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Systematic Review/Meta-analysis

Left Ventricular Systolic Dysfunction and Cardiovascular Outcomes in Tetralogy of Fallot: Systematic Review and Meta-analysis

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See editorial by Wald and Oechslin, pages 1623–1625 of this issue.

ABSTRACT

Background: Although there are robust data about the pathophysiology and prognostic implications of left ventricular (LV) systolic dysfunction in patients with acquired heart disease, similar prognostic data about LV systolic dysfunction are sparse in the tetralogy of Fallot (TOF) population. The purpose of this study was to perform a meta-analysis of all studies that assessed the relationship between LV ejection fraction (LVEF) and cardiovascular adverse events (CAEs) defined as death, aborted sudden death, or sustained ventricular tachycardia.

Methods: We used random-effects models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Of the 1,809 citations, 7 studies with 2,854 patients (age 28 ± 4 years) were included. During 5.6 ± 3.4 years' follow-up, there were 82 deaths, 17 aborted sudden cardiac deaths, and 56 sustained ventricular tachycardia events. Overall, CAEs occurred in 5.1% (144 patients). As a continuous variable, LVEF was a predictor of CAE (HR

RÉSUMÉ

Contexte : Bien que l'on dispose de données solides sur la physiopathologie de la dysfonction systolique ventriculaire gauche (VG) et sur ses répercussions sur le pronostic des patients présentant une maladie cardiaque acquise, de telles données sur le pronostic associé à la dysfonction systolique VG chez les patients présentant une tétralogie de Fallot sont rares. La présente étude consiste en une méta-analyse de toutes les études qui ont évalué la relation entre la fraction d'éjection VG (FEVG) et les événements cardiovasculaires indésirables (ECI) que sont le décès, la mort cardiaque subite avortée et la tachycardie ventriculaire soutenue.

Méthodologie : Nous avons utilisé des modèles à effets aléatoires pour calculer les rapports des risques instantanés (RRI) et les intervalles de confiance (IC) à 95 %.

Résultats : Des 1 809 publications trouvées, 7 études portant sur un nombre total de 2 854 patients (âge : 28 ± 4 ans) ont été retenues. Au cours de la période de suivi de 5,6 ± 3,4 ans, 82 décès, 17 morts

Right ventricular (RV) systolic dysfunction is one of the late complications after repair of tetralogy of Fallot (TOF), and it is associated with mortality and other adverse outcomes.[1,2] The etiology of RV systolic dysfunction is multifactorial and results from cyanosis and pressure overload before repair, intraoperative hypoxic injury at the time of surgical intervention, and ongoing hemodynamic stress from residual/recurrent hemodynamic lesions.[1-3] The same factors that result in RV systolic dysfunction can potentially lead to left ventricular (LV) systolic dysfunction as well.[4] Although there are robust data about the pathophysiologic mechanisms and prognostic implications of LV systolic dysfunction in patients with acquired heart disease,[5] similar prognostic data about LV systolic dysfunction are sparse in the TOF population.[6,7] This is an important knowledge gap because an in-depth understanding of the mechanism and prognostic implication of LV systolic dysfunction is a fundamental step toward the exploration of novel prophylactic and therapeutic interventions to address this problem and improve survival.

To understand and treat LV systolic dysfunction in patients with repaired TOF, it is important to review the existing literature about the clinical implications of LV systolic dysfunction in this population. To the best of our knowledge, there are no systematic reviews of studies addressing the

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1.29, 95% CI, 1.09-1.53, $P = 0.001$) per 5% decrease in LVEF. Similarly, LVEF < 40% was also a predictor of CAE (HR 3.22, 95% CI, 2.16-4.80, $P < 0.001$).

Conclusions: LV systolic dysfunction was an independent predictor of CAE, and we observed a 30% increase in the risk of CAE for every 5% decrease in LVEF, and a 3-fold increase in the risk of CAE in patients with LVEF <40% compared with other patients. These findings underscore the importance of incorporating LV systolic function in clinical risk stratification of patients with TOF and the need to explore new treatment options to address this problem.

cardiaques subites avortées et 56 cas de tachycardie ventriculaire soutenue ont été relevés. Dans l'ensemble, des ECI sont survenus chez 5,1 % (144) des patients. En tant que variable continue, la FEVG était un prédicteur d'ECI (RRI de 1,29; IC à 95 % : de 1,09 à 1,53; $p = 0,001$), pour chaque diminution de 5 % de la FEVG. De même, une FEVG < 40 % était aussi un prédicteur d'ECI (RRI de 3,22; IC à 95 % : de 2,16 à 4,80; $p < 0,001$).

Conclusions : La dysfonction systolique VG était un prédicteur indépendant d'ECI; nous avons observé une hausse de 30 % du risque d'ECI pour chaque diminution de 5 % de la FEVG, et un risque d'ECI trois fois plus élevé chez les patients présentant une FEVG < 40 % que chez les autres patients. Ces constatations font ressortir l'importance de tenir compte de la fonction systolique VG dans la stratification du risque clinique chez les patients présentant une tétralogie de Fallot, ainsi que la nécessité d'explorer de nouvelles options thérapeutiques pour résoudre ce problème.

prognostic importance of LV systolic dysfunction in the TOF population; hence, the current review. The purpose of this study was therefore to review and meta-analyze the existing body of knowledge about the association of LV systolic dysfunction and clinical outcomes.

Methods

Literature search and study eligibility

We searched Medline, PubMed, Embase, and Google Scholar by medical subject heading through January 2019, using the following key words: tetralogy of Fallot, left ventricular dysfunction, left ventricular ejection fraction, mortality, death, and outcomes. The search was restricted to articles published in English, and we excluded duplicate publications, case reports, reviews, and abstracts published more than 2 years before this search. One of the investigators (A.C.E) screened all citations for relevance, based on review of titles and abstracts. This same investigator (A.C.E) reviewed the full-length text and reference lists of the relevant abstracts to determine eligibility. A study was considered eligible if all 4 criteria were met: (1) study included patients with TOF; (2) study reported LV function assessment using LV ejection fraction (LVEF) by echocardiogram or cardiac magnetic resonance imaging (CMRI); (3) study reported any of the following clinical outcomes: death, aborted sudden cardiac death, or sustained ventricular tachycardia; (4) study had a follow-up longer than1 year from the time of LVEF assessment. A second investigator (E.A.) reviewed the titles and abstracts of a random sample of 10 citations for relevance and of a random sample of 10 relevant abstracts for eligibility to assess interobserver agreement.

Data extraction

The following baseline data were extracted from the eligible studies: age, gender, history of palliative shunt, transannular patch repair, age at the time of TOF repair, inclusion of TOF-pulmonary atresia diagnosis, history of pulmonary valve replacement, LVEF, and CMRI-derived volumetric indices. The following outcome data were also extracted: duration of follow-up, ventricular arrhythmia, resuscitated cardiac arrest or aborted sudden cardiac death, and death. Data extraction was performed by A.C.E and verified by R.A. The corresponding authors of all the eligible studies were contacted via email, and they were provided with a detailed spread sheet containing the variables extracted from their studies. The corresponding authors were given the opportunity to verify accuracy of the variables and provide missing data if necessary.[8-14] Four of the 7 of the corresponding authors responded and verified accuracy of the data used in this analysis.[9-12]

Summary measure

The primary outcome was the association between LVEF and cardiovascular adverse events (CAEs), which is a composite endpoint of death, aborted sudden cardiac death, or sustained ventricular tachycardia. In the studies that included both LVEF and RV ejection fraction (RVEF) in the multivariate model, we performed exploratory analysis comparing the effect size (using hazard ratio [HR] and 95% confidence interval [CI]) of the association between LVEF and CAE, vs the association between RVEF and CAE.

Statistical analysis

Variables were expressed as means ± standard deviation, median (interquartile range), and counts (%) as appropriate. The interobserver agreements for study relevance and study eligibility were assessed using kappa (κ) statistic. The eligible studies were assessed for risk of bias using the Newcastle-Ottawa scale.[15] Of the 7 eligible studies, 3 studies used LVEF as a continuous predictor variable in the multivariate regression models, whereas the other 4 studies used LVEF as binary predictor variable (LVEF < 40% vs ≥ 40%) in the regression models. As a result, we performed a meta-analysis of the 3 studies that reported LVEF as a continuous predictor variable and a separate meta-analysis of the 4 studies that reported LVEF as a binary predictor variable. Heterogeneity was assessed using Cochrane's Q test via a χ^2 test and was quantified with the I^2 test. All statistical analyses were performed with OpenMetaAnalyst (Biostat, Englewood, NJ) using random effects models. A P value < 0.05 was considered statistically significant.

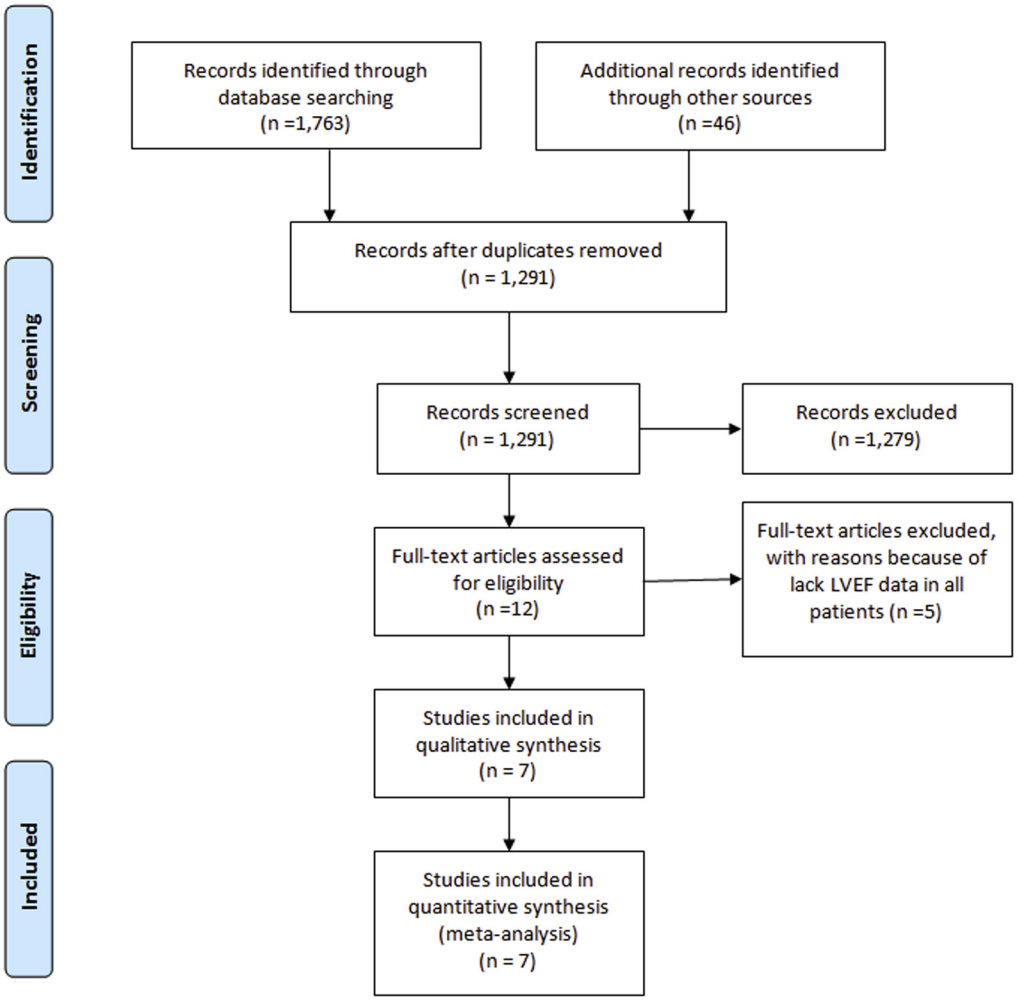

Figure 1. Flowchart showing search results and article selection.

Results

The literature search yielded 1,809 citations, of which 7 articles were eligible based on the study inclusion criteria (Fig. 1). All 7 studies were retrospective cohort studies, and Table 1 shows the risk of bias for the different studies. There was an excellent interobserver agreement for study relevance (κ 0.89, 95% CI, 0.84-0.93) and for study eligibility (κ 0.86, 95% CI, 0.82-0.91). A total of 2,854 patients from 7 studies were included in this review. Table 2 shows the demographics and baseline clinical data, and Table 3 shows the echocardiographic and CMRI data of the studies. The number of patients per study ranged from 81 to 873 patients. LVEF was assessed by CMRI in 6 studies[8-13] and by echocardiogram in 1 study.[14] Table 4 shows the demographics of the pooled cohort.

During a mean follow-up of 5.6 ± 3.4 years (11,982 patient-years), 2.9% (82 patients from 7 studies) died, 0.6% (17 patients from 4 studies) had aborted sudden cardiac death, and 2.0% (56 patients from 6 studies) had sustained ventricular tachycardia. Overall, CAE occurred in 5.1% (144 patients). Figures 2 and 3 show a summary of the effect estimates of the relationship between LVEF and CAE using LVEF as continuous predictor variable and binary predictor variable, respectively. As a continuous variable, LVEF was a predictor of CAE (HR 1.29, 95% CI, 1.09-1.53, $P = 0.001$)

Table 1. Test of bias

	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome absent at baseline	Comparability	Assessment of outcome	Adequacy of follow-up
Westhoff-Bleck et al.[10] (2016)	1	1	1	1	0	1	1
Geva et al.[8] (2018)	1	1	1	1	1	1	1
Valente et al.[9] (2014)	1	1	1	1	1	1	1
Orwat et al.[11] (2016)	1	1	1	1	0	1	0
Bokma et al.[12] (2017)	1	1	1	1	1	1	1
Knauth et al.[13] (2008)	1	0	1	1	0	1	0
Diller et al.[14] (2012)	1	1	1	1	1	1	1

Table 2. Baseline characteristics

	N	Age, y	TOF repair	Palliative shunt	TAP repair	TOF-PA	PVR
Westhoff-Bleck et al.[10] (2016)	81	26 ± 7	2.5 ± 2.1	—	67 (83%)	N	38 (47%)
Geva et al.[8] (2018)	452	26 (19 to 38)	2.2 (0.5 to 6.0)	—	—	Y	452 (100%)
Valente et al.[9] (2014)	873	24 (0.2 to 72)	2.9 (0.6 to 7.2)	314 (36%)	442 (51%)	Y	315 (36%)
Orwat et al.[11] (2016)	372	16 (12 to20)	1 (0.1 to 3.0)	204 (55%)	—	Y	—
Bokma et al.[12] (2017)	575	31 ± 1 1	3 (1.4 to 6.7)	191 (33%)	283 (49%)	Y	—
Knauth et al.[13] (2008)	88	24 (10 to 43)	3.0 (0.3 to 9.8)	—	—	Y	—
Diller et al.[14] (2012)	413	36 ± 13	8 (2 to 10)	—	—	Y	—

Data presented as mean ± standard deviation, median (interquartile range), and count (%).

PVR, pulmonary valve replacement; TAP, transannular patch; TOF, tetralogy of Fallot; TOF-PA, tetralogy of Fallot with pulmonary atresia; y, years;

per 5% decrease in LVEF. Similarly, LVEF < 40% was also a predictor of CAE (HR 3.22, 95% CI, 2.16-4.80, $P < 0.001$).

There was significant heterogeneity ($I^2 = 67$ %, $P = 0.047$) in the meta-analysis of the studies that reported LVEF as continuous predictor variable. The study by Westhoff-Bleck et al.[10] had an effect size that was much higher than the other 2 studies. A possible explanation for the observed difference in effect size may due to differences in sample size and population demographics. The study by Westhoff-Bleck et al.[10] was based on only 81 patients, and these patients had relatively smaller RV volumes. In contrast, the studies by Orwat et al.[11] and Diller et al.[14] had more than 370 patients in each of the studies, and the RV volumes were relatively larger. Of the studies that reported LVEF as binary variable, the study by Knauth et al.[13] had an effect size that was much larger compared with the other studies. This difference may also be related to the small sample size of 88 patients compared with more than 400 patients in each of the other 3 studies and relatively smaller RV volumes in that study.

Only 1 of the 7 studies, (Orwat et al.[11]) assessed the effect of LVEF and RVEF on the occurrence of CAE in the same multivariate model. Based on this model, LV dysfunction was an independent predictor of CAE (HR 1.28, 95% CI. 1.10-1.54) per 5% decrease in LVEF, whereas RV dysfunction was also an independent predictor of CAE (HR 1.61, 95% CI, 1.05-2.29) per 5% decrease in RVEF. There was no significant difference in the effect size of LVEF vs RVEF on the incidence of CAE, based on a comparison of the confidence intervals of the estimates.

Discussion

Based on the meta-analysis of 7 studies involving 2854 patients with TOF, we demonstrated that LV systolic dysfunction was an independent predictor of CAE. This effect was consistent throughout all studies. There was a 30% increase in the risk of CAE for every 5% decrease in LVEF. Similarly, there was more than a 3-fold increase in the risk of CAE in patients with LVEF < 40% compared with other patients. LV systolic dysfunction and RV systolic dysfunction had similar effect size in predicting CAEs.

LV systolic dysfunction is a known predictor of mortality and other adverse events in patients with acquired heart disease, and there are extensive studies in strategies for preventing and treating LV systolic dysfunction in that population.[5] Unfortunately, the clinical implications of LV systolic dysfunction in the TOF population are understudied and under-reported as evidence by the small number of studies that integrated LVEF in their risk models.[8-14] This is most likely because TOF repair results primarily in a right heart disease, and most of the residual or recurrent lesions such as pulmonary regurgitation typically affect the RV.[3] As a result, the RV has been the central focus of research in the TOF population, and the effect of RV systolic dysfunction on adverse outcomes is well studied.[1-3,12,16,17] Based on the robust data from these studies, progressive RV systolic dysfunction is 1 of the criteria for surgical or transcatheter intervention in this population.[6,7,18] In this study, we demonstrated that LV systolic dysfunction is also an important determinant of clinical outcomes and that the risk of adverse outcomes increased by roughly the same magnitude per unit change in EF for the LV and the RV. Although this comparison was only reported in 1 study, and hence is prone to bias, it suggests that perhaps the current risk stratification models used in clinical practice can be optimized by integrating LVEF as one of the indices.

The pathogenesis and pathophysiology of LV systolic dysfunction after TOF repair is likely multifactorial, and there are several potential mechanisms underlying this problem.

The first is longstanding cyanosis and chronic LV volume overload due to palliative shunt before TOF repair, especially in the older cohort of patients that underwent late TOF

Table 3. Noninvasive hemodynamic data

	LVEF %	RVEDVI mL/m^2	RVESVI mL /m^2	RVEF %	RVSP* mm Hg	> Mod TR*	> Mod PR*
Westhoff-Bleck et al.[10] (2016)	61 ± 7	98 ± 27	51 ± 20	47 ± 11	—	8 (10%)	40 (49%)
Geva et al.[8] (2018)	56 ± 8	176 ± 48	96 ± 36	46 ± 9	36 (27 to 55)	35 (8%)	452 (100%)
Valente et al.[9] (2014)	58 ± 8	153 ± 49	79 ± 35	49 ± 9	—	—	—
Orwat et al.[11] (2016)	58 (53 to 63)	116 (97 to 140)	57 (44 to 74)	51 (45 to 57)	—	—	—
Bokma et al.[12] (2017)	53 ± 8	126 ± 38	88 ± 23	44 ± 10	36 (27 to 55)	35 (6%)	452 (79%)
Knauth et al.[13] (2008)	60 ± 9	129 ± 27	66 ± 33	48 ± 12	—	Y	—
Diller et al.[14] (2012)	55 ± 10*	—	—	—	—	17 (4%)	210 (51%)

Data presented as mean ± standard deviation, median (interquartile range), and count (%).

PVR, pulmonary valve replacement; TAP, transannular patch; TOF, tetralogy of Fallot; TOF-PA, tetralogy of Fallot with pulmonary atresia; Y, years.

*Signifies echocardiographic data (all other data were derived from cardiac magnetic resonance image)

Table 4. Demographics of pooled cohort

	Values	N of studies providing data	N of included patients
Male	1451 (51%)	7	2854
Age, years	28 ± 4	7	2854
Age at TOF repair, years	3.2 ± 1.1	7	2854
Palliative shunt	709 (39%)	3	1820
Transannular patch repair	792 (52%)	3	1529
Mean follow-up, years	5.6 ± 3.4	7	2854
Total follow-up, patient-years	11,982	7	2854

Data presented as mean ± standard deviation and count (%).
N, number; TOF, tetralogy of Fallot.

repair.[19] This is followed by intraoperative hypoxic injury to the myocardium at the time of TOF repair and subsequent surgical interventions.[20] Another potential mechanism is ventricular-ventricular interaction, and this occurs because both ventricles share myocardial fibers, ventricular septum, and pericardial space.[4] Finally, dyssynchrony due to conduction disturbance and RV pacing can also result in LV systolic dysfunction in this population.[4]

Clinical implications and future directions

The presence of LV systolic dysfunction is a *soft* indication to support pulmonary valve replacement in a patient that already has other indications for pulmonary valve replacement.[6] There is a statistically significant—but perhaps not clinically significant—improvement in LVEF by 2 percentage points after pulmonary valve replacement (PVR), mostly due to increase in LV end-diastolic dimension.[21] A more important clinical question is how to manage patients with LV systolic dysfunction who have persistent LV systolic dysfunction after PVR. There are guideline directed medical therapies for the management of heart failure with reduced LVEF due to ischemic and nonischemic cardiomyopathies.[5,22,23] The cornerstone of these therapies is the combination of beta blockers and renin-angiotensin-aldosterone system inhibitors at the maximal tolerated doses. Although these medications are often used in the TOF population, it is unclear whether dosages are optimized for maximal clinical benefit because of limited data from published studies.[1-3,7-14,16] A recent clinical trial demonstrated that angiotensin receptor-neprilysin inhibitors reduced the incidence of cardiovascular death and hospitalization for heart failure in patients with heart failure and reduced EF compared with standard therapy with renin-angiotensin-aldosterone system inhibitors alone.[24] Although it would be inappropriate to extrapolate data directly from this trial to the TOF population because of significant differences in population demographics, the significant effect of LV dysfunction on adverse events demonstrated in this meta-analysis (30% increase in event rate for every 5% decrease in LVEF) calls for more focused research on medical therapies to address this problem. There is no evidence that this therapy will be effective in patients with TOF, and, at the same time, there is no evidence that it will not work. Hence, we have equipoise. Our goal was to stimulate clinicians and researchers to expand their horizons beyond only replacing the pulmonary valve as the only definitive therapy in TOF.

More importantly, the observation that LV systolic dysfunction and RV systolic dysfunction had approximately the same magnitude of effect on the incidence of adverse events underscores the need for reevaluation of the current management paradigm in this population. Another therapy that demands further study is cardiac resynchronization therapy for LV systolic dysfunction in patients with TOF. Although the maximum benefits of cardiac resynchronization therapy have been reported in patients with left bundle branch block,[5,22,23] perhaps similar strategies should be explored in the TOF population.

Limitations

This meta-analysis was limited by the small number of eligible studies, which resulted in our inability to perform subgroup analysis. We could not assess for the effects of therapies such as PVR, implanted cardioverter-defibrillators, and cardiac resynchronization therapy, all of which can potentially confound event rates in the different studies. Finally, the different studies did not provide data about the use of heart failure medical therapy in the subset of patients with LV systolic dysfunction in their cohorts. Notwithstanding, the association between LVEF and adverse events was consistent in all studies, suggesting that differences in the use of heart failure therapy may not be a significant confounder.

Conclusions

LV systolic dysfunction was an independent predictor of CAEs in patients with repaired TOF, and we observed a 30% increase in the risk of CAEs for every 5% decrease in LVEF and a 3-fold increase in the risk of CAEs in patients with LVEF < 40% compared with other patients. LV systolic

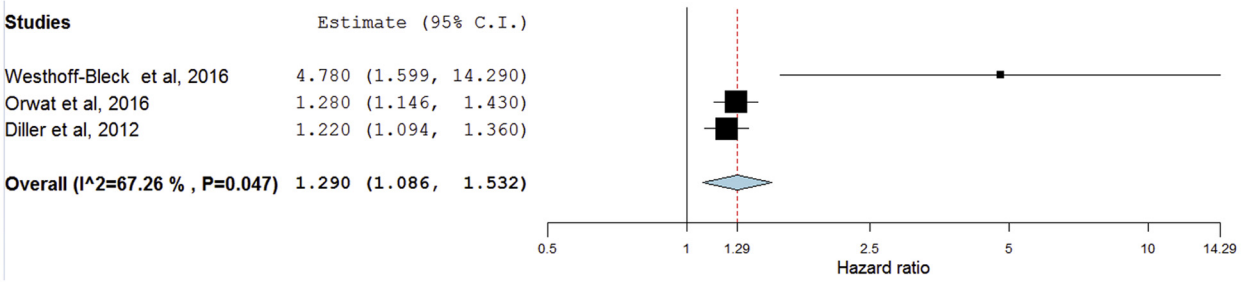

Figure 2. Forest plot showing pooled effect of left ventricular ejection fraction (as continuous variable) on the incidence of cardiovascular adverse events.

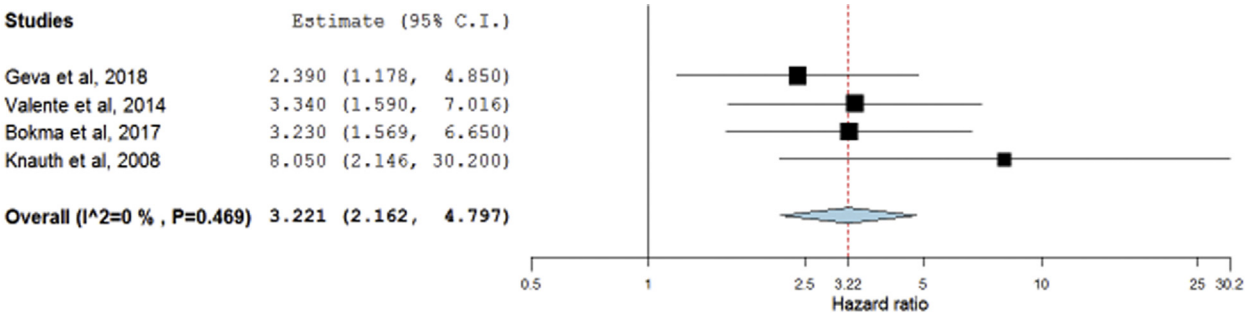

Figure 3. Forest plot showing pooled effect of left ventricular ejection fraction (as categorical variable) on the incidence of cardiovascular adverse events.

dysfunction and RV systolic dysfunction had similar magnitudes of effect on the incidence of CAEs. These findings underscore the importance of incorporating LV systolic function in clinical risk stratification of patients with TOF. It also highlights the need for further studies to explore the efficacy of standard heart failure therapy (medications and cardiac resynchronization therapy), and novel strategies (early pulmonary valve replacement for pulmonary regurgitation) in this population

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Disclosures

The authors have no conflicts of interest to disclose.

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