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CLINICAL RESEARCH
Congenital heart disease

End-stage heart failure in congenitally corrected transposition of the great arteries: a multicentre study

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Abstract

Background and Aims For patients with congenitally corrected transposition of the great arteries (ccTGA), factors associated with progression to end-stage congestive heart failure (CHF) remain largely unclear.

Methods This multicentre, retrospective cohort study included adults with ccTGA seen at a congenital heart disease centre. Clinical data from initial and most recent visits were obtained. The composite primary outcome was mechanical circulatory support, heart transplantation, or death.

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Results From 558 patients (48% female, age at first visit 36 ± 14.2 years, median follow-up 8.7 years), the event rate of the primary outcome was 15.4 per 1000 person-years (11 mechanical circulatory support implantations, 12 transplantations, and 52 deaths). Patients experiencing the primary outcome were older and more likely to have a history of atrial arrhythmia. The primary outcome was highest in those with both moderate/severe right ventricular (RV) dysfunction and tricuspid regurgitation ($n = 110$, 31 events) and uncommon in those with mild/less RV dysfunction and tricuspid regurgitation ($n = 181$, 13 events, $P < .001$). Outcomes were not different based on anatomic complexity and history of tricuspid valve surgery or of subpulmonic obstruction. New CHF admission or ventricular arrhythmia was associated with the primary outcome. Individuals who underwent childhood surgery had more adverse outcomes than age- and sex-matched controls. Multivariable Cox regression analysis identified older age, prior CHF admission, and severe RV dysfunction as independent predictors for the primary outcome.

Conclusions Patients with ccTGA have variable deterioration to end-stage heart failure or death over time, commonly between their fifth and sixth decades. Predictors include arrhythmic and CHF events and severe RV dysfunction but not anatomy or need for tricuspid valve surgery.

Structured Graphical Abstract

Key Question

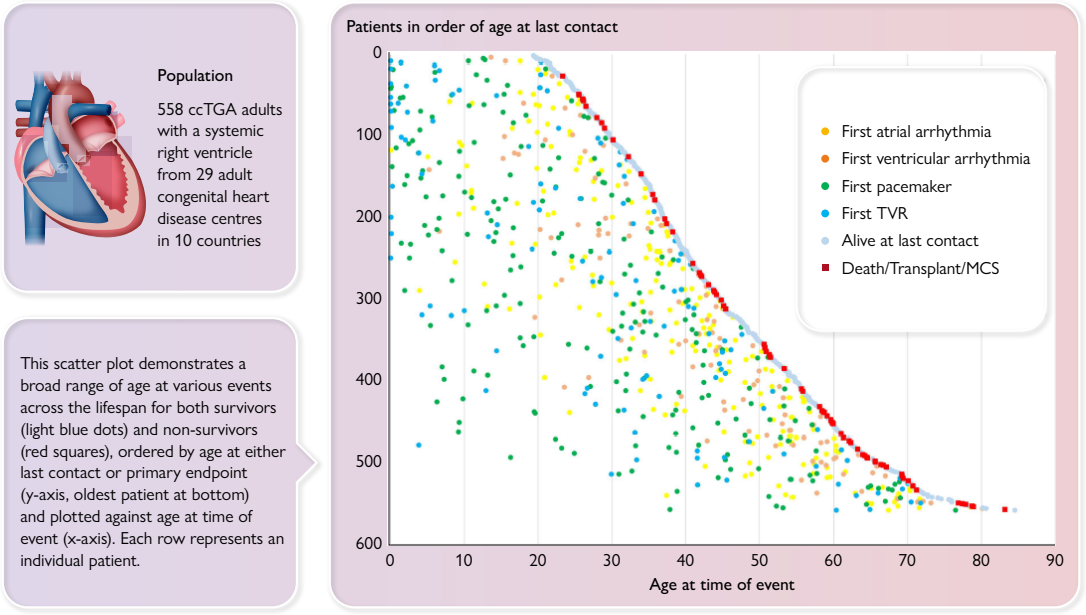
What is the incidence of and factors associated with end-stage clinical heart failure events, namely need for mechanical circulatory support (MCS), heart transplantation, or death, in patients with congenitally corrected transposition of the great arteries (ccTGA)?

Key Finding

The event rate of the primary outcome was low: 15.4 per 1000 persons-years (11 MCS, 12 transplantations, 52 deaths). Multivariable Cox regression analysis identified older age, prior congestive heart failure (CHF) admission, and severe right ventricular (RV) dysfunction as independent predictors for the primary outcome.

Take Home Message

Patients with ccTGA have variable deterioration to end-stage heart failure or death over time, commonly between the ages of 51 and 69. Predictors included arrhythmic and CHF events and severe RV dysfunction, but not anatomy or need for tricuspid valve surgery.



The magnitude and broad range of events in the entire ccTGA cohort. The scatter plot demonstrates that clinical events such as arrhythmia, pacemaker implantation, tricuspid valve surgery, need for heart transplant or MCS and occurrence of death were common and occurred throughout the lifespan of patients. ccTGA, congenitally corrected transposition of the great arteries; MCS, mechanical circulatory support; TVR, tricuspid valve repair/replacement.

Keywords Adult congenital heart disease • Transposition of the great arteries • Systemic right ventricle • Congestive heart failure • Mechanical circulatory support • Heart transplantation

Introduction

For individuals with a systemic right ventricle due to congenitally corrected transposition of the great arteries (ccTGA), systolic function is expected to progressively decline, eventually leading to congestive heart failure (CHF). Yet, the disease course is variable and the factors contributing to deterioration remain poorly understood. In some, deterioration to end-stage heart failure occurs early, while others may remain asymptomatic for decades despite right ventricular (RV) systolic dysfunction.[1–4]

The rarity of this condition has limited research. Studies are challenged by the variable age at presentation and a diversity of associated lesions and comorbidities. There is considerable heterogeneity; those with substantial coexisting heart defects including pulmonary stenosis (PS) or ventricular septal defect (VSD) are usually diagnosed in early life, whereas those without such complexity may not be detected until adulthood. For either group, prognostic predictors are lacking. Prior research leaves several other knowledge gaps as well in areas of medical therapy,[5,6] the role of mechanical assist devices,[7,8] and transplantation,[9,10] as reflected by recommendations in current guidelines.[11,12]

This multicentre study gathered clinical data on a large adult ccTGA cohort to quantify the incidence of and factors associated with end-stage clinical heart failure events, namely need for mechanical circulatory support (MCS), heart transplantation, or death.

Methods

Study population and design

We performed a multicentre, retrospective cohort study in parallel with an equivalent study on outcomes of patients with a systemic right ventricle in the setting of d-loop transposition (D-TGA) after atrial switch.[13] The study was proposed within the Alliance for Adult Research in Congenital Cardiology (www.aarcc.net). Oregon Health & Science University (OHSU) oversaw study administration and data collection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in approval by each participating site's ethical regulatory body. Requirement for informed consent was waived given the study design. The study adhered to the Health Insurance Portability and Accountability Act (HIPAA) standards and principles outlined by the International Council of Harmonization Guidelines for Good Clinical Practice. Inclusion criteria were ccTGA, age $\geq$ 18 years at time of first assessment, and seen at least twice at the adult congenital heart disease (ACHD) outpatient clinic over a period of a year or more (in order to exclude those referred late in their clinical course or those lost to follow-up). Exclusion criteria were single ventricle anatomy or palliation and prior Rastelli or double switch operation (anatomic repair; only one patient underwent anatomical repair during adulthood and was censored at time of operation). Patients were considered complex with a coexisting VSD, valvular or subvalvular PS, double outlet right ventricle, or situs/heterotaxy abnormalities. Coarctation and atrial septal defect (ASD) were considered separately. The first outpatient ACHD encounter since 1 January 2002 was identified as the initial visit. This date was selected to provide up to at least 15 years of follow-up and was based on pilot data of (i) frequency of follow-up events and (ii) expected variation in frequency of relevant clinical tests [such as cardiovascular magnetic resonance (CMR) or exercise studies] due to different practice patterns over time.

Data elements

Data were extracted from medical records by local investigators and entered into a secure online database. We recorded anatomic, interventional, and medical history, including arrhythmia, presence of a pacemaker or implantable cardioverter defibrillator (ICD), and heart failure admissions prior to the initial visit. Clinical data most temporally related to the initial visit ('baseline visit') and most recent visit ('follow-up visit') were recorded including vital signs, medications, comorbidities, laboratory, electrocardiography, echocardiography, CMR, and cardiopulmonary exercise testing. We gathered semi-quantitative designations (normal, mild, moderate, or severe) for RV systolic dysfunction and tricuspid regurgitation (TR). From cardiopulmonary exercise studies (cycle or treadmill), the peak heart rate and oxygen consumption (VO_2) were collected. For patients with one of the primary outcome events (need for MCS, heart transplantation, or death), we obtained the most recent findings as above preceding the outcome event. The date of last known contact was recorded for each patient. Patients with similar age, gender, and history from more than one centre were flagged and checked for potential duplicates, but no duplicates were found.

Arbitration of events was done by site investigators based on stated pre-study definitions. The cause of death was categorized as sudden/arrhythmic, worsening heart failure, other causes, or unknown based on available information. Follow-up data included hospitalization for clinical CHF, arrhythmia, major cardiac surgery, and new device [pacemaker, ICD, and biventricular/cardiac resynchronization therapy (CRT)] placement. Hospitalization for clinical CHF was defined as non-elective admission related to heart failure symptoms with elevated B-type natriuretic peptide (BNP) or need for diuretics. Atrial arrhythmia was defined as requiring an emergent visit, cardioversion, new medication prescription, and ablation or sustained and deemed permanent. Ventricular arrhythmia was defined as at least three consecutive ventricular beats of >100 b.p.m. associated with symptoms, >30 s with or without symptoms, or any ventricular arrhythmia prompting intervention such as ablation or ICD shock. Description of arrhythmia during follow-up was obtained and adjudicated by two investigators (C.S.B. and P.K.) to determine inclusion as major adverse ventricular arrhythmias and related events (MARE) as defined previously.[14]

Statistical analysis

Data quality checks consisted of identifying and tracking missing, incomplete, or inconsistent information. Questioned inputs were flagged, and data queries were issued to clarify and resolve discrepancies on a per-patient basis by site investigators. For those with paced rhythms, QRS duration was not used in analyses. The BNP ratio was derived by dividing BNP by the upper limit of normal for the assay used to account for different assays, with natural log transformation to account for skewing. The RV and left ventricular (LV) volumes from CMR were indexed to the body surface area, and the predicted peak VO_2 was calculated based on age, weight, and gender using published reference equations,[15] from which the percent of predicted VO_2 was calculated.

The primary outcome was the first occurrence of MCS, heart transplantation, or death. Simple comparisons between groups were compared using the χ^2 or Student's t-test as appropriate. Means and standard deviations (SD), median and interquartile range (IQR, 25th–75th percentiles), or counts/percentages were used to summarize data distributions. Kaplan–Meier plots were constructed to estimate survival (freedom from the primary outcome) curves from occurrence of specified sentinel events [arrhythmia, pacemaker placement, and tricuspid valve replacement (TVR)/repair], and the Cox proportional hazards model was used for initial univariate comparisons of variables measured at baseline with time to the primary outcome. Univariate hazard ratios (HR) and 95% confidence intervals (CI) were used to estimate individual associations with the primary outcome. Cardiovascular magnetic resonance and cardiopulmonary exercise testing were less reliably obtained in conjunction with the initial visit, and thus, the date of testing was always used rather than the date of initial visit for univariate HR calculations.

Further analysis was performed by fitting a multivariable Cox proportional hazards model (fitted by backwards elimination using a threshold of $P < .1$ for elimination) after checking assumptions of proportionality, including predictors with <20% missingness that were significant in univariable analysis ($P < .05$) and that were considered clinically relevant.

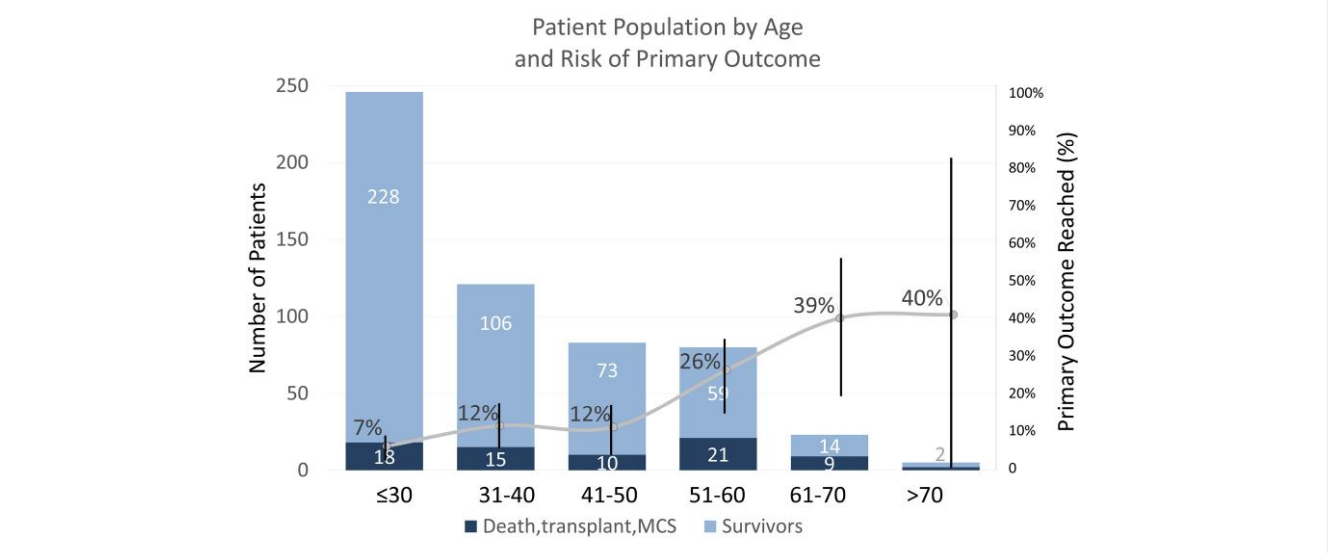


Figure 1 Patient sample by age decade at initial visit. Light blue blocks represent patients not reaching the primary outcome (mechanical circulatory support, transplantation, or death), and dark blue blocks represent those reaching the primary outcome in follow-up (*n* given for each block). Percentages of those reaching the primary outcome for each age decile are superimposed (horizontal line) with 95% confidence interval lines perpendicularly.

For multivariable analysis, values within 2 years of the initial visit were included.

A subgroup sensitivity analysis was performed in a cohort where each patient with childhood surgery ('case') was matched to two patients of the same sex and similar age at initial visit who did not require childhood surgery ('controls'). Univariate Cox proportional hazards models were fit in this subgroup for time to first atrial arrhythmia, first ventricular arrhythmia, first pacemaker placement, or ICD implantation. Comparisons between surgery and non-surgery groups were performed with *t*-tests and χ^2 tests where appropriate. Limited predictors were tested due to the sample size and fewer events. Comparisons were also made for individuals >40 years old at the time of initial visit.

Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) and R (R Project for Statistical Computing, Vienna, Austria).

Results

Study cohort

The final cohort included 558 individuals (48% female) from 29 participating centres. Age distribution by decade is shown (*Figure 1*). The median age at initial visit was 32.8 (IQR 23.5–47.1) years and at last follow-up in the clinic was 42.1 (IQR 32.5–55.6) years. Complex anatomy as defined above was present in 283 (51%), which included VSD (228, 41%), PS (146, 26%), situs abnormalities including heterotaxia (55, 10%), or any combination of these. There were 41 (7%) born with an ASD, 10 (2%) with coarctation of the aorta, 86 (15%) with dextro- or mesocardia, and 31 (6%) with an Ebstein-like tricuspid valve (TV). The cohort included 92 (16%) patients who underwent one or more childhood cardiac surgeries (age < 18 years) usually for pulmonary blood flow augmentation or VSD closure.

Primary outcome

The follow-up duration was 8.7 ± 4.9 years (minimum 1.0, maximum 19.1 years) and similar between those who did and did not reach the primary outcome (*Table 1*). There were 75/558 individuals who experienced a primary outcome (13.4%, 95% CI 11%–17%, 15.4 events per 1000 person-years). These included 11 MCS implantations (three of whom were subsequently transplanted, and one of whom died within 2 weeks), 12 transplanted without MCS (one of whom did not survive to hospital discharge), and 52 deaths without prior MCS or transplantation. Heart failure deaths accounted for 25 (48%) of these, and sudden unexplained or arrhythmic death accounted for seven (13%), including two who had recently undergone TV surgery. Additional causes of death included complications of liver transplantation for viral cirrhosis, endocarditis, pneumonia, intracranial haemorrhage after a fall, colon cancer, and Parkinson's disease. One died of complications from a pulmonary vein isolation procedure. There were 12 (23%) deaths from unknown causes.

The median age at time of the primary outcome was 51.3 (IQR 37.2–62.9) years, which was older than the median age of last contact for surviving patients [41.5 (IQR 32.7–55.0) years] ($P < .001$). Although deaths occurred across a wide range of ages, the proportion of patients reaching the primary outcome increased with age, from 4.2 (95% CI 1.6%–6.7%) for age < 30 years up to 34.6 (95% CI 16.3–52.9) for those aged 60–70 years (*Figure 1*). There were five patients over age 70 years at inclusion, two of whom died during the follow-up period.

Factors associated with the primary outcome (mechanical circulatory support/heart transplantation/death)

Descriptive features of those who did or did not reach the primary outcome of MCS, heart transplantation, or death are shown in *Table 2*, and univariate analysis for HR is given for each. Those who did reach the primary outcome were older at the initial visit, were more likely to have diabetes, and had greater weight and body mass index (BMI). They also had a slightly higher resting heart rate and lower oxygen saturation at rest. The primary outcome was more common in those taking beta-blockers, diuretics, or aspirin but not anticoagulants or either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/

Table 1 Primary outcome events

	n	%	Age at initial visit	Age at outcome
MCS	11	15	46.4 (28.0–51.5)	51.1 (36.7–58.1)
Transplantation	12	16	41.9 (33.1–51.3)	46.6 (36.7–58.7)
Death without MCS/transplantation	52	69	50.7 (30.0–58.7)	57.3 (40.9–66.5)
Heart failure	23	44	56.5 (29.9–61.6)	59.6 (43.7–69.0)
Sudden/arrhythmic	9	17	31.6 (22.8–55.5)	44.8 (30.7–60.4)
Other	8	15	41.6 (19.9–62.8)	52.0 (26.9–72.9)
Unknown	12	23	45.7 (34.5–56.6)	56.4 (41.0–65.6)
Total	75	100	**46.1 (31.0–56.6)**	**51.1 (37.2–62.9)**

Data are expressed as number, percentage of total, and median (25th–75th IQR).
MCS, mechanical circulatory support.

ARB). Those reaching the primary outcome had a higher serum creatinine, lower estimated glomerular filtration rate (eGFR), higher BNP ratio (reported value/upper limit of normal), ln BNP ratio, and lower albumin.

The primary outcome was also associated with a higher prevalence of atrial arrhythmia prior to the initial visit but not of ventricular arrhythmia, syncope, or catheter ablation (*Table 2*). A pacemaker placed before adulthood, a pacemaker in place at the initial visit, or having a paced rhythm at the time of the initial visit did not differ between groups. An implanted ICD or CRT at the initial visit was more common in those reaching the primary outcome (*Table 2*).

Echocardiographic, exercise, and CMR testing results are similarly shown (*Table 3*). Almost all patients had reported echocardiographic findings coinciding with the initial visit ($n = 542$, 97%). Severe RV systolic dysfunction was proportionally more common in those reaching the primary outcome, both on initial and follow-up echocardiograms (*Figure 2*), despite shorter follow-up. Excluding patients with TVR prior to their initial visit ($n = 62$), event rates were lowest in those with both RV dysfunction and TR in the normal–mild range (13/181, 7%) and highest in those with RV dysfunction and TR in the moderate–severe range (31/110, 28%, $P < .001$, *Figure 3*, though not accounting for follow-up time). Left ventricular outflow tract (LVOT) velocity did not differentiate groups.

Among those with reported cardiopulmonary exercise testing ($n = 238$, 43%), those reaching the primary outcome had a lower peak VO_2 as a percentage of standardized predicted values. The peak heart rate and ventilatory efficiency slope (VE/VCO_2) did not differ (*Table 3*). Data from CMR studies with volume measurements were reported in 181 (32% of the complete cohort or 47% of those without a pacemaker/ICD at initial visit). The RV and LV end-diastolic and end-systolic indices were larger in those who experienced the primary outcome, and RV and LV ejection fractions were lower (*Table 3*). The stroke volume index and cardiac index were not different in those reaching the primary outcome.

Events during follow-up

Those who met the primary outcome were more likely to have been started on either a loop diuretic (32% vs. 13%, $P < .001$) or an aldosterone antagonist (28% vs. 11%, $P < .001$) during the follow-up period but no more likely to have been newly prescribed either beta-blockers or ACEi/ARB. Events occurring during follow-up included new heart failure admission (51% vs. 11% of those with vs. without the primary outcome, respectively, $P < .001$), major adverse rhythm events[12] (47% vs. 11%, $P < .001$), and need for ICD placement (32% vs. 11%, $P < .001$), whereas new occurrence of atrial arrhythmia, non-sustained ventricular tachycardia, pacemaker placement, and need for new cardiac surgery including TVR during follow-up were not different. Both intra-atrial re-entrant (flutter) and atrial fibrillation were common: 22% of new atrial arrhythmias were flutter, 49% fibrillation, and 20% atrial tachycardia. Patients with atrial fibrillation were older compared with those with flutter (45.0 ± 13.1 vs. 38.3 ± 11.5 years, $P < .001$). Few patients ($n = 47$) underwent ablation procedures during follow-up.

First-time TV surgery (i.e. excluding redo TV surgery) during the follow-up period was performed in 58 patients (10% of the total cohort), all but one with reported echocardiographic data. Of these, 41% had moderate–severe RV dysfunction before surgery; this proportion increased to 70% (40/57) at follow-up. There was not a substantial difference in reaching the primary outcome between those with or without moderate–severe RV dysfunction before surgery (10% vs. 8%). Of the 120 individuals undergoing any TV intervention during the study period, 71 (59%) also had atrial arrhythmia ($P < .001$). For those with both, there was a linear relationship between age at TVR and age at first atrial arrhythmia ($R = .75$, $P < .001$).

To determine the comparative impact on survival over time, Kaplan–Meier curves were constructed for first occurrence of pacemaker placement, TVR, atrial arrhythmia, and ventricular arrhythmia (*Figure 4*), each treated as a separate exposure event, using time of first occurrence of each event as time zero (whether before or after the initial clinic visit). Fifty percent survival after ventricular arrhythmia was met at 20 years. The pace of deterioration was much slower after pacemaker placement, TVR, or atrial arrhythmia, with <50% reaching the primary outcome after 40 years.

To visualize the magnitude of events in the entire cohort, we plotted patients ordered by their age at last contact (by row) along with first experience with atrial arrhythmia, ventricular arrhythmia, pacemaker placement, or TVR (*Figure 5*). Clinical events were common and occurred throughout the lifespan.

Potential impact of need for early surgery

There were 92 patients needing major cardiac intervention in childhood, including 23 with pulmonary atresia, and 32 needing TV

Table 2 Descriptive features of those who did or did not reach the primary outcome and univariate Cox analysis for the primary outcome

	Primary outcome		Univariate Cox analysis		
	Yes ($n = 75$)	No ($n = 483$)	HR	95% CI	*P*-value
Follow-up duration (years)	8.0 ± 4.6	8.8 ± 4.9			
Baseline characteristics					
Age at initial visit (years)	46.1, 25.6	31.8, 21.2	1.04	(1.03–1.06)	<.001
Female sex	32, 43%	238, 49%	0.81	(0.51–1.28)	
VSD	31, 41%	197, 41%	1.04	(0.66–1.65)	
PS/LVOT obstruction	26, 35%	120, 25%	1.26	(0.78–2.03)	
Anatomic complexity present (any)	41, 55%	234, 48%	1.13	(0.72–1.78)	
Ebstein-like tricuspid valve designation	7, 9%	24, 5%	2.06	(0.85–4.90)	
Prior tricuspid valve surgery	7, 9%	55, 11%	0.73	(0.33–1.62)	
Prior VSD surgery	21, 28%	123, 25%	1.10	(0.67–1.82)	
Prior LVOT/PS surgery	19, 25%	101, 21%	1.23	(0.73–2.08)	
Tobacco smoking history	11, 15%	85, 18%	0.96	(0.89–1.04)	
Systemic hypertension	10, 13%	33, 7%	1.12	(0.85–1.46)	
Pulmonary hypertension	1, 1%	7, 1%	1.52	(0.21–10.97)	
Diabetes mellitus	11, 15%	12, 2%	6.67	(2.80–15.80)	<.001
Vitals and body measures at time of initial visit					
Weight (kg)[a]	80 ± 26	75 ± 18	1.01	(1.00–102)	
Height (cm)[a]	170 ± 11	170 ± 10	0.91	(0.73–1.12)	
Body mass index (g/m^2)	27.7 ± 7.8	25.7 ± 5.9	1.04	(1.01–1.07)	.015
Body surface area (m^2)	1.85 ± 0.4	1.83 ± 0.3	1.68	(0.64–4.43)	
Heart rate (b.p.m.)[a]	78 ± 15	73 ± 13	1.23	(1.05–1.44)	.014
Systolic blood pressure (mmHg)[a]	116 ± 14	117 ± 14	0.95	(0.80–1.12)	
Diastolic blood pressure (mmHg)[a]	70 ± 11	70 ± 10	0.97	(0.78–1.22)	
Oxygen saturation (%)	96 ± 4	97 ± 3	0.92	(0.86–0.997)	.019
Medications used at time of initial visit					
Beta-blocker	28, 37%	111, 23%	2.78	(1.72–4.49)	<.001
ACEi/ARB	36, 38%	207, 43%	1.18	(0.75–1.86)	
Diuretic	33, 44%	71, 15%	4.82	(3.03–7.69)	<.001
Aldosterone antagonist	13, 17%	25, 5%	4.41	(2.41–8.06)	<.001
Pulmonary arterial hypertension therapy	1, 1%	7, 1%	1.52	(0.21–10.97)	
Aspirin	25, 33%	80, 1%	3.00	(1.84–4.89)	<.001
Anticoagulant	17, 23%	74, 15%	1.67	(0.96–2.88)	
Laboratory					
Sodium (mmol/L)	138.4 ± 3.1	138.8 ± 2.6	0.97	(0.86–1.08)	
Creatinine (g/dL)	1.0 ± 0.3	0.9 ± 0.2	9.34	(3.97–21.97)	<.001
eGFR (mL/min/1.73 m^2)	80 ± 25.0	101 ± 29.0	0.97	(0.96–0.98)	<.001
Haemoglobin (g/dL)	14.0 ± 2.6	14.2 ± 1.8	0.95	(0.80–1.12)	
Albumin (g/dL)	4.0 ± 0.5	4.2 ± 0.5	0.46	(0.19–1.09)	.080

Continued

Table 2 *Continued*

	Primary outcome		Univariate Cox analysis		
	Yes ($n = 75$)	No ($n = 483$)	HR	95% CI	*P*-value
BNP (ratio)	7.6 ± 10.2	3.6 ± 7.3	1.03	(1.00–1.06)	.053
ln BNP ratio	1.3 ± 1.4	0.2 ± 1.5	1.46	(1.13–1.89)	.004
Electrophysiology					
Prior syncope	7, 10%	31, 7%	1.42	(0.65–3.13)	
Prior atrial arrhythmia	28, 37%	103, 21%	2.09	(1.31–3.34)	.002
Prior ventricular arrhythmia	8, 11%	34, 7%	1.67	(0.80–3.48)	
Pacemaker implanted	24, 32%	137, 28%	0.97	(0.59–1.57)	
Paced rhythm at initial visit	14, 19%	107, 28%	0.79	(0.44–1.41)	
Implantable cardioverter defibrillator	8, 11%	15, 3%	3.32	(1.59–6.92)	.001
Biventricular pacing lead present	3, 4%	9, 2%	3.31	(1.04–10.56)	.043
Prior electrophysiology study/ablation	4, 5%	14, 3%	1.37	(0.59–3.19)	
QRS duration (ms)[b]	122 ± 25	113 ± 25	1.01	(1.00–1.02)	.025

Data are expressed as mean ± SD, median with IQR, or *n* with percentage.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MCS, mechanical circulatory support; PS, pulmonary stenosis; LV, left ventricle/ventricular; LVOT, left ventricular outflow tract; RV, right ventricle/ventricular; VSD, ventricular septal defect.
[a]Covariate per 10 units for univariate analysis.
[b]Non-paced rhythm, $n = 438$.

intervention. Compared with age- and sex-matched controls, the proportion with an Ebstein-like TV was similar (7% vs. 5%), but those with childhood intervention included more with prior TVR (as expected) and thus less severe TR and more anticoagulation use at the time of the initial visit (*Table 4*). The proportion of patients with moderate–severe RV dysfunction was not different. The groups did not differ with respect to prescribed medications. Thirteen (14%) cases met the primary outcome at a median age of 33.7 (IQR 26.0–44.2) years vs. 11 (6.4%) controls ($P < .004$) at a median age of 43.8 (IQR 35.3–56.5) years. Those with early surgery were more likely to have atrial or ventricular arrhythmia in follow-up. Need for childhood surgery differentiated patients based on time to first atrial arrhythmia (univariate HR 2.62, 95% CI 1.81–3.8, $P < .001$), first ventricular arrhythmia (HR 4.67, 95% CI 2.9–7.53, $P < .001$), first pacemaker placement (HR 2.12, 95% CI 1.49–3.02, $P < .001$), or ICD implantation (HR 3.75, 95% CI 2.22–6.35, $P < .001$) compared with age- and sex-matched controls.

Multivariable analysis

In multivariable modelling using initial visit findings, the only independent predictors of the composite primary outcome were older age at initial visit (HR 1.44 per decade, 95% CI 1.21–1.70, $P < .001$), prior heart failure admission (HR 4.44, 95% CI 2.61–7.56, $P < .001$), and severe RV dysfunction designation by echocardiography (HR 3.50, 95% CI 1.98–6.21, $P < .001$). Factors not independently predictive included atrial arrhythmia, ventricular arrhythmia, QRS duration, beta-blocker use, diuretic use, and eGFR. These same variables were significant when excluding those with childhood surgery and remained independent when limited to patients ≥40 years old at initial visit, with the sole exception that eGFR was significant and diuretic use was not. For patients with childhood surgery considered separately, ICD placement prior to initial visit was the only univariate predictor. Models are shown in *Table 5*.

Discussion

In this study of 558 adults with ccTGA and a systemic right ventricle seen at 1 of 29 ACHD centres, 75 (13%) experienced MCS, transplantation, or death over an average observation period of ∼8 years, and heart failure was the most common cause of death (*Structured Graphical Abstract*). There is considerable heterogeneity in associated defects, need for intervention, and timeline towards clinical heart failure. Mortality rates rose sharply between the fifth and sixth decades of life.

Our primary aim was to determine which factors were most strongly associated with clinical deterioration including death. Atrial arrhythmia, beta-blocker use, ICD, increased BMI, and diabetes were associated with the primary endpoint in univariate analysis. Laboratory findings such as elevated BNP, a drop in sodium, or rising creatinine over time were also associated with the primary outcome in univariate analyses. All these factors are frequently encountered in those with progressive heart failure. Yet, on multivariable analysis, age, prior heart failure admission, and severe RV systolic dysfunction were the sole factors independently associated with the primary outcome. Lower exercise tolerance and adverse ventricular volume and function by CMR were similarly associated but could not be included in multivariable models due to a high proportion of missing data.

Our findings are congruent with previous smaller studies, including the overall makeup of our cohort such as a broad age range,[16]

Table 3 Echocardiographic, exercise, and cardiovascular magnetic resonance testing features of those who did or did not reach the primary outcome and univariate Cox analysis for the primary outcome

	Primary outcome		Univariate Cox analysis		
	Yes ($n = 75$)	No ($n = 483$)	HR	95% CI	*P*-value
Echocardiography ($n = 542$)					
Moderate–severe RV systolic dysfunction	44/71, 62%	145/471, 31%	3.44	(2.13–5.56)	<.001
Moderate–severe tricuspid regurgitation	44/69, 64%	210/460, 46%	1.93	(1.18–3.16)	.009
LVOT velocity (m/s)	2.1 ± 1.4	1.7 ± 1.1	1.20	(0.82–1.78)	
Exercise testing ($n = 238$)					
Peak heart rate at exercise (b.p.m.)[a]	142 ± 26	149 ± 31	0.95	(0.85–1.06)	
Oxygen saturation at peak exercise (%)	94 ± 9	96 ± 5	0.99	(0.92–1.06)	
VE/VCO_2 slope	31.9 ± 5.2	28.8 ± 6.5	1.00	(0.97–1.04)	
Percent of predicted maximum VO_2 (%)	66 ± 42	75 ± 27	0.99	(0.97–1.01)	
Magnetic resonance ($n = 197$)					
RV end-diastolic volume index (mL/m^2)[a]	139 ± 50	113 ± 40	1.14	(1.06–1.23)	<.001
RV end-systolic volume index (mL/m^2)[a]	79 ± 43	58 ± 29	1.21	(1.10–1.32)	<.001
RV stroke volume index (mL/m^2)[a]	60 ± 18	56 ± 19	1.08	(0.91–1.28)	
RV ejection fraction (%)	46 ± 13	50 ± 10	0.96	(0.92–0.99)	.018
LV end-diastolic volume index (mL/m^2)[a]	96 ± 32	78 ± 31	1.24	(1.09–1.39)	.001
LV end-systolic volume index (mL/m^2)[a]	48 ± 26	32 ± 19	1.42	(1.23–1.64)	<.001
LV stroke volume index (mL/m^2)[a]	48 ± 19	46 ± 18	0.99	(0.73–1.33)	
LV ejection fraction (%)	51 ± 13	60 ± 11	0.92	(0.89–0.95)	<.001
Systemic cardiac index ($L/min/m^2$)	3.5 (2.7–3.8)	3.3 (2.8–4.0)	0.89	(0.60–1.33)	

Data are expressed as mean ± SD, median with IQR, or *n*/total with percentage. *P*-value is given if significant.
CI, confidence interval; HR, hazard ratio; LV, left ventricular; LVOT, left ventricular outflow tract; RV, right ventricular; VO_2, oxygen consumption.
[a]Covariate per 10 units for univariate analysis.

frequency of coexisting defects (VSD, PS, etc.), and use of pacemakers.[4,17,18] Overall survival herein also largely parallels prior research, such as one showing 74% survival at 20 years of observed follow-up.[17] Smaller studies have also explored factors associated with transplantation or death. The most consistent predictors have been TR and RV dysfunction,[4,17,19] whereas prior cardiac surgery, age, and complete heart block were not significant.[17]

Both atrial and ventricular arrhythmias were common in our study. Others have reported atrial fibrillation to be associated with worse survival,[16] as do we, though progress from the first event to the primary outcome was slow and thus weakens its utility as a predictor. Heart failure admission was independent of atrial arrhythmia as a predictor in our sample. Pacing has been shown to be associated with RV dysfunction over time based on single-centre echocardiograms.[18] We did not find similar results in our cohort, though RV function assessment was not uniform. Further, there was similarly a long duration between the need for pacing and the primary outcome, making it less significant as a predictor. In other studies, systemic RV dysfunction has been shown to increase the risk of clinically significant ventricular arrhythmias.[20] Sudden/arrhythmic death was the second most common cause of death and occurred in 17% of deaths in our cohort. One expects several unexplained deaths may also be arrhythmic, as other smaller series have shown a considerably higher prevalence of arrhythmic death than we report.[21] Future studies are still needed to determine which patients benefit from ICD implantation.

Two categories of patients with congenitally corrected transposition of the great arteries

We made a distinction of two phenotypes of ccTGA: those with early diagnoses needing surgery in childhood vs. those not needing such intervention and likely diagnosed later in life. Despite the need for early surgeries, often several, outcome differences seemed largely a function of age, which in part reflects the gradual emergence of interventional options in the latter half of the prior century when many of our cohort were born. Older patients with anatomic complexity would have had limited survival and be less represented in a sample such as this. After controlling for age, we found a higher

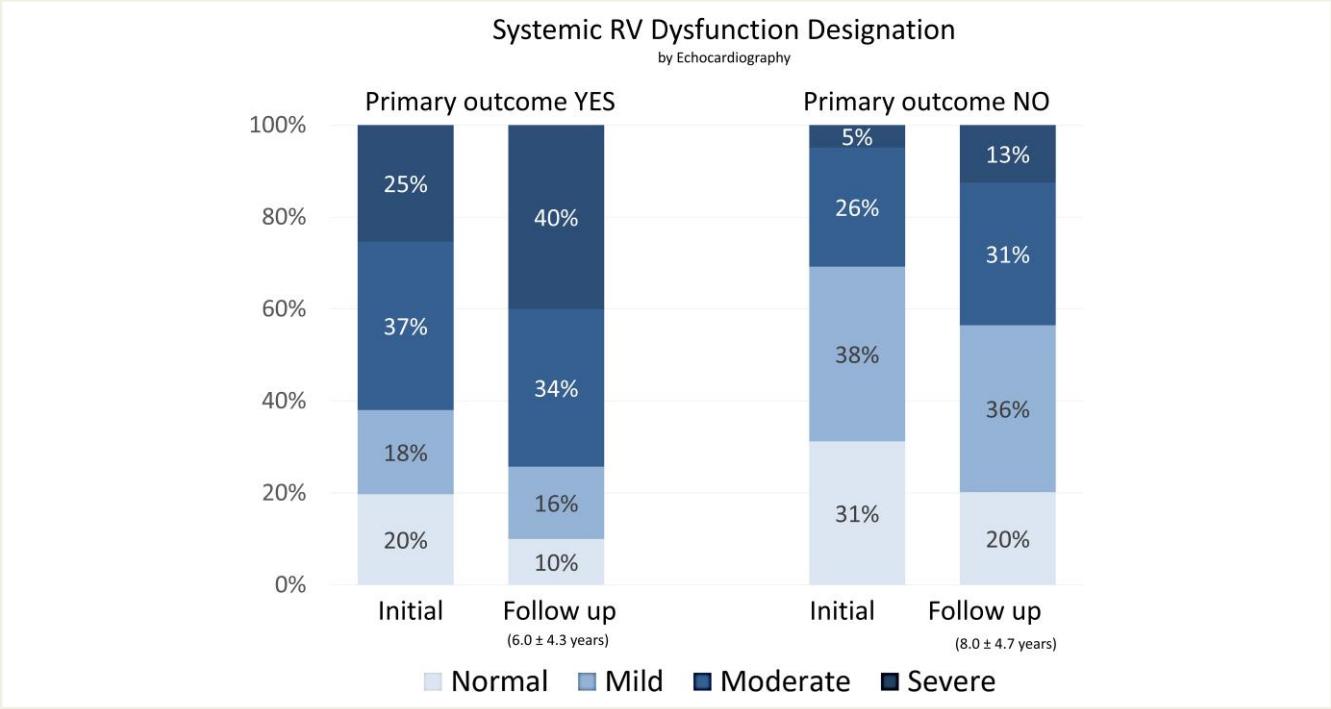


Figure 2 Breakdown of systemic right ventricular systolic function, semi-quantitatively assessed by echocardiography at initial visit and most recent echo at follow-up, comparing those who did (left) and did not (right) reach the primary outcome (mechanical circulatory support, transplantation, or death). Follow-up time (between echocardiograms) is given for both groups and was longer for those not reaching the primary outcome ($P < .001$). Clinical follow-up time was not different.

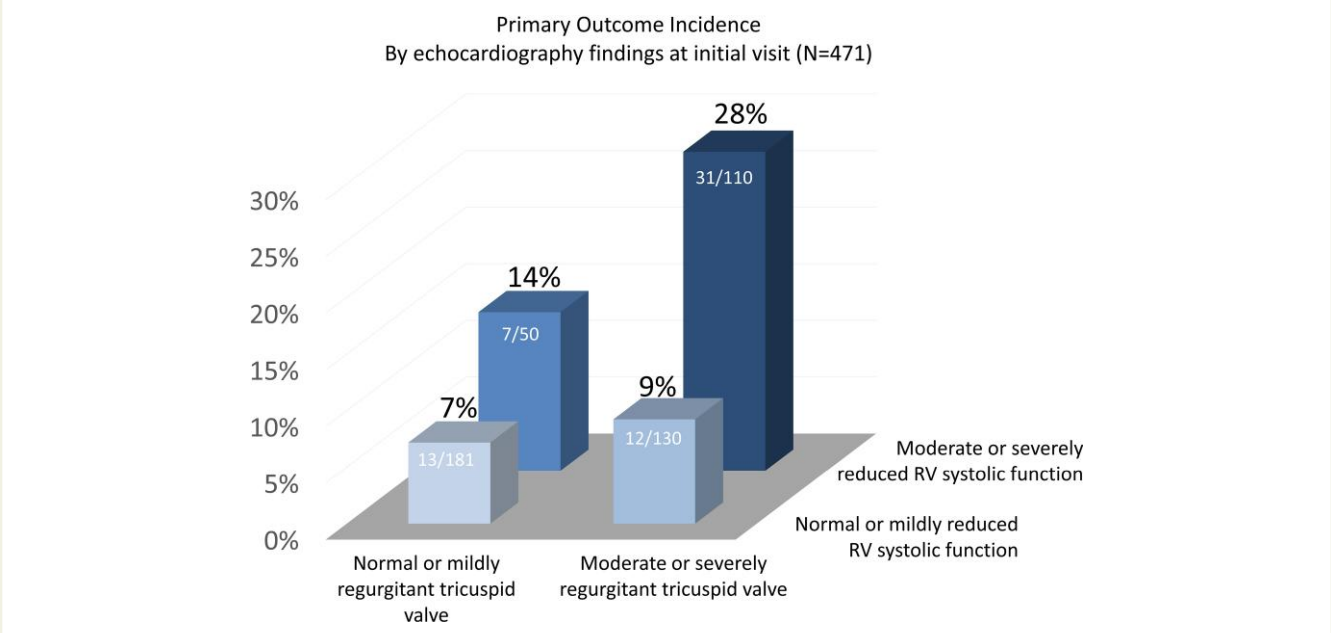


Figure 3 Occurrence of the primary outcome (mechanical circulatory support, transplantation, or death) by designation of right ventricular dysfunction and tricuspid valve regurgitation designations at the time of the initial echocardiogram. Excludes patients with prior tricuspid valve surgery.

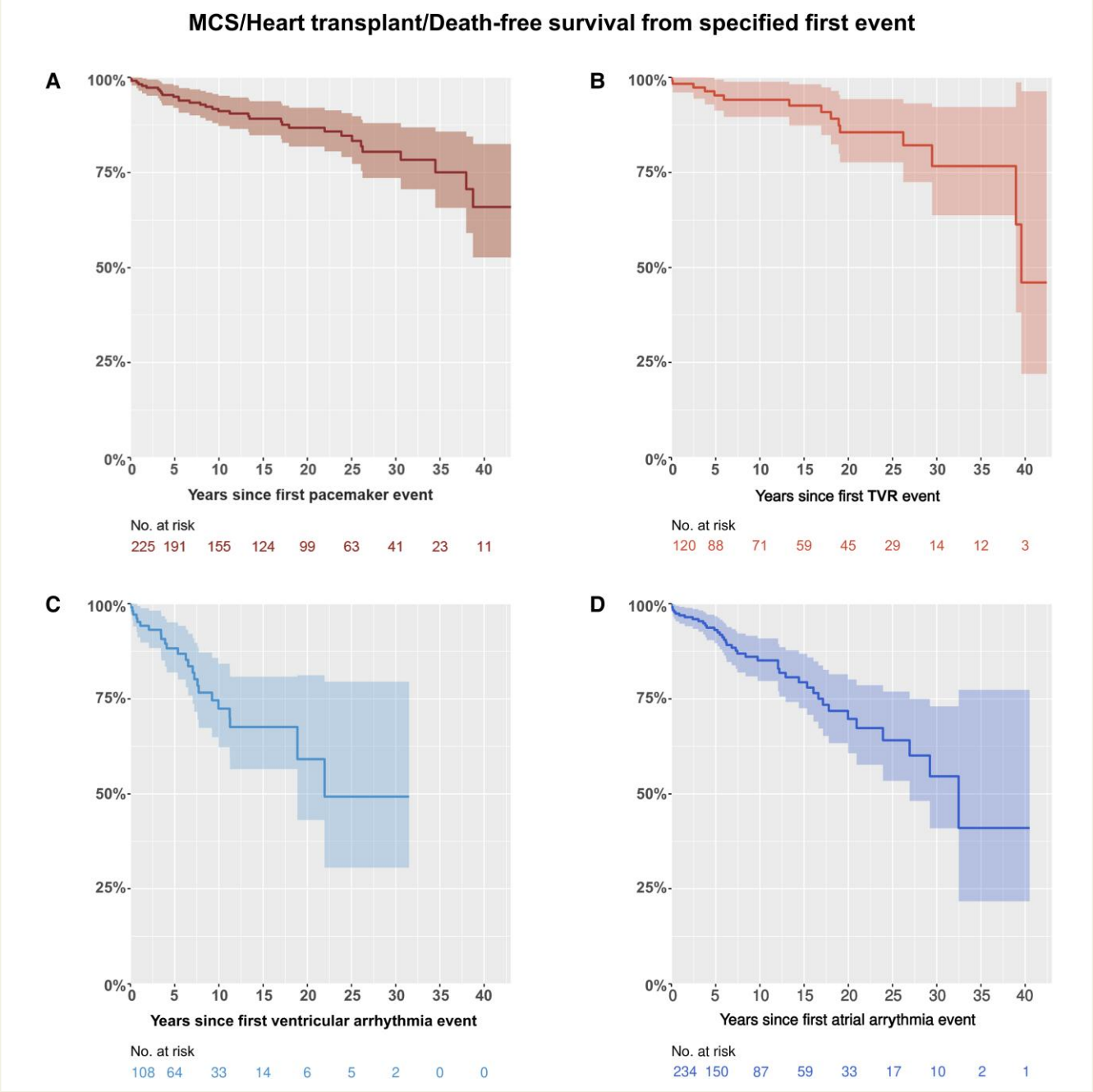


Figure 4 Superimposed Kaplan–Meier curves with 95% confidence interval lines perpendicularly for subgroups of patients who have experienced various clinical events (pacemaker placement, tricuspid valve replacement, atrial arrhythmia, and ventricular arrhythmia) and progression to end-stage heart failure (% freedom from mechanical circulatory support, transplantation, or death) based on time of first occurrence of a specified clinical event as time zero. (*A*) Freedom from the primary outcome since first pacemaker implantation. (*B*) Freedom from the primary outcome since first tricuspid valve repair/replacement. (*C*) Freedom from the primary outcome since first ventricular arrhythmia. (*D*) Freedom from the primary outcome since first atrial arrhythmia.

proportion reaching the primary endpoint, as well as more atrial and ventricular arrhythmias and pacemaker/ICD implantation in those with early surgery, even though such events seem to occur broadly across the lifespan of all types of patients in our cohort (*Figure 5*).

Others similarly have differentiated phenotypes along similar lines. In one sample, roughly half of the cohort required early cardiac surgery,[17] with no difference in survival demonstrated in this group compared with those not needing cardiac surgery. In another study, there were no major differences between those with or without associated lesions, particularly TR or RV function, other than clinical CHF defined as cardiomegaly, oedema, congestion, gallop rhythm, or need for medical therapy.[4] One expects that as the patients with more complex anatomy age, heart failure manifestations will become more pronounced sooner than in patients with simpler anatomy.

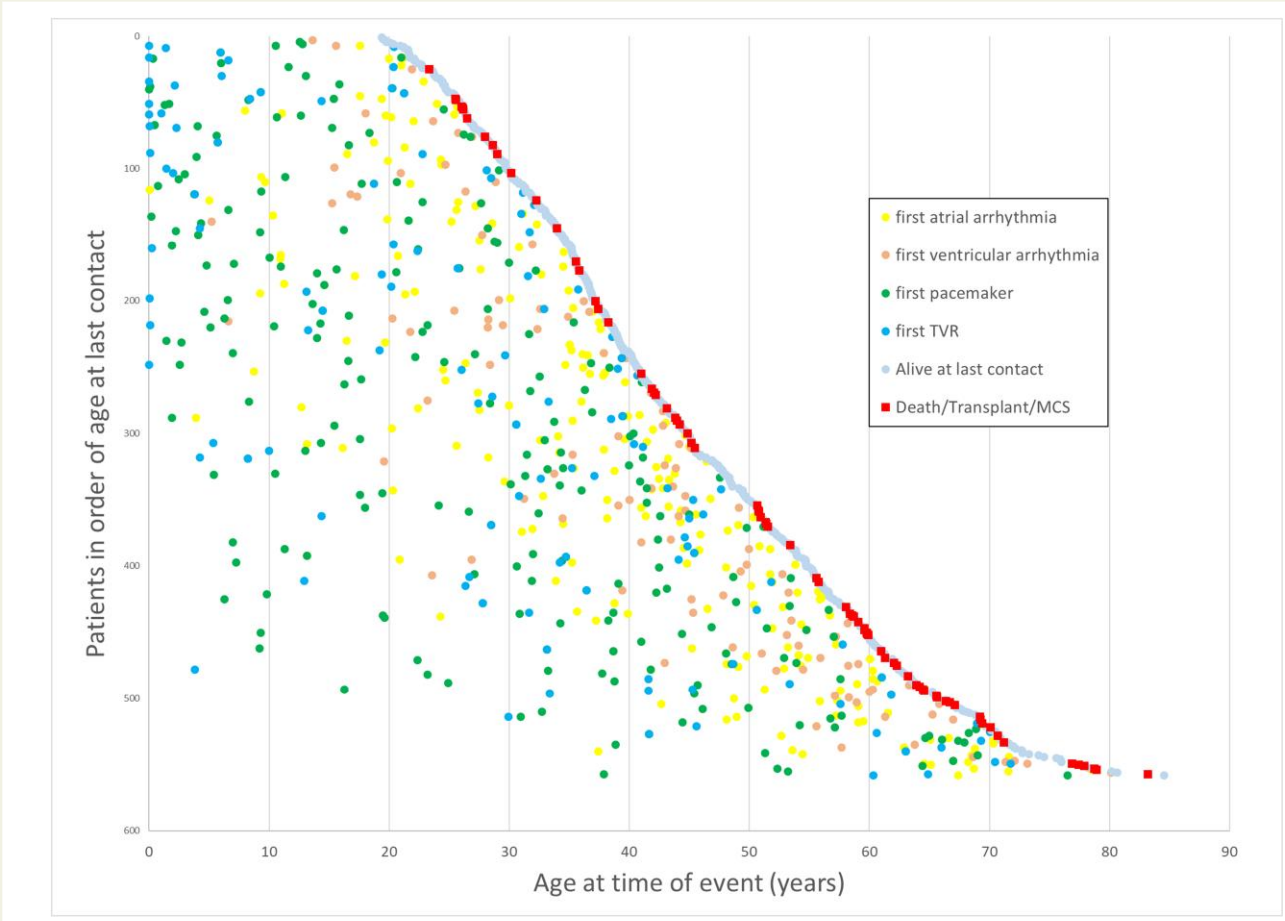


Figure 5 Scatter plot of the entire cohort ordered by age at either last contact or primary endpoint (*y*-axis, oldest patient at bottom) plotted against age at time of event (*x*-axis) such that each row represents an individual patient. Red squares represent those who met the mechanical circulatory support, transplantation, or death primary endpoint, whereas blue circles represent those who did not. Additional circles show age at first atrial arrhythmia (yellow), ventricular arrhythmia (orange), pacemaker placement (green), or tricuspid valve repair/replacement (blue) as applicable for each patient. The scatter plot demonstrates a broad range of age at various events across the lifespan for both survivors and non-survivors.

Tricuspid valve intervention and outcome

As expected, the presence of TR with RV systolic dysfunction is associated with development of heart failure. Several previous studies have demonstrated a relationship between TR and RV function.[22] Morphologic abnormalities of the TV are common, and late referral for TVR after progression of RV dysfunction is associated with worse 10-year survival.[16] Recently, a single-centre study with 186 ccTGA patients showed that TVR was associated with improvement in RV systolic function when performed before onset of RV dysfunction.[23] Yet, our larger study did not demonstrate an association between early TVR (i.e. before development of moderate–severe RV systolic dysfunction) and improved survival or even preserved RV function. It is possible that practice patterns in participating centres reflected improved decision-making based on prior published experience and guidance such that TVR was performed before RV dysfunction developed or avoided when function was significantly reduced. Consistent with this possibility, we found that only 18% of those with moderate–severe TR by time of the initial visit underwent TV intervention during follow-up. The study design did not include all echocardiographic reports or a core lab to standardize assessment of function or changes over time, and more nuanced distinctions may not be captured herein.

We found a correlation between age of onset of atrial arrhythmia and subsequent need for TVR, implying a physiologic relationship between the two, which is in line with our understanding of the significant adverse role played by atrioventricular valve regurgitation in the occurrence of atrial arrhythmias.

Reports suggest that the presence of LVOT obstruction can be favourable by way of minimizing TR severity.[19] We did not observe a relationship between the two herein, even excluding those with previous TVR. The impact of subpulmonary LVOT obstruction on survival remains uncertain. A recent study observed that the risk of sudden cardiac death was significantly increased for patients with a systemic right ventricle and subpulmonary LVOT obstruction, although this correlation was only observed in the D-TGA subgroup.[14] Moreover, a recent study in both D-TGA and ccTGA patients demonstrated that adverse remodelling of the subpulmonary left ventricle was associated with a worse clinical outcome.[24] On the contrary, others have shown that LVOT obstruction did not affect survival in ccTGA patients,[16] consistent with our findings. It may be that LVOT obstruction affects the severity of TR or LV hypertrophy (as a potential ventricular arrhythmia substrate) substantially in a small subset of cases, not well accounted for in our group analysis.

Table 4 Comparison of those with major childhood surgery ('cases') vs. matched controls

	Cases ($n = 92$)	Matched controls ($n = 171$)
Baseline characteristics		
Age at initial visit (years)	26.2 ± 8.3	27.2 ± 8.8
Ebstein-like tricuspid valve designation	6, 7%	8, 5%
Prior tricuspid valve surgery	29, 32%	10, 6%
Prior VSD surgery	62, 67%	35, 21%
Prior LVOT/PS surgery	56, 61%	31, 18%
Medications used at time of initial visit		
Beta-blocker	17, 19%	35, 15%
ACEi/ARB	43, 47%	57, 33%
Diuretic	12, 13%	20, 12%
Aldosterone antagonist	8, 9%	6, 4%
Pulmonary arterial hypertension therapy	1, 1%	3, 2%
Aspirin	24, 26%	26, 15%
Anticoagulant	25, 27%	11, 6%
Electrophysiology at time of initial visit		
Prior syncope	4, 4%	11, 6%
Prior atrial arrhythmia	22, 24%	29, 17%
Prior ventricular arrhythmia	11, 12%	9, 5%
Pacemaker implanted	32, 35%	48, 28%
Paced rhythm at initial visit	20, 22%	41, 24%
Implantable cardioverter defibrillator	6, 7%	6, 4%
Biventricular pacing lead present	3, 3%	3, 2%
Echocardiography at time of initial visit		
Moderate–severe RV systolic dysfunction	34, 37%	48, 29%
Moderate–severe tricuspid regurgitation	32, 37%	73, 45%

Data are expressed as mean ± SD or *n* with percentage.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PS, pulmonary stenosis; LVOT, left ventricular outflow tract; RV, right ventricular; VSD, ventricular septal defect.

Table 5 Multivariable Cox analysis

	HR	95% CI	*P*-value
Model with the entire population			
Age at initial visit per decade (years)	1.44	(1.21–1.70)	<.001
Heart failure admission prior to initial visit	4.44	(2.61–7.56)	<.001
Severe RV dysfunction	3.50	(1.98–6.21)	<.001
Model excluding patients with childhood surgery			
Age at initial visit per decade (years)	1.59	(1.30–1.94)	<.001
Heart failure admission prior to initial visit	5.16	(2.93–9.10)	<.001
Severe RV dysfunction	3.19	(1.70–5.99)	<.001
Model limited to patients >40 years at initial visit			
Age at initial visit per decade (years)	2.04	(1.32–3.15)	<.001
Heart failure admission prior to initial visit	4.38	(2.22–8.65)	<.001
Severe RV dysfunction	2.94	(1.41–6.14)	.004

CI, confidence interval; HR, hazard ratio; RV, right ventricular.

Medications

As with a similar cohort of d-loop transposition, we found worse outcomes among those prescribed diuretics and beta-blockers, with no difference in outcomes based on use of ACEi/ARB. Others, and we, have shown that ACEi/ARB and beta-blockers are used frequently (25% and 43%, respectively), regardless of RV dysfunction,[16] though patterns vary between institutions. We expect multiple confounders to play a role in whether these medications are prescribed (e.g. blockers were more likely used in those with prior atrial arrhythmia in our study) and therefore cannot make strong inferences about effectiveness from these observational data. We did not find that initiation of these medications during follow-up was associated with reaching end-stage heart failure and suspect that any effect is likely to be modest. Blood pressure tended to be lower in those reaching the primary endpoint, perhaps raising questions about the theoretical benefits of these therapies.

Our study focused on heart failure outcomes, but the data can be used to explore predictors of other major events. Notably, predictors of ventricular arrhythmia/sudden cardiac death are needed and warrant separate analysis. Others have previously shown that systemic RV dysfunction increases the risk of sudden cardiac death and ventricular tachycardia.[20] While longer QRS duration has been reported to be associated with lower RV ejection fraction (and presumably larger ventricles) in prior research,[20] we did not observe an association between QRS duration and RV volumes herein, even after excluding paced patients.

Limitations

Interpretation of these data requires consideration of the underlying study design. Our study should not be interpreted as a natural history study, as patients with this diagnosis are discovered across the lifespan without a uniform 'event' for comparison of timelines related to natural progression. Both survivorship and referral bias affect our sample, and the magnitude of such biases is impossible to determine. Our study is skewed towards younger age, likely reflecting an enriched sample of both younger and more complex patients. Deaths in the 18–30 age category were rare (4%). Thus, one might expect a low proportion to be

missing from our sample. Healthy or undiagnosed ccTGA patients would less likely be referred for care at an ACHD centre. While it may not be representative of all patients living with ccTGA, our study is representative of the typical makeup of patients seen and followed in ACHD centres, where these findings are likely to be most relevant to decision-making. Loss to follow-up is an expected occurrence in any study of this kind, yet it was considered unlikely to have a significant impact on our results as the date of last contact was similar or close to the date of follow-up visit in the large majority of patients (508/558, 91%, with a median duration of 2.1 months).

In addition to the expected heterogeneity of patient characteristics, practice patterns vary widely between centres. There was no specific definition for what constituted an initial visit, and we expect variation in frequency of testing (e.g. CMR, exercise testing, and laboratory tests) and use of medications. Our inclusion of patients from 2002 onwards was based on pilot data giving expected numbers of events in follow-up as well as likelihood of clinical testing performed, though practice variation is expected. We attempted to mitigate these inherent differences by including patients from multiple and variably sized ACHD centres to more broadly represent the ccTGA population now in specialty care. There are also differences in methodologies across centres (e.g. CMR quantification or exercise protocols) that may also contribute to the heterogeneity of our study population. Attrition is an expected limitation. We recorded the date of last contact to help account for patients who had become lost to clinical follow-up and thus for whom clinical events may have been missed. We found only seven patients who had not had follow-up since 2010. Missing data are always a limitation of retrospective studies of this nature. Our multivariable modelling for risk calculation was limited in part due to missing data (such as QRS duration, exercise, or CMR findings). Multivariable modelling was also potentially impacted by expected associations (beta-blockers and arrhythmia or diuretics and creatinine, for example). Some factors that would be expected to have independent significance were not identified as such. Thus, the creation of a robust risk prediction model was not feasible in our view.

Conclusions

Individuals with ccTGA seen in ACHD centres are susceptible to end-stage heart failure commonly in their fifth and sixth decades or before. Independent predictors included older age, worsening RV function, and prior heart failure admission but not anatomic complexity, history of TV surgery, or history of subpulmonic obstruction. Despite the relatively large multicentre cohort, it remains difficult to reliably predict which patients are most likely to rapidly progress towards end-stage heart failure. Additional analyses of this dataset will further elucidate predictors for worse outcomes in ccTGA patients.

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Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

Data Availability

Per AHA policy, the repository will be posted to an open-source repository (either IntACT or Open Science Framework) as a spreadsheet file without any identifiable information. Data will include all appropriate metadata (namely variable definitions, eligibility criteria, and contributing centres). The spreadsheet will be granted without restriction on research reuse after finishing the current analysis for subsequent papers. The anticipated date of availability will be in the year 2025.

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Ethical Approval

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in approval by each participating site's ethical regulatory body. Requirement for informed consent was waived given the study design. The study adhered to the Health Insurance Portability and Accountability Act (HIPAA) standards and principles outlined by the International Council of Harmonization Guidelines for Good Clinical Practice.

Pre-registered Clinical Trial Number

None supplied.

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