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Clinical Research

The 30-Year Outcomes of Tetralogy of Fallot According to Native Anatomy and Genetic Conditions

Samuel Blais, BSc,[a,b] Ariane Marelli, MD, MPH,[c] Alain Vanasse, MD, PhD,[b,d] Nagib Dahdah, MD,[e] Adrian Dancea, MD,[f] Christian Drolet, MD,[g] Jaime Colavincenzo, BSc,[h] Esther Vaugon, MD,[f] and Frederic Dallaire, MD, PhD[a,b]

[a] *Department of Pediatrics, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Québec, Canada*

[b] *Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec, Canada*

[c] *McGill Adult Unit for Congenital Heart Disease Excellence, McGill University Health Centre, Montréal, Québec, Canada*

[d] *Department of Family Medicine and Emergency Medicine, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Québec, Canada*

[e] *Division of Pediatric Cardiology, Centre Hospitalier Universitaire Sainte-Justine, Montréal, Québec, Canada*

[f] *Division of Pediatric Cardiology, McGill University Health Centre, Montréal, Québec, Canada*

[g] *Division of Pediatric Cardiology, Centre Hospitalier Universitaire de Québec, Québec, Québec, Canada*

[h] *Faculty of Medicine, McGill University, Montréal, Québec, Canada*

See editorial by Chetan and Mertens, pages 825–826 of this issue.

ABSTRACT

Background: The reported survival of tetralogy of Fallot (TOF) is > 97%. Patients with pulmonary atresia and/or genetic conditions have worse outcomes, but long-term estimates of survival and morbidity for these TOF subgroups are scarce. The objective of this study was to describe the 30-year outcomes of TOF according to native anatomy and the coexistence of genetic conditions.

Methods: The TRIVIA (Tetralogy of Fallot Research for Improvement of Valve Replacement Intervention: A Bridge Across the Knowledge Gap) study is a retrospective population-based cohort including all TOF subjects born from 1980 to 2015 in Québec. We evaluated all-cause mortality by means of Cox proportional hazards regression, and

RÉSUMÉ

Contexte : Le taux de survie raporté des patients présentant une tétralogie de Fallot (TdF) est supérieur à 97 %. Le pronostic est plus sombre chez les patients souffrant en plus d'atrésie pulmonaire ou de troubles génétiques, mais les estimations de la survie et de la morbidité à long terme pour ces sous-groupes de patients atteints de la TdF sont rares. Notre étude visait à décrire les résultats à 30 ans chez les patients présentant une TdF en fonction des caractéristiques anatomiques naturelles et de la coexistence de troubles génétiques.

Méthodologie : L'étude TRIVIA (*Tetralogy of Fallot Research for Improvement of Valve Replacement Intervention: A Bridge Across the Knowledge Gap*) est une étude de cohorte rétrospective

Today, tetralogy of Fallot (TOF) is often diagnosed prenatally or during infancy. In the past decades, advances in surgical and critical care have increased survival of TOF subjects following correction to approximately 97%.[1-6] However, these favourable results have generally been described for the classic stenotic TOF type. It is accepted that TOF subjects with pulmonary atresia (PA) or those with a concomitant genetic condition have poorer outcomes.[7-11] However, the impact of the native anatomy and that of genetic syndromes has mostly been measured on relatively small populations with short-term follow-ups. Studies have often reported the impact of these conditions on outcomes as relative ratios compared with classic TOF, but long-term survival and expected numbers of cardiovascular interventions and hospitalisations stratified for these specific TOF subgroups have seldom been reported.

Nevertheless, approximately one-fifth of TOF subjects are born with PA and 28% to 39% with a concomitant genetic condition.[7,8,11-13] To provide adequate counselling to families facing a new diagnosis of TOF, we need long-term outcomes based on information available in the perinatal period. Such outcomes should be based on robust real-world observational data from a large unselected population followed from birth to

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Corresponding author: Dr Frederic Dallaire, Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine and Health Sciences, University of Sherbrooke, 3001, 12e Avenue Nord, Sherbrooke, Québec J1H 5N4, Canada. Tel.: +1-819-346-1110 ext 70454; fax: +1-819-564-5398.

E-mail: frederic.a.dallaire@usherbrooke.ca

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cumulative mean number of cardiovascular interventions and unplanned hospitalisations with the use of marginal means/rates models. We computed 30-year estimates of outcomes according to TOF types, ie, classic TOF (cTOF) and TOF with pulmonary atresia (TOF-PA), and the presence of genetic conditions.

Results: We included 960 subjects. The median follow-up was 17 years (interquartile range, 8-27). Nonsyndromic cTOF subjects had a 30-year survival of 95% and had undergone a mean of 2.8 interventions and 0.5 hospitalisations per subject. In comparison, TOF-PA subjects had a lower 30-year survival of 78% and underwent a mean of 8.1 interventions, with 4 times as many hospitalisations. The presence of a genetic condition was associated with lower survival (< 85% for cTOF and < 60% for TOF-PA) but similar numbers of interventions and hospitalisations.

Conclusions: The anatomic types and the presence of genetic conditions strongly influence the long-term outcomes of TOF. We provided robust 30-year estimates for key markers of prognosis that may be used to improve risk stratification and provide more informed counselling to families.

populationnelle incluant tous les sujets présentant une TdF nés au Québec entre 1980 et 2015. Nous avons évalué la mortalité toutes causes confondues au moyen d'un modèle de régression à risques proportionnels de Cox, et déterminé le nombre cumulatif moyen d'interventions cardiovasculaires et d'hospitalisations imprévues à l'aide de modèles de moyennes et de fréquences marginales. Nous avons estimé les résultats à 30 ans en fonction du type de TdF, soit une TdF classique (TdFc) ou une TdF accompagnée d'une atrésie pulmonaire (TdF-AP), et de la présence de troubles génétiques.

Résultats : Notre étude comprenait 960 sujets. La durée médiane du suivi était de 17 ans (1er quartile et 3e quartile: 8-27). Les sujets présentant une TdFc non syndromique affichaient un taux de survie à 30 ans de 95 % et avaient subi en moyenne 2,8 interventions et 0,5 hospitalisation chacun. En revanche, les sujets présentant une TdF-AP affichaient un taux de survie à 30 ans de 78 % et avaient subi en moyenne 8,1 interventions et 4 fois plus d'hospitalisations. La présence d'un trouble génétique a été associée à un taux de survie inférieur (< 85 % en cas de TdFc et < 60 % en cas de TdF-AP), mais à un nombre comparable d'interventions et d'hospitalisations.

Conclusions : Les caractéristiques anatomiques et la présence de troubles génétiques ont une grande influence sur l'évolution à long terme de la TdF. Nous fournissons des estimations robustes des résultats à 30 ans à l'égard des facteurs déterminants du pronostic, qui pourraient se révéler utiles pour améliorer la stratification du risque et prodiguer des conseils plus éclairés aux familles.

adulthood and stratified for clinical variables accessible at the time of diagnosis.

The TRIVIA (**T**etralogy of Fallot **R**esearch for **I**mprovement of **V**alve Replacement **I**ntervention: **A** Bridge Across the Knowledge Gap) study was initiated to study the long-term outcomes of TOF by leveraging data from the Québec Congenital Heart Disease (CHD) database and merging it with granular clinical data from all pediatric cardiology institutions in Québec. The objective of the present analysis was to describe the long-term outcomes of TOF subjects from birth to 30 years of age according to native anatomy and the presence of genetic syndromes. We aimed to provide estimates of survival and expected cumulative numbers of interventions and hospitalisations based on variables available at the time of perinatal diagnosis to improve patient counseling.

Methods

Study design and population

The rationale and design of the TRIVIA study were described previously.[14] Briefly, it is a retrospective population-based cohort combining detailed clinical information and long-term administrative follow-up for all TOF subjects born from 1980 to 2015 in Québec, Canada. TOF was defined as a ventricular septal defect by malalignment of the conal septum or overriding of the aorta with at least mild obstruction of the right ventricular outflow tract. We also included patients with TOF and PA and patients with double-outlet right ventricle (DORV) of the TOF type that satisfied the definition above. We excluded subjects with a concomitant severe heart defect, such as atrioventricular septal defect, and patients with TOF and absent pulmonary valve.

Data collection

The final cohort consisted of detailed clinical data from birth to 18 years of age extracted from the 4 pediatric cardiology health care centers following TOF patients in Québec, enriched with > 35 years of health care administrative follow-up data. Clinical data were manually abstracted from patients' charts with the use of a standardised collection form. Administrative data were extracted from the Québec CHD database.[15,16] The project was approved by each participating institution's ethics review board and by the Commission d'Accès à l'Information du Québec, the governing entity regulating access to administrative data in Québec. Given the retrospective nature of the study and deidentification of the records, the requirement for individual consent was waived.

Outcomes

The observation period started at birth and ended at death or in 2017. The primary outcome was all-cause mortality. The causes of death were extracted from administrative data or from manual revision of patients' chart and death certificate, when available. Secondary outcomes were cardiovascular interventions and cardiovascular unplanned hospitalisations for adverse cardiac events. Cardiovascular interventions were defined as all surgical, percutaneous, or electrophysiologic interventions performed on the heart or the major thoracic blood vessels and were identified by physicians' and surgeons' billing codes. Unplanned hospitalisations were defined as all nonelective hospitalisations for adverse cardiovascular events and were identified by International Classification of Disease codes (ICD-9 and ICD-10), thus excluding planned hospitalisations for elective procedures. The algorithms and the lists of codes used to identify interventions and hospitalisations as

well as the definition of the causes of death are described in detail in the Supplementary Material.

Predictive variables

Predictive variables of interest were the TOF anatomic type and the presence of genetic conditions. The TOF anatomic type was identified according to the first echocardiogram report after birth or a catheterisation report if an echocardiogram was unavailable and was confirmed by the corrective surgery report. We defined 2 TOF types: 1) classic stenotic TOF (cTOF); and 2) TOF with PA (TOF-PA), depending on the presence or absence of forward flow in the right ventricle outflow tract at birth. DORV was inconsistently documented and affected a small proportion of the population. It was included in the cTOF or TOF-PA categories according to the presence of forward flow in the right ventricle outflow tract.

The presence of a genetic condition was divided into 4 categories: 1) trisomy 21 (T21); 2) 22q11 deletion (22q11); 3) subjects with a clinical or genetic diagnosis other than T21 and 22q11; and 4) nonsyndromic subjects, defined as the absence of a clinical suspicion of a genetic condition for whom no referral for genetic testing was requested. For 6.8% of subjects, information on genetic condition was unknown (unclear if genetic condition was suspected and no testing available) and was predicted with the use of multiple imputation (see Statistical analysis).

We included a covariable representing the surgical era based on the year of birth. In preliminary analyses, a 4-category variable representing each decade from 1980 to 2010 was tested. However, in the final analyses, we used a binary variable (1980-1999 and 2000-2015) because the effect sizes were similar to those obtained with a 4-category variable for all outcomes. We tested for sex-specific differences, but no association was found in all models so the variable was excluded from analyses.

Statistical analysis

All analyses were performed with the use of SAS v9.4. Statistical significance was defined as a 2-sided P value < 0.05. Descriptive statistics are presented as frequency and proportion for categoric variables. Continuous variables are summarised as median and interquartile range.

We used a multivariable Cox proportional hazard model to evaluate mortality. For interventions and hospitalisations, we used marginal means/rates models for recurrent events, which are a semiparametric extension of the Cox model.[17,18] The marginal means/rates regression models the cumulative mean number of events per subjects over time. All models were adjusted for surgical era. We used stratified models for TOF types when the annualised risk curves were qualitatively different between TOF types. Furthermore, we tested for the presence of interaction between genetic conditions and TOF types and added an interaction term if needed.

Results from the Cox model are presented as hazard ratios (HRs), and results from the marginal means/rates models are presented as mean ratios (MRs) with their respective 95% confidence intervals (CIs). We computed the estimated survival and the estimated cumulative mean number of interventions and unplanned hospitalisations per subjects from birth to 30 years of age according to 8 TOF clinical profiles (the 2 TOF types and the 4 categories of genetic conditions). The proportional hazard assumption was verified by plotting Schoenfeld residuals against time. The potential for multicollinearity was verified and ruled out before analysis.

Because information on genetic conditions was missing for part of the cohort, we used multiple imputation with a fully conditional specification method to create 50 imputed datasets. We performed analyses in parallel for each of the imputed datasets and used the SAS Proc Mianalyze module to generate the final models' coefficients and estimated curves. More information on the imputation model specifications are presented in the Supplementary Material.

Results

We identified 972 TOF subjects who met the inclusion criteria. Of those, we excluded 12 subjects with missing follow-up information. The remaining 960 subjects (98.8%) were included in final analyses. The median follow-up duration was 17.1 years (range, 7.5-26.7), including 158 subjects (16%) followed > 30 years, for a total of 16,515 patient-years.

The population characteristics according to TOF types are presented in Table 1. As expected, cTOF was more prevalent than TOF-PA (78.5% and 21.5%, respectively) and 55.6% of the subjects were male. The prevalence of subjects with a genetic condition was higher for subjects with TOF-PA than with cTOF (28.2% and 17.5%, respectively). This was explained by a higher prevalence of 22q11 deletions and other syndromes in subjects with TOF-PA compared with with cTOF (13.1% vs 5.8%, respectively, for 22q11 and 12.7% vs 6.9% for other syndromes). The proportion of subjects with

Table 1. Population characteristics according to TOF type

Characteristic	All subjects (n = 960; 100%)	cTOF (n = 754; 78.5%)	TOF-PA (n = 206; 21.5%)
Male sex	534 (55.6%)	429 (56.8%)	105 (51.0%)
Genetic condition			
Nonsyndromic	704 (73.3%)	568 (75.3%)	136 (66.0%)
Trisomy 21	41 (4.3%)	36 (4.8%)	5 (2.4%)
22q11 deletion	71 (7.4%)	44 (5.8%)	27 (13.1%)
Other syndromes	78 (8.1%)	52 (6.9%)	26 (12.7%)
Unknown	66 (6.9%)	54 (7.2%)	12 (5.8%)
Follow-up length, y (median [Q25-Q75])	17.1 (7.5-26.7)	18.1 (8.8-27.0)	13.4 (2.7-25.6)

Results are presented as n (%) or median (interquartile range).
cTOF, classic stenotic tetralogy of Fallot; TOF-PA, tetralogy of Fallot with pulmonary atresia.

T21 was higher in subjects with cTOF (4.8%) than with TOF-PA (2.4%). Only 5 subjects had T21 in the TOF-PA group, leading to the exclusion of this subgroup from the final statistical analysis owing to insufficient sample size.

The distribution of TOF clinical profiles is presented in Figure 1, along with the modelled survival and cumulative mean number of interventions and hospitalisations from birth to 30 years, adjusted for surgical era. The detailed estimates at 5, 10, 20, and 30 years with their 95% CIs are presented in Supplemental Tables S3-S5. Figure 2 presents the annualised risk of mortality and annualised rates of interventions and hospitalisations according to TOF types.

Survival

There were 142 deaths. The causes of death according to TOF types are shown in Figure 3. The distribution of the causes of death was similar between cTOF and TOF-PA. The majority of deaths (64.8%) were attributable to cardiovascular causes. For both cTOF and TOF-PA, the most common causes of death were perioperative complications (eg, inability to come off bypass, early postoperative arrhythmia, or heart failure) (26.5% and 33.8%, respectively) and respiratory disease or infections (11.8% and 12.2%, respectively). The HRs from the Cox multivariable model are presented in Table 2.

Interestingly, nearly half of the deaths (49%) occurred before surgical correction. This proportion remained constant across surgical eras for both cTOF and TOF-PA subjects. Of those, 23% received neonatal palliative care (ie, active treatment was withheld owing to poor prognosis) and 57% underwent a palliative procedure (surgical shunt or stenting) but died before definitive repair. For cTOF, the proportion of preoperative deaths and the causes of death before surgical correction differed according to the presence of genetic conditions. In nonsyndromic cTOF subjects, only 8 subjects died before correction (25% of deaths) and 5 of those 8 deaths were due to noncardiovascular causes. In comparison, for syndromic cTOF, 73% of deaths occurred before surgical correction and of them, nearly 70% were for cardiovascular causes, including 35% receiving neonatal palliative care. For TOF-PA subjects, around 75% of the deaths before surgical correction were from cardiovascular causes, with 30% receiving neonatal palliative care.

The 30-year survival varied greatly according to clinical profiles, highlighting the strong independent effect of TOF types and genetic conditions (see Figure 1). Nonsyndromic subjects with cTOF had the highest estimated 30-year survival (95%). In comparison, nonsyndromic TOF-PA subjects had a lower survival of 78% (HR 4.5, 95% CI 2.9-7.1). We observed significant heterogeneity in the effect of genetic conditions on the risk of mortality between TOF types. Compared with nonsyndromic cTOF, subjects with 22q11 had a similar 30-year survival of 93% (HR 1.3, 95% CI 0.4-4.0), while subjects with T21 and other syndromes had lower survivals of 85% and 77% (HR 3.1 [95% CI 1.4-6.6] and 4.8 [95% CI 2.6-8.7], respectively). On the other hand, the 30-year survival was lower in subjects with TOF-PA and 22q11 deletions (57%, HR 2.3, 95% CI 1.2-4.3) or other syndromes (40%, HR 3.8, 95% CI 2.1-6.8) compared with nonsyndromic TOF-PA (78%).

Cardiovascular interventions

We recorded 2305 cardiovascular interventions during follow-up. Of them, 866 were surgical correction of TOF. The proportions of other intervention types are described in Figure 3. Aside from correction of TOF, the most common interventions were percutaneous pulmonary valvuloplasty (40% of all interventions for both cTOF and TOF-PA). The most common surgical interventions were pulmonary valve replacements (17.5% for cTOF and 15.8% for TOF-PA) and systemic-to-pulmonary shunts (8.2% for cTOF and 11.2% for TOF-PA). Overall, when excluding surgical correction, percutaneous procedures accounted for 45% of interventions for TOF-PA subjects, independently from surgical era. On the other hand, the proportion of percutaneous procedures in cTOF increased from 52% to 65% when comparing interventions performed before and after the year 2000. The mean ratios from the stratified multivariable marginal means/rates model are presented in Table 3.

The 30-year cumulative mean number of interventions markedly varied according to TOF types (see Fig. 1). Nonsyndromic TOF-PA subjects had an estimated 8.1 interventions per subject at 30 years, while nonsyndromic cTOF subjects underwent a mean of 2.8 interventions during the same period. For cTOF, the annualised rate of intervention (Fig. 2) was initially high but decreased to nearly zero between the age of 6 to 12 years, corresponding to a plateauing of the number of interventions. In comparison, the rate of intervention remained high for TOF-PA, resulting in a steady increase in the number of interventions. The presence of genetic conditions was not associated with the number of cardiovascular interventions in either TOF type, except for 22q11 deletions in subjects with TOF-PA, who had a higher number of interventions, compared with nonsyndromic subjects (10.6 interventions, MR 1.3, 95% CI 1.0-1.7).

Hospitalisations for adverse cardiovascular events

There were 357 unplanned hospitalisations for cardiac adverse events. The causes of hospitalisation are shown in Figure 3. The proportions of the causes of hospitalisation were similar between both TOF types. The most common causes of hospitalisation were cardiac infections, including endocarditis ($\sim$ 40%), arrhythmias ($\sim$ 25%), and heart failure ($\sim$ 7%). The MRs from the stratified multivariable marginal means/rates model are presented in Table 4.

Overall, the rate of unplanned hospitalisations for an adverse cardiac event was low in both TOF types, with a mean rate of < 0.1 hospitalisations per patient-year after 3 years of age (Fig. 2). For nonsyndromic cTOF, we estimated that approximately half of the subjects were hospitalised once before reaching 30 years of age (see Fig. 1). In comparison, nonsyndromic TOF-PA subjects had a cumulative number of 1.8 hospitalisations during the same period. The presence of either T21 or 22q11 was not associated with an increased number of hospitalisations. However, compared with nonsyndromic subjects, subjects with other syndromes had a higher mean number of hospitalisations: 0.8 hospitalisations for cTOF (MR 2.0, 95% CI 1.2-3.2) and 2.5 hospitalisations for TOF-PA (MR 1.4, 95% CI 0.6-2.9), albeit not statistically significant for TOF-PA. Of note, when all-cause

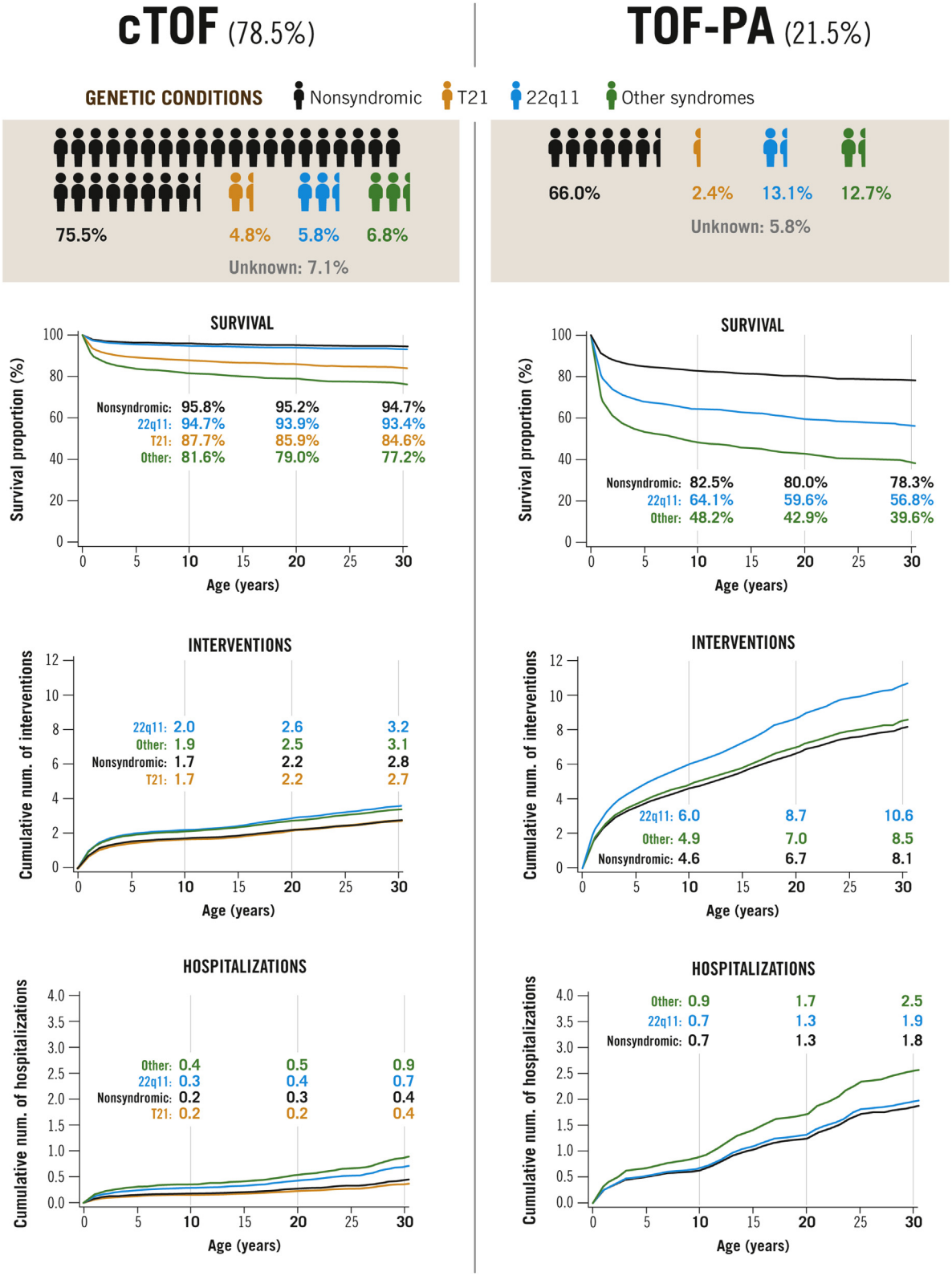

Figure 1. Prevalence of anatomic types and genetic conditions in subjects with tetralogy of Fallot (TOF) with associated estimated survival and estimated cumulative mean number of interventions and hospitalisations from birth to 30 years for each clinical profile. Results are divided by TOF types: left: classic stenotic TOF (cTOF); right: TOF with pulmonary atresia (TOF-PA). The **lines** represent locally weighted scatter plot smoothed curves fitted on the predicted values from the regression models.

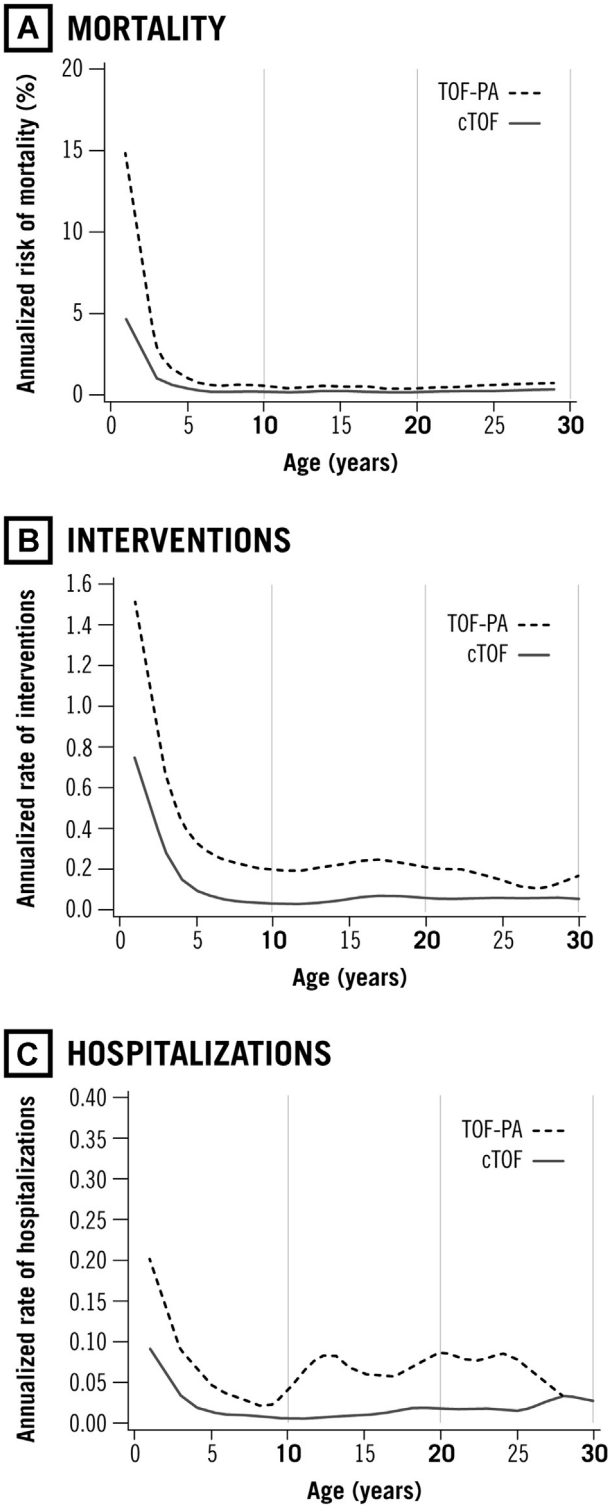

Figure 2. Annualised risk of mortality (**A**) and annualised rates of cardiovascular interventions (**B**) and unplanned hospitalisations for adverse cardiac events (**C**). Results are presented according to tetralogy of Fallot (TOF) type: classic stenotic TOF (cTOF), **solid grey lines**; TOF with pulmonary atresia (TOF-PA), **dashed black lines**. The lines represent locally weighted scatter plot smoothed curves fitted on the predicted values from the regression models.

hospitalisations were analysed, we found similar differences between clinical profiles (data not shown).

Post hoc analyses for DORV and systemic-to-pulmonary collaterals

We performed post hoc analyses to evaluate the impact of the presence of systemic-to-pulmonary collaterals and DORV of the TOF type. There were 23 subjects clearly identified as having a DORV in the cTOF group and 4 in the TOF-PA group. We were unable to detect any differences in survival, interventions, and hospitalisations compared with subjects without DORV. As stated in the methods, the presence of DORV was inconsistently documented and likely underestimated.

We identified 25 subjects (3%) with systemic-to-pulmonary collaterals in the cTOF group and 102 (50%) in the TOF-PA group. The presence of collaterals was associated with an increased cumulative number of interventions (MR 1.2, 95% CI 1.1-1.4) without differences between cTOF and TOF-PA. For survival and hospitalisations, the number of events was insufficient to reliably analyse the influence of collaterals with sufficient statistical power.

Furthermore, we identified a phenotype of subjects with cTOF who had poorer outcomes than subjects with TOF-PA. Patients with cTOF and collaterals, pulmonary tree hypoplasia, and receiving a right ventricle—to—pulmonary artery conduit (n = 40) had an increased cumulative number of interventions and hospitalisations (MR 1.7 and MR 2.6, respectively [$P < 0.001$]), which was similar to subjects with TOF-PA. Because of a limited number of events, we were unable to identify a difference in survival.

Discussion

We have provided 30-year estimates of survival and cumulative numbers of interventions and hospitalisations, stratified for native cardiac anatomy and the coexistence of specific genetic conditions, in a large unselected cohort of TOF patients. To our knowledge, this is the first study to enrich long-term population-based administrative data with granular clinical information. In recent years, there has been a gradual shift in CHD research from single-centre cohorts and administrative registries[4-6,19] toward larger multicentre cohorts, enabling the evaluation of longer-term outcomes after repair of TOF.[2,3,20] Consequently, several studies have reported the long-term survival for TOF,[1-5] but TOF outcomes often remain limited to postoperative survival, and long-term morbidity outcomes have seldom been reported. Because TOF is a chronic disease that evolves over multiple decades, it is of paramount importance to study outcomes over the entire lifespan.[21] We have provided long-term estimates of survival that include presurgical correction mortality as well as the rarely reported long-term morbidity outcomes. We think that our study provides an accurate representation of the true life trajectory of patients with TOF as it is based on an uncontrolled and unselected population in a real-world setting.

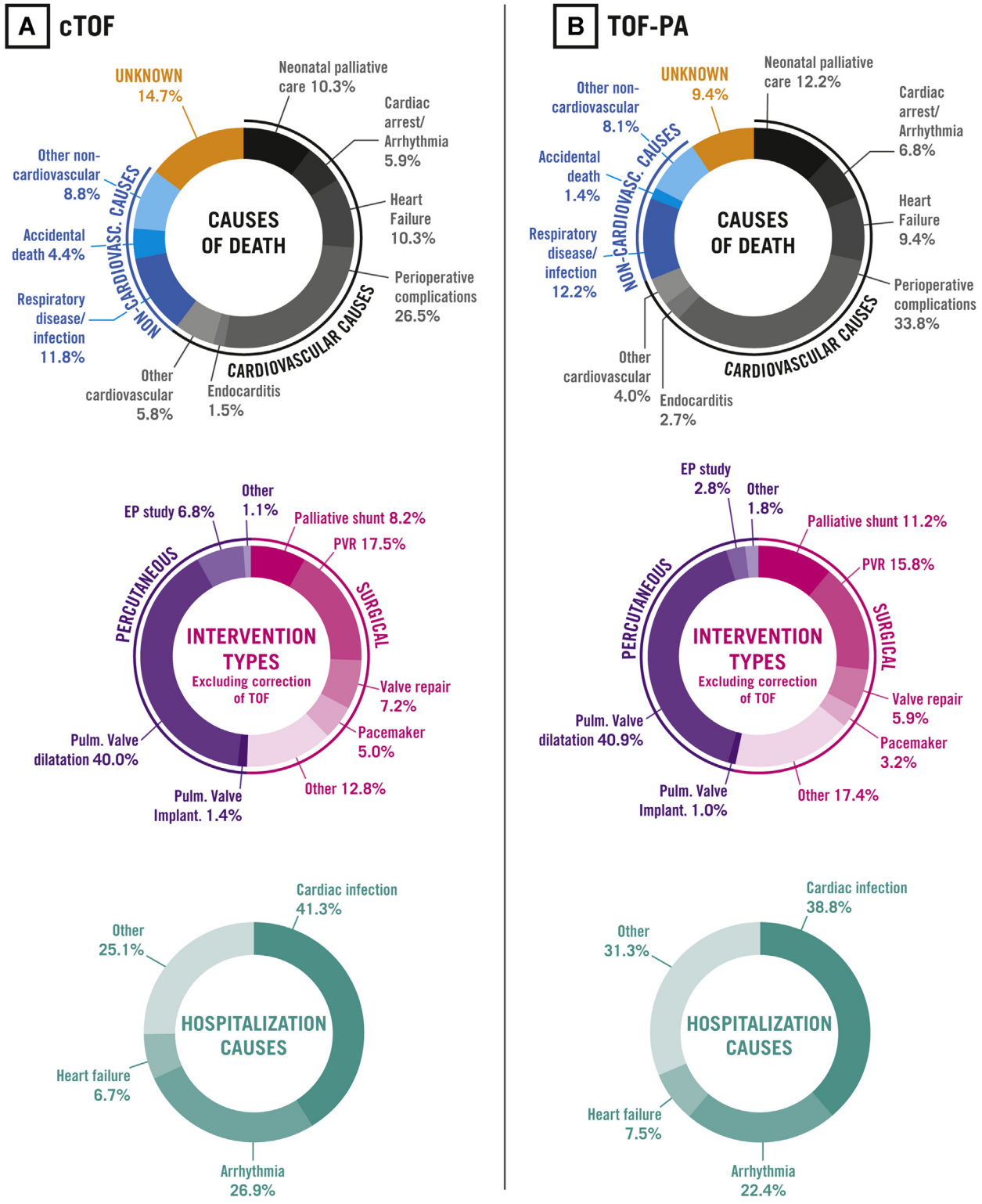

Figure 3. Description of the causes of death, types of cardiovascular interventions performed, and causes of unplanned hospitalisations for adverse cardiovascular events. Results are divided by tetralogy of Fallot (TOF) types: (**A**) classic stenotic TOF (cTOF); (**B**) TOF with pulmonary atresia (TOF-PA). EP, electrophysiology; PVR, pulmonary valve replacement.

Table 2. Mortality HRs according to predictive variables in the Cox multivariable model

Variable	HR (95% CI)	*P* value
TOF type		
cTOF	Reference	Reference
TOF-PA	4.5 (2.9-7.1)	< 0.001
Genetic condition (effect for cTOF)		
Nonsyndromic	Reference	Reference
Trisomy 21	3.1 (1.4-6.6)	0.004
22q11 deletion	1.3 (0.4-4.0)	0.703
Other syndromes	4.8 (2.6-8.7)	0.001
Genetic condition (effect for TOF-PA)		
Nonsyndromic	Reference	Reference
22q11 deletion	2.3 (1.2-4.4)	0.009
Other syndromes	3.8 (2.1-6.8)	< 0.001
Surgical era		
1980-1999	Reference	Reference
2000-2015	0.6 (0.4-0.9)	0.012

An interaction term between genetic condition and TOF type was included in the model. HRs for genetic syndromes are presented separately for each type.

CI, confidence interval; cTOF, classic stenotic tetralogy of Fallot; HR, hazard ratio; TOF-PA, tetralogy of Fallot with pulmonary atresia.

Clinical implications

For nonsyndromic cTOF subjects, we corroborate past studies showing that survival is excellent. We showed that even in the more recent decades, for both cTOF and TOF-PA, mortality before surgical correction represents approximately half of the overall mortality during the first 30 years of life but is less frequent in nonsyndromic patients. The expected number of interventions and hospitalisations during the first 30 years of life also remains low overall. We are currently conducting a separate analysis on long-term survival and burden of care according to the choice of corrective surgery and their associated residual lesions using the same cohort.

The expected survival and morbidity for subjects with genetic conditions and those with TOF-PA are considerably poorer. We estimated that subjects with TOF-PA will undergo a mean of at least 8 interventions over 30 years, with more than half of these being open-heart surgeries, even in the recent surgical era. This rate of approximately 1 intervention every 4 years as well as an overall decreased survival are critical pieces of information to convey to new or expecting parents.

Table 3. MRs for the cumulative mean number of interventions according to predictive variables in marginal means/rates models stratified for TOF types

	Model for cTOF		Model for TOF-PA	
Variable	MR (95% CI)	*P* value	MR (95% CI)	*P* value
Genetic condition				
Nonsyndromic	Reference	Reference	Reference	Reference
Trisomy 21	1.0 (0.7-1.3)	0.917	—	—
22q11 deletion	1.2 (0.9-1.4)	0.126	1.3 (1.0-1.7)	0.045
Other syndromes	1.1 (0.9-1.4)	0.373	1.1 (0.8-1.4)	0.737
Surgical era				
1980-1999	Reference	Reference	Reference	Reference
2000-2015	1.0 (0.9-1.2)	0.410	1.6 (1.4-2.0)	< 0.001

CI, confidence interval; cTOF, classic stenotic tetralogy of Fallot; MR, mean ratio; TOF-PA, tetralogy of Fallot with pulmonary atresia.

Table 4. MRs for the cumulative mean number of hospitalisations according to predictive variables in marginal mean/rates models stratified for TOF types

	Model for cTOF		Model for TOF-PA	
Variable	MR (95% CI)	*P* value	MR (95% CI)	*P* value
Genetic condition				
Nonsyndromic	Reference	Reference	Reference	Reference
Trisomy 21	0.8 (0.3-2.0)	0.680	—	—
22q11 deletion	1.6 (0.9-2.9)	0.113	1.1 (0.5-2.1)	0.873
Other syndromes	2.0 (1.2-3.2)	0.005	1.4 (0.6-2.9)	0.421
Surgical era				
1980-1999	Reference	Reference	Reference	Reference
2000-2015	1.0 (0.7-1.4)	0.945	1.9 (1.3-3.0)	0.003

CI, confidence interval; cTOF, classic stenotic tetralogy of Fallot; MR, mean ratio; TOF-PA, tetralogy of Fallot with pulmonary atresia.

Prevalence of TOF types and genetic conditions

We found a 20% proportion of TOF-PA among TOF subjects and an increased prevalence of genetic conditions in TOF-PA compared with cTOF, which is similar to previously published data.[7,10] However, we found overall lower proportions of genetic conditions than what was previously reported.[8,11-13] The reported prevalence of 22q11 deletions ranged from 21% to 40% for TOF-PA subjects and from 8% to 25% for cTOF subjects, whereas we found a prevalence of 13% for TOF-PA subjects and 6% for cTOF subjects.[7,8,13,22,23] The difference may be explained by the selection of more complex cases in studies from high-volume tertiary centres and by variation in the rate of termination of pregnancies among fetuses with TOF and a concomitant genetic condition. The proportion of T21 in our sample was, however, similar to what has been previously reported.[7,8]

Influence of TOF types and genetic conditions on survival

Most authors have reported lower short-term survival in subjects with TOF-PA and genetic conditions compared with nonsyndromic cTOF.[7-9,24,25] Others have evaluated long-term survival of TOF[1-5] and have, in general, showed that patients operated on after 1980 had 20- to 30-year survival between 90% and 95%. Hickey et al.[5] found an overall survival of 80% at 30 years for patients operated on between 1960 and 1998, but predicted that survival would be greater than 90% if early mortality was reduced. This prediction is well in line with our results. A recent study by the Pediatric Cardiac Care Consortium reported a 25-year survival of 94.5% for nonsyndromic subjects after correction of TOF and a decreased survival of 84% for subjects with a genetic condition. We report a similar long-term survival for the cTOF nonsyndromic group and cTOF with genetic conditions. Our survival estimates included preoperative deaths, which accounted for nearly half of overall deaths, whereas most other studies did not. Furthermore, our time at risk extended to 2017, compared with the early 2000s for most other studies. On one hand, including preoperative mortality will increase overall mortality, but we think that this is a better reflection of the true survival of infants born with TOF. On the other hand, including recent survival data with shorter time at risk could show reduced mortality, but it is difficult to know whether subjects operated on in 2015 will have similar

30-year survival compared with the data reported in this study, because improvements in care could occur in the following years.

A recent study by van Mil et al. evaluated the influence of 22q11 deletion syndrome on mortality in adult repaired TOF patients. They reported a 5-fold increase in the risk of mortality for subjects with 22q11 after adjusting for the presence of pulmonary atresia.[26] Unlike those results, we found no influence of 22q11 on the risk of mortality in cTOF subjects from birth to 30 years of age, suggesting a shift in the mortality risk of these patients later in life. Our study adds to the current literature by providing stratified survival estimates and morbidity outcomes for TOF-PA and for specific genetic conditions such as T21, 22q11 deletions, and complex syndromes.

Burden of interventions and hospitalisations

We elected to measure the global burden of cardiovascular interventions and hospitalisations as the cumulative mean number of events. Others have sometimes used the freedom from reintervention to evaluate outcomes.[19] Although that may be adequate for short-term follow-ups or rare events, it is restricted to the evaluation of the time to first event and does not take into account the burden of multiple interventions over time.

The study by Hickey et al.[5] evaluated freedom from reintervention after corrective surgery and found a higher risk of reoperation in TOF-PA subjects. Although we cannot directly compare our results owing to the divergent methodology used and our inclusion of presurgical correction interventions, we observed that the cumulative number of interventions were significantly higher in subjects with TOF-PA but were, for the most part, independent from the presence of genetic conditions. On one hand, in cTOF, the rate of intervention decreased to nearly zero between 6 and 12 years of age but rose slightly thereafter, which corresponded to pulmonary valve replacements progressively being performed in adolescents and young adults. On the other hand, subjects with TOF-PA had a steady rise in the cumulative number of interventions due, in large part, to percutaneous pulmonary valve balloon dilations, surgical valvuloplasties, and conduit replacements.

We showed an overall low incidence of unplanned hospitalisations for cardiovascular events in the first 30 years of life, especially for subjects with cTOF, highlighting the familiar scarcity of hard outcomes in CHD research. The most common cause of hospitalisations was cardiac infections, with a higher incidence in TOF-PA subjects, a consequence of the increased risk of endocarditis on prosthetic valves and synthetic conduits in the pulmonary position.[27,28] The other frequent causes of hospitalisations were arrhythmias and heart failure, both consequences of longstanding right ventricular pressure and volume overload.[29,30]

Study limitations and mitigation strategies

This study has inherent limitations attributable to its retrospective nature. Information on genetic conditions was missing for a small proportion of subjects, most of whom died early, which might have affected the prevalence reported. To reduce the potential bias from missing values, we used multiple imputation, a method now recognised as being able to produce robust and valid results. Moreover, some confounders, such as identification of preterm and low-weight births, were not available, which may have influenced the results. This study spans several decades. This has many benefits, but it also captures the effect of improvements in the quality of care over time. We controlled for surgical era, but any long-term survival analysis would likely have an inherent residual effect of the surgical eras. Finally, we chose to evaluate all-cause mortality because the cause of death was not available for 12% of the subjects. Furthermore, noncardiovascular mortality could be precipitated or partly caused by the cardiovascular condition (eg, death from a respiratory infection that would not have occurred had the TOF not been present). We cannot exclude that results would have differed if cardiovascular death could have been evaluated.

Conclusion

This paper presents results from the TRIVIA study, a novel approach that leverages the Canadian universal health care system by linking granular subject-level clinical data and long-term administrative follow-up. We provided 30-year estimates of survival and cumulative numbers of cardiovascular interventions and hospitalisations according to native cardiac anatomy and the presence of genetic conditions in a large unselected population of TOF subjects. This will refine risk stratification for TOF subjects and improve counselling in the setting of a new perinatal diagnosis. Upcoming results from the TRIVIA study include long-term outcomes according to the type of corrective surgery and an analysis on the efficacy and timing of pediatric pulmonary valve replacement.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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