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

Tricuspid 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. 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. Current guidelines do not suggest when concomitant tricuspid valve intervention (TVI) should be recommended. Nonetheless, severe TR is strongly associated with an increased risk of adverse outcomes in ACHD. Therefore, we aimed to evaluate early results of concomitant TVI at the time of PVR.
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-analyses and Meta-analysis of Observational Studies in Epidemiology. 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 end-systolic 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. 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 I² 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 publications16–21 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; P=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; P=94%) and PVR (MD, −0.99; 95% CI, −1.81 to −0.16; P=0.026; P=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% CI, −0.75 to −0.05, P=0.031; P=75%). As a result, postoperative TR grade was comparable between both groups (MD, 0.08; 95% CI, −0.14 to 0.29; P=0.342; P=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; P=36%) and PVR (MD, −2.52; 95% CI, −3.03 to −2.02, P=0.010; P=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; P=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; P=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 qualitative score for RV dilatation compared with PVR (MD, 0.14; 95% CI, 0.08 to 0.19; P=0.020; P=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...
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; I²=62%) and RVESV (MD, −0.37; 95% CI, −11.84 to 11.09; P=0.901; I²=12%). No evidence of effects of either treatment nor differences between the effects could be observed with regard to RVEF (Table 4).
NYHA Class

NYHA class was only reported by a single study. Roubertie et al\textsuperscript{19} 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 al\textsuperscript{19} 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 random-effects 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% CI, –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 (\(I^2\) 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
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.\(^2\) 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 al.\(^2\) 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 al.\(^2\) 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 al.\(^1\) 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 al.\(^1\) 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
| Author Group | Original congenital diagnosis | Trans-aortic patch | Age at initial repair, y | Interval time, y | Age at PVR, y | TOF | PS | PA | Other |
|--------------|-----------------------------|-------------------|------------------------|----------------|--------------|-----|-----|-----|-------|
| Deshaies 2020 | All patients                | 293               | 542                    | 314            | 4.8±0.91     | ND  |     |     |       |
| PVR          |                             | 89                | 293                    | 36±8.2±4       | 35.6±3.4     | ND  |     |     |       |
|              |                             | 255               | 293                    | 542            | 4.8±0.91     | ND  |     |     |       |
|              |                             | 293               | 314                    | 4.8±0.91       | 35.6±3.4     | ND  |     |     |       |
| TVI+PVR      |                             | 180               | 89                     | 16             | 6±1±4        | ND  |     |     |       |
|              |                             | 293               | 314                    | 4.8±0.91       | 35.6±3.4     | ND  |     |     |       |
| PVR          |                             | 362               | 89                     | 40             | 35.6±3.4     | ND  |     |     |       |
|              |                             | 293               | 314                    | 4.8±0.91       | 35.6±3.4     | ND  |     |     |       |
| TVI+PVR      |                             | 140               | 293                    | 40             | 35.6±3.4     | ND  |     |     |       |
|              |                             | 314               | 314                    | 6±1±4          | 35.6±3.4     | ND  |     |     |       |
| PVR          |                             | 180               | 293                    | 40             | 35.6±3.4     | ND  |     |     |       |
|              |                             | 314               | 314                    | 6±1±4          | 35.6±3.4     | ND  |     |     |       |
| TVI+PVR      |                             | 10               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
|              |                             | 314               | 314                    | 6±1±4          | 35.6±3.4     | ND  |     |     |       |
| PVR          |                             | 18               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
|              |                             | 314               | 314                    | 6±1±4          | 35.6±3.4     | ND  |     |     |       |
| TVI+PVR      | TVI+PVR (low gradient TR)   | 10               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
|              | TVI+PVR (moderate TR)       | 18               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
|              | TVI+PVR (severe TR)         | 9                | 293                    | 0              | 6±1±4        | ND  |     |     |       |
| PVR          | PVR (moderate TR)           | 18               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
|              | PVR (severe TR)             | 18               | 293                    | 0              | 6±1±4        | ND  |     |     |       |
| Cramer 2015  | All patients                | 62                | 36                     | 50             | 6±1±4        | ND  |     |     |       |
| PVR          |                             | 36                | 36                     | 50             | 6±1±4        | ND  |     |     |       |
| TVI+PVR      |                             | 16                | 36                     | 50             | 6±1±4        | ND  |     |     |       |
| TVI+PVR      |                             | 19                | 36                     | 50             | 6±1±4        | ND  |     |     |       |
| PVR          |                             | 19                | 36                     | 50             | 6±1±4        | ND  |     |     |       |

DORV indicates double outlet right ventricle; ND, not determined; PA, pulmonary atresia; PS, pulmonary stenosis; PVR, pulmonary valve replacement; TR, tricuspid regurgitation; TVI, tricuspid valve intervention; and VSD, ventricular septal defect.
Table 4. Summary of Outcomes

| Variable (unit) | Comparison | No. of (sub)studies (No. of patients) | MD (95% CI) | P value | I² (%) | P value |
|----------------|------------|--------------------------------------|-------------|---------|--------|---------|
| TR grade (0–3) | Preoperative TVI+PVR vs PVR | 4 (82 TVI+PVR/84 PVR) | 0.64 (−0.18 to 1.45) | 0.090 | 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;0.92) | 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) | −8.46 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) | −7.45 mL (−32.94 to 23.43) | 0.898 | 62 | 0.072 |

(Continued)
who undergo TVI. With the exception of Liecke et al., the left atrium was replaced in only 78% (79/100) of their patients undergoing TVI. In the remaining 22% (21/100) of patients, the study was performed in 6% (25/25) of those who underwent TVI+PVR, replacing the left atrium in 21% (21/100). Overall, 6% (21/25) of patients required reintervention, with a mortality of 2% (2/25) in the TVI+PVR group. Furthermore, 6% (21/25) of patients had atrial arrhythmias, 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 al. 19 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 at latest follow-up (4.95 years; 77 patients). In this cohort, the patients with severe preoperative TR were associated with a higher risk of residual postoperative TR (OR, 9.43; 95% CI, 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, patients who underwent isolated TVI in this cohort had a higher rate of atrial arrhythmias following TVI, regardless of surgical approach. 12

In our analysis of 109 TV repairs and 19 replacements in 128 patients with ACHD other than Ebstein anomaly, Lo Rito et al. 20 found that those who underwent isolated TVI+PVR had a higher rate of atrial arrhythmias (OR, 6.00; 95% CI, 3.44–22.45; P < 0.001). In an analysis of 109 TV repairs and 19 replacements in 128 patients with ACHD other than Ebstein anomaly, Lo Rito et al. 20 found that those who underwent isolated TVI+PVR had a higher rate of atrial arrhythmias (OR, 6.00; 95% CI, 3.44–22.45; P < 0.001). In this cohort, 4 patients required reintervention, with a mortality of 2% (2/25) in the TVI+PVR group. Overall, 6% (21/25) of patients required reintervention, with a mortality of 2% (2/25) in the TVI+PVR group. Furthermore, 6% (21/25) of patients had atrial arrhythmias, regardless of surgical approach. 25,26

Table 4. Continued

| Variable (unit) | Comparison | No. of (sub)studies (No. of patients) | MD (95% CI) | P value | P (%) | 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 | 90 | <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 | 99 | <0.001 |

MD indicates mean difference; PR, pulmonary regurgitation; PVR, pulmonary valve regurgitation; RV, right ventricular; RVESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; TR, tricuspid regurgitation; TV, tricuspid valve; and TVI, tricuspid valve intervention.

*(Difference in change with TVI+PVR vs PVR)=(Change from preoperative to postoperative in TVI+PVR)−(Change from preoperative to postoperative in PVR).
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 in 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 al\(^7\) intervened on 46% (16/35) of patients with moderate or greater TR, stating bias toward a conservative approach based on their prior work\(^7\) showing improvement in TV function without concomitant TVI, a view shared by Cramer et al\(^8\). In contrast, Taejung Kim et al\(^9\) 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\(^1\), 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, reflecting a more aggressive approach to TR at their center. 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 al\(^1\) and

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**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.
Taejung Kim et al. 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. 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, IRCSS 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. H.C.: data interpretation, critical revision of article, approval of article. A.R.: data 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 interpretation, critical revision of article, approval of article. M.P.S.: concept/design, data analysis/interpretation, statistics, drafting article, critical revision of article, approval of article; S.K.: data interpretation, critical revision of article, approval of article.

Sources of Funding

None.

Disclosures

J. Van den Eynde was supported by the Belgian American Educational Foundation. Dr Budts is proctor for Abbott and Occuthec. 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

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SUPPLEMENTAL MATERIAL
Supplemental Methods

Search strategy.

PubMed (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")

Scopus (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).

| Study              | Risk of bias domains |
|--------------------|----------------------|
|                    | D1      | D2      | D3      | D4      | D5      | D6      | D7      |
| Deshaies 2020      | +       | -       | +       | +       | +       | +       | +       |
| Taejung Kim 2019   | -       | -       | +       | +       | -       | -       | +       |
| Lueck 2018         | -       | -       | +       | +       | +       | -       | +       |
| Roubertie 2017     | -       | -       | +       | +       | ↓       | -       | +       |
| Cramer 2015        | -       | -       | +       | +       | ↓       | -       | +       |
| Kogon 2015         | -       | X       | +       | +       | ↓       | +       | +       |

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement:
- Critical
- Serious
- Moderate
- Low
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

| Study          | TVI+PVR Total Mean | TVI+PVR Mean Difference | PVR Total Mean | PVR Mean Difference | Weight (fixed) | Weight (random) |
|----------------|--------------------|-------------------------|----------------|--------------------|----------------|-----------------|
| Taeging Kim 2019 | 38                 | 2.79 ± 0.95             | 29             | 1.45 ± 0.50        | 1.34 ± 0.98    | 1.70 ± 1.03     |
| Lueck 2018      | 10                 | 2.00 ± 0.77             | 18             | 1.94 ± 0.62        | 0.06 ± 0.50    | 0.62 ± 0.60     |
| Cramer 2015     | 18                 | 2.70 ± 0.50             | 15             | 2.20 ± 0.60        | 0.50 ± 0.20    | 0.80 ± 0.20     |
| Kogon 2015      | 16                 | 2.63 ± 0.43             | 19             | 2.06 ± 0.26        | 0.55 ± 0.31    | 0.97 ± 0.79     |

Fixed effect model: 0.65 (0.65, 1.00) = 100%
Random effects model: 0.65 (0.65, 1.00) = 100%
Heterogeneity: I² = 65%, p = 0.001
Test for overall effect (random effects): z = 2.47 (p = 0.000)

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

| Study          | TVI+PVR Total Mean | TVI+PVR Mean Difference | PVR Total Mean | PVR Mean Difference | Weight (fixed) | Weight (random) |
|----------------|--------------------|-------------------------|----------------|--------------------|----------------|-----------------|
| Taeging Kim 2019 | 30                 | 1.42 ± 0.63             | 29             | 1.25 ± 0.45        | 0.14 ± 0.12    | 0.41 ± 0.41     |
| Lueck 2018      | 10                 | 1.00 ± 0.40             | 18             | 1.72 ± 0.56        | -0.12 ± 0.12   | 0.28 ± 0.28     |
| Cramer 2015     | 16                 | 0.94 ± 0.00             | 18             | 0.71 ± 0.00        | 0.23 ± 0.03    | 0.71 ± 0.03     |
| Kogon 2015      | 16                 | 1.31 ± 0.01             | 19             | 1.20 ± 0.30        | 0.02 ± 0.14    | 0.41 ± 0.41     |

Fixed effect model: 0.08 (0.01, 0.29) = 100%
Random effects model: 0.08 (0.01, 0.29) = 100%
Heterogeneity: I² = 67%, p = 0.001
Test for overall effect (random effects): z = 4.67 (p = 0.000)

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

| Study          | TE | seTE | Mean Difference | MD | Weight (fixed) | Weight (random) |
|----------------|----|-----|-----------------|----|----------------|-----------------|
| Dohares 2020 (mild TR) | 0.40 | 0.20 | 0.00 ± 0.00 | 0.40 | 0.00 ± 0.00 | 10.0% |
| Dohares 2020 (moderate TR) | 0.30 | 0.03 | 0.00 ± 0.00 | 0.30 | 0.00 ± 0.00 | 10.0% |
| Dohares 2020 (severe TR) | 0.20 | 0.02 | 0.00 ± 0.00 | 0.20 | 0.00 ± 0.00 | 10.0% |

Fixed effect model: 0.00 (0.00, 0.00) = 100%
Random effects model: 0.00 (0.00, 0.00) = 100%
Heterogeneity: I² = 99%, p = 0.001
Test for overall effect (fixed effects): z = 19.57 (p < 0.001)
Test for overall effect (random effects): z = 19.57 (p < 0.001)

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

| Study          | TE | seTE | Mean Difference | MD | Weight (fixed) | Weight (random) |
|----------------|----|-----|-----------------|----|----------------|-----------------|
| Dohares 2020 (mild TR) | 0.40 | 0.20 | 0.00 ± 0.00 | 0.40 | 0.00 ± 0.00 | 10.0% |
| Dohares 2020 (moderate TR) | 0.30 | 0.03 | 0.00 ± 0.00 | 0.30 | 0.00 ± 0.00 | 10.0% |
| Dohares 2020 (severe TR) | 0.20 | 0.02 | 0.00 ± 0.00 | 0.20 | 0.00 ± 0.00 | 10.0% |

Fixed effect model: 0.00 (0.00, 0.00) = 100%
Random effects model: 0.00 (0.00, 0.00) = 100%
Heterogeneity: I² = 99%, p = 0.001
Test for overall effect (fixed effects): z = 19.57 (p < 0.001)
Test for overall effect (random effects): z = 19.57 (p < 0.001)

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

| Study          | TVI+PVR Total Mean | TVI+PVR Mean Difference | PVR Total Mean | PVR Mean Difference | Weight (fixed) | Weight (random) |
|----------------|--------------------|-------------------------|----------------|--------------------|----------------|-----------------|
| Dohares 2020 (mild TR) | 19 | 0.33 ± 0.50 | 235 | 1.35 ± 0.50 | -0.07 ± 0.44 | 0.30 ± 0.41 |
| Dohares 2020 (moderate TR) | 20 | 1.07 ± 0.71 | 97 | 0.71 ± 0.71 | -0.36 ± 0.68 | 0.14 ± 0.24 |
| Dohares 2020 (severe TR) | 25 | 4.89 ± 0.48 | 135 | 1.25 ± 0.43 | -4.24 ± 0.68 | 0.97 ± 0.68 |

Fixed effect model: 0.34 (0.24, 0.62) = 100%
Random effects model: 0.00 (0.00, 0.00) = 100%
Heterogeneity: I² = 70%, p = 0.001
Test for overall effect (random effects): z = 2.79 (p = 0.000)
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

| Study  | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD 95% CI | Weight (fixed) | Weight (random) |
|--------|--------------------|----|----------------|----|----------------|-----------|---------------|-----------------|
| 2015 Cramer | 16 3.00 0.10 | 0.01 | 16 3.00 0.10 | 0.01 | -0.10 [-0.05, 0.05] | 16.3% 20.3% | 37 | 100.0% |
| 2015 Kogos | 16 3.00 0.10 | 0.01 | 16 3.00 0.10 | 0.01 | 0.00 [-0.07, 0.07] | 83.7% 73.7% | 37 | 100.0% |

Fixed effect model

Random effects model

Test for overall effect (fixed effect): z = -0.53 (p = 0.597)
Test for overall effect (random effects): t = -0.60 (p = 0.508)

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

| Study  | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD 95% CI | Weight (fixed) | Weight (random) |
|--------|--------------------|----|----------------|----|----------------|-----------|---------------|-----------------|
| 2015 Cramer | 16 0.50 0.50 | 0.00 | 16 0.50 0.50 | 0.00 | 0.00 [0.00, 0.00] | 65.9% 65.9% | 37 | 100.0% |
| 2015 Kogos | 16 0.37 0.47 | 0.00 | 16 0.41 0.87 | 0.00 | -0.04 [-0.09, 0.01] | 34.1% 34.1% | 37 | 100.0% |

Fixed effect model

Random effects model

Test for overall effect (fixed effect): z = -0.10 (p = 0.920)
Test for overall effect (random effects): t = -0.72 (p = 0.477)

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

| Study  | Postop Total Mean | SD | Preop Total Mean | SD | Mean Difference | MD 95% CI | Weight (fixed) | Weight (random) |
|--------|-------------------|----|------------------|----|----------------|-----------|---------------|-----------------|
| 2015 Cramer | 16 2.96 0.31 | 0.00 | 16 2.00 0.10 | 0.01 | -2.46 [-2.71, -2.13] | 45.5% 45.5% | 34 | 100.0% |
| 2015 Kogos | 16 3.00 0.10 | 0.00 | 16 3.00 0.10 | 0.01 | -2.63 [-2.87, -2.38] | 54.5% 54.5% | 34 | 100.0% |

Fixed effect model

Random effects model

Test for overall effect (fixed effect): z = -2.81 (p = 0.006)
Test for overall effect (random effects): t = -2.05 (p = 0.042)

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

| Study  | Postop Total Mean | SD | Preop Total Mean | SD | Mean Difference | MD 95% CI | Weight (fixed) | Weight (random) |
|--------|-------------------|----|------------------|----|----------------|-----------|---------------|-----------------|
| 2015 Cramer | 16 2.00 0.10 | 0.01 | 16 2.00 0.10 | 0.01 | 0.00 [-0.07, 0.07] | 20.3% 20.3% | 37 | 100.0% |
| 2015 Kogos | 16 3.00 0.10 | 0.01 | 16 3.00 0.10 | 0.01 | -2.59 [-3.86, -2.32] | 26.4% 26.4% | 37 | 100.0% |

Fixed effect model

Random effects model

Test for overall effect (fixed effect): z = -2.47 (p = 0.013)
Test for overall effect (random effects): t = -6.09 (p = 0.010)

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

| Study  | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD 95% CI | Weight (fixed) | Weight (random) |
|--------|--------------------|----|----------------|----|----------------|-----------|---------------|-----------------|
| 2015 Cramer | 16 2.50 0.14 | 0.00 | 16 2.50 0.12 | 0.00 | 0.10 [0.02, 0.19] | 52.9% 52.9% | 37 | 100.0% |
| 2015 Kogos | 16 2.60 0.12 | 0.00 | 16 2.59 0.20 | 0.00 | -0.04 [-0.10, 0.02] | 38.2% 38.2% | 37 | 100.0% |

Fixed effect model

Random effects model

Test for overall effect (fixed effect): z = 1.57 (p = 0.122)
Test for overall effect (random effects): t = -0.49 (p = 0.622)
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          | TV+PVR Total Mean | PVR Total Mean | Weight (fixed) | Weight (random) |
|----------------|-------------------|----------------|----------------|-----------------|
| Taixiang Kim 2019 | 38.21 ± 3.40      | 39.21 ± 5.30   | 30.0%          | 30.0%           |
| Cramer 2015     | 18.31 ± 2.00      | 18.29 ± 4.00   | 64.0%          | 64.0%           |

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

| Study          | TV+PVR Total Mean | PVR Total Mean | Weight (fixed) | Weight (random) |
|----------------|-------------------|----------------|----------------|-----------------|
| Taixiang Kim 2019 | 38.14 ± 3.50      | 39.17 ± 4.60   | 40.7%          | 40.7%           |
| Cramer 2015     | 18.24 ± 3.00      | 18.24 ± 3.00   | 59.3%          | 59.3%           |

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

| Study          | Preop Total Mean | Postop Total Mean | Weight (fixed) | Weight (random) |
|----------------|------------------|-------------------|----------------|-----------------|
| Taixiang Kim 2019 | 38.21 ± 3.40     | 38.21 ± 3.40      | 32.4%          | 32.4%           |
| Cramer 2015     | 18.31 ± 2.00     | 18.31 ± 2.00      | 67.6%          | 67.6%           |

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

| Study          | Preop Total Mean | Postop Total Mean | Weight (fixed) | Weight (random) |
|----------------|------------------|-------------------|----------------|-----------------|
| Taixiang Kim 2019 | 29.17 ± 5.60     | 29.17 ± 6.30      | 39.0%          | 39.0%           |
| Cramer 2015     | 18.24 ± 3.00     | 18.24 ± 3.00      | 62.0%          | 62.0%           |

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

| Study          | TV+PVR Total Mean | PVR Total Mean | Weight (fixed) | Weight (random) |
|----------------|-------------------|----------------|----------------|-----------------|
| Taixiang Kim 2019 | 38.21 ± 3.40      | 39.21 ± 5.30   | 51.5%          | 51.5%           |
| Cramer 2015     | 18.31 ± 2.00      | 18.29 ± 4.00   | 49.7%          | 49.7%           |
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

| Study  | TV+PVR | Mean | SD  | Total Mean | SD  | PVR | Mean | SD  | Weight (fixed) | Weight (random) |
|--------|--------|------|-----|------------|-----|-----|------|-----|---------------|----------------|
| Lueck  | 10     | 1.70| 0.90| 18        | 1.50| 0.96| 0.20 | 0.90| 0.06          | 0.06           |
| Kugon  | 19     | 1.50| 0.96| 19        | 2.54| 0.96| 0.05 | 0.90| 0.06          | 0.06           |
| Fixed effect model | 26     | 0.08| 0.06| 0.08 | 0.06| 100.0% | 100.0% |
| Random effects model | 37     | 0.08| 0.06| 0.08 | 0.06| 100.0% | 100.0% |

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

| Study  | TV+PVR | Mean | SD  | Total Mean | SD  | PVR | Mean | SD  | Weight (fixed) | Weight (random) |
|--------|--------|------|-----|------------|-----|-----|------|-----|---------------|----------------|
| Lueck  | 10     | 2.11| 0.90| 18        | 1.70| 0.92| 0.33 | 0.21| 0.10          | 0.04           |
| Kugon  | 19     | 1.70| 0.92| 19        | 2.27| 0.92| 0.33 | 0.21| 0.04          | 0.04           |
| Fixed effect model | 26     | 0.22| 0.04| 0.22 | 0.04| 100.0% | 100.0% |
| Random effects model | 37     | 0.22| 0.04| 0.22 | 0.04| 100.0% | 100.0% |

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

| Study  | Postop | Total Mean | SD  | Total Mean | SD  | Preop | Total Mean | SD  | MD  | 95%-CI | Weight (fixed) | Weight (random) |
|--------|--------|------------|-----|------------|-----|--------|------------|-----|-----|--------|---------------|----------------|
| Lueck  | 10     | 2.11| 0.90| 18        | 1.70| 1.00| 0.41 | 0.46| 0.10| 0.00  | 0.01           | 0.01           |
| Kugon  | 19     | 1.70| 0.90| 19        | 2.27| 0.92| 0.07 | 0.14| 0.00| 0.01  | 0.01           | 0.01           |
| Fixed effect model | 26     | 0.18| 0.04| 0.18 | 0.04| 100.0% | 100.0% |
| Random effects model | 37     | 0.18| 0.04| 0.18 | 0.04| 100.0% | 100.0% |

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

| Study  | Postop | Total Mean | SD  | Total Mean | SD  | Preop | Total Mean | SD  | MD  | 95%-CI | Weight (fixed) | Weight (random) |
|--------|--------|------------|-----|------------|-----|--------|------------|-----|-----|--------|---------------|----------------|
| Lueck  | 10     | 1.70| 0.90| 18        | 1.70| 0.92| 0.28 | 0.33| 0.09| 0.00  | 0.01           | 0.01           |
| Kugon  | 19     | 1.70| 0.92| 19        | 2.27| 0.92| 0.07 | 0.14| 0.00| 0.01  | 0.01           | 0.01           |
| Fixed effect model | 37     | 0.37| 0.04| 0.37 | 0.04| 100.0% | 100.0% |
| Random effects model | 37     | 0.37| 0.04| 0.37 | 0.04| 100.0% | 100.0% |

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

| Study  | TV+PVR | Mean | SD  | Total Mean | SD  | PVR | Mean | SD  | Weight (fixed) | Weight (random) |
|--------|--------|------|-----|------------|-----|-----|------|-----|---------------|----------------|
| Lueck  | 10     | 0.41| 0.90| 18        | 0.28| 0.31| 0.13 | 0.18| 0.04| 0.14  | 0.01           | 0.01           |
| Kugon  | 19     | 0.28| 0.31| 19        | 0.71| 0.23| 0.14 | 0.21| 0.02| 0.14  | 0.01           | 0.01           |
| Fixed effect model | 26     | 0.14| 0.01| 0.14 | 0.01| 100.0% | 100.0% |
| Random effects model | 37     | 0.14| 0.01| 0.14 | 0.01| 100.0% | 100.0% |
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

| Study | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD | 95%-CI | Weight (fixed) | Weight (random) |
|-------|--------------------|----|----------------|----|----------------|----|--------|---------------|----------------|
| Luck 2018 | 1.00 ± 0.07 | 10 | 1.56 ± 0.06 | 18 | -0.56 | 0.24 | [-0.46; 0.94] | 45.0% | 45.1% |
| Kögren 2015 | 1.93 ± 1.04 | 16 | 1.42 ± 0.03 | 19 | 0.51 | 0.51 | [0.22; 1.11] | 50.0% | 50.9% |
| Fixed effect model | 25 | 37 | 0.39 | [0.08; 0.80] | 100.0% | -- | -- | 100.0% | 100.0% |
| Random effects model | -- | -- | 0.39 | [0.13; 0.66] | 80.0% | -- | -- | 100.0% | 100.0% |

Test for overall effect (fixed effect): z = 1.60 (p = 0.104)
Test for overall effect (random effects): z = 2.09 (p = 0.021)

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

| Study | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD | 95%-CI | Weight (fixed) | Weight (random) |
|-------|--------------------|----|----------------|----|----------------|----|--------|---------------|----------------|
| Luck 2018 | 2.44 ± 1.07 | 10 | 2.06 ± 1.03 | 18 | 0.38 | 0.38 | [0.44; 1.20] | 32.6% | 32.6% |
| Kögren 2015 | 1.90 ± 0.63 | 16 | 1.03 ± 0.68 | 19 | 0.87 | 0.87 | [0.30; 1.44] | 67.4% | 67.4% |
| Fixed effect model | 26 | 37 | 0.71 | [0.24; 1.18] | 100.0% | -- | -- | 100.0% | 100.0% |
| Random effects model | -- | -- | 0.71 | [0.21; 1.20] | 80.0% | -- | -- | 100.0% | 100.0% |

Test for overall effect (fixed effect): z = 2.39 (p = 0.017)
Test for overall effect (random effects): z = 3.09 (p = 0.001)

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

| Study | Postop Total Mean | SD | Preop Total Mean | SD | Mean Difference | MD | 95%-CI | Weight (fixed) | Weight (random) |
|-------|-------------------|----|------------------|----|----------------|----|--------|---------------|----------------|
| Luck 2018 | 2.44 ± 1.07 | 10 | 1.90 ± 0.63 | 16 | 0.64 | 0.64 | [0.21; 1.20] | 36.0% | 41.1% |
| Kögren 2015 | 1.90 ± 0.63 | 16 | 1.03 ± 0.68 | 19 | 0.87 | 0.87 | [0.30; 1.44] | 67.4% | 67.4% |
| Fixed effect model | 26 | 37 | 0.71 | [0.24; 1.18] | 100.0% | -- | -- | 100.0% | 100.0% |
| Random effects model | -- | -- | 0.71 | [0.24; 1.18] | 80.0% | -- | -- | 100.0% | 100.0% |

Test for overall effect (fixed effect): z = 2.43 (p = 0.015)
Test for overall effect (random effects): z = 3.09 (p = 0.001)

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

| Study | Postop Total Mean | SD | Preop Total Mean | SD | Mean Difference | MD | 95%-CI | Weight (fixed) | Weight (random) |
|-------|-------------------|----|------------------|----|----------------|----|--------|---------------|----------------|
| Luck 2018 | 2.06 ± 1.03 | 16 | 1.50 ± 0.90 | 18 | 0.56 | 0.56 | [0.15; 1.11] | 41.2% | 47.9% |
| Kögren 2015 | 1.90 ± 0.86 | 19 | 1.42 ± 0.83 | 19 | 0.38 | 0.38 | [0.00; 0.76] | 61.2% | 52.1% |
| Fixed effect model | 37 | 37 | 0.38 | [0.00; 0.76] | 100.0% | -- | -- | 100.0% | 100.0% |
| Random effects model | -- | -- | 0.38 | [0.00; 0.76] | 80.0% | -- | -- | 100.0% | 100.0% |

Test for overall effect (fixed effect): z = 0.41 (p = 0.970)
Test for overall effect (random effects): z = 0.48 (p = 0.634)

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

| Study | TVI+PVR Total Mean | SD | PVR Total Mean | SD | Mean Difference | MD | 95%-CI | Weight (fixed) | Weight (random) |
|-------|--------------------|----|----------------|----|----------------|----|--------|---------------|----------------|
| Luck 2018 | 0.64 ± 0.44 | 10 | 0.50 ± 0.33 | 18 | 0.14 | 0.14 | [0.01; 0.27] | 30.4% | 35.4% |
| Kögren 2015 | 0.00 ± 0.33 | 16 | 0.39 ± 0.28 | 19 | 0.36 | 0.36 | [0.19; 0.53] | 69.6% | 64.0% |
| Fixed effect model | 26 | 37 | 0.29 | [0.12; 0.46] | 100.0% | -- | -- | 100.0% | 100.0% |
| Random effects model | -- | -- | 0.29 | [0.12; 0.46] | 80.0% | -- | -- | 100.0% | 100.0% |

Test for overall effect (fixed effect): z = 2.31 (p = 0.001)
Test for overall effect (random effects): z = 2.08 (p = 0.027)
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

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

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

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

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

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

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

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

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

| Study            | Total Mean | SD Total | Mean Difference | MD     | 95% CI   | Weight (fixed) | Weight (random) |
|------------------|------------|----------|-----------------|--------|----------|----------------|-----------------|
| Rolantes 2017    | 8          | 39.10    | 6.00            | 10.56  | -4.92    | 3.81           | 0.81            |
| Rolantes 2017    | 8          | 42.50    | 5.00            | 9.56   | -4.61    | 3.81           | 0.81            |
| Cramer 2015      | 10         | 500.00   | 11.00           | 13.50  | -1.14    | 3.81           | 0.81            |
| Pooled mean      | 8           | 41.00    | 6.00            | 10.50  | -4.92    | 3.81           | 0.81            |
| Random effects   | 43          | 43       |                 | 9.50   | -1.14    | 3.81           | 0.81            |

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

| Study            | Total Mean | SD Total | Mean Difference | MD     | 95% CI   | Weight (fixed) | Weight (random) |
|------------------|------------|----------|-----------------|--------|----------|----------------|-----------------|
| Rolantes 2017    | 8          | 43.00    | 6.00            | 10.56  | -4.92    | 3.81           | 0.81            |
| Rolantes 2017    | 8          | 44.50    | 5.00            | 9.56   | -4.61    | 3.81           | 0.81            |
| Cramer 2015      | 10         | 500.00   | 11.00           | 13.50  | -1.14    | 3.81           | 0.81            |
| Pooled mean      | 8           | 41.00    | 6.00            | 10.50  | -4.92    | 3.81           | 0.81            |
| Random effects   | 43          | 43       |                 | 9.50   | -1.14    | 3.81           | 0.81            |

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

| Study            | Total Mean | SD Total | Preop Mean | Preop SD | Mean Difference | MD     | 95% CI   | Weight (fixed) | Weight (random) |
|------------------|------------|----------|------------|----------|-----------------|--------|----------|----------------|-----------------|
| Rolantes 2017    | 8          | 43.00    | 6.00       | 10.56    | -4.92           | 3.81   | 0.81     | 6.00           | 6.00            |
| Rolantes 2017    | 8          | 44.50    | 5.00       | 9.56     | -4.61           | 3.81   | 0.81     | 6.00           | 6.00            |
| Cramer 2015      | 10         | 500.00   | 11.00      | 13.50    | -1.14           | 3.81   | 0.81     | 6.00           | 6.00            |
| Pooled mean      | 8           | 41.00    | 6.00       | 10.50    | -4.92           | 3.81   | 0.81     | 6.00           | 6.00            |
| Random effects   | 43          | 43       | 3.00       | 3.00     | -1.14           | 3.81   | 0.81     | 6.00           | 6.00            |

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

| Study            | Total Mean | SD Total | Preop Mean | Preop SD | Mean Difference | MD     | 95% CI   | Weight (fixed) | Weight (random) |
|------------------|------------|----------|------------|----------|-----------------|--------|----------|----------------|-----------------|
| Rolantes 2017    | 8          | 43.00    | 6.00       | 10.56    | -4.92           | 3.81   | 0.81     | 6.00           | 6.00            |
| Rolantes 2017    | 8          | 44.50    | 5.00       | 9.56     | -4.61           | 3.81   | 0.81     | 6.00           | 6.00            |
| Cramer 2015      | 10         | 500.00   | 11.00      | 13.50    | -1.14           | 3.81   | 0.81     | 6.00           | 6.00            |
| Pooled mean      | 8           | 41.00    | 6.00       | 10.50    | -4.92           | 3.81   | 0.81     | 6.00           | 6.00            |
| Random effects   | 43          | 43       | 3.00       | 3.00     | -1.14           | 3.81   | 0.81     | 6.00           | 6.00            |

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

| Study            | Total Mean | SD Total | Mean Difference | MD     | 95% CI   | Weight (fixed) | Weight (random) |
|------------------|------------|----------|-----------------|--------|----------|----------------|-----------------|
| Rolantes 2017    | 8          | 5.30     | 4.51            | 15.00  | 2.50     | 1.40           | 0.81            |
| Rolantes 2017    | 8          | 3.00     | 1.00            | 5.50   | -1.40    | 1.00           | 0.81            |
| Cramer 2015      | 10         | 17.00    | 3.67            | 10.00  | -2.50    | 1.40           | 0.81            |
| Pooled mean      | 8           | 3.50     | 4.51            | 15.00  | 2.50     | 1.40           | 0.81            |
| Random effects   | 43          | 43       |                 | 10.00  | -2.50    | 1.40           | 0.81            |
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 Events | PVR Total | Odds Ratio | OR    | 95% CI       | Weight (fixed) | Weight (random) |
|------------------|----------------|--------------|-----------|------------|-------|--------------|----------------|-----------------|
| Roubertie 2017   | 0              | 16           | 2         | 25         | 0.28  | [0.01; 6.33] | 33.2%          | 11.3%           |
| Cramer 2015      | 0              | 18           | 0         | 18         | 0.00  | [0.00; 0.00] | 0.00           | 0.00            |
| Kogon 2015       | 0              | 16           | 0         | 19         | 0.00  | [0.00; 0.00] | 0.00           | 0.00            |
| Deshales 2020    | 6              | 180          | 5         | 362        | 2.46  | [0.74; 8.18] | 55.6%          | 75.6%           |
| Lueck 2018       | 1              | 10           | 1         | 18         | 1.89  | [0.11; 33.89] | 11.1%          | 13.1%           |

Fixed effect model: 240 / 442
Random effects model: 1.67 [0.62; 4.62] 100.0% --

Heterogeneity, $I^2 = 0\%$, $p = 0.437$
Test for overall effect (fixed effect): $z = 1.02$ ($p = 0.309$)
Test for overall effect (random effects): $I^2 = 1.30$ ($p = 0.324$)