Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort

Tal Geva MD,[1] Barbara Mulder, MD,[2] Kimberlee Gauvreau, ScD,[1] Sonya V. Babu-Narayan, MBBS,[3] Rachel M. Wald, MD,[4] Kelsey Hickey, BA,[1] Andrew J. Powell, MD,[1] Michael A. Gatzoulis, MD,[3] Anne Marie Valente, MD.[1]

[1]Department of Cardiology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, MA, USA
[2]Department of Cardiology, Academic Medical Centre, Amsterdam, The Netherlands
[3]Royal Brompton and Harefield NHS Foundation Trust, National Heart and Lung Institute, Imperial College, London
[4]Division of Cardiology, University of Toronto, Peter Munk Cardiac Centre, Toronto, ON, Canada

Short title: Outcome predictors after PVR

Word count: 3478

Address for correspondence: Tal Geva, MD
Department of Cardiology
Boston Children's Hospital
300 Longwood Avenue
Boston, MA 02115
Phone: 617-355-7655
Fax: 617-739-6282
Email: tal.geva@cardio.chboston.org

Abstract

Background: Risk factors for adverse clinical outcomes have been identified in patients with repaired tetralogy of Fallot (rTOF) before pulmonary valve replacement (PVR). However, pre-PVR predictors for post-PVR sustained ventricular tachycardia (VT) and death have not been identified.

Methods: Patients with rTOF enrolled in the INDICATOR cohort—a 4-center international cohort study— who had a comprehensive preoperative evaluation and subsequently underwent PVR were included. Pre-procedural clinical, electrocardiogram, cardiovascular magnetic resonance (CMR), and postoperative outcome data were analyzed. Cox proportional hazards multivariable regression analysis was used to evaluate factors associated with time from pre-PVR CMR until the primary outcome—death, aborted sudden cardiac death, or sustained VT.

Results: Of the 452 eligible patients (median age at PVR 25.8 years), 36 (8%) reached the primary outcome (27 deaths, 2 resuscitated death, and 7 sustained VT) at a median time after PVR of 6.5 years. Cox proportional hazards regression identified pre-PVR right ventricular (RV) ejection fraction < 40% (hazard ratio [HR] 2.39; 95% confidence interval [CI] 1.18 to 4.85; P = 0.02), RV mass-to-volume ratio ≥ 0.45 g/mL (HR 4.08; 95%, CI 1.57 to 10.6; P = 0.004), and age at PVR ≥ 28 years (HR 3.10; 95% CI 1.42 to 6.78; P = 0.005) as outcome predictors. In a subgroup analysis of 230 patients with Doppler data, predicted RV systolic pressure ≥40 mm Hg was associated with the primary outcome (HR 3.42; 95% CI 1.09 to 10.7; P = 0.04). Preoperative predictors of a composite secondary outcome—postoperative arrhythmias and heart failure—included older age at PVR, pre-PVR atrial tachyarrhythmias, and a higher left ventricular end-systolic volume index.

Conclusions: In this observational investigation of patients with rTOF, an older age at PVR and pre-PVR RV hypertrophy and dysfunction were predictive of shorter time to postoperative death and sustained VT. These findings may inform the timing of PVR if confirmed by prospective clinical trials.

Keywords: Tetralogy of Fallot; pulmonary valve replacement; risk factors; outcomes

Clinical Perspective

What is New?

- This study was designed to identify preoperative predictors of poor clinical outcomes after pulmonary valve replacement in a cohort of patients with repaired tetralogy of Fallot (rTOF) from a large multicenter cohort.
- Older age at PVR and preoperative right ventricular dysfunction or hypertrophy predicted shorter postoperative time to death or sustained ventricular tachycardia. Elevated right ventricular pressure was associated with additional risk. The likelihood of a poor outcome increased substantially when multiple risk factors coexist.
- Moderate or severe tricuspid regurgitation and impaired left ventricular parameters were associated with postoperative atrial tachyarrhythmias and heart failure symptoms.

What Are the Clinical Implications?

- Indications for pulmonary valve replacement in repaired tetralogy of Fallot have relied on markers of postoperative right ventricular remodeling, with paucity of information regarding predictors of clinical outcomes.
- This study identified preoperative demographic predictors and imaging biomarkers associated with poor clinical outcomes after pulmonary valve replacement, which may be useful for guiding clinical recommendations for valve implantation in this population.

Surgical management of tetralogy of Fallot (TOF) often results in right ventricular (RV) outflow tract dysfunction, including stenosis and regurgitation, which leads to a complex cascade of pathophysiologic events resulting in RV dilatation and dysfunction, left ventricular (LV) dysfunction, exercise intolerance, arrhythmia, and premature death.[1-3] Several studies have shown that while the rate of these complications is low during childhood, it increases substantially in adulthood.[4-6] Since the great majority of young patients with TOF survive surgical management early in life, the number of adult patients facing adverse clinical outcomes late after TOF repair (rTOF) is rising rapidly.[7]

Pulmonary valve replacement (PVR) is increasingly performed in patients with rTOF to restore valve function and to halt or reverse the adverse ventricular remodeling, with the expectation that this will lead to improvements in the quality of life and longevity. Although the effects of PVR on ventricular remodeling, electrocardiographic markers, exercise capacity, and symptoms have been studied extensively,[8-13] preoperative predictors of clinically important post-PVR outcomes such as death or sustained ventricular tachycardia (VT) have not been evaluated in detail. As a result, guidelines for PVR have relied on preoperative markers of suboptimal postoperative ventricular remodeling as opposed to clinical outcomes.[14, 15]

Information on risk factors for poor clinical outcomes after PVR would be valuable because it may inform clinical decisions regarding the optimal timing of PVR. Therefore, the goal of this study was to identify preoperative predictors of poor clinical outcomes after PVR in a large cohort of rTOF patients from the International Multicenter TOF Registry (INDICATOR) cohort who underwent PVR.

METHODS

Patients

A detailed description of the methodology of the INDICATOR registry, including recruitment protocol, inclusion and exclusion criteria, data collection, and data analysis in the core laboratory has been published.[16, 17] Briefly, participating centers in Toronto, London, Amsterdam, and Boston identified patients fulfilling the following inclusion criteria: 1) repaired TOF; 2) PVR either by catheter or surgery; 3) Pre-PVR cardiovascular magnetic resonance (CMR) with assessment of left and right ventricular volumes and mass according to the study protocol; and 4) clinical follow-up ≥1 year after PVR or occurrence of a primary outcome. Patients with prior PVR less than 10 years from the index procedure and those with incomplete CMR data were excluded. Each participating center received Institutional Review or Ethical Board approval. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Collection

Deidentified data were sent to the coordinating center, which included a data repository, CMR core laboratory, and a statistical core center. The registry collected data on patient demographics (date of birth, sex, race), anatomic type of TOF (classified as TOF with pulmonary stenosis, pulmonary atresia, atrioventricular canal, or absent pulmonary valve), associated cardiovascular anomalies, non-cardiac morbidities, genetic abnormalities, surgical and catheter interventions, and clinical outcomes. Clinical history and dates of any arrhythmias were recorded. One center also collected Doppler echocardiographic data to quantify RV systolic pressure based on peak velocities of the tricuspid regurgitation jet and RV outflow. The electrocardiogram (ECG) was analyzed for heart rate and QRS duration. The 24-hour Holter monitor was analyzed for sustained atrial arrhythmia (categorized as supraventricular tachycardia, atrial fibrillation, or

atrial flutter) and for ventricular ectopy (defined as >100 premature ventricular contractions, >20 couplets, or nonsustained VT lasting <30 s).

Deidentified copies of the CMR examinations were sent to the CMR core laboratory for analysis. The technical details of the CMR imaging protocol, analysis methods, and quality assurance procedures have been published.[1, 17] Measurements included diastolic and systolic RV and LV volumes, mass, and pulmonary regurgitation fraction. Calculations included ventricular stroke volumes and ejection fractions (EF). Measurements were adjusted to body surface area calculated using the Haycock formula and z-scores were calculated based on published normal values.[18]

Outcomes

The composite primary outcome was defined as all-cause mortality (classified as sudden cardiac death, heart failure-related death, cardiac other, or non-cardiac), aborted sudden cardiac death (defined as resuscitated pulseless cardiac event), or sustained VT (lasting ≥30 s or requiring cardioversion). The composite secondary outcome included New York Heart Association (NYHA) class III or IV and/or sustained atrial tachyarrhythmia such as atrial flutter or fibrillation. Outcomes were ascertained through periodic reviews of clinical records and electronic searches of death records in each participating center.

Statistical Analysis

Categorical variables were summarized using frequencies and percentages, and compared for patients with and without the outcomes using Fisher's exact test. Continuous variables were summarized using either the mean and standard deviation, or median and 25^{th}, 75^{th} percentiles; they were compared using the unpaired *t* test or Wilcoxon rank-sum test. Cox proportional hazards regression was used to evaluate factors associated with time from pre-PVR CMR until

death, aborted sudden cardiac death, or sustained VT. Patients who did not experience the primary outcome were censored at the time of last follow-up. Hazard ratios are reported with 95% confidence intervals. Harrell's C-index for time to event outcomes was used to quantify how well the Cox regression model discriminates between patients who experienced the outcome and those who did not; C-indices are presented with 95% confidence intervals. Considering variables significant at the 0.20 level in univariable analysis, stepwise forward selection was used to fit a multivariable model that maximized the C-index; only factors significant at the 0.05 level by the likelihood ratio test were retained in the final model. Once the factors with the highest discrimination for the primary outcome were identified, cut points were considered for continuous variables if restricted cubic splines suggested a threshold effect rather than a linear relationship. The cut point that maximized the Wald chi-square statistic was chosen. Survival functions stratified by categorical variables included in the final Cox regression model were estimated using the Kaplan–Meier method, and compared by the log-rank test. Plots of Schoenfeld residuals versus time were used to evaluate the proportional hazards assumption. In order to evaluate the relationship between RV systolic pressure and outcome, a subgroup analysis was performed for patients in whom RV pressure and tricuspid regurgitation data were available within 1 year of the CMR and before PVR. Cox proportional hazards regression was also used to evaluate factors associated with the secondary outcome time from pre-PVR CMR until NYHA class III or IV or sustained atrial tachyarrhythmia, and a combined outcome, which was met if a patient experienced either the primary or secondary outcome. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata 15 (StataCorp, College Station, TX).

RESULTS

Patients

Of the 1,418 patients enrolled in the INDICATOR database, 788 underwent PVR. Of those, 452 fulfilled inclusion criteria, and thus formed the study cohort. Figure 1 shows the reasons for exclusion, and Table 1 summarizes the demographic and clinical characteristics of the study patients stratified by presence or absence of the primary outcome. The median age at PVR was 25.8 years and the median length of hospital stay was 5 days. Except for one patient who received a mechanical valve, the remaining 451 patients received biological valves (surgically implanted bioprosthesis in 297 [66%], homograft in 87 [19%], and a transcatheter stented valve in 66 [15%]). CMR was performed a median of 7 months before PVR and contemporaneous Doppler assessment of RV pressure and tricuspid regurgitation was available in 230 patients from 1 center. Table 2 summarizes the CMR and Doppler data stratified by presence or absence of the primary outcome.

Outcomes

The 452 study patients were followed after PVR for a median of 6.5 years (4.5, 9.2 years). Of those, 36 (8%) reached the primary outcome at a median time after PVR of 3.9 years (0.8, 6.5 years) at a median age of 42.7 years (29.5, 52 years). Of those, 27 patients died, 2 experienced a resuscitated pulseless cardiac arrest, and 7 had documented sustained VT. The mode of death was classified as cardiac in 17 (5 heart failure, 5 arrhythmic, 7 other cardiac), non-cardiac in 7, and unknown in 3 patients. The composite secondary outcome was reached after PVR in 42 patients (9%): 36 had atrial flutter or fibrillation, and 8 had NYHA class III or IV (including 2 who had atrial or ventricular tachyarrhythmias). The combined outcome was reached in 69

patients, 36 experienced the primary outcome and 42 experienced the secondary outcome (of those, 9 also experienced the primary outcome).

Preoperative predictors of post-PVR death and sustained VT

Demographic, clinical, CMR, ECG, and Doppler variables associated with the primary outcome by univariable analysis are shown in Table 3. Among the examined demographic and clinical variables, an older age at PVR ($p = 0.002$), obesity (body mass index ≥ 30 kg/m^2) ($p = 0.02$), and documented pre-PVR atrial flutter or fibrillation ($p = 0.007$) were associated with a higher risk of postoperative death or sustained VT. Sex was not found to be a significant risk factor of the outcome in univariable analysis, nor when forced into the multivariable model. Among the CMR parameters, RV dysfunction (measured as decreased EF), RV hypertrophy (measured either as increased mass index or mass-to-volume ratio), and LV dilation and hypertrophy were associated with the primary outcome. Among echocardiographic variables, predicted RV systolic pressure by Doppler ≥ 40 mm Hg was associated with post-PVR death and sustained VT. A higher RV end-systolic volume index and longer QRS duration had borderline associations with the primary outcome ($p = 0.06$ and 0.07, respectively). Notably, pre-PVR RV end-diastolic volume, pulmonary regurgitation fraction, and LV EF were not associated with post-PVR death or sustained VT.

By Cox regression multivariable analysis (Table 4), the best model for predicting death and sustained VT after PVR included RV EF <40% (HR 2.39, 95% CI 1.18 to 4.84, $p = 0.02$), RV mass-to-volume ratio ≥ 0.45 g/mL (HR 4.08, 95% CI 1.57 to 10.6, $p = 0.004$), and age at PVR 28 years or older (HR 3.1, 95% CI 1.42 to 6.78, $p = 0.005$) with a model C-index of 0.75 (95% CI: 0.68, 0.83). Using RV EF as a continuous variable, for every 10-percentage EF point decrease the outcome risk increased 49% (95% CI 4% to 215%, $p = 0.03$). To examine whether

risk factors for death or sustained VT are different in patients with a documented cardiac death as oppose to all-cause mortality, we performed a sensitivity analysis excluding the 7 non-cardiac deaths and 3 unknown causes from the primary outcome group. The analysis showed the same risk factors to be associated with the outcome with a model C-index of 0.77.

Kaplan-Meier analysis demonstrated that the 5- and 10-year freedom from death or sustained VT after PVR was 98% in patients with none of the above risk factors (Figure 2). In contrast, the 5- and 10-year freedom from the outcome were 92% and 85%, respectively, in those with 1 risk factor, and 85% and 71% in those with at least 2 risk factors (Log-rank $p < 0.001$). Figure 3 demonstrates the decrease in freedom from the primary outcome associated with a lower threshold for preoperative RV EF (Figure 3A), with a higher threshold for RV mass-to-volume ratio (Figure 3B), and with older age at PVR (Figure 3C).

Among the 230 patients with available contemporaneous Doppler data, 18 reached the primary outcome. By univariable analysis, the same parameters that predicted the primary outcome in the entire cohort were associated with the outcome in this subgroup. In addition, a higher RV systolic pressure determined by the peak velocity of the tricuspid regurgitation jet was associated with the outcome. Specifically, the HR for RV systolic pressure ≥40 mm Hg was 3.42 (95% CI 1.09, 10.7; $p = 0.04$). Notably, moderate or severe tricuspid regurgitation was not significantly associated with the primary outcome.

Preoperative predictors of the secondary outcome

By univariable analysis, several demographic, CMR, and echocardiographic variables were associated with the composite secondary outcome (NYHA class III or IV and/or sustained atrial tachyarrhythmia [n= 42]). Among demographic and clinical variables, older age at PVR (HR 2.07 for each 10-year increase, 95% CI: 1.64, 2.60; $p < 0.001$) and pre-PVR sustained atrial

tachyarrhythmia (HR 4.99, 95% CI: 2.70, 9.23; p <0.001) were associated with the secondary outcome. Among CMR parameters, lower RV EF (HR 1.22 for each 5-percentage EF point decrease, 95% CI: 1.03, 1.46; p = 0.02), higher LV end-diastolic and end-systolic volumes z-score (HR 1.40 for 1 unit increase in end-diastolic volume z-score and 1.38 for end-systolic z-score; p <0.001 for both), lower LV EF (HR 1.30 for 5% decrease, 95% CI: 1.04, 1.63; p = 0.02), and higher LV mass index (HR 1.43 for 10 g/m^2 increase, 95% CI: 1.16, 1.75; p = 0.001) were associated with the outcome. Among the patients with Doppler data, moderate or severe TR was associated with the outcome (HR 3.50, 95% CI: 1.41, 8.73; p = 0.007).

By Cox regression multivariable analysis, the best model for predicting the composite secondary outcome included older age at PVR (HR 1.63 for each decade, 95% CI: 1.23, 2.15; p = 0.001), pre-PVR atrial flutter or fibrillation (HR 2.15, 95% CI: 1.01, 4.55; p = 0.046), and higher LV end-systolic volume z-score (HR 1.21 for 1 unit, 95% CI: 1.02, 1.43; p = 0.03) with a model C-index of 0.81 (95% CI: 0.74, 0.88).

Preoperative predictors of the combined outcome

Figure 4 shows freedom from the combined outcome. By Cox regression multivariable analysis, the best model for predicting the combined primary and secondary outcomes included older age at PVR (HR 1.47 for each decade, 95% CI: 1.19, 1.81; p <0.001), higher RV mass-to-volume ratio (HR 1.26 for each 0.1 g/mL, 95% CI 1.05 to 1.53, p = 0.01), higher LV end-systolic volume index (HR 1.21 for each 10 mL/m^2, 95% CI: 1.09, 1.33; p <0.001), and pre-PVR atrial flutter or fibrillation (HR 1.94, 95% CI: 1.04, 3.61; p = 0.04) with a model C-index of 0.75 (95% CI: 0.68, 0.82).

DISCUSSION

Clinical guidelines for the timing of PVR in patients with rTOF have mostly relied on studies examining pre-PVR markers of adequate reverse remodeling of the RV after valve implantation.[14, 15, 19, 20] Such focus on pre-PVR threshold values of RV size stems from the low frequency of clinically important adverse clinical outcomes, precluding most single-center studies from having sufficient power for statistical analysis. In this large multicenter observational cohort study, we identified pre-PVR RV hypertrophy and dysfunction and older age at PVR as predictors of shorter time to death or sustained VT after PVR. Importantly, patients with 2 or 3 of these risk factors were at substantially higher risk for poor clinical outcomes. Furthermore, subgroup analysis of patients with Doppler data showed that higher systolic RV pressure was associated with the primary outcome. In addition, older age at PVR, preoperative sustained atrial tachyarrhythmias, elevated LV end-systolic volume index, and moderate or severe TR were associated with the composite secondary outcome of postoperative heart failure and arrhythmias.

The preoperative risk factors for adverse post-PVR outcomes identified in this study extend our previous findings from the INDICATOR cohort wherein the majority of patients did not undergo PVR.[16] Both in the previous and current analyses, RV dysfunction and hypertrophy were independently associated with the primary outcome. However, in the current study, which focused on pre-PVR predictors of postoperative clinical outcomes, older age at PVR was found to be a new risk factor for post-PVR death or sustained VT (primary outcome) as well as postoperative atrial tachyarrhythmias and heart failure symptoms (secondary outcome). Furthermore, coexistence of 2 or 3 risk factors was incrementally associated with a shorter time to occurrence of the primary outcome. Also, in keeping with the previous study, increased RV systolic pressure before PVR was found by univariable analysis to be associated with higher risk

of death and sustained VT after PVR. However, in contrast to the earlier report, LV dysfunction was not predictive of the primary outcome after PVR. Instead, along with other predictors, LV end-systolic volume, which represents both ventricular size and function, was associated with both primary and secondary outcomes. It is conceivable that with stronger statistical power, lower preoperative LV ejection fraction may be associated with post-PVR clinical outcomes.

Our results highlight several observations pertaining to timing of PVR. Although identification of preoperative imaging and clinical markers of poor outcomes after PVR is undoubtedly informative with regard to risk stratification, it does not fully define the inflection point of the individual predictors. Instead, the cutoff values were chosen to maximize their sensitivity and specificity for predicting the primary outcome. From the clinician's perspective, it would be helpful to define the "window" during which the risk of poor outcome begins to increase while the disease process has not transitioned from reversible to irreversible. In other words, given that all currently available bioprosthetic valves deteriorate over time and are associated with side effects (e.g., endocarditis), it would be ideal not to implant a pulmonary valve too early in asymptomatic patients with stable disease who are at low risk for adverse outcomes. Evidence supporting this reasoning was recently reported by Bokma et al. who found no benefit and even potential harm from PVR performed before reaching proactive criteria for valve implantation.[21] At the same time, delaying PVR until the mechanoelectrical cardiomyopathy of rTOF has advanced to become irreversible is also suboptimal.[8, 22, 23] Our findings suggest that delaying PVR until the RV is hypertrophied and dysfunctional, or until patients fulfilling criteria are older may be considered too late as these patients are at high risk for premature death or sustained VT after PVR. Therefore, it is reasonable to consider PVR before patients reach these risk indicators. However, data on the evolution of these risk factors

over time, before and after PVR, will provide further insight into causality, pathophysiology, and impact of PVR on clinical outcomes in this patient population. Finally, it is worth noting that although our study identified key clinical and imaging markers of poor outcomes after PVR, further research is required to determine whether modifying these risk factors through pharmacologic or other interventions would lead to improved outcomes.

Several commonly suspected risk factors for the primary outcome were notably not found to be predictive in the current study. Specifically, LV dysfunction, RV volumes, and PR fraction were not associated with the primary outcome. However, with regard to the composite secondary outcome, several clinical and imaging markers were associated with the outcome, including older age at PVR, preexisting atrial flutter or fibrillation, higher RV and LV volumes, and decreased ejection fractions. Among patients with Doppler data, moderate or severe tricuspid regurgitation was also associated with the secondary outcome, which is in accord with the findings of Bokma et al.[24]

Our study has several limitations. By design, the cohort is restricted to patients who have undergone CMR; this limitation is partially mitigated by the routine use of CMR in this patient group at the participating centers. In accordance with the requirement for CMR data, patients with pacemakers or defibrillators implanted before CMR were excluded. The indications for PVR in this cohort were not standardized, which might lead to selection bias. However, the patient characteristics in this cohort are consistent with studies that did not require CMR.[25] We also note the although this is the largest study of its kind in post-PVR patients with rTOF, the number of outcomes is modest, which limits statistical power to detect some less robust but potentially clinically relevant predictors. Finally, we chose all-cause mortality as a component of the composite primary outcome in keeping with the literature on clinical outcomes in patients

with heart disease.[26-28] To determine whether risk factors for mortality differed between those whose death was clearly attributable to cardiac causes vs. those with non-cardiac or uncertain mode of death, we performed a sensitivity analysis excluding patients in the latter group. The analysis found that the risk factors for the primary outcome were the same as for the entire cohort.

In conclusion, in this multicenter cohort of rTOF patients undergoing PVR, preoperative RV dysfunction or hypertrophy measured by CMR and older age at PVR predicted shorter postoperative time to death or sustained VT. The likelihood of a poor outcome increased substantially when multiple risk factors coexist. Elevated RV systolic pressure may confer an additional risk. In addition, LV dilation and dysfunction and moderate or severe tricuspid regurgitation were associated with postoperative atrial tachyarrhythmias and heart failure symptoms. To further refine the optimal time window for PVR, future studies should be designed to study the time course of these risk factors, to identify the inflection point of risk, to identify specific criteria for surgical vs. transcatheter valve implantation, and to explore new predictors of at-risk patients such as myocardial strain,[29] diffuse fibrosis by CMR T1 mapping,[30] serum biomarkers such as microRNA, and genetic markers. Observations from this study may be used to generate hypotheses that can be tested in clinical trials designed to determine the clinical benefits of interventions such as pulmonary valve insertion.

Acknowledgment: The authors are grateful to Emily Harris for artwork and Sarah Ghonim, PhD for assistance with data collection.

Funding sources: Higgins Family Noninvasive Research Fund at Boston Children's Hospital (TG, AMV, AJP), the Dunlevie Foundation (AMV), the Lerner Research award (AMV), the

Sarah Marie Liamos Fund (KH), the Canadian Institutes of Health Research MOP 119353 (RMW), and the British Heart Foundation FS/11/38/28864 (SVB-N).

Disclosures: none

REFERENCES

1. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. *J Cardiovasc Magn Reson*. 2011;13:9.

2. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, Webb GD and McCrindle BW. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg*. 2009;35:156-164.

3. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD and Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *The Lancet*. 2000;356:975-981.

4. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W and Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30:1374-1383.

5. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ and Broberg CS. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation*. 2010;122:868-875.

6. Chiu SN, Wang JK, Chen HC, Lin MT, Wu ET, Chen CA, Huang SC, Chang CI, Chen YS, Chiu IS, Chen CL and Wu MH. Long-term survival and unnatural deaths of patients with repaired tetralogy of Fallot in an Asian cohort. *Circulation Cardiovascular quality and outcomes*. 2012;5:120-125.

7. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N and Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749-756.

8. Geva T, Gauvreau K, Powell AJ, Cecchin F, Rhodes J, Geva J and del Nido P. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. *Circulation*. 2010;122:S201-208.

9. Hallbergson A, Gauvreau K, Powell AJ and Geva T. Right ventricular remodeling after pulmonary valve replacement: early gains, late losses. *Ann Thorac Surg*. 2015;99:660-666.

10. O'Byrne ML, Glatz AC, Mercer-Rosa L, Gillespie MJ, Dori Y, Goldmuntz E, Kawut S and Rome JJ. Trends in pulmonary valve replacement in children and adults with tetralogy of fallot. *Am J Cardiol*. 2015;115:118-124.

11. Ferraz Cavalcanti PE, Sa MP, Santos CA, Esmeraldo IM, de Escobar RR, de Menezes AM, de Azevedo OM, Jr., de Vasconcelos Silva FP, Lins RF and Lima Rde C. Pulmonary valve replacement after operative repair of tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. *J Am Coll Cardiol*. 2013;62:2227-2243.

12. Babu-Narayan SV, Diller GP, Gheta RR, Bastin AJ, Karonis T, Li W, Pennell DJ, Uemura H, Sethia B, Gatzoulis MA and Shore DF. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. *Circulation*. 2014;129:18-27.

13. Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC, Diller GP, McCarthy KP, Ho SY, Li W, Wright P, Spadotto V, Kilner PJ, Oldershaw P, Pennell DJ, Shore DF and Babu-Narayan SV. Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot: A Prospective Cardiovascular Magnetic Resonance and Clinical Study. *Circulation*. 2017;136:1703-1713.

14. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of fallot: the quest continues. *Circulation*. 2013;128:1855-1857.

15. Tretter JT, Friedberg MK, Wald RM and McElhinney DB. Defining and refining indications for transcatheter pulmonary valve replacement in patients with repaired tetralogy of Fallot: Contributions from anatomical and functional imaging. *Int J Cardiol*. 2016;221:916-925.

16. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, Landzberg MJ, Mulder B, Powell AJ, Wald R and Geva T. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart*. 2014;100:247-253.

17. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Evans SP, Gatzoulis M, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, Landzberg MJ, Mulder B, Powell AJ, Wald R and Geva T. Rationale and design of an International Multicenter Registry of patients with repaired tetralogy of Fallot to define risk factors for late adverse outcomes: the INDICATOR cohort. *Pediatr Cardiol*. 2013;34:95-104.

18. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP and Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging*. 2003;17:323-329.

19. Boudjemline Y. Pulmonary valve replacement: extending the indications to the whole spectrum of pulmonary valve disease. *Future Cardiol*. 2007;3:35-41.

20. Cheung MM, Konstantinov IE and Redington AN. Late complications of repair of tetralogy of Fallot and indications for pulmonary valve replacement. *Semin Thorac Cardiovasc Surg*. 2005;17:155-159.

21. Bokma JP, Geva T, Sleeper LA, Babu Narayan SV, Wald R, Hickey K, Jansen K, Wassall R, Lu M, Gatzoulis MA, Mulder BJ and Valente AM. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Heart*. 2018;104:738-744.

22. Gatzoulis MA, Till JA, Somerville J and Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231-237.

23. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG and Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of fallot: are we operating too late? *J Am Coll Cardiol*. 2000;36:1670-1675.

24. Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, Koolbergen DR, Groenink M, Mulder BJ and Bouma BJ. Severe tricuspid regurgitation is predictive for adverse events in tetralogy of Fallot. *Heart*. 2015;101:794-799.

25. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SE, van Domburg RT, Utens LM, Simoons ML and Bogers AJ. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. *J Thorac Cardiovasc Surg*. 2008;135:50-55.

26. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS and Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. 2014;64:472-481.

27. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner J, Shah DJ, Jue J, White BE, Shenoy C and Farzaneh-Far A. Association of Feature-Tracking Cardiac Magnetic Resonance Imaging Left Ventricular Global Longitudinal Strain With All-Cause Mortality in Patients With Reduced Left Ventricular Ejection Fraction. *Circulation*. 2017;135:2313-2315.

28. Mauermann E, Bolliger D, Fassl J, Grapow M, Seeberger EE, Seeberger MD, Filipovic M and Lurati Buse GAL. Postoperative High-Sensitivity Troponin and Its Association With 30-Day and 12-Month, All-Cause Mortality in Patients Undergoing On-Pump Cardiac Surgery. *Anesth Analg*. 2017;125:1110-1117.

29. Orwat S, Diller GP, Kempny A, Radke R, Peters B, Kuhne T, Boethig D, Gutberlet M, Dubowy KO, Beerbaum P, Sarikouch S, Baumgartner H and German Competence Network for Congenital Heart Defects I. Myocardial deformation parameters predict outcome in patients with repaired tetralogy of Fallot. *Heart*. 2016;102:209-215.

30. Chen CA, Dusenbery SM, Valente AM, Powell AJ and Geva T. Myocardial ECV fraction assessed by CMR is associated with type of hemodynamic load and arrhythmia in repaired tetralogy of Fallot. *JACC Cardiovasc Imaging*. 2016;9:1-10.

Table 1: Demographic, anatomic, and surgical characteristics

	All Patients (n = 452)	Primary Outcome (n = 36)	No Outcome (n = 416)	*P* value
Median age at TOF repair (years)	2.3 (0.5 - 6.0)	5.6 (1.2 - 10.0)	2.1 (0.5 - 5.7)	0.002
Median age at pre-PVR CMR (years)	24.7 (17.3 - 36.6)	38.5 (26.1 - 44.8)	24.3 (17.2 - 34.7)	0.001
Time from CMR to PVR (years)	0.6 (0.2 - 1.1)	0.5 (0.2 - 1.4)	0.6 (0.2 - 1.1)	0.61
Median age at PVR (years)	25.8 (18.6 - 37.6)	38.9 (26.6 - 45.6)	25.2 (18.3 - 36.1)	<0.001
Follow-up time after PVR (years)	6.5 (4.5 - 9.2)	5.2 (1.2 - 8.8)	6.5 (4.6 - 9.2)	0.02
Sex, male	257 (57%)	21 (58%)	236 (57%)	1.0
Body surface area (m^2) (n=421)	1.71 ± 0.39	1.76 ± 0.41	1.70 ± 0.39	0.48
Body mass index (kg/m^2)	24.2 ± 6.30	26.7 ± 6.63	24.0 ± 6.23	0.03
Body mass index ≥30 kg/m^2	69 (17%)	10 (30%)	59 (16%)	0.05
Diagnosis				0.26
Tetralogy of Fallot, PS	353 (78%)	26 (72%)	327 (79%)	
Tetralogy of Fallot, PA	86 (19%)	10 (28%)	76 (18%)	
Tetralogy of Fallot, AV canal	13 (3%)	0 (0%)	13 (3%)	
Chromosomal anomaly	18 (4%)	3 (9%)	15 (4%)	0.17
Associated genetic syndrome	18 (4%)	2 (6%)	16 (4%)	0.65
Pre-PVR history of atrial arrhythmia	66 (15%)	11 (31%)	55 (13%)	0.01
Pre-PVR history of ventricular arrhythmia	100 (22%)	11 (31%)	89 (21%)	0.21
PVR valve type (n=451)				0.36
Bioprosthetic	297 (66%)	20 (56%)	277 (67%)	
Homograft	87 (19%)	10 (28%)	77 (19%)	
Transcatheter	66 (15%)	6 (17%)	60 (14%)	
Mechanical	1 (<1%)	0 (0%)	1 (<1%)	
Prior RV-PA conduit	90 (20%)	10 (28%)	80 (19%)	0.27
Valve size (mm) (n=295)	25 (24 - 27)	26 (25 - 27)	25 (24 - 27)	0.68
Length of hospital stay (days) (n=256)	5 (4 - 7)	8 (7 - 10)	5 (4 - 7)	0.007

Data are count (percentage), mean ±SD, or median (25^{th} – 75^{th} percentiles).
AV, atrioventricular; CMR, cardiac magnetic resonance; PA, pulmonary atresia; PS, pulmonary stenosis; PVR, pulmonary valve replacement; RV, right ventricle; TOF, tetralogy of Fallot; VT, ventricular tachycardia

Table 2: Pre-PVR CMR and echocardiographic data

CMR variables	All Patients (n = 452)	Primary Outcome (n = 36)	No Outcome (n = 416)	*P* value
RV end-diastolic volume index (mL/m^2)	176 ± 48	180 ± 69	176 ± 46	0.72
RV end-systolic volume index (mL/m^2)	96 ± 36	107 ± 51	95 ± 35	0.20
RV ejection fraction (%)	46 ± 9	43 ± 10	47 ± 9	0.04
RV ejection fraction Z-score	-2.56 ± 2.09	-3.48 ± 2.47	-2.48 ± 2.04	0.03
RV mass index (g/m^2)	37 ± 13	47 ± 21	36 ± 12	0.008
RV mass/volume (g/mL)	0.22 ± 0.11	0.29 ± 0.21	0.21 ± 0.09	0.02
RV stroke volume index (mL/m^2)	80 ± 21	74 ± 26	81 ± 21	0.11
Pulmonary regurgitation (%)	42 ± 14	40 ± 17	42 ± 14	0.37
LV end-diastolic volume index (mL/m^2)	88 ± 23	97 ± 45	87 ± 19	0.24
LV end-systolic volume index (mL/m^2)	39 ± 16	47 ± 35	38 ± 12	0.17
LV ejection fraction (%)	56 ± 8	55 ± 11	56 ± 7	0.54
LV ejection fraction Z-score	-1.71 ± 1.64	-1.97 ± 2.30	-1.68 ± 1.57	0.49
LV mass index (g/m^2)	54 ± 16	65 ± 29	52 ± 14	0.02
LV mass/volume (g/mL)	0.62 ± 0.20	0.75 ± 0.41	0.61 ± 0.16	0.06
LV stroke volume index (mL/m^2)	49 ± 11	50 ± 17	49 ± 10	0.74
RV/LV end-diastolic volume ratio	2.07 ± 0.59	2.00 ± 0.76	2.08 ± 0.57	0.57
QRS duration	151 ± 28	162 ± 29	151 ± 28	0.03
Echocardiographic variables	**All Patients (n = 230)**	**Primary Outcome (n = 18)**	**No Outcome (n = 212)**	***P* value**
Predicted RV pressure by TR (mm Hg)	36 (27 - 55)	43 (38 - 72)	35 (26 - 54)	0.09
Tricuspid regurgitation				0.21
None/trivial	60 (26%)	3 (17%)	57 (27%)	
Mild	130 (57%)	9 (50%)	121 (57%)	
Moderate	30 (13%)	5 (28%)	25 (12%)	
Severe	5 (2%)	0 (0%)	5 (2%)	
Not reported	5 (2%)	1 (6%)	4 (2%)	

CMR, cardiovascular magnetic resonance; LV, left ventricle; RV, right ventricle; TR, tricuspid regurgitation.

Table 3: Predictors of the primary outcome by univariable analysis

		HR (95% CI)	Wald Chi-Square Statistic	*P* value	C index (95% CI)
Demographic and clinical variables					
Age at PVR (years)	↑ 10	1.46 (1.15, 1.87)	9.43	0.002	0.63 (0.52, 0.74)
Age at pre-PVR CMR (years)	↑ 10	1.45 (1.14, 1.85)	9.12	0.003	0.63 (0.51, 0.74)
Pre-PVR history of atrial arrhythmia		2.69 (1.32, 5.50)	7.37	0.007	0.59 (0.51, 0.67)
Body mass index (kg/m^2)	↑ 1	1.06 (1.01, 1.11)	5.45	0.02	0.64 (0.54, 0.74)
Body mass index ≥30 kg/m^2		2.37 (1.12, 5.01)	5.08	0.02	0.58 (0.49, 0.67)
Chromosomal anomaly		2.54 (0.78, 8.31)	2.38	0.12	0.53 (0.48, 0.57)
Diagnosis of TOF/PA		1.71 (0.82, 3.56)	2.07	0.15	0.56 (0.48, 0.65)
CMR variables					
LV ESVi (mL/m^2)	↑5	1.11 (1.05, 1.17)	13.82	<0.001	0.55 (0.43, 0.67)
LV mass index (g/m^2)	↑10	1.34 (1.14, 1.57)	12.35	<0.001	0.58 (0.44, 0.72)
LV EDVi (mL/m^2)	↑5	1.09 (1.03, 1.15)	9.96	0.002	0.52 (0.40, 0.64)
RV mass index (g/m^2)	↑10	1.33 (1.10, 1.62)	8.40	0.004	0.56 (0.43, 0.69)
RV ejection z-score	↓1	1.20 (1.04, 1.38)	6.43	0.01	0.67 (0.56, 0.78)
RV mass/volume (g/mL)	↑0.1	1.26 (1.05, 1.51)	6.01	0.01	0.58 (0.47, 0.69)
RV ejection fraction (%)	↓5	1.22 (1.03, 1.44)	5.08	0.02	0.67 (0.56, 0.77)
LV mass/volume (g/mL)	↑0.1	1.11 (0.98, 1.23)	3.83	0.05	0.50 (0.38, 0.63)
RV ESVi, mL/m^2)	↑5	1.04 (0.99, 1.08)	3.53	0.06	0.55 (0.42, 0.67)
QRS duration (ms)	↑10	1.13 (0.99, 1.28)	3.28	0.07	0.55 (0.45, 0.65)
RV stroke volume index (mL/m^2)	↓10	1.14 (0.97, 1.33)	2.53	0.11	0.59 (0.48, 0.71)
Echocardiographic variables					
Predicted RV pressure ≥40 mm Hg (n= 177)		3.42 (1.09, 10.7)	4.41	0.04	0.70 (0.60, 0.80)
Moderate or severe TR (n= 225)		2.28 (0.80, 6.49)	2.39	0.12	0.59 (0.47, 0.71)

CMR, cardiovascular magnetic resonance; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LV, left ventricle; PVR, pulmonary valve replacement; RV, right ventricle; RV-PA, right ventricle-to-pulmonary artery; TOF/PA, tetralogy of Fallot with pulmonary atresia; TR, tricuspid regurgitation

Table 4: Multivariable predictors of the primary outcome

	HR (95% CI)	*P* value	C index (95% CI)
Model 1			
RV ejection fraction < 40%	2.39 (1.18, 4.85)	0.02	0.75 (0.68, 0.83)
RV mass/volume ratio ≥ 0.45 g/mL	4.08 (1.57, 10.6)	0.004	
Age at PVR ≥ 28 years	3.10 (1.42, 6.78)	0.005	
Model 2			
RV ejection fraction (↓10%)	1.49 (1.04, 2.15)	0.03	0.75 (0.67, 0.83)
RV mass/volume ratio ≥ 0.45 g/mL	4.80 (1.80, 12.8)	0.002	
Age at PVR ≥ 28 years	3.06 (1.40, 6.71)	0.005	

HR, hazard ratio; PVR, pulmonary valve replacement; RV, right ventricle

Figure Legends

Figure 1. Flow chart showing patient selection and reasons for exclusion.

Abbreviations: MRI, magnetic resonance imaging; PVR, pulmonary valve replacement; VT, ventricular tachycardia

Figure 2. Kaplan-Meier analysis of freedom from death or sustained VT stratified by number of risk factors summed for each patient. The 3 risk factors for the primary outcome identified by multivariable analysis included RV ejection fraction < 40%, RV mass-to-volume ratio ≥ 45 g/mL, and age at PVR ≥28 years.

Abbreviations: RV, right ventricle; PVR, pulmonary valve replacement; VT, ventricular tachycardia

Figure 3. Kaplan-Meier analysis of freedom from death or sustained VT stratified by different threshold values of RV ejection fraction (A), RV mass-to-volume ratio (B), and age at PVR (C).

Abbreviations: PVR, pulmonary valve replacement; RV, right ventricle; RVEF, right ventricular ejection fraction; VT, ventricular tachycardia

Figure 4. Kaplan-Meier analysis of freedom from the combined primary and secondary outcomes stratified by number of risk factors summed for each patient. The 4 risk factors for the combined outcome identified by multivariable analysis included age at PVR ≥ 28 years, RV mass-to-volume ratio ≥ 28 g/mL, LV end-systolic volume index ≥ 48 mL/m^2, and pre-PVR atrial flutter or fibrillation.

Abbreviations: LV, left ventricle; PVR, pulmonary valve replacement; RV, right ventricle; VT