

# Pulmonary Valve Replacement in Tetralogy of Fallot: An Updated Meta-Analysis

Jef Van den Eynde, BSc,\* Michel Pompeu B. O. Sá, MD, PhD,\* Dominique Vervoort, MD, Leonardo Roever, MSc, PhD, Bart Meyns, MD, PhD, Werner Budts, MD, PhD, Marc Gewillig, MD, PhD, Arjang Ruhparwar, MD, PhD, Konstantin Zhigalov, MD, PhD, and Alexander Weymann, MD, PhD

Unit of Cardiac Surgery, Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium; Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco, PROCAPE, University of Pernambuco, Recife, Pernambuco, Brazil; Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Department of Clinical Research, Federal University of Uberlândia, Minas Gerais, Uberlândia, Brazil; Congenital and Structural Cardiology University Hospitals Leuven and Department of Cardiovascular Sciences, Catholic University Leuven, Leuven, Belgium; Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium; and Department of Thoracic and Cardiovascular Surgery, West German Heart and Vascular Center, Essen, Germany

## ABSTRACT

**BACKGROUND** The benefits of pulmonary valve replacement (PVR) for pulmonary insufficiency in patients with repaired tetralogy of Fallot are still incompletely understood, and optimal timing remains challenging.

**METHODS** We systematically reviewed databases (PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials /Cochrane Controlled Trials Register, [ClinicalTrials.gov](https://www.clinicaltrials.gov), Scientific Electronic Library Online, Literatura Latino Americana em Ciências da Saúde, and Google Scholar) and reference lists of relevant articles for studies about PVR in repaired tetralogy of Fallot patients that reported any of the following outcomes: mortality and redo PVR rates, right ventricular (RV) and left ventricular measures, QRS duration, cardiopulmonary exercise test results, or brain natriuretic peptide. In addition to calculating the pooled treatment effects using a random-effects meta-analysis, we evaluated the effect of preoperative measures on PVR outcomes using meta-regressions.

**RESULTS** Eighty-four studies involving 7544 patients met the eligibility criteria. Pooled mortality at 30 days, 5 years, and 10 years after PVR was 0.87% (63 of 7253 patients, 80 studies), 2.7% (132 of 4952 patients, 37 studies), and 6.2% (510 of 2765 patients, 15 studies), respectively. Pooled 5- and 10-year redo PVR rates were 3.7% (141 of 3755 patients, 23 studies) and 16.8% (172 of 3035 patients, 16 studies), respectively. The results of the previous meta-analysis could be confirmed. In addition, we demonstrated that after PVR (1) QRS duration, cardiopulmonary exercise test results, and RV and left ventricular measures longitudinal strain do not significantly change; (2) brain natriuretic peptide decreases; and (3) greater indexed RV end-diastolic and end-systolic volumes are associated with lower chances of RV volume normalization after PVR.

**CONCLUSIONS** This updated meta-analysis provides evidence about the benefits of PVR.

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One of the most common late consequences in patients with repaired tetralogy of Fallot (TOF) is pulmonary valve insufficiency.<sup>1</sup> Significant pulmonary insufficiency results in progressive right ventricular (RV) dilatation and dysfunction, arrhythmias, heart failure, a decrease in exercise tolerance, and increased risk of sudden and premature death. The current indications of pulmonary valve replacement (PVR) for pulmonary insufficiency in patients with repaired TOF according to the most recent

guidelines<sup>2-4</sup> are based overall on the presence of symptoms (class I). The indications for asymptomatic patients

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\*Mr Van den Eynde and Dr Pompeu contributed equally to this work and are co-first authors.

Address correspondence to Mr Van den Eynde, Department of Cardiovascular Diseases, University Hospitals Leuven, KU Leuven, Herestraat 49, 3000 Leuven, Belgium; email: [jef.vandeneinde@student.kuleuven.be](mailto:jef.vandeneinde@student.kuleuven.be).

**Abbreviations and Acronyms**

BNP	= brain natriuretic peptide
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
LVEDV	= left ventricular end-diastolic volume
LVESV	= left ventricular end-systolic volume
MRI	= magnetic resonance imaging
PRF	= pulmonary regurgitation fraction
PVR	= pulmonary valve replacement
RV	= right ventricle/ventricular
RVEDV	= right ventricular end-diastolic volume
RVEF	= right ventricular ejection fraction
RVESV	= right ventricular end-systolic volume
TOF	= tetralogy of Fallot
$V_E/V_{CO_2}$	= expired volume per unit time/volume of $CO_2$
$Vo_2$	= volume of oxygen uptake

are restricted to the following situations: decrease in objective exercise capacity, progressive RV dilation, progressive RV systolic dysfunction, progressive tricuspid regurgitation (at least moderate), RV outflow tract obstruction with RV systolic pressure exceeding 80 mm Hg (tricuspid regurgitation velocity  $>4.3$  m/s), and sustained atrial/ventricular arrhythmias (class IIa).

Optimal timing of PVR remains challenging. A balance should be made between intervening too early and risking complications, such as endocarditis, as well as redo PVR procedures due to the limited durability of prosthetic valves vs intervening too late with no potential for RV and functional recovery, with late arrhythmia and heart failure.

Despite the recommendation classes, the levels of evidence still remain low (level B and C).<sup>2-4</sup> A review of the current state of published medical data on this subject is therefore necessary. In 2013, a meta-analysis about PVR in 3118 patients with repaired TOF was published.<sup>5</sup> Since then, several studies have been added to the literature. The present meta-analysis reevaluates the state of evidence together with additional analyses not conducted in the prior meta-analysis.

**MATERIAL AND METHODS**

This analysis was planned in accordance with current guidelines for performing comprehensive systematic reviews and meta-analysis with regression, including the PRISMA (Preferred Reporting Items for Systematic reviews Meta-Analyses)<sup>6</sup> and MOOSE (Meta-analysis Of Observational Studies in Epidemiology)<sup>7</sup> guidelines for randomized and nonrandomized studies, respectively. We aimed to determine the outcomes after PVR and its effect on indexed ventricular volumes, ventricular function, QRS duration, cardiopulmonary exercise test (CPET) results, ventricular strain, and brain natriuretic peptide (BNP) in pediatric and adult patient populations after initial repair of TOF.

**ELIGIBILITY CRITERIA.** Using the PICOS (Participants, Interventions, Comparisons and Outcomes) strategy, studies were considered if:

1. The population comprised patients with total repaired TOF who developed at least moderate pulmonary valve insufficiency; and
2. Patients were admitted to the hospital for PVR; and
3. Patients were assessed before and after PVR; and
4. Outcomes studied included any of the following: 30-day, 5-year, and 10-year mortality rates, 5-year and 10-year redo PVR rate, indexed RV end-diastolic volume (RVEDV), indexed RV end-systolic volume (RVESV), corrected RV ejection fraction (RVEF), indexed left ventricular (LV) end-diastolic volume (LVEDV), indexed LV end-systolic volume (LVESV), LV ejection fraction (LVEF), pulmonary regurgitation fraction (PRF), RV/LV ratio, QRS duration, peak oxygen uptake ( $Vo_2$ ), ventilatory efficiency (expired volume per unit time [ $V_E$ ]/volume of  $CO_2$  [ $V_{CO_2}$ ]), RV longitudinal strain, LV longitudinal strain, or BNP; and
5. Studies were prospective or retrospective or non-randomized or randomized controlled trials.

**INFORMATION SOURCES.** The following databases were used (until March 2020): PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials/Cochrane Controlled Trials Register, [ClinicalTrials.gov](https://www.clinicaltrials.gov); Scientific Electronic Library Online, Literatura Latino Americana em Ciências da Saúde, Google Scholar, and reference lists of relevant articles.

**SEARCH.** The Medical Subject Headings terms that were used for this search are given in the [Supplemental Methods](#).

**STUDY SELECTION.** The following steps were taken: (1) identification of titles of records through databases 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 (J.V.d.E. and M.P.B.O.S.). Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer made the final decision.

**DATA ITEMS.** The crude end points were 30-day mortality (%), 5-year mortality (%), 10-year mortality (%), 5-year redo PVR (%), and 10-year redo PVR (%). The following mean values of comparative data were also collected with regard to preoperative and postoperative periods: indexed RVEDV ( $mL/m^2$ ), indexed RVESV ( $mL/m^2$ ), corrected RVEF, indexed LVEDV ( $mL/m^2$ ), indexed LVESV ( $mL/m^2$ ), LVEF, PRF (%), RV/LV ratio, QRS duration (ms), peak  $Vo_2$  ( $mL/kg/min$  and % predicted),  $V_E/V_{CO_2}$ , RV lateral longitudinal

strain (%), LV global longitudinal strain (%), and BNP (ng/L).

Studies were screened for potential overlap of 2 or more patient cohorts. When this was the case, the study containing the largest number of patients was considered, and other studies were excluded. Only if the selected article did not report a specific data item, data from these other articles were considered.

**DATA COLLECTION PROCESS.** Two independent reviewers extracted the data (J.V.d.E. and M.P.B.O.S.). When there was disagreement about data, a third reviewer checked the data and made the final decision. From each study, we extracted patient characteristics, study design, and outcomes.

**SUMMARY MEASURES.** The principal summary measures were difference in means with 95% confidence intervals (CI) and *P* values (considered statistically significant when  $P < .05$ ). The meta-analysis was completed with Comprehensive Meta-Analysis 2 software (Biostat, Inc, Englewood, NJ).

**SYNTHESIS OF RESULTS.** Forest plots were generated for graphical presentations of clinical outcomes, and we performed the  $I^2$  test and  $\chi^2$  test for assessment of heterogeneity across the studies.<sup>8</sup> Each study was summarized by differences in means before and after PVR. The differences in means were combined across studies with the weighted DerSimonian-Laird random-effects model.<sup>9</sup>

**RISK OF BIAS ACROSS STUDIES.** To assess publication bias, a funnel plot was generated and statistically assessed by the Begg and Mazumdar test<sup>10</sup> and the Egger test.<sup>11</sup>

**META-REGRESSION ANALYSIS.** Meta-regression analyses were performed to determine whether the effects of PVR were modulated by prespecified factors. Meta-regression graphs describe the effect of PVR on the outcome (plotted on the *y*-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the *x*-axis).

In addition, meta-regression analyses were performed to determine whether RV volume normalization was modulated by prespecified factors. RV normalization was defined as postoperative indexed RVEDV of less than 108 mL/m<sup>2</sup>.<sup>12</sup> Meta-regression graphs describe the logit event rate of RV volume normalization (plotted on the *y*-axis) as a function of a given factor (plotted as a mean of proportion of that factor on the *x*-axis).

The predetermined modulating factors to be examined were age at TOF repair, interval between TOF repair and PVR, age at PVR, sex, preoperative indexed RVEDV, preoperative indexed RVESV and PRF changes, and QRS duration.

## RESULTS

**STUDY SELECTION.** We identified 10,640 citations, of which 143 studies were potentially relevant and retrieved as full text. Of these, 84 publications ([Supplemental Results](#)) fulfilled our eligibility criteria ([Figure 1](#)).

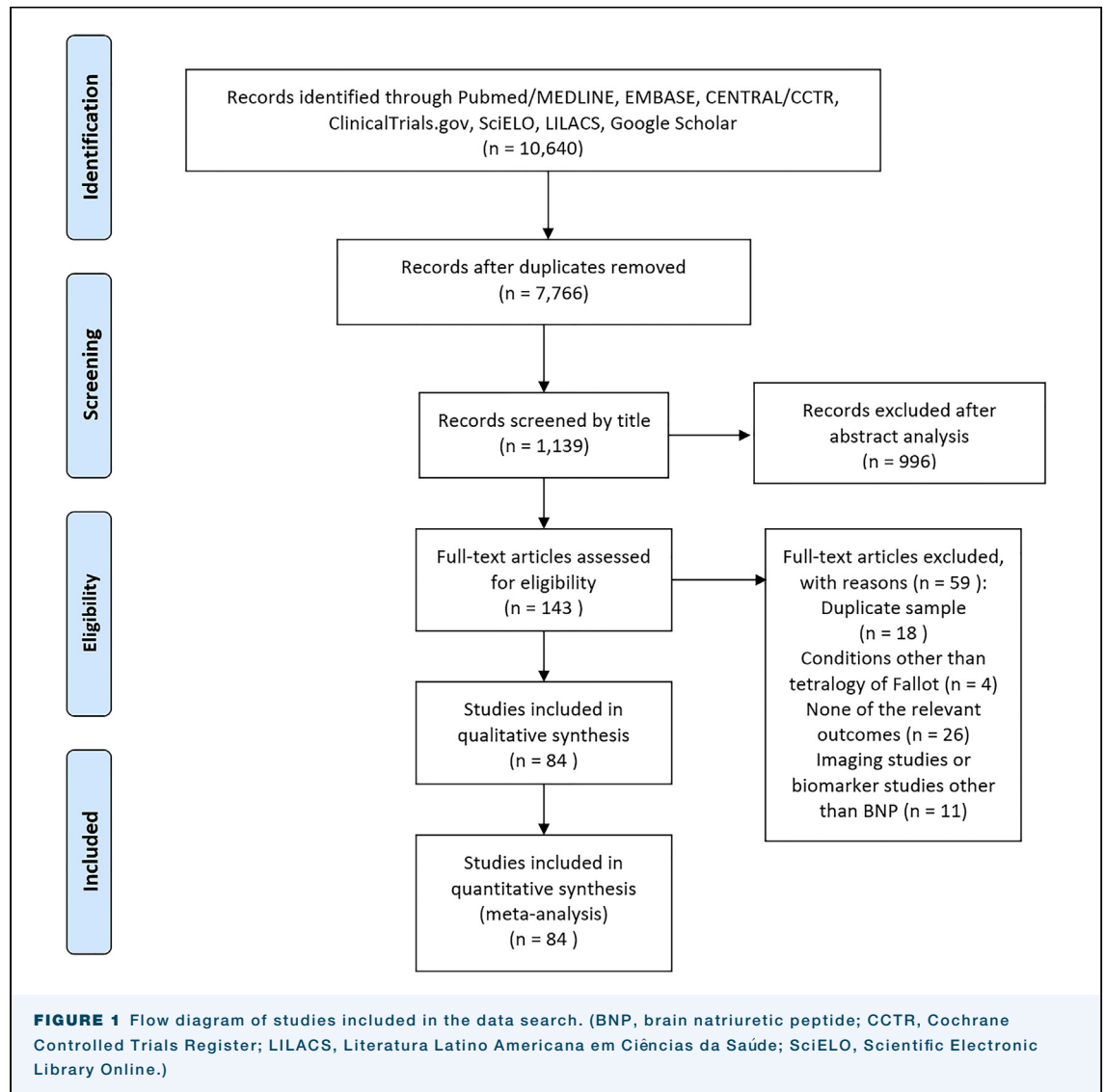
**STUDY CHARACTERISTICS.** Characteristics of each study are summarized in the [Supplemental Table](#). Included were 7544 patients from studies dating from 1997 to 2020 that involved patients enrolled from 1960 to 2018. Among these studies, 18 were prospective (21.4%), 2 were randomized (2.4%), and 13 were multicenter (15.5%). Most studies consisted of patients (mostly men) whose mean or median age at PVR was approximately the first and third decade of life. Ten studies (11.9%) consisted of an exclusively pediatric population, 23 (27.4%) were of an exclusively adult population, and 51 (60.7%) were of a mixed population. In general, we have observed that PVR has been indicated in the following situations: presence of symptoms and/or exercise intolerance during tests and/or those who had RV impairment, taking into account imaging data, with more attention given to cardiac magnetic resonance imaging (MRI) for detecting RV dilation.

**SYNTHESIS OF RESULTS.** The pooled mortality at 30 days, 5 years, and 10 years after PVR was 0.87% (63 of 7253 patients, 80 studies), 2.7% (132 of 4952 patients, 37 studies), and 6.2% (510 of 2765 patients, 15 studies), respectively. The pooled 5-year and 10-year redo PVR rates were 3.7% (141 of 3755 patients, 23 studies) and 16.8% (172 of 3035 patients, 16 studies), respectively. MRI scans were obtained after a median follow-up of 12 months (interquartile range, 5.9-23.4 months) after PVR.

**ANALYSES OF PREVIOUS META-ANALYSIS.** Results from the previous meta-analysis<sup>5</sup> could be confirmed and are reported in the [Supplemental Results](#). The corresponding forest plots are given in [Supplemental Figures 1-3](#).

**CPET RESULTS.** The difference in means for peak  $\dot{V}_{O_2}$  (in mL/kg/min) after PVR in each study is reported in [Figure 2A](#). Ten studies reported the data. There was evidence for low heterogeneity of treatment effect among the studies for peak  $\dot{V}_{O_2}$  (in mL/kg/min). The overall difference in means of peak  $\dot{V}_{O_2}$  (in mL/kg/min) showed no significant difference after PVR (random-effects model, 0.639; 95% CI, -0.615 to 1.894;  $P = .318$ ).

The difference in means for peak  $\dot{V}_{O_2}$  (in % predicted) after PVR in each study is reported in [Figure 2B](#). Five studies reported the data. There was evidence for low heterogeneity of treatment effect among the studies for peak  $\dot{V}_{O_2}$  (in mL/kg/min). The overall difference in means of peak  $\dot{V}_{O_2}$  (in mL/kg/min) showed no significant



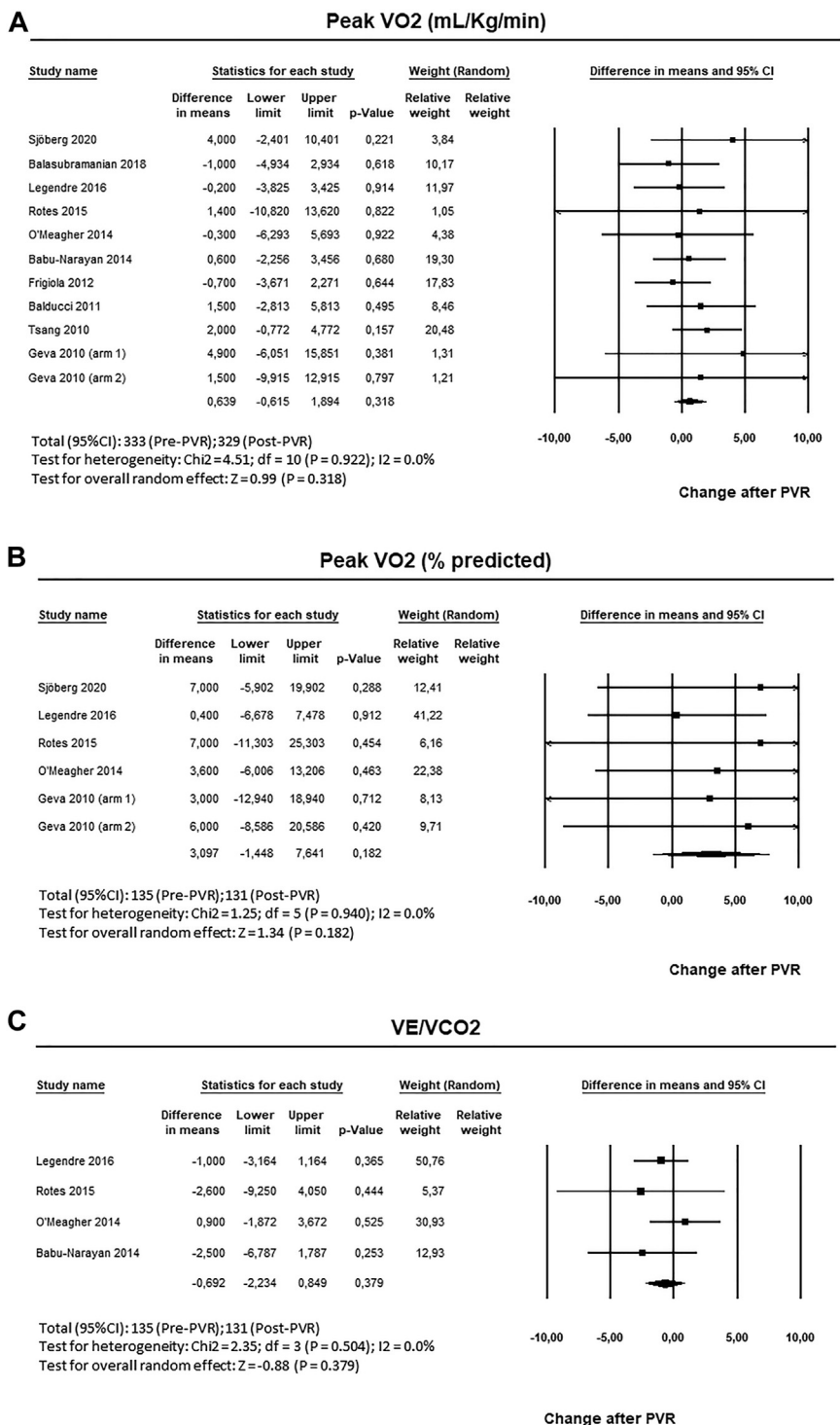
difference after PVR (random-effects model, 3.097; 95% CI, -1.448 to 7.641;  $P = .182$ ).

The difference in means for  $V_E/V_{CO_2}$  after PVR in each study is reported in Figure 2C. Only 4 studies reported the data. There was evidence for low heterogeneity of treatment effect among the studies for  $V_E/V_{CO_2}$ . The overall difference in means of  $V_E/V_{CO_2}$  showed no significant difference after PVR (random-effects model, -0.692; 95% CI, -2.234 to 0.849;  $P = .379$ ).

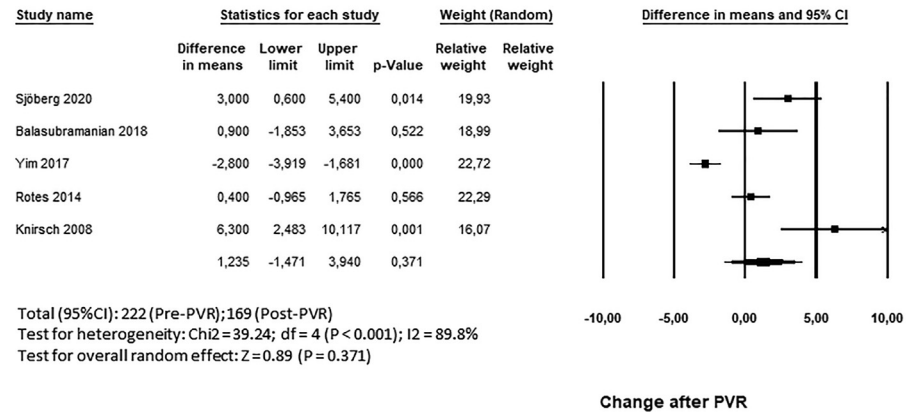
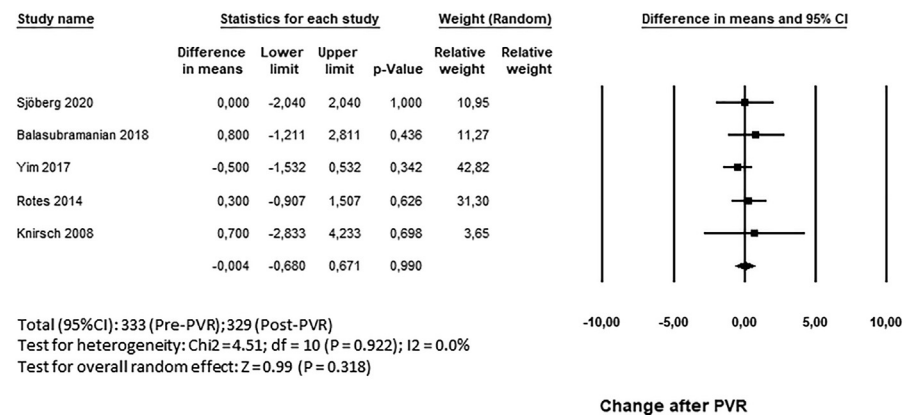
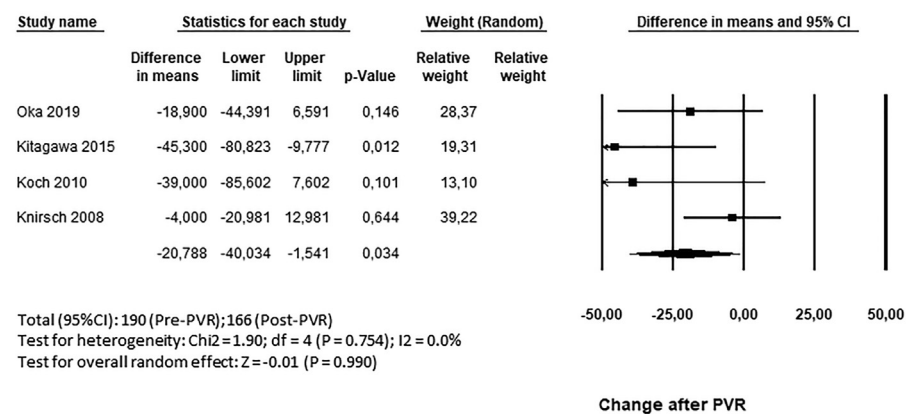
**STRAIN.** The difference in means for RV longitudinal strain after PVR in each study is reported in Figure 3A. Five studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for RV longitudinal strain. The overall difference in means of RV longitudinal strain showed no significant difference after PVR (random-effects model, 1.235; 95% CI, -1.471 to 3.940;  $P = .371$ ).

The difference in means for LV longitudinal strain after PVR in each study is reported in Figure 3B. Five studies reported the data. There was evidence for low heterogeneity of treatment effect among the studies for LV longitudinal strain. The overall difference in means of LV longitudinal strain showed no significant difference after PVR (random-effects model, -0.004; 95% CI, -0.680 to 0.671;  $P = .990$ ).

**BNP RESULTS.** BNP measurements were obtained at a median follow-up of 9 months (interquartile range 6-15.9 months). The difference in means for BNP after PVR in each study is reported in Figure 3C. Only 4 studies reported the data. There was evidence for nonsignificant heterogeneity of treatment effect among the studies for BNP. The overall difference in means of BNP showed a significant reduction after PVR (random-effects model, -20.788; 95% CI, -40.034 to -1.541;  $P = .034$ ).



**FIGURE 2** Forest plots of clinical outcomes related to cardiopulmonary exercise test results. Pooled difference in means for (A) peak oxygen uptake ( $V_{O_2}$ ) in mL/kg/min, (B) peak  $V_{O_2}$  (% predicted), and (C) ventilatory efficiency (expired volume per unit time [ $V_E$ ]/volume of  $CO_2$  [ $V_{CO_2}$ ]). The size of the solid square corresponds to the relative weight assigned in the pooled analysis. The horizontal lines represent the 95% confidence intervals (CIs). The diamond denotes the weighted mean differences, and the lateral tips of the diamond indicate the associated CI. (PVR, pulmonary valve replacement.)

**A** RV longitudinal strain (%)**B** LV longitudinal strain (%)**C** BNP (ng/L)

**FIGURE 3** Forest plots of clinical outcomes. Pooled difference in means for (A) right ventricular (RV) longitudinal strain, (B) left ventricular (LV) longitudinal strain, and (C) brain natriuretic peptide (BNP). The size of the solid square corresponds to the relative weight assigned in the pooled analysis. The horizontal lines represent the 95% confidence intervals (CIs). The diamond denotes the weighted mean differences, and the lateral tips of the diamond indicate the associated CI. (PVR, pulmonary valve replacement.)

**RISK OF BIAS ACROSS STUDIES.** Funnel plot analysis (Supplemental Figures 4-6) disclosed asymmetry around the axis for the treatment effect in the following outcomes: indexed RVEDV, indexed RVESV, QRS, and peak  $\text{Vo}_2$  (as % predicted). Consequently, publication bias related to these outcomes is not unlikely. Publication biases were not found in the other outcomes.

**META-REGRESSION ANALYSIS.** Results from the previous meta-regression<sup>5</sup> could be confirmed and are reported in the Supplemental Results. The corresponding forest plots are given in Supplemental Figures 7 and 8. In addition, with regard to the preoperative indexed RVEDV and RVESV, we observed statistically significant coefficients for RV volume normalization ( $P < .001$  [Figure 4A] and  $P < .001$  [Figure 4B], respectively). We can observe that the greater the preoperative indexed RVEDV and RVESV in a population undergoing PVR after TOF repair, the lower the logit event rate for RV volume normalization.

## COMMENT

**SUMMARY OF EVIDENCE.** Updating the initial meta-analysis about PVR in repaired TOF<sup>5</sup> with the studies published since its release, the current meta-analysis provides incremental value by demonstrating that patients with repaired TOF who developed pulmonary insufficiency over time after PVR (1) have a clear decrease in PRF, (2) present RV improvement of its indexed volumes and corrected RVEF, (3) present LV improvement of its systolic function measured by EF, despite the increasing of its indexed volumes, (4) have no significant change in QRS duration, (5) have no improvement in CPET results, (6) present no changes in RV or LV longitudinal strain, and (7) have a decrease in plasma BNP levels. Furthermore, if we consider the effect of preoperative variables on PVR outcomes, we observe that (8) RVs with greater preoperative indexed RVEDV measures presented the greatest responses in RV geometry and RV/LV ratio in the postoperative period but were correlated with a lower chance of RV volume normalization after PVR, (9) RVs with greater preoperative indexed RVESV measures presented the greatest responses in RV volumes in the postoperative period despite a lower increase in RVEF and a lower chance of RV volume normalization after PVR, (10) hearts with greater PRF decrease presented the greatest responses in terms of RV geometry in the postoperative period, (11) almost all of these observations are under important influence of heterogeneity of the effects, and (12) we found only limited publication bias.

**MORTALITY.** Our crude results with regard to pooled 30-day, 5-year, and 10-year mortality show that the rates

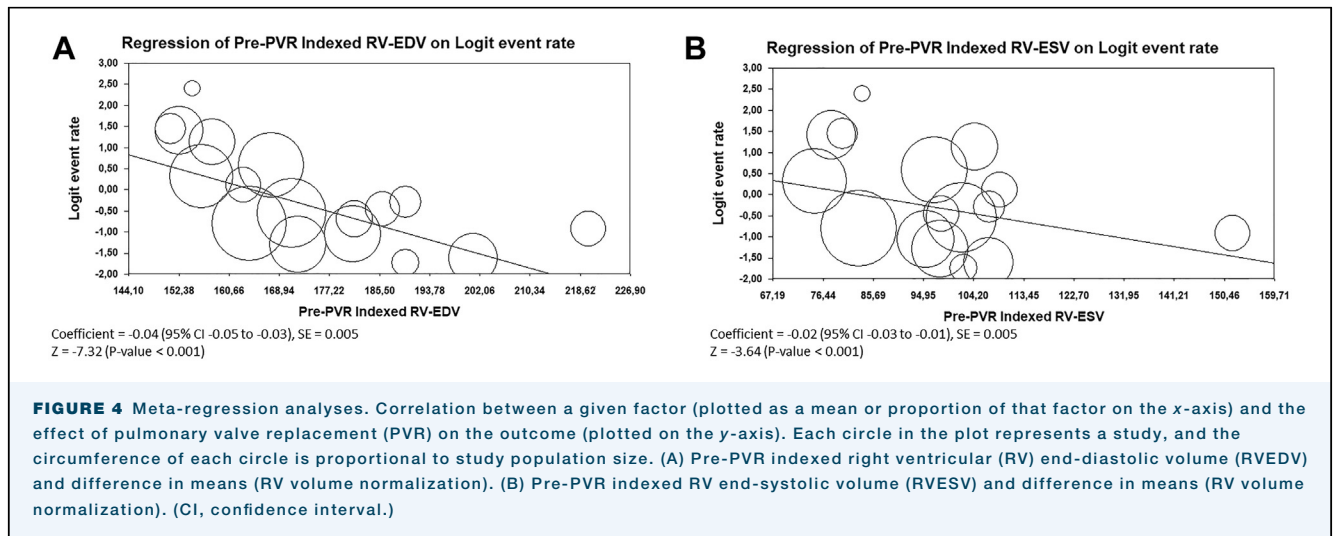
seem to be acceptable, because they are all low. The low reporting of data about 20-year mortality limits longer-term analyses. Taking into consideration that almost all of the studies reported data for symptomatic patients, these results must not be used to stimulate aggressive management in asymptomatic patients.

**CONFIRMATION OF FINDINGS FROM THE PREVIOUS META-ANALYSIS.** A further comment on the findings that could be confirmed from the previous meta-analysis can be found in the Supplemental Comment.

**EFFECT OF PVR ON RV.** As demonstrated in the initial meta-analysis,<sup>5</sup> as well as a meta-analysis by Cheung and colleagues<sup>13</sup> in 2010 and further confirmed in the present meta-analysis, variables of RV volumes and function, as assessed by cardiac MRI, significantly improve in response to PVR. It is a generally accepted observation, however, that some ventricles respond to PVR more than others and that not all of them reach RV volume normalization. On the other hand, the invasive nature of surgical PVR and the limited durability of prosthetic valves urge to delay the procedure as much as possible. Optimal timing of PVR, therefore, remains challenging, and there is a large need for good predictors of RV volume normalization after PVR.

In response to this need, various authors have tried to find an upper threshold above which there would be no normalization of the ventricle.<sup>14-22</sup> These thresholds have been based mostly around indexed RVEDV and RVESV measures, ranging between 150 and 170 mL/m<sup>2</sup> for indexed RVEDV and between 80 and 120 mL/m<sup>2</sup> for RVESV. The addition of studies that reported RV volume normalization (defined as postoperative indexed RVEDV <108 mL/m<sup>2</sup>)<sup>12</sup> in recent years allowed us to perform a meta-regression to determine predictors of RV volume normalization. Although it might be argued that indexed RVESV and RVEF should also be considered for the definition of normalization, most studies did not consistently do this, and thus, no data were available for this analysis. Based on our analyses, we found that greater a preoperative indexed RVEDV in a population undergoing PVR after TOF repair was associated with a lower chance of RV normalization, despite a greater numerical decrease in the indexed RVEDV. Similarly, we found that a greater preoperative RVESV significantly reduced the chances of RV normalization, despite a greater response in the numerical decrease in the indexed RVESV.

These results, pooling together data from various studies, demonstrate a clear negative correlation between RV volumes and chances of RV volume normalization in response to PVR. It is suggested that PVR should not be delayed until the point where the RV dilates too much, because this might limit benefits of the



procedure on clinical outcomes, adverse events, and mortality. The inability of severely dilated RVs to regain normal volume and function after PVR might indicate that these ventricles have already gone into a state of dysfunction characterized by underlying irreversible myocardial damage due to chronic volume and pressure overload.

Furthermore, we observed that all studies that had a preoperative indexed RVEDV below 160 mL/m<sup>2</sup> had RV volume normalization in at least 70% of patients. This supports the European Society of Cardiology Guidelines for the management of grown-up congenital heart disease published in 2010,<sup>2</sup> as these state that “Normalization of RV size after re-intervention becomes unlikely as soon as the indexed RVEDV exceeds 160 mL/m<sup>2</sup>,” referring to the study by Oosterhof and colleagues.<sup>15</sup>

An important matter of discussion is which of both better predicts outcomes: indexed RVEDV or indexed RVESV. Although most studies have reported cutoff values for indexed RVEDV, Henkens and colleagues<sup>23</sup> and Geva and colleagues<sup>16</sup> reasoned that indexed RVESV incorporates both RV volume overload and systolic function, variables strongly related to clinical status, and suggested that indexed RVESV would, therefore, be the most important preoperative measure for planning PVR. After having observed a strong correlation between postoperative indexed RVESV and RVEF but only a modest correlation between postoperative indexed RVEDV and RVEF, Lee and colleagues<sup>21</sup> concluded that more emphasis should be placed on the indexed RVESV rather than the indexed RVEDV in determining the timing of PVR. Other studies have demonstrated that the PR fraction is more closely associated with the indexed RVEDV compared with indexed RVESV.<sup>24,25</sup>

These last 2 findings taken together might reflect the pathophysiological sequence with RV dilatation as a response to volume overload occurring first (with

indexed RVEDV as a variable), followed by RV dysfunction (with indexed RVESV as a variable). As such, indexed RVEDV might be an earlier measure in the pathophysiological sequence, whereas indexed RVESV is more directly related to RV function and potentially clinical outcomes. Whether the use of one or the other cutoff also translates into superior clinical outcomes (including reduced mortality, heart failure, and arrhythmias) remains to be seen and will require well-designed management studies.

Interestingly, age at PVR and the interval between TOF repair and PVR were not significant predictors of RV volume normalization. There was a large spread in the proportions of patients showing normalization within each age category. Chances of normalization might, therefore, primarily be a function of preoperative RV volumes rather than age, in a way that young patients with severely dilated RVs still have a high risk of showing incomplete RV reverse remodeling in response to PVR. It has to be taken into account, however, that the studies were characterized by a heterogeneity of indications for PVR, with some centers opting for “early” PVR and other centers delaying PVR as long as possible. This might have limited the ability of our meta-analysis to infer the true relationship between age and outcomes after PVR.

**EFFECT OF PVR ON CPET RESULTS.** An important goal of PVR is to reach improvement of symptoms, thereby optimizing quality of life for the patient.<sup>2-4</sup> However, most of the diagnostic studies for the evaluation of patients with repaired TOF are completed at rest. These have the disadvantage that they are load dependent, and previous reports of studies have shown poor correlation of RV function at rest with objective and subjective measures of exercise capacity.<sup>26,27</sup> On the other hand, it has been



demonstrated TOF patients with normal resting RV function variables can already have impaired response to exercise, characterized by an inability to maintain sufficient right effective stroke volume and LV filling during effort.<sup>28</sup>

For this reason, CPET has been proposed as a tool to identify subclinical ventricular dysfunction in patients with repaired TOF. Decreased  $\dot{V}O_2$ <sup>29</sup> and decreased  $\dot{V}_E/\dot{V}CO_2$ <sup>30-32</sup> have both been identified as predictors of unfavorable outcomes in patients with congenital heart disease. Our meta-analysis, however, showed no effect of PVR on CPET results ( $\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$ ). As such, we could provide no evidence for the use of CPET for timing of PVR. However, CPET may be useful to improve risk stratification by identifying those patients who are incapable of sufficiently augmenting their cardiac output during exercise. Furthermore, future research should investigate whether a subgroup exists of patients who may benefit from PVR with regard to CPET outcomes. Lastly, adequate postintervention rehabilitation might be required to achieve improved CPET performance.

**EFFECT OF PVR ON RV AND LV LONGITUDINAL STRAIN.** Feature tracking is an image processing technology that quantifies myocardial tissue deformation and has been increasingly adapted over the past decade. Several studies have demonstrated its capability of characterizing ventricular mechanics in a more sensitive way than global volumetric variables.<sup>33,34</sup>

In our meta-analysis, we investigated the effect of PVR on RV and LV longitudinal strain but were unable to show any significant differences between measures before and after PVR. Given the limited studies that reported circumferential and radial strain data, we were unable to perform meta-analyses for these variables, which limits a complete understanding of the physiology.

Interestingly, Balasubramanian and colleagues<sup>35</sup> reported improved LV circumferential strain after PVR even in the absence of appreciable changes in LVEF, suggesting that changes in LV circumferential strain might precede responses of the LVEF to PVR. No changes in RV circumferential or longitudinal strain could be demonstrated in this study. However, more studies are needed to achieve a more complete understanding of the role of feature tracking strain variables in TOF patients undergoing PVR.

**EFFECT OF PVR ON BNP.** Plasma BNP levels have received significant interest as a biomarker for the degree of cardiac impairment in various conditions. BNP is synthesized and released by ventricular myocytes in response to pressure overload, volume expansion, and increased myocardial wall stress, all of which are important issues in TOF patients. A systematic review by

Eindhoven and colleagues<sup>36</sup> demonstrated that BNP levels are indeed elevated in TOF patients and are correlated with RV end-diastolic dimensions as well as severity of pulmonary valve insufficiency. Our meta-analysis found a significant decrease in plasma BNP levels in response to PVR, reflecting RV reverse remodeling and reduction of pulmonary valve insufficiency.

How BNP can be used as tool for defining the optimal timing of PVR is presently unclear. Kitagawa and colleagues<sup>37</sup> suggested in their study that the optimal BNP cutoff value for considering PVR was 32.15 pg/mL (with a sensitivity of 85.7% and a specificity of 83.3%), because these patients were more likely to have cardiac symptoms. More studies are needed to further investigate the prognostic relevance of BNP and its potential use in planning PVR. In the future, BNP might be used as a screening tool on routine follow-up to identify patients who should be considered for further investigation with echocardiography, cardiac catheterization, or MRI to properly assess the timing of PVR.

**RISK OF BIAS AND LIMITATIONS.** This meta-analysis included data from nonrandomized and/or observational studies, which reflects the “real world,” but the studies are limited by treatment bias, confounders, and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes nonrandomized studies obviously less robust.

Comparing and grouping these studies is difficult because of many factors: patients might have been referred for surgery at different ages and times after the primary repair, with different indications to PVR, different centers have different operative routines, a considerable number of patients have additional lesions leading to a high percentage of additional procedures at the time of PVR, there is a wide range of valves or valved conduits, and there is variability of follow-up length as well as techniques used to assess RV function and volume after PVR.

There are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups.

Furthermore, limited follow-up in the included studies restricted our reporting of mortality and redo PVR rates to 10 years. Because longer outcomes are of interest, future studies should aim to include longer follow-up. Besides, the lack of data about catheter-based reintervention rates and rates of endocarditis limits our ability to evaluate these aspects.

**CONCLUSION.** PVR in patients after TOF repair has been associated with low 30-day and 5-year mortality rates, an acceptable 5-year redo PVR rate, significant decreases in RV volumes and increases in RV systolic function, increases in LV systolic function and volume, and decreases in BNP. No changes are seen in QRS duration, CPET results, or longitudinal strain. Greater initial indexed RVEDV and RVESV are associated with lower chances of RV volume normalization after PVR.

In the end, the real clinical end point is cardiac event-free survival until the eighth or ninth decade. All surrogate end points should therefore be validated as a predictor of this end point. Furthermore, the indication for PVR should always be weighed against the durability of the valve, the risk of endocarditis, procedural morbidity and mortality, and costs. Because all of these factors are continuously evolving, PVR in repaired TOF should be seen as a dynamic field. It is certain that the last word has not been spoken.

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