JACC: ADVANCES VOL. 3, NO. 4, 2024

ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Cardiovascular Outcomes in Fontan Patients With Right vs Left Univentricular Morphology

A Multicenter Study

Nabil Dib, MD,[a] Marie-A. Chaix, MD, PhD,[a] Michelle Samuel, MPH, PhD,[a] Sewanou Hermann Honfo, PhD,[a] Robert M. Hamilton, MD,[b] Jamil Aboulhosn, MD,[c] Craig S. Broberg, MD,[d] Scott Cohen, MD,[e] Stephen Cook, MD,[f] Annie Dore, MD,[a] Susan M. Jameson, LPD, PA-C,[g] Anne Fournier, MD,[h] Reda Ibrahim, MD,[a] Joseph Kay, MD,[i] François-Pierre Mongeon, MD, SM,[a] Alexander R. Opotowsky, MD, MMSc,[j] Ali Zaidi, MD,[k] Nancy Poirier, MD,[a] Paul Khairy, MD, PhD[a]

ABSTRACT

BACKGROUND There is a paucity of data on long-term outcomes after Fontan palliation in patients with a dominant morphological univentricular right (uRV) vs left (uLV) ventricle.

OBJECTIVES The purpose of this study was to compare the incidence of atrial arrhythmias, thromboembolic events, cardiac transplantation, and death following Fontan palliation in patients with uRV vs uLV.

METHODS The Alliance for Adult Research in Congenital Cardiology conducted a multicenter retrospective cohort study on patients with total cavopulmonary connection Fontan palliation across 12 centers in North America. All components of the composite outcome, that is, atrial arrhythmias, thromboembolic events, cardiac transplantation, and death, were reviewed and classified by a blinded adjudicating committee. Time-to-event analyses were performed that accounted for competing risks.

RESULTS A total of 384 patients were followed for 10.5 ± 5.9 years. The composite outcome occurred in 3.7 vs 1.7 cases per 100 person-years for uRV (N = 171) vs uLV (N = 213), respectively ($P < 0.001$). In multivariable analyses, uRV conferred a >2-fold higher risk of the composite outcome (HR: 2.17, 95% CI: 1.45-3.45, $P < 0.001$). In secondary analyses of components of the primary outcome, uRV was significantly associated with a greater risk of cardiac transplantation or death (HR: 9.09, 95% CI: 2.17-38.46, $P < 0.001$) and atrial arrhythmias (HR: 2.17, 95% CI: 1.20-4.00, $P = 0.010$) but not thromboembolic events (HR: 1.64, 95% CI: 0.86-3.16, $P = 0.131$).

CONCLUSIONS Fontan patients with uRV vs uLV morphology have a higher incidence of adverse cardiovascular events, including atrial arrhythmia, cardiac transplantation, and all-cause mortality. (JACC Adv 2024;3:100871) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Montreal Heart Institute, Université de Montréal, Quebec, Canada; [b]The Hospital for Sick Children, University of Toronto, Toronto, Canada; [c]Ahmanson/UCLA Adult Congenital Heart Program, University of California, Los Angeles, USA; [d]Knight Cardiovascular Institute, Oregon Health and Science University, Portland, USA; [e]The Wisconsin Adult Congenital Heart (WAtCH) Program, Medical College of Wisconsin, Milwaukee, USA; [f]The Philadelphia Adult Congenital Heart Center, Children's Hospital of Pittsburgh, Pittsburgh, USA; [g]Adult Congenital Heart Program, Stanford University, Palo Alto, USA; [h]Hôpital Sainte-Justine, Université de Montréal, Montreal, Canada; [i]Division of Cardiology, University of Colorado Denver, Aurora, USA; [j]Boston Adult Congenital Heart Service, Boston Children's Hospital and Brigham and Women's Hospital, Harvard Medical School, Boston, USA; and the [k]Nationwide Children's Hospital, Ohio State University, Columbus, USA.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.100871

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

CI = confidence interval

HLHS = hypoplastic left heart syndrome

HR = hazard ratio

IART = intra-atrial re-entrant tachycardia

uRV = morphological univentricular right ventricle

uLV = morphological univentricular left ventricle

TACTIC = The AntiCoagulation Therapy In Congenital heart disease study

Fontan surgery was originally performed to address tricuspid atresia[1] and has subsequently been extended to a broad category of patients with complex congenital heart disease in whom biventricular repair is not feasible.[2,3] The primary objective is to direct deoxygenated blood into the pulmonary arteries without the need for a functional sub-pulmonary ventricle. Expanding indications for Fontan surgery have given rise to a growing population of patients with systemic morphological right ventricles. Intrinsic differences in ventricular morphology render the univentricular heart with a dominant systemic right ventricle (uRV) less adapted to generating long-term systemic pressures than a dominant univentricular left ventricle (uLV).[4] Some studies indicate that the uRV is associated with worse perioperative outcomes, prolonged requirements for inotropic drugs or mechanical ventilation,[5] suboptimal postoperative hemodynamics,[6] longer hospitalizations, and increased mortality.[7] Nevertheless, there is a paucity of studies reporting comparative outcomes beyond the perioperative period in patients with uRV vs uLV with results that are inconsistent or unclear.[7-14]

Common longer-term complications in patients with Fontan surgery include atrial arrhythmias, thromboembolic events, Fontan circulatory failure requiring transplantation, and death.[15] The Alliance for Adult Research in Congenital Cardiology sought to quantify and compare these adverse cardiovascular events, along with individual components of this composite outcome, among Fontan patients with uRV vs uLV in a North American multicenter retrospective cohort study.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT POPULATION. Details of TACTIC (The AntiCoagulation Therapy In Congenital Heart Disease) study have previously been described.[15,16] In brief, TACTIC is a North American (3 Canadian and 9 American centers) multicenter retrospective cohort study conducted by the Alliance for Adult Research in Congenital Cardiology of patients with heterogenous forms of congenital heart disease.[16,17] Data were collected over a 26-month period ending in March 2016. The current TACTIC substudy was limited to patients with single ventricle physiology who were born in 2011 or earlier, underwent total cavopulmonary connection Fontan surgery, survived their index surgery, and were followed at the same institution that performed the procedure.

DATA COLLECTION. Data were retrospectively collected from medical and surgical records by the 12 participating centers. Time 0 was defined as the time of Fontan completion. Baseline characteristics were captured at the time of Fontan completion and included age, sex, dominant morphological type of single ventricle, prior surgical- and catheter-based interventions, preoperative heart failure, pulmonary hypertension, and comorbidities including respiratory, renal, hepatic, and endocrine conditions. Classification of the univentricular heart was based on a previously described taxonomy system in which the terms left and right do not imply sidedness or position but, rather, refer to the morphological pattern of the predominant ventricle regardless of whether or not a second ventricular chamber is present.[18] Preoperative heart failure was defined as chronic diuretic use or as NYHA functional class III or IV symptoms, independent of medical therapy. Diagnosis of pulmonary arterial hypertension was made in accordance with clinical guidelines available at the time of enrollment.[19]

OUTCOMES. The primary outcome is a composite metric consisting of a sustained atrial arrhythmia, thromboembolic event, cardiac transplantation, or all-cause death occurring after the index hospitalization. Atrial arrhythmias required documentation of an atrial rate ≥100 beats/min for ≥30 seconds by electrocardiograms or rhythm strips. If well-formed P waves were distinguishable electrocardiographically and separated by an isoelectric interval, or if an electrophysiology study identified a point source with radial spread of activation, the tachycardia was classified as focal atrial tachycardia.[20] Otherwise, a diagnosis of intra-atrial re-entrant tachycardia (IART) was retained, which incorporates all types of typical and atypical atrial flutter.[20] Atrial fibrillation was characterized by the absence of uniform P waves, with fibrillatory waves varying in amplitude, contour, and timing.[21]

Thromboembolic complications included both systemic and venous events. Systemic

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 22, 2023; revised manuscript received November 27, 2023, accepted January 2, 2024.

thromboemboli were classified as cardiac, neurological, peripheral arterial, renal, or mesenteric.[16,17,22,23] Systemic cardiac thromboemboli included thrombus within native cardiac chambers in the systemic circulation (ie, pulmonary venous atrium or ventricle) and coronary embolism. Neurological events comprised transient ischemic attacks and strokes. Transient ischemic attacks were characterized by sudden focal deficits lasting <24 hours without any visible signs of infarction on imaging. Strokes were defined as deficits that lasted 24 hours or longer, with or without confirmatory imaging, or that persisted <24 hours but were associated with positive imaging or an invasive treatment strategy.[24] Diagnosis of peripheral arterial complications was based on the 6 cardinal signs of acute limb ischemia: pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia.[25] The diagnosis of renal and mesenteric events necessitated confirmation through imaging techniques. Venous thromboemboli were further characterized into cardiac, peripheral venous, and pulmonary events.[16,17] Thrombus within the Fontan pathway was considered a venous cardiac event. These events were detected and described by various imaging techniques, including echocardiography, magnetic resonance imaging, computed tomography, and angiography. For the diagnoses of deep venous thromboses and pulmonary emboli, appropriate confirmatory imaging studies were mandated.

ADJUDICATION. All components of the primary outcome, that is, atrial arrhythmias, thromboembolic events, cardiac transplantations, and deaths, were independently adjudicated by a blinded committee consisting of 4 physicians. Any inconsistencies were thoroughly reviewed against the case report forms and all other necessary documents, as required by the protocol. Committee discussions were held to arrive at a final adjudication. The Montreal Health Innovations Coordinating Center was responsible for monitoring the process of data collection, integration, and entry and also conducted regular quality assurance checks. The observed error rate of 0.02% before the database lock was much lower than the acceptable limit defined a priori at <0.5%. The study protocol received approval from the ethics committee at every participating institution, with a waiver of informed consent. The research followed the principles set forth by the Declaration of Helsinki and the International Council of Harmonization Tripartite Guidelines for Good Clinical Practice.

STATISTICAL ANALYSIS. Continuous variables were expressed as median (IQR) or mean ± SD, as appropriate. Categorical variables were presented as frequencies and percentages. Continuous baseline characteristics of the 2 Fontan groups (ie, uRV vs uLV) were compared using analyses of variance or Wilcoxon rank sum tests, depending on whether or not they were normally distributed. Comparisons of categorical variables were performed using chi-square or Fisher exact tests, as appropriate.

TABLE 1 Predominant Type of Congenital Heart Disease

	All (N = 384)	uRV (n = 171)	uLV (n = 213)
Hypoplastic left heart syndrome	76 (19.8)	76 (44.4)	-
Tricuspid atresia	62 (16.1)	-	62 (29.1)
Double inlet left ventricle	34 (8.9)	-	34 (16.0)
Double outlet right ventricle/mitral atresia	61 (15.9)	61 (35.7)	
Pulmonary atresia with intact ventricular septum	51 (13.3)	-	51 (23.9)
Unbalanced atrioventricular septal defect	23 (6.0)	9 (5.3)	14 (6.6)
Other	77 (20.1)	25 (14.6)	52 (24.4)

Values are n (%).
uLV = univentricular heart of left ventricular morphology; uRV = univentricular heart of right ventricular morphology.

The list of potential independent variables considered in regression models was based on subject-specific knowledge and events-per-variable considerations. Univariable and multivariable Cox regression models were used to assess the composite primary outcome, along with its components. Cardiac transplantation was combined with death into a single outcome. Diagnostic testing was performed to verify modeling assumptions, including the proportionality of hazards (test of independence between Schoenfeld residuals and time), linearity of continuous predictors (Martingale residuals plot), and detection of influential observations (index plots of *dfbetas*). Assumptions were met for the primary analysis and all secondary analyses, except for the model with cardiac transplantation or death as the dependent variable and uRV vs uLV as the independent variable. This was addressed by detecting and removing influential observations and refitting the Cox model, which subsequently met all assumptions. For analyses in which atrial arrhythmias and thromboembolic events were the dependent variables, cardiac transplants and deaths were modeled as competing risks.

The impact of study site on outcomes was assessed in 2 ways, that is, by adding site as a cluster term and by including a variance component in random site effect models. No significant site effect was detected using either approach. After pruning to identify redundant covariates, mediators, and colliders, retained variables associated with P values <0.2 in univariable analyses were included in multivariable

TABLE 2 Baseline Characteristics

	All (N = 384)	uRV (n = 171)	uLV (n = 213)	*P* Value
Clinical characteristics				
Age at Fontan completion, y	3.3 (2.2-5.6)	3.0 (2.1-4.6)	3.7 (2.5-5.8)	0.068
Female	160 (41.7)	73 (42.7)	87 (40.9)	0.755
Oxygen saturation post-Fontan, %	88.9 ± 7.1	87.3 ± 8.7	90.0 ± 5.6	0.006
Preoperative comorbidities				
Congestive heart failure	10 (2.6)	3 (1.8)	7 (3.3)	0.349
Pulmonary arterial hypertension	2 (0.5)	1 (0.6)	1 (0.5)	0.876
Chronic lung disease	1 (0.3)	1 (0.6)	0 (0.0)	0.445
Thyroid disorder	2 (0.5)	1 (0.6)	1 (0.5)	0.876
Surgical history				
Systemic-pulmonary shunt[a]	168 (43.8)	63 (36.8)	105 (49.3)	0.017
Blalock Taussig shunt	165 (43.0)	61 (35.7)	104 (48.8)	0.013
Waterston	5 (1.3)	4 (2.3)	1 (0.5)	0.108
Norwood procedure	109 (28.4)	85 (49.7)	24 (11.3)	<0.001
Pulmonary artery banding	50 (13.0)	15 (8.8)	35 (16.4)	0.032
Superior cavopulmonary anastomosis[a]	330 (85.9)	148 (88.6)	182 (85.5)	0.770
Bidirectional Glenn	294 (76.6)	130 (76.0)	164 (77.0)	0.823
Hemi-Fontan	41 (10.7)	21 (12.3)	20 (9.4)	0.407
No prior staging procedure	19 (5.0)	9 (5.3)	10 (4.7)	0.799
Surgical Fontan fenestration	266 (69.3)	131 (76.6)	135 (63.4)	0.005
Fontan types				
Intracardiac lateral tunnel	201 (52.3)	97 (56.7)	104 (48.8)	0.123
Extracardiac conduit	183 (47.7)	74 (43.3)	109 (51.2)	0.123

Values are n (%). [a]Subcategories of systemic-pulmonary shunt and superior cavopulmonary anastomosis are not mutually exclusive.

uLV = univentricular heart of left ventricular morphology; uRV = univentricular heart of right ventricular morphology.

TABLE 3 Adjudicated Adverse Cardiovascular Events

	All (N = 384)	uRV (n = 171)	uLV (n = 213)	*P* Value
Death or cardiac transplantation	15 (3.9)	13 (7.6)	2 (0.9)	<0.001
Death	7 (1.8)	7 (4.4)	0 (0.0)	0.002
Transplantation	8 (2.1)	6 (3.5)	2 (0.9)	0.061
Atrial arrhythmias	42 (10.9)	25 (14.6)	17 (8.0)	0.020
Atrial fibrillation	6 (1.5)	5 (2.9)	1 (0.5)	
Focal atrial tachycardia	12 (3.0)	6 (3.5)	6 (2.8)	
Intra-atrial re-entrant tachycardia	24 (5.9)	14 (8.2)	10 (4.7)	
Thromboembolic events	32 (8.3)	18 (10.5)	14 (6.6)	0.221
Systemic	21 (5.5)	12 (7.0)	9 (4.2)	0.696
Neurologic	9 (2.3)	4 (2.3)	5 (2.4)	
Cardiac systemic circulation	6 (1.6)	4 (2.3)	2 (0.9)	
Renal	3 (0.8)	2 (1.2)	1 (0.5)	
Peripheral	3 (0.8)	2 (1.2)	1 (0.5)	
Fontan pathway/pulmonary arterial	11 (2.9)	6 (3.5)	5 (2.4)	0.335
Fontan pathway	10 (2.6)	5 (2.9)	5 (2.4)	
Pulmonary arterial circulation	1 (0.3)	1 (0.6)	0 (0.0)	
Follow-up duration, y	10.6 ± 5.9	10.2 ± 5.7	10.9 ± 6.0	0.239
Age at last follow-up, y	15.5 ± 8.0	14.6 ± 7.7	16.2 ± 8.2	0.049

Values are n (%).

uLV = univentricular heart of left ventricular morphology; uRV = univentricular heart of right ventricular morphology.

backward selection models with forced retention of the main independent variable, that is, uRV vs uLV morphology. Cumulative incidence function curves were generated from these analyses. Two-sided *P* values <0.05 were considered statistically significant. All analyses were performed using Stata software 17.0 (StataCorp, USA).

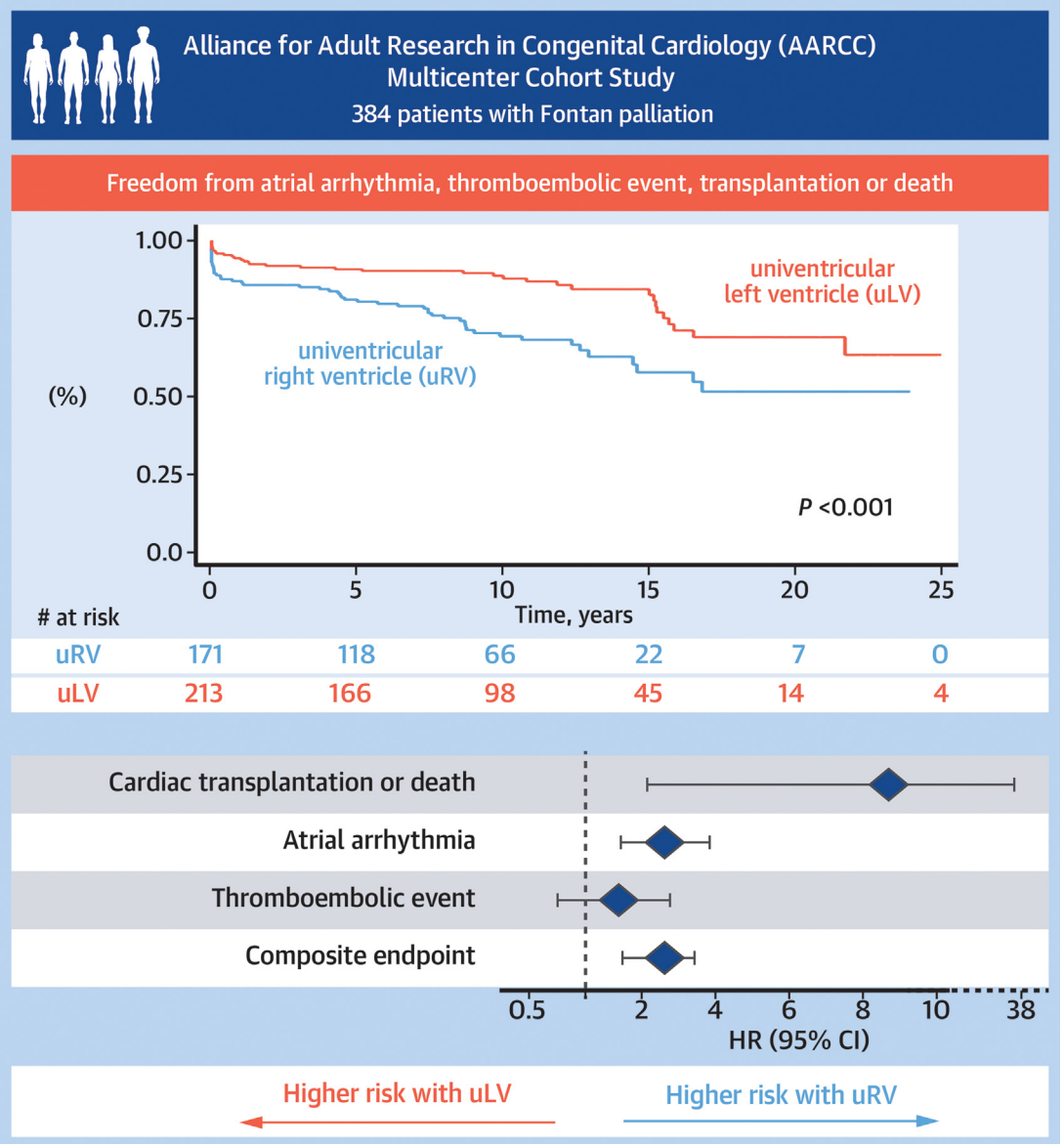
RESULTS

BASELINE CHARACTERISTICS. A total of 522 patients were enrolled in the TACTIC Fontan study of whom 112 had an atriopulmonary connection Fontan. Among the 410 patients with a total cavopulmonary connection, the dominant ventricular morphology was unknown or uncertain in 26 (6.3%) patients. The study population consisted of the remaining 384 eligible patients, 41.7% female, who had Fontan palliation at a median age of 3.3 (IQR: 2.2-5.6) years. The univentricular heart was of dominant uRV morphology in 171 (44.5%) and of dominant uLV morphology in 213 (55.5%). Predominant underlying types of congenital heart disease are summarized in Table 1. The most common diagnoses were hypoplastic left heart syndrome (HLHS) (44.4%) and double outlet right ventricle/mitral atresia (35.7%) in patients with uRV and tricuspid atresia (29.1%) and pulmonary atresia with an intact ventricular septum (23.9%) in those with uLV.

Baseline characteristics are summarized in Table 2. There were no significant differences among patients with uRV vs uLV in age at Fontan completion, sex, preoperative comorbidities, and type of total cavopulmonary connection surgery. However, patients with uRV had a higher prevalence of Fontan fenestration with a lower postoperative oxygen saturation level, fewer Blalock-Taussig shunts, and more Norwood procedures.

ADVERSE CARDIOVASCULAR EVENTS. The 89 adjudicated adverse cardiovascular events that occurred over a mean follow-up of 10.6 ± 5.9 years are summarized in Table 3. As shown in the Central Illustration, the incidence of the composite endpoint of atrial arrhythmia, thromboembolic event, cardiac transplantation, or death was 3.7 vs 1.7 cases per 100 person-years for uRV vs uLV, respectively ($P < 0.001$). Corresponding cumulative rates of the composite endpoint 10, 15, and 20 years after Fontan surgery were 30.8%, 41.9%, and 48.5% in patients with uRV vs 12.3%, 17.4%, and 31.2% in those with uLV, respectively. Factors associated with the composite endpoint in univariable and multivariable analyses are listed in Table 4. In multivariable analyses, uRV remained independently associated with

CENTRAL ILLUSTRATION **Cardiovascular Outcomes in Fontan Patients With Right vs Left Univentricular Morphology**



Dib N, et al. JACC Adv. 2024;3(4):100871.

atrial arrhythmia, thromboembolic event, cardiac transplantation, or death (HR: 2.17, 95% CI: 1.45-3.45, $P < 0.001$). In addition, the non-adjudicated complication of lymphatic failure (ie, protein-losing enteropathy, plastic bronchitis, and/or chylothorax) occurred in 26 (6.8%) patients, with no difference according to the dominant ventricular morphology, that is, 6.4% vs 7.0% with uRV vs uLV, $P = 0.813$.

CARDIAC TRANSPLANTATION AND DEATH. Over the course of follow-up, 7 (1.8%) patients died and 8 (2.1%) underwent cardiac transplantation. Cumulative rates of cardiac transplantation or death 10, 15, and 20 years after Fontan surgery were 3.4%, 5.1%, and 13.0%, respectively, corresponding to an overall incidence of 0.4 cases per 100 person-years. The incidence of cardiac transplantation or death, plotted in Figure 1, was significantly higher among patients with uRV vs uLV, that is, 0.80 vs 0.09 cases per 100 person-years, HR: 9.09 (95% CI: 2.17-38.46, $P < 0.001$). Other factors significantly associated with cardiac transplantation or death in univariable analyses were number of prior

TABLE 4 Factors Associated With Atrial Arrhythmias, Thromboembolic Events, Cardiac Transplantation, or Death in Univariable and Multivariable Cox Regression Analyses

	Univariable Analysis[a]	Multivariable Analysis[b]	*P* Value
uRV	2.22 (1.45-3.45)	2.17 (1.45-3.45)	<0.001
Female	0.86 (0.56-1.32)		
Age at Fontan completion, y	1.01 (0.97-1.05)		
Surgical Fontan fenestration	0.93 (0.60-1.46)		
Number of prior surgeries	1.20 (0.99-1.44)	1.20 (1.00-1.44)	0.055
Number of prior catheterizations	1.06 (0.90-1.25)		
Systemic-pulmonary shunt	0.66 (0.42-1.02)		
Blalock-Taussig shunt	0.63 (0.40-0.99)		
Superior cavopulmonary anastomosis	1.10 (0.66-1.84)		
Bidirectional Glenn	0.87 (0.56-1.35)		
No surgical staging	0.82 (0.40-1.72)		
Norwood procedure	1.46 (0.92-2.32)		
Extracardiac conduit vs intracardiac lateral tunnel	1.13 (0.73-1.75)		
Pulmonary artery banding	1.29 (0.73-2.28)		

[a]Values are HR (95% CI). [b]Values are adjusted HR (95% CI).
uRV = univentricular heart of right ventricular morphology.

cardiac surgeries (HR: 1.93, 95% CI: 1.35-2.76, $P < 0.001$]), number of prior catheterization procedures (HR: 1.91, 95% CI: 1.45-2.53, $P < 0.001$), and prior Norwood procedure (HR: 4.28, 95% CI: 1.54-11.89, $P = 0.005$). Given the limited number of events, multivariable analysis was not performed.

ATRIAL ARRHYTHMIAS. A total of 42 (10.9%) patients experienced an atrial arrhythmia over the course of follow-up, the most common subtype being IART (57.1%), followed by focal atrial tachycardia (28.6%) and atrial fibrillation (14.3%). Non-mutually exclusive symptoms included palpitations in 24 (57.1%) patients, dyspnea in 18 (42.9%), chest discomfort in 5 (11.9%), dizziness/pre-syncope in 3 (7.1%), and syncope in 1 (2.4%). A sustained atrial arrhythmia was detected by routine surveillance in 9 (21.4%) patients with minimal symptoms of whom 1 (uRV) had tachycardia-induced cardiomyopathy due to persistent IART. Cumulative rates of atrial arrhythmias at 10, 15, and 20 years after Fontan surgery were 12.3%, 18.3%, and 24.2%, respectively, corresponding to an overall incidence of 1.4% per 100 person-years. The incidence rate for atrial arrhythmias was significantly higher among patients with uRV vs uLV, that is, 2.1 vs 0.9 per 100 person-years, respectively ($P = 0.006$). In multivariable analyses, summarized in Table 5, uRV remained independently associated with a higher risk of atrial arrhythmias (HR: 2.17, 95% CI: 1.20-4.00, $P = 0.010$).

THROMBOEMBOLIC COMPLICATIONS. At total of 32 (8.3%) patients experienced a thromboembolic event, of which 21 were in the systemic circulation and 11 within the Fontan pathway/pulmonary circulation. Subtypes of thromboembolic events are summarized in Table 3. Cumulative thromboembolic event rates in the entire cohort 10, 15, and 20 years after Fontan surgery were 8.4%, 11.5%, and 16.8%, respectively, corresponding to an overall incidence of 0.8% per 100 person-years. Thromboembolic event rates among patients with uRV vs uLV were 1.0% and 0.6% per 100 person-years, respectively (HR: 1.64, 95% CI: 0.86-3.16, $P = 0.131$). No other factor was retained in the multivariable model.

DISCUSSION

This North American multicenter study of patients with a total cavopulmonary connection-type of Fontan palliation revealed that those with a dominant uRV vs uLV morphology had a >2-fold increased risk of the composite endpoint of cardiac transplantation, all-cause mortality, atrial arrhythmias, and thromboembolic events. Nearly half the patients with a uRV experienced an event by 20 years of follow-up. Moreover, in analyses of the components of the composite outcome, the uRV was significantly associated with a higher rate of cardiac transplantation or death and atrial arrhythmias.

CARDIAC TRANSPLANTATION AND DEATH. Overall, a transplant-free survival rate of 87% at 20 years of follow-up was observed in our study, which compares favorably to prior publications.[12,26,27] Nevertheless, the proportion of patients with uRV reaching adulthood is on the rise[27] rendering it plausible that survival trends will be adversely impacted in the foreseeable future as the ratio of the Fontan population with a uRV increases over time.[28] Our findings call attention to the different lifespan trajectories experienced by patients with uRV vs uLV.[14,27,29]

HLHS is the most common anatomic lesion in children with univentricular hearts.[30] Survival to adulthood with HLHS in the current era has been reported to reach 70%.[31] Our findings are consistent with prior publications that identified HLHS to be a poor prognostic factor.[32-34] Norwood repair, which was performed in 50% of our population with uRV, has also been linked to higher mortality.[35] In addition, patients with HLHS undergo numerous concomitant surgical repairs[14,30] that could increase complication risks. Compounded with the disadvantages of the morphologically right ventricle in sustaining long-term systemic pressures,[4] the rate of Fontan circulatory failure and cardiac transplantation needs are likely to further increase as the uRV

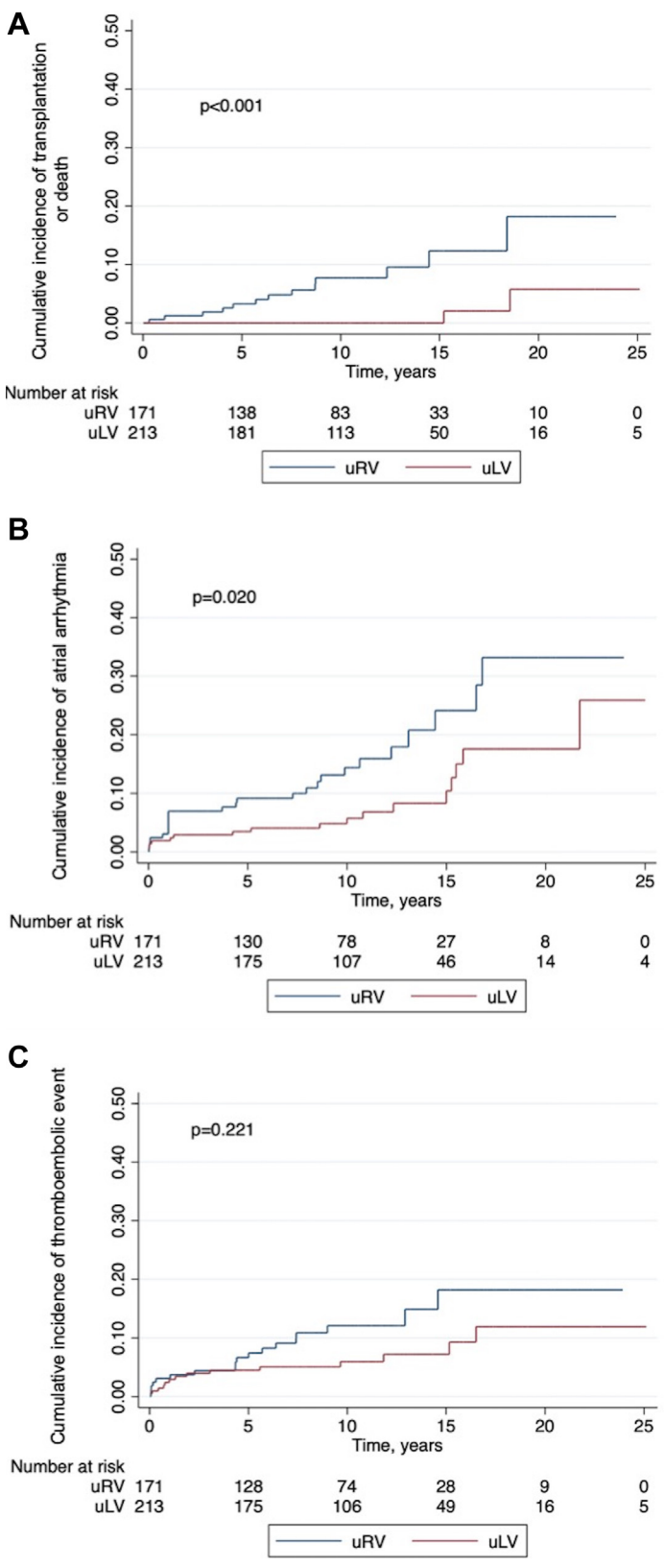
population ages.[28] Appropriate planning of resources will, therefore, be required to face this important upcoming challenge. Indeed, in the current study, 75% of patients who underwent cardiac transplantation had a uRV.

ATRIAL ARRHYTHMIA. Atrial arrhythmia is a well-established and frequent complication associated with Fontan palliation.[32] The prevalence of atrial arrhythmias is particularly high in patients with atriopulmonary connection Fontan surgery, exceeding 90% by 30 years of follow-up.[15] The total cavopulmonary connection technique has been associated with a substantially lower cumulative incidence of atrial arrhythmias at up to 20 years of follow-up.[15] Nevertheless, these complications remain a major concern[36] with the current analysis revealing a cumulative incidence of 24% 20 years after Fontan palliation. Atrial arrhythmias can result from suture lines,[37] injury to the sinus node or arterial supply, and atrial remodeling.[38] Any new onset or worsening atrial arrhythmia may herald a hemodynamic issue that should be identified and addressed.

Factors that have previously been associated with atrial arrhythmias in the Fontan population include an atriopulmonary connection, older age at the time of surgery, preoperative and early postoperative atrial tachycardia, moderate or severe atrioventricular valve regurgitation, and longer follow-up duration.[27,32,33] Male sex, right atrial isomerism, and loss of sinus rhythm have also been proposed to be associated factors, but less consistently so.[39,40] Herein, we expand the list of associated factors to include uRV. Reasons as to why atrial arrhythmias are more common in the uRV remain speculative. It may be hypothesized that the uRV, which is morphologically less adapted to withstand systemic pressures, is subject to a greater degree of ventricular dilation, systolic and diastolic dysfunction, and annular stretch with subsequent AV valve regurgitation.[4] In turn, these physiological changes can lead to pressure and volume overload of the atrial chamber,[36,38] with attendant adverse structural and electrical remodeling changes that enhance arrhythmogenicity.

THROMBOEMBOLIC EVENTS. The incidence of thromboembolic complications would be expected to be higher with uRV vs uLV given that atrial arrhythmias are more common in the setting of a uRV and that arrhythmias, particularly IART and atrial fibrillation, are strongly linked to thromboemboli. The nonsignificantly higher rates in patients with uRV vs uLV observed in the current study (eg, 1.0% vs 0.6% per 100 patient-years, HR: 1.56) are consistent with this notion. Possible explanations as to why

FIGURE 1 Cumulative Incidence of Cardiac Transplantation or Death, Atrial Arrhythmias, and Thromboembolic Events According to Univentricular Morphology



Cumulative incidence of (A) cardiac transplantation or death, (B) atrial arrhythmias, and (C) thromboembolic events according to univentricular morphology. uLV = univentricular heart of left ventricular morphology; uRV = univentricular heart of right ventricular morphology.

TABLE 5 Factors Associated With Atrial Arrhythmias and Thromboembolic Events in Multivariable Cox Regression Analyses

	Adjusted HR (95% CI)	*P* Value
Atrial arrhythmias		
uRV	2.17 (1.20-4.00)	0.010
Number of prior cardiac catheterizations	0.82 (0.65-1.04)	0.108
Systemic-pulmonary shunt	0.58 (0.31-1.06)	0.075
Thromboembolic events		
uRV	1.64 (0.86-3.16)	0.131

uRV = univentricular heart of right ventricular morphology.

differences did not achieve significance include insufficient statistical power and mitigating effects of thromboprophylaxis. Although anticoagulation modeled as a time-dependent variable was not significantly associated with thromboembolic events, up to 75% of patients with total cavopulmonary connection Fontan surgery received some form of therapy (ie, anticoagulation, antiplatelet therapy, or dual therapy) at any given point during follow-up.[15] Further studies are required to definitively exclude an association between dominant single ventricle morphology and thromboembolic events.

STUDY LIMITATIONS. The study is observational and retrospective and is, therefore, subject to limitations related to potential unmeasured or unknown confounders, missing data on covariates not captured by medical records, and non-standardized surveillance testing. The study was not designed to assess subcategories of uLV and uRV. To maximize data quality, data standards classically applied to randomized trials were incorporated, including quality control measures and independent blinded adjudication of all events included in the composite outcome. In order to focus on longer-term outcomes and maximize data completeness, the study was deliberately limited to patients who survived complete Fontan palliation and were followed in tertiary centers. As such, results should not be generalized to patients not meeting these inclusion criteria, such as those progressing along various Fontan stages or not followed by specialized centers.

CONCLUSIONS

In this North American multicenter cohort of patients with Fontan surgery, a dominant uRV vs uLV morphology was associated with a >2-fold higher risk of adverse cardiovascular events, including atrial arrhythmia, cardiac transplantation, and all-cause mortality. These findings should raise awareness about the prevalence of these complications and the need for further studies to identify strategies to mitigate risks in patients with uRV.

ACKNOWLEDGMENTS The authors thank Marie-Claude Villeneuve, MSc (Montreal Health Innovations Coordinating Center); Aynun Naher, MBBS, MS (Oregon Health and Science University); William R. Davidson, Jr, MD, John J. Kelleman, MD, Elizabeth E. Adams, DO, Jennifer Ting, MD, and Dena Jefferson RN, BSN, CCRC (Hershey Medical Center); Morgan Hindes (Children's Hospital of Pittsburgh); Ryan Williams and Gwen Derk (University of California-Los Angeles); Michael G. Earing, MD, Jonathan W. Cramer, MD, and Emily Reinhardt, RN (Medical College of Wisconsin).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The TACTIC study was funded by an investigator-initiated unrestricted grant from Boehringer Ingelheim. The sponsor had no role in the study design, data collection, analysis, interpretation, writing of the paper, and decision to submit the manuscript for publication. Dr Dib is supported by the French Federation of Cardiology (FFC) and ADETEC grants. Dr Khairy is supported by the André Chagnon research chair in electrophysiology and congenital heart disease. All other have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Paul Khairy, Montreal Heart Institute, 5000 Belanger Street, Montreal, H1T 1C8 Quebec, Canada. E-mail: paul.khairy@umontreal.ca.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The risk for adverse cardiovascular events, including all-cause mortality, cardiac transplantation, and atrial arrhythmias is more than 2-fold higher in patients with univentricular hearts with a dominant morphological right vs left ventricle following Fontan palliation.

TRANSLATIONAL OUTLOOK: In light of the rising prevalence of dominant morphological right ventricles in the Fontan population reaching adulthood, the cardiology community should anticipate an increase in long-term complications and direct research efforts toward identifying strategies to mitigate risks.

REFERENCES

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240-258.

2. Gersony WM. Fontan operation after 3 decades: what we have learned. *Circulation*. 2008;117:13-15.

3. Mondesert B, Marcotte F, Mongeon FP, et al. Fontan circulation: success or failure? *Can J Cardiol*. 2013;29:811-820.

4. Ghelani SJ, Colan SD, Azcue N, et al. Impact of ventricular morphology on fiber stress and strain in Fontan patients. *Circ Cardiovasc Imaging*. 2018;11:e006738.

5. Nordmeyer S, Rohder M, Nordmeyer J, et al. Systemic right ventricular morphology in the early postoperative course after extracardiac Fontan operation: is there still a need for special care? *Eur J Cardiothorac Surg*. 2017;51:483-489.

6. Pollak U, Abarbanel I, Salem Y, Serraf AE, Mishaly D. Dominant ventricular morphology and early postoperative course after the Fontan procedure. *World J Pediatr Congenit Heart Surg*. 2022;13:346-352.

7. McGuirk SP, Winlaw DS, Langley SM, et al. The impact of ventricular morphology on midterm outcome following completion total cavopulmonary connection. *Eur J Cardiothorac Surg*. 2003;24:37-46.

8. Gentles TL, Mayer JE Jr, Gauvreau K, et al. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. *J Thorac Cardiovasc Surg*. 1997;114:376-391.

9. Julsrud PR, Weigel TJ, Van Son JA, et al. Influence of ventricular morphology on outcome after the Fontan procedure. *Am J Cardiol*. 2000;86:319-323.

10. Khairy P, Fernandes SM, Mayer JE Jr, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation*. 2008;117:85-92.

11. Khairy P, Poirier N, Mercier LA. Univentricular heart. *Circulation*. 2007;115:800-812.

12. Tweddell JS, Nersesian M, Mussatto KA, et al. Fontan palliation in the modern era: factors impacting mortality and morbidity. *Ann Thorac Surg*. 2009;88:1291-1299.

13. Zhou Z, Malhotra SP, Yu X, et al. Moderate altitude is not associated with adverse postoperative outcomes for patients undergoing bidirectional cavopulmonary anastomosis and Fontan operation: a comparative study among Denver, Edmonton, and Toronto. *J Thorac Cardiovasc Surg*. 2013;146:1165-1171.

14. Moon J, Shen L, Likosky DS, et al. Relationship of ventricular morphology and atrioventricular valve function to long-term outcomes following Fontan procedures. *J Am Coll Cardiol*. 2020;76:419-431.

15. Deshaies C, Hamilton RM, Shohoudi A, et al. Thromboembolic risk after atriopulmonary, lateral tunnel, and extracardiac conduit Fontan surgery. *J Am Coll Cardiol*. 2019;74:1071-1081.

16. Khairy P, Aboulhosn J, Broberg CS, et al. Thromboprophylaxis for atrial arrhythmias in congenital heart disease: a multicenter study. *Int J Cardiol*. 2016;223:729-735.

17. Labombarda F, Hamilton R, Shohoudi A, et al. Increasing prevalence of atrial fibrillation and permanent atrial arrhythmias in congenital heart disease. *J Am Coll Cardiol*. 2017;70:857-865.

18. Jacobs JP, Franklin RC, Jacobs ML, et al. Classification of the functionally univentricular heart: unity from mapped codes. *Cardiol Young*. 2006;16 Suppl 1:9-21.

19. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573-1619.

20. Saoudi N, Cosio F, Waldo A, et al. A classification of atrial flutter and regular atrial tachycardia according to electrophysiological mechanisms and anatomical bases; a statement from a Joint Expert Group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 2001;22:1162-1182.

21. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1-e76.

22. Khairy P, Landzberg MJ, Gatzoulis MA, et al. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. *Circulation*. 2006;113:2391-2397.

23. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (Writing Committee to develop cardiovascular endpoints data standards). *J Am Coll Cardiol*. 2015;66:403-469.

24. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack-proposal for a new definition. *N Engl J Med*. 2002;347:1713-1716.

25. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;58:2020-2045.

26. d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. *Circulation*. 2014;130:S32-S38.

27. d'Udekem Y, Xu MY, Galati JC, et al. Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance. *J Am Coll Cardiol*. 2012;59:1178-1185.

28. Wald RM, Mertens LL. Hypoplastic left heart syndrome across the lifespan: clinical considerations for care of the fetus, child, and adult. *Can J Cardiol*. 2022;38:930-945.

29. Anderson PA, Sleeper LA, Mahony L, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network Multicenter Study. *J Am Coll Cardiol*. 2008;52:85-98.

30. Barron DJ, Kilby MD, Davies B, Wright JG, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. *Lancet*. 2009;374:551-564.

31. Feinstein JA, Benson DW, Dubin AM, et al. Hypoplastic left heart syndrome: current considerations and expectations. *J Am Coll Cardiol*. 2012;59:S1-S42.

32. Kverneland LS, Kramer P, Ovroutski S. Five decades of the Fontan operation: a systematic review of international reports on outcomes after univentricular palliation. *Congenit Heart Dis*. 2018;13:181-193.

33. Hirsch JC, Goldberg C, Bove EL, et al. Fontan operation in the current era: a 15-year single institution experience. *Ann Surg*. 2008;248:402-410.

34. Yimer MA, Tisma-Dupanovic S, Malloy-Walton L, et al. Post-operative arrhythmias in patients with hypoplastic left heart syndrome and anatomic variants: incidence, type, and course. *Cardiol Young*. 2021;31:1412-1418.

35. Ohye RG, Schranz D, D'Udekem Y. Current therapy for hypoplastic left heart syndrome and related single ventricle lesions. *Circulation*. 2016;134:1265-1279.

36. Ghai A, Harris L, Harrison DA, Webb GD, Siu SC. Outcomes of late atrial tachyarrhythmias in adults after the Fontan operation. *J Am Coll Cardiol*. 2001;37:585-592.

37. Collins KK, Love BA, Walsh EP, Saul JP, Epstein MR, Triedman JK. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. *Am J Cardiol*. 2000;86:969-974.

38. Fishberger SB, Wernovsky G, Gentles TL, et al. Factors that influence the development of atrial flutter after the Fontan operation. *J Thorac Cardiovasc Surg*. 1997;113:80-86.

39. Poh CL, Cordina RL, Iyengar AJ, et al. Pre- and Post-operative determinants of transplantation-free survival after Fontan. The Australia and New Zealand experience. *Int J Cardiol Heart Vasc*. 2021;35:100825.

40. Ota N, Fujimoto Y, Murata M, et al. Improving outcomes of the surgical management of right atrial isomerism. *Ann Thorac Surg*. 2012;93:832-838.

KEY WORDS atrial arrhythmia, Fontan surgery, thromboembolic events, univentricular heart