.08	[-0.14; 0.29]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.670										
Test for overall effect (fixe	ed effect)	z = 0.1	81 (p	= 0.417	5		-0.6-0.4-0.2 0 0.2 0.4 0.6				
Test for overall effect (ran	dom effe	ects): ta	= 1.1	3 (p = (0.342)						

C. Change from pre-op to post-op TR grade (0-3) in TVI+PVR

Study	TE	seTE	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)	
Deshaies 2020 (mild TR)	-0.40	0.0910	1 1 1	-0.40	[-0.58; -0.22]	60.2%	16.2%	
Deshaies 2020 (moderate TR) -1.45	0.1590		-1.45	[-1.76; -1.14]	19.7%	15.8%	
Deshaies 2020 (severe TR)	-2.35	0.2910		-2.35	[-2.92: -1.78]	5.9%	14.7%	
Taejung Kim 2019	-1.68	0.2690		-1.68	[-2.21: -1.15]	6.9%	14.9%	
Lueck 2018	-0.56	0.4590	→ +++	-0.56	[-1.46; 0.34]	2.4%	12.7%	
Cramer 2015	-2.36	0.4450			[-3.23; -1.49]		12.9%	
Kogon 2015	-2.10	0.4520			[-2.99; -1.21]		12.8%	
Fixed effect model			-	-0.90	[-1.04: -0.77]	100.0%	-	
Random effects model Heterogeneity: $I^2 = 94\%$, $p < 0.0$	01			-1.53	[-2.28; -0.79]	-	100.0%	
Test for overall effect (fixed effect		12.81 (p	<30.00.12 -1 0 1 2	3				
Test for overall effect (random e				0				

D. Change from pre-op to post-op TR grade (0-3) in PVR

Study	TE	seTE	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
Deshaies 2020 (mild TR)	-0.40	0.0260		-0.40	[-0.45; -0.35]	91.3%	21.7%
Deshaies 2020 (moderate TR) -0.93	0.0970	+1	-0.93	[-1.12; -0.74]	6.6%	20.9%
Deshaies 2020 (severe TR)	-2.89	1.4430		-2.89	[-5.72; -0.06]	0.0%	2.2%
Taejung Kim 2019	-0.33	0.2650	i-++	-0.33	[-0.85; 0.19]	0.9%	16.6%
Lueck 2018	-0.36	0.3360	÷++-	-0.36	[-1.02; 0.30]	0.5%	14.6%
Cramer 2015	-2.56	0.4610		-2.56	[-3.46; -1.66]	0.3%	11.3%
Kogon 2015	-1.94	0.4010		-1.94	[-2.73; -1.15]	0.4%	12.8%
Fixed effect model				-0.45	[-0.50; -0.40]	100.0%	
Random effects model			\$	-0.99	[-1.81; -0.16]		100.0%
Heterogeneity: $I^2 = 91\%$, $p < 0.0$							
Test for overall effect (fixed effect	ct): z = -	17.99 (p	< 0.02(1) -2 0 2 4				
Test for overall effect (random e	ffects): I	e = -2.94	(p = 0.026)				

E. Difference in change in TR grade (0-3) between TVI+PVR and PVR

		TVI	PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Deshaies 2020 (mild TR)	19	-0.32	0.80	235	-0.25	0.61		-0.07	[-0.44; 0.30]	10.4%	14.6%
Deshaies 2020 (moderate TR)	83	-1.07	0.74	92	-0.71	0.76		-0.36	[-0.58; -0.14]	28.3%	17.9%
Deshaies 2020 (severe TR)	65	-1.49	0.64	4	-1.25	0.43		-0.24	[-0.69; 0.21]	6.9%	12.7%
Taejung Kim 2019	38	-1.37	0.95	29	-0.17	0.68	I	-1.20	[-1.59: -0.81]	9.2%	14.1%
Lueck 2018	10	-0.40	0.29	18	-0.22	0.20	3 1	-0.18	[-0.38: 0.02]	34.8%	18.3%
Cramer 2015	18	-1.76	0.96	18	-1.49	0.74		-0.27	[-0.83: 0.29]	4.4%	10.5%
Kogon 2015	16	-1.32	0.87	19	-0.79	0.52		-0.53	[-1.02; -0.04]	5.9%	12.0%
Fixed effect model	249			415				-0.34	[-0.46; -0.22]	100.0%	
Random effects model							<u></u>	-0.40	[-0.75; -0.05]		100.0%
Heterogeneity: $I^2 = 75\%$, $p < 0.00$	1										
Test for overall effect (fixed effect): z = -	5.66 (p	< 0.00	01)			1.5 -1 -0.5 0 0.5 1	1.5			
Test for overall effect (random eff	ects): (= -2.7	9 (p =	0.031)	K						

Figure S3. Forest plots for PR grade (0-3). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op PR grade (0-3) between TVI+PVR and PVR

	TVI	PVR			PVR								Weight	Weight
Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
18	2.90	0.31	18	3.00	0.10		*		- 3		-0.10	[-0.25; 0.05]	16.3%	26.3%
16	3.00	0.10	19	3.00	0.10		<u></u>		_		0.00	[-0.07; 0.07]	83.7%	73.7%
34			37				*	-			-0.02	[-0.08; 0.04]	100.0%	-
= 0.23	4		_		-	-	T	Ŧ	Т	7	-0.03	[-0.59; 0.53]	-	100.0%
effect)	z = -0					-0.2	-0.1	0	0.1	0.2				
	18 16 34 = 0.23 effect)	Total Mean 18 2.90 16 3.00 34 = 0.234 effect): z = -0	18 2.90 0.31 16 3.00 0.10 34 = 0.234 effect): z = -0.53 (p	Total Mean SD Total 18 2.90 0.31 18 16 3.00 0.10 19 34 37 = 0.234 effect); z = -0.53 (p = 0.59)	Total Mean SD Total Mean 18 2.90 0.31 18 3.00 16 3.00 0.10 19 3.00 34 37	Total Mean SD Total Mean SD 18 2.90 0.31 18 3.00 0.10 16 3.00 0.10 19 3.00 0.10 34 37	Total Mean SD Total Mean SD 18 2.90 0.31 18 3.00 0.10 16 3.00 0.10 19 3.00 0.10 34 37 effect); z = -0.53 (p = 0.599) -0.2	Total Mean SD Total Mean SD Mean 18 2.90 0.31 18 3.00 0.10 - 16 3.00 0.10 19 3.00 0.10 - - 34 37 -	Total Mean SD Total Mean SD Mean Differ 18 2.90 0.31 18 3.00 0.10 16 3.00 0.10 19 3.00 0.10 34 37 = 0.234	Total Mean SD Total Mean SD Mean Difference 18 2.90 0.31 18 3.00 0.10 16 3.00 0.10 10 10 10 34 37 10 10 10 10 effect): z = -0.53 (p = 0.599) -0.2 -0.1 0 0.1	Total Mean SD Total Mean SD Mean Difference 18 2.90 0.31 18 3.00 0.10 16 3.00 0.10 19 3.00 0.10 34 37	Total Mean SD Total Mean SD Mean Difference MD 18 2.90 0.31 18 3.00 0.10 -0.10 16 3.00 0.10 1 0.00 0.00 0.00 34 37 -0.02 -0.10 0.01 0.00 effect); z = -0.53 (p = 0.599) -0.2 -0.1 0 0.1 0.2	Total Mean SD Total Mean SD Mean Difference MD 95%-Cl 18 2.90 0.31 18 3.00 0.10 -0.10 [-0.25; 0.05] 16 3.00 0.10 19 3.00 0.10 -0.02 [-0.07; 0.07] 34 37 -0.02 [-0.08; 0.04] -0.03 [-0.59; 0.63] = 0.234 -0.10 0.10 0.10 0.10 0.2 -0.10 0.10 -0.2	Total Mean SD Total Mean SD Mean Difference MD 95%-CI (fixed) 18 2.90 0.31 18 3.00 0.10 -0.10 [-0.25; 0.05] 16.3% 16 3.00 0.10 19 3.00 0.10 -0.02 [-0.08; 0.04] 100.0% 34 37 -0.02 [-0.08; 0.04] 100.0% -0.03 [-0.59; 0.53] -0.02 effect); z = -0.53 (p = 0.599) -0.2 -0.1 0 0.1 0.2

B. Difference in post-op PR grade (0-3) between TVI+PVR and PVR

		TVI	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Cramer 2015	18	0.50	0.50	18	0.50	0.50			-		_	0.00	[-0.33; 0.33]	65.9%	65.9%
Kogon 2015	16	0.37	0.47	19	0.41	0.87			-			-0.04	[-0.49; 0.41]	34.1%	34.1%
Fixed effect model	34			37				_	4	_		-0.01	[-0.28; 0.25]	100.0%	
Random effects model	1								\$	-		-0.01	[-0.25; 0.23]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.889							1	1	1					
Test for overall effect (fixed	d effect)	z = -0	.10 (p	= 0.92	0)		-0.4	-0.2	0	0.2	0.4				
Test for overall effect (rand	dom effe	ects): t,	= -0.1	72(p =	0.603)										

C. Change from pre-op to post-op PR grade (0-3) in TVI+PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Cramer 2015	18	0.50	0.50	18	2.90	0.31	-		T			-2.40	[-2.67; -2.13]	42.9%	45.5%
Kogon 2015	16	0.37	0.47	16	3.00	0.10	7					-2.63	[-2.87; -2.39]	57.1%	54.5%
Fixed effect model	34			34			\$					-2.53	[-2.71; -2.35]	100.0%	
Random effects model						-		-				-2.53	[-3.98; -1.07]		100.0%
Heterogeneity: $I^2 = 36\%$, p	= 0.21	0					Г			1					
Test for overall effect (fixed			7.88 (p < 0.0	01)		-2	-1	0	1	2				
Test for overall effect (rand	lom effe	ects): t1	= -22	.05 (p :	= 0.029)									

D. Change from pre-op to post-op PR grade (0-3) in PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence	e	MD	95%-CI	(fixed)	(random)
Cramer 2015	18	0.50	0.50	18	3.00	0.10	÷.		T			-2.50	[-2.74; -2.26]	73.6%	73.6%
Kogon 2015	19	0.41	0.87	19	3.00	0.10	+					-2.59	[-2.98; -2.20]	26.4%	26.4%
Fixed effect model	37			37			\$					-2.52	[-2.73; -2.32]	100.0%	
Random effects model							0					-2.52	[-3.03; -2.02]		100.0%
Heterogeneity: $I^2 = 0\%$, $p =$	0.701							1		1					
Test for overall effect (fixed							-2	-1	0	1	2				
Test for overall effect (rand	lom effe	ects): t1	= -63	.65 (p =	= 0.010)									

E. Difference in change in PR grade (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Cramer 2015	18	-2.40	0.14	18	-2.50	0.12		0.10	[0.02: 0.18]	61.8%	52.9%
Krogon 2015	16	-2.63	0.12	19	-2.59	0.20		-0.04	[-0.15; 0.07]	38.2%	47.1%
Fixed effect model	34			37				0.05	[-0.02; 0.11]	100.0%	
Random effects model Heterogeneity: $I^2 = 75\%$, p		5				-		0.03	[-0.86; 0.92]		100.0%
Test for overall effect (fixed	d effect)	: z = 1.3					-0.15 -0.05 0 0.05 0.1 0.15				
Test for overall effect (rand	dom effe	ects): t1	= 0.4	9 (p = 1	0.711)						

Figure S4. Forest plots for TV annulus (mm). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; SD, standard deviation; TV, tricuspid valve; TVI, tricuspid valve intervention.

A. Difference in pre-op TV annulus (mm) between TVI+PVR and PVR

Study	TVI+PVR Total Mean SD	PVR Total Mean SD	Mean Difference	Weight Weight MD 95%-Cl (fixed) (random)
Taejung Kim 2019 Cramer 2015	38 21.30 4.80 18 31.10 2.00	29 21.10 6.30 18 29.50 4.00		0.20 [-2.55; 2.95] 36.0% 36.0% - 1.60 [-0.47; 3.67] 64.0% 64.0%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, p Test for overall effect (fixed Test for overall effect (rand	= 0.425 d effect): z = 1.30 (p =		-3 -2 -1 0 1 2 3	1.10 [-0.56; 2.75] 100.0%

B. Difference in post-op TV annulus (mm) between TVI+PVR and PVR

		TVI+	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Differ	rence		MD	95%-CI	(fixed)	(random)
Taejung Kim 2019	38	14.40	3.50	29	17.50	4.60		. :				-3.10	[-5.11;-1.09]	40.7%	48.3%
Cramer 2015	18	24.90	2.00	18	24.90	3.00		Ť	1	_		0.00	[-1.67; 1.67]	59.3%	51.7%
Fixed effect model	56			47				-	>			-1.26	[-2.54; 0.02]	100.0%	
Random effects mode	-											-1.50	[-21.18; 18.19]		-100.0%
Heterogeneity: $I^2 = 82\%$,	p = 0.02	0						1	1						
Test for overall effect (fixe	d effect)	: z = -1	.93 (p	= 0.05	4)		-4	-2	0	2	4				
Test for overall effect (ran	dom effe	ects): t1	= -0.9	97 (p =	0.511)										

C. Change from pre-op to post-op TV annulus (mm) in TVI+PVR

		Po	stop		Р	reop				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Taejung Kim 2019	38	14.40	3.50	38	21.30	4.80	<u> </u>	-6.90	[-8.79; -5.01]	32.4%	32.4%
Cramer 2015	18	24.90	2.00	18	31.10	2.00	+	-6.20	[-7.51; -4.89]	67.6%	67.6%
Fixed effect model	56			56			↓	-6.43	[-7.50; -5.35]	100.0%	
Random effects model								-6.43	[-10.59; -2.27]		100.0%
Heterogeneity: $I^2 = 0\%$, $p =$	0.550						1 1 1				
Test for overall effect (fixed	effect)	: z = -11	1.72 (o < 0.00	01)		-5 0 5				
Test for overall effect (rand	om effe	ects): t1	= -19	.62 (p =	= 0.032)						

D. Change from pre-op to post-op TV annulus (mm) in PVR

		Po	stop		P	reop										Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		М	ean	Diff	erend	ce		MD	95%-CI	(fixed)	(random)
Taejung Kim 2019	29	17.50	4.60	29	21.10	6.30		1.		-				-3.60	[-6.44;-0.76]	39.8%	39.8%
Cramer 2015	18	24.90	3.00	18	29.50	4.00		•	_					-4.60	[-6.91; -2.29]	60.2%	60.2%
Fixed effect model	47			47			~	⇐	-					-4.20	[-5.99; -2.41]	100.0%	
Random effects mode	1				_		_	÷	_	-+-	-			-4.20	[-10.42; 2.02]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.592							1	1	1		1					
Test for overall effect (fixe	d effect)	: z = -4	.60 (p	< 0.00	1)		-6	-4	-2	0	2	4	6				
Test for overall effect (ran	dom effe	ects): t ₁	= -8.5	58 (p =	0.074)												

E. Difference in change in TV annulus (mm) between TVI+PVR and PVR

Study	Total	TVI+ Mean	PVR SD	Total	Mean	PVR SD	Mean	Differ	ence	MD	95%-CI	Weight (fixed)	Weight (random)
Taejung Kim 2019	38	-6.90	0.96	29	-3.60	1.45				-3.30	[-3.91; -2.69]	51.3%	50.1%
Cramer 2015	18	-6.20	0.67	18	-4.60	1.18				-1.60	[-2.23; -0.97]	48.7%	49.9%
Fixed effect model	56			47			-				[-2.91; -2.03]		
Random effects model Heterogeneity: $I^2 = 93\%$, p		1	_					Ŧ		-2.45	[-13.25; 8. 35]		100.0%
Test for overall effect (fixed Test for overall effect (rande	effect)	: z = -1					-2	0	2				

Figure S5. Forest plots for RV dilatation (0-3). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; RV, right ventricular; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op RV dilatation (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR						Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean	n Differ	ence	MD	95%-CI	(fixed)	(random)
Lueck 2018	10	1,70	1.00	18	1.50	0.96		- H a		- 0.20	[-0.56; 0.96]	29.3%	29.3%
Kogon 2015	16	2.27	0.86	19	2.24	0.56				0.03	[-0.46; 0.52]	70.7%	70.7%
Fixed effect model	26			37			-	4		0.08	[-0.33; 0.49]	100.0%	-
Random effects mode	1					2		<u> </u>		- 0.08	[-0.90; 1.06]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.713							1					
Test for overall effect (fixe	d effect)	z = 0.3	38 (p	= 0.705)		-0.5	0	0.5				
Test for overall effect (rand	dom effe	ects): t1	= 1.0	3 (p = (0.490)								

B. Difference in post-op RV dilatation (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	ence		MD	95%-CI	(fixed)	(random)
Lueck 2018	10	2.11	0.99	18	1.78	0.92		_		10		0.33	[-0.42; 1.08]	33.3%	33.3%
Kogon 2015	16	1.70	0.77	19	1.53	0.82		-	- 18			0.17	[-0.36; 0.70]	66.7%	66.7%
Fixed effect model	26			37					-	-		0.22	[-0.21; 0.65]	100.0%	
Random effects model									-		-	0.22	[-0.73; 1.18]		100.0%
Heterogeneity: $I^2 = 0\%$, p =	= 0.732							1	1	1					
Test for overall effect (fixed	d effect)	: z = 1.	02 (p =	= 0.310))		-1	-0.5	0	0.5	1				
Test for overall effect (rand	dom effe	ects): t1	= 2.9	6 (p = 1	0.207)										

C. Change from pre-op to post-op RV dilatation (0-3) in TVI+PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Lueck 2018	10	2.11	0.99	10	1.70	1.00		\rightarrow	-	- 181		- 0.41	[-0.46; 1.28]	29.6%	44.0%
Kogon 2015	16	1.70	0.77	16	2.27	0.86	1	-				-0.57	[-1.14; 0.00]	70.4%	56.0%
Fixed effect model	26			26					4	-		-0.28	[-0.75; 0.19]	100.0%	
Random effects mode	-		_	_	_			-	-			-0.14	[-6.32; 6.04]		100.0%
Heterogeneity: $I^2 = 71\%$, μ	= 0.06	5							1				ecours income		
Test for overall effect (fixe	d effect)	z = -1	.16 (p	= 0.24	8)		-1	-0.5	0	0.5	1				
Test for overall effect (ran	dom effe	ects): t	= -0.2	28 (p =	0.823)										

D. Change from pre-op to post-op RV dilatation (0-3) in PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Lueck 2018	18	1.78	0.92	18	1.50	0.96		H	-			0.28	[-0.33; 0.89]	34.6%	47.6%
Kogon 2015	19	1.53	0.82	19	2.24	0.56		-				-0.71	[-1.16; -0.26]	65.4%	52.4%
Fixed effect model	37			37				-	-			-0.37	[-0.73; -0.01]	100.0%	
Random effects mod Heterogeneity: $I^2 = 85\%$.			-						+	-	7	-0.24	[-6.62; 6.04]		100.0%
Test for overall effect (fix			00 (p	= 0.046	6)		-1	-0.5	0	0.5	1				
Test for overall effect (ra							- 1	-0.5	0	0.5					

E. Difference in change in RV dilatation (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	N	lean D	ifferenc	e		MD	95%-CI	(fixed)	(random)
Lueck 2018	10	0.41	0.44	18	0.28	0.31		-	*		— (0.13	[-0.18: 0.44]	24.0%	24.0%
Kogon 2015	16	-0.57	0.29	19	-0.71	0.23		-	- 191	_	(0.14	[-0.03; 0.31]	76.0%	76.0%
Fixed effect model	26			37						-	(0.14	[-0.01; 0.29]	100.0%	-
Random effects mod	lel								\diamond		(0.14	[0.08; 0.19]		100.0%
Heterogeneity: $I^2 = 0\%$, μ	p = 0.956							1		1			a		
Test for overall effect (fix	(ed effect)	z = 1.7	77 (p =	= 0.077)		0.4 -0).2	0 0	2	0.4				
Test for overall effect (ra	ndom effe	ects): t.	= 32.	24(p =	0.020)										

Figure S6. Forest plots for RV dysfunction (0-3). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; RV, right ventricular; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op RV dysfunction (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Lueck 2018	10	1.80	0.87	18	1.56	0.96		_	-1-1		_	0.24	[-0.46; 0.94]	45.0%	45.0%
Kogon 2015	16	1.93	1.04	19	1.42	0.83			+	100		0.51	[-0.12; 1.14]	55.0%	55.0%
Fixed effect model	26			37					+	4	-	0.39	[-0.08; 0.86]	100.0%	
Random effects mode	1					_	_				_	0.39	[-1.32, 2.10]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.574						L		1	1					
Test for overall effect (fixe	d effect)	z = 1.6	63 (p :	= 0.104)		-1	-0.5	0	0.5	1				
Test for overall effect (ran	dom effe	ects): t1	= 2.8	9(p = 0)	0.212)										

B. Difference in post-op RV dysfunction (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence	•	MD	95%-CI	(fixed)	(random)
Lueck 2018	10	2.44	1.07	18	2.06	1.03		-	+	- 10		0.38	[-0.44; 1.20]	32.6%	32.6%
Kogon 2015	16	1.90	0.83	19	1.03	0.88				-	1	- 0.87	[0.30; 1.44]	67.4%	67.4%
Fixed effect model	26			37						-	-	0.71	[0.24; 1.18]	100.0%	-
Random effects mode	1				_	_		_			_	0.71	[-2.21; 3.63]		100.0%
Heterogeneity: $I^2 = 0\%$, p	= 0.334								1	1					
Test for overall effect (fixe	d effect)	z = 2.9	99 (p	= 0.003)		-1	-0.5	0	0.5	1				
Test for overall effect (ran	dom effe	ects): t1	= 3.0	9(p = 0)	0.199)										

C. Change from pre-op to post-op RV dysfunction (0-3) in TVI+PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	erence	e	MD	95%-CI	(fixed)	(random)
Lueck 2018	10	2.44	1.07	10	1.80	0.87			+	÷ .	2	- 0.64	[-0.21; 1.49]	36.8%	41.1%
Kogon 2015	16	1.90	0.83	16	1.93	1.04			<u>-</u>			-0.03	[-0.68; 0.62]	63.2%	58.9%
Fixed effect model	26			26					-			0.22	[-0.30; 0.73]	100.0%	-
Random effects model		-	-				-		-	-		0.25	[-3.94; 4.43]		100.0%
Heterogeneity: 12 = 33%, p	= 0.223	2					- <u>k</u>	1	1		1				
Test for overall effect (fixed	d effect)	: z = 0.1	32 (p :	= 0.413	3)		-1	-0.5	0	0.5	1				
Test for overall effect (rand	lom effe	ects): t	= 0.7	5(p = 0)	0.592)										

D. Change from pre-op to post-op RV dysfunction (0-3) in PVR

		Po	stop		P	reop								Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	Diffe	rence		MD	95%-CI	(fixed)	(random)
Lueck 2018	18	2.06	1.03	18	1.56	0.96			-1:			0.50	[-0.15; 1.15]	41.2%	47.9%
Kogon 2015	19	1.03	0.88	19	1.42	0.83			-			-0.39	[-0.93; 0.15]	58.8%	52.1%
Fixed effect model	37			37				-	÷	-		-0.02	[-0.44; 0.39]	100.0%	
Random effects mod	ei							_			_	0.04	[-5.61; 5.69]		100.0%
Heterogeneity: 12 = 76%	p = 0.04	0					1	1	1	1	1				
Test for overall effect (fix	ed effect)	z = -0.	11 (p	= 0.91	1)		-1	-0.5	0	0.5	1				
Test for overall effect (ra	ndom effe	ects): t,	= 0.0	8(p = 0)	0.948)										

E. Difference in change in RV dysfunction (0-3) between TVI+PVR and PVR

		TVI+	PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Lueck 2018	10	0.64	0.44	18	0.50	0.33		0.14	[-0.17; 0.45]	30.4%	35.4%
Kogon 2015	16	-0.03	0.33	19	-0.39	0.28		- 0.36	[0.15; 0.57]	69.6%	64.6%
Fixed effect model	26			37				0.29	[0.12; 0.46]	100.0%	
Random effects mode				- 27	_	_		0.28	[-1.05; 1.62]		- 100.0%
Heterogeneity: $I^2 = 25\%$, μ	= 0.24	7									
Test for overall effect (fixe	d effect)	z = 3.3	35 (p -	< 0.001)		-0.4 -0.2 0 0.2 0.4				
Test for overall effect (ran	dom effe	ects): t1	= 2.6	B(p = 0)	0.227)						

Figure S7. Forest plots for RVEDV (mL). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; RVEDV, right ventricular end-diastolic volume; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op RVEDV (mL) between TVI+PVR and PVR

		TV	+PVR			PVR				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(fixed)	(random)
Roubertie 2017 (moderate TR group)	8	166.40	33.00	16	160.20	19.00		6.20	[-18.49; 30.89]	42.6%	42.6%
Roubertie 2017 (severe TR group)	8	168.00	15.00	9	179.00	35.00		-11.00	[-36.12: 14.12]	41.1%	41.1%
Cramer 2015	18	175.40	62.00	18	157.30	60.00		- 18.10	[-21.76; 57.96]	16.3%	16.3%
Fixed effect model	34			43			4	1.07	[-15.04; 17.18]	100.0%	
Random effects model								1.07	[-32.04; 34.18]		100.0%
Heterogeneity: $I^2 = 0\%$, $p = 0.416$											
Test for overall effect (fixed effect): z = 0	.13 (p :	= 0.896)					-40 -20 0 20 40				
Test for overall effect (random effects): t	2 = 0.1	4(p = 0)	902)								

B. Difference in post-op RVEDV (mL) between TVI+PVR and PVR

Study	Total		+PVR SD	Total	Mean	PVR SD		Mean	Diffe	rence		MD	95%-C	Weight (fixed)	Weight (random)
Roubertie 2017 (moderate TR group)	8	98.00	45.00	16	86.00	32.00		-	-11			12.00	[-22.90; 46.90	10.9%	10.9%
Roubertie 2017 (severe TR group)	8	80.00	9.00	9	86.80	18.00		-	-			-6.80			74.6%
Cramer 2015	18	106.90	42.00	18	100.70	50.00		<u>11</u>			-	6.20	[-23.97; 36.37	14.5%	14.5%
Fixed effect model	34			43				-	4	-		-2.87	[-14.37; 8.63]	100.0%	-
Random effects model												-2.87	[-23.83; 18.09]		100.0%
Heterogeneity: $I^2 = 0\%$, $p = 0.502$								1	1	- U			The Control of States		
Test for overall effect (fixed effect): z = -	0.49 (p	= 0.625	÷				-40	-20	0	20	40				
Test for overall effect (random effects): I	2 = -0.5	59(p = 0	615)												

C. Change from pre-op to post-op RVEDV (mL) in TVI+PVR

Study	Total	P Mean	ostop SD			Preop SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
Roubertie 2017 (moderate TR group)	8	98.00	45.00	8	166.40	33.00	-++- I	-68.40	[-107.07; -29.73]	8.0%	8.0%
Roubertie 2017 (severe TR group)	8	80.00	9.00	8	168.00	15.00	*	-88.00	[-100.12: -75.88]	81.9%	81.9%
Cramer 2015	18	106.90	42.00	18	175.40	62.00	+	-68.50	[-103.10; -33.90]	10.1%	10.1%
Fixed effect model	34			34			\$	-84.46	[-95.43; -73.49]	100.0%	-
Random effects model									[-107.36; -61.57]		100 001
Heterogeneity: $I^2 = 0\%$, $p = 0.405$											
Test for overall effect (fixed effect): z = -	15.09 (0.00	1)				100 -50 0 50 10)			
Test for overall effect (random effects): t	2 = -15	.87 (p =	0.004)								

D. Change from pre-op to post-op RVEDV (mL) in PVR

Study	Total		ostop SD	Total		Preop SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
Roubertie 2017 (moderate TR group)			32.00		160.20			74.20		56.9%	50.3%
Roubertie 2017 (severe TR group)	9		18.00		179.00				[-117.91; -66.49]	28.6%	31.5%
Cramer 2015	18	100.70	50.00	18	157.30	60.00		56.60	[-92.68; -20.52]	14.5%	18.2%
Fixed effect model	43			43			. ↓	76.79	[-90.54; -63.04]	100.0%	
Random effects model								76.66	[-114.22; -39.11]		100.0%
Heterogeneity: $l^2 = 25\%$, $p = 0.264$											
Test for overall effect (fixed effect): z = -	10.94 (p < 0.00	1)				-100 -50 0 50 100				
Test for overall effect (random effects):	12 = -8.	78 (p = 0	.013)								

E. Difference in change in RVEDV (mL) between TVI+PVR and PVR

		TV	+PVR			PVR									Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Mean	n Diffe	rence		MD	9	5%-CI	(fixed)	(random)
Roubertie 2017 (moderate TR group)	8	-68.40	19.73	16	-74.20	9.30		-				5.80	[-8.61;	20.21]	21.0%	28.1%
Roubertie 2017 (severe TR group)	8	-88.00	6.18	9	-92.20	13.10				•		4.20	[-5.37;	13.77]	47.6%	38.4%
Cramer 2015	18	-68.50	17.65	18	-56.60	18.40			-			-11.90	[-23.68	-0.12]	31.4%	33.4%
Fixed effect model	34			43				4	4	-		-0.52	[-7.12;	6.08]	100.0%	-
Random effects model								_	-	_	_	-0.74	[-24.90;	23.43]		100.0%
Heterogeneity: $l^2 = 62\%$, $p = 0.072$																
Test for overall effect (fixed effect): z = - Test for overall effect (random effects): t							-20	-10	0	10	20					

Figure S8. Forest plots for RVESV (mL). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; RVESV, right ventricular end-systolic volume; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op RVESV (mL) between TVI+PVR and PVR

Study	Total	TV Mean	I+PVR SD	Total	Mean	PVR SD		M	ean D	Diffe	renc	e		MD		9	95%-CI	Weig (fixe		Weight random)	
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	8		28.00 20.00 27.00	9	86.40	17.00 26.00 45.00		_	×	1	-		_	-11.00	[-32	2.92	30.32] 10.92] 30.24]	34.5	%	37.2% 34.5% 28.2%	
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $p = 0.388$ Test for overall effect (fixed effect): $z = 0$ Test for overall effect (random effects): t				43			-30	-20	-10		10	20	30				14.20] 28.82]	100.0		 100.0%	

B. Difference in post-op RVESV (mL) between TVI+PVR and PVR

	TVI+PVR	PVR				Weight Weight
Study	Total Mean SD	Total Mean SD	Mean Difference	MD	95%-CI	(fixed) (random)
Roubertie 2017 (moderate TR group)	8 58.00 29.00	16 49.00 22.00		- 9.00	[-13.80; 31.80]	19.6% 19.6%
Roubertie 2017 (severe TR group)	8 47.70 14.00	9 53.80 17.00		-6.10	[-20.85; 8.65]	46.8% 46.8%
Cramer 2015	18 47.90 24.00	18 45.80 29.00		2.10	[-15.29; 19.49]	33.6% 33.6%
Fixed effect model	34	43		-0.39	[-10.47; 9.70]	100.0%
Random effects model				-0.39	[-18.28; 17.51]	100.0%
Heterogeneity: $I^2 = 0\%$, $p = 0.520$		Г				
Test for overall effect (fixed effect): z = -0	0.08 (p = 0.940)	-30	-20 -10 0 10 20	30		
Test for overall effect (random effects): t	$_2 = -0.09 (p = 0.934)$					

C. Change from pre-op to post-op RVESV (mL) in TVI+PVR

Study	Postop Total Mean SD T	Preop Total Mean SD	Mean Difference	MD 95%-C	Weight Weight (fixed) (random)
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	8 58.00 29.00 8 47.70 14.00 18 47.90 24.00	8 80.50 28.00 8 75.40 20.00 18 79.20 27.00		-22.50 [-50.43; 5.43 -27.70 [-44.62; -10.78 -31.30 [-47.99; -14.61	41.8% 41.8%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $p = 0.863$ Test for overall effect (fixed effect): $z = -1$ Test for overall effect (random effects): l		34	-40 -20 0 20 40	-28.45 [-39.38; -17.52 -28.45 [-37.65; -19.25	

D. Change from pre-op to post-op RVESV (mL) in PVR

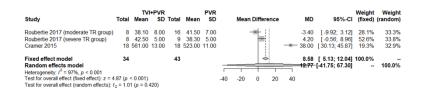
Study	Postop Total Mean SD T	Preop Total Mean SD	Mean Difference	MD	95%-CI	Weight Weight (fixed) (random)
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	16 49.00 22.00 9 53.80 17.00 18 45.80 29.00	16 71.30 17.00 9 86.40 26.00 - 18 73.20 45.00 -		-32.60 [-52	5.92; -8.68] 2.90; -12.30] 2.13; -2.67]	57.0% 57.0% 25.7% 25.7% 17.3% 17.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $p = 0.704$ Test for overall effect (fixed effect): $z = -1$ Test for overall effect (random effects): t		43	-40 -20 0 20 40		5.11; -15.54] 0.20; -12.46]	100.0% 100.0%

E. Difference in change in RVESV (mL) between TVI+PVR and PVR

Study	TVI+PVR Total Mean SD 1	PVR Total Mean SD	Mean Difference	Weight Weight MD 95%-Cl (fixed) (random)
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	8 -22.50 14.25 8 -27.70 8.63 18 -31.30 8.51	16 -22.30 6.95 9 -32.60 10.35 18 -27.40 12.62		-0.20 [-10.65; 10.25] 22.0% 23.3% - 4.90 [-4.13; 13.93] 29.5% 30.3% -3.90 [-10.93; 3.13] 48.5% 46.4%
Fixed effect model Random effects model Heterogeneity: $l^2 = 12\%$, $p = 0.320$ Test for overall effect (fixed effect): $z = -$ Test for overall effect (random effects): 1		43	-10 -5 0 5 10	-0.49 [-5.39; 4.41] 100.0% -0.37 [-11.84; 11.09] 100.0%

Figure S9. Forest plots for RVEF (%). Pooled mean difference and conclusions plot for all comparisons. CI, confidence interval; MD, mean difference; PVR, pulmonary valve replacement; RVEF, right ventricular ejection fraction; SD, standard deviation; TVI, tricuspid valve intervention.

A. Difference in pre-op RVEF (%) between TVI+PVR and PVR



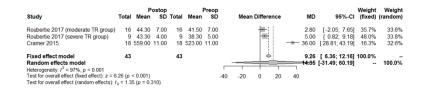
B. Difference in post-op RVEF (%) between TVI+PVR and PVR

Study	Total M	TVI+PV lean S	R D Total	Mean	PVR SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	8 4	3.40 11.0 6.10 2.0 8.00 10.0	0 9	44.30 43.30 559.00	4.00		-0.90 2.80 19.00	[-9.26; 7.46] [-0.16; 5.76] [12.13; 25.87]		30.7% 36.6% 32.7%
Fixed effect model Random effects model Heterogeneity: $I^2 = 90\%$, $p < 0.001$ Test for overall effect (fixed effect): $z = 3$ Test for overall effect (random effects): t			43			-20 -10 0 10 20		[2.16; 7.32] [-18.98; 32.89]	100.0% 	 100.0%

C. Change from pre-op to post-op RVEF (%) in TVI+PVR

Study	Total M	Postop Mean SD	Total	Preop SD		Mean D	lifferen	ce	MD	95%-CI	Weight (fixed)	Weight (random)
Roubertie 2017 (moderate TR group) Roubertie 2017 (severe TR group) Cramer 2015	8 4	43.40 11.00 46.10 2.00 78.00 10.00	8	 5.00		_	-		3.60	[-4.13; 14.73] [-0.13; 7.33] [9.42; 24.58]	11.2% 71.5% 17.3%	28.2% 39.6% 32.1%
Fixed effect model Random effects model Heterogeneity: $i^2 = 79\%$, $p = 0.008$ Test for overall effect (fixed effect): $z = 3$ Test for overall effect (random effects):			34		-20	-10	0 1	0 20		[2.96; 9.27] [-9.77; 26.54]	100.0% 	 100.0%

D. Change from pre-op to post-op RVEF (%) in PVR



E. Difference in change in RVEF (%) between TVI+PVR and PVR

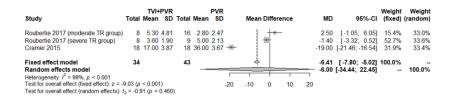


Figure S10. Forest plot for 30-day mortality. Pooled odds ratio and conclusions plot. CI,

confidence interval; OR, odds ratio; PVR, pulmonary valve replacement; TVI, tricuspid valve intervention.

Study	TVI+PVR Events Total Event	PVR s Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Roubertie 2017 Cramer 2015 Kogon 2015 Deshaies 2020 Lueck 2018		2 25 — 0 18 0 19 5 362 1 18		2.46 [0.	01; 6.33] 74; 8.18] 11; 33.89]	33.2% 0.0% 0.0% 55.6% 11.1%	11.3% 0.0% 0.0% 75.6% 13.1%
			0.1 0.51 2 10	-	62; 4.52] 4; 14.61]	100.0% 	 100.0%