Received: 21 February 2021 | Revised: 4 August 2021 | Accepted: 20 August 2021

DOI: 10.1002/joa3.12630

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Increasing age and atrial arrhythmias are associated with increased thromboembolic events in a young cohort of adults with repaired tetralogy of Fallot

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Funding information
UBC Cardiology Academic Practice Plan (CAPP)

Abstract

Background: Adults with repaired Tetralogy of Fallot (rTOF) comprise one of the largest cohorts among adults with congenital heart disease (ACHD). These patients have a higher burden of atrial arrhythmias (AA), leading to increased adverse events, including stroke and transient ischemic attack (TIA). However, the data on factors associated with stroke/TIA in rTOF are limited, and classic risk factors may not apply. We studied event rates and associated factors for thromboembolism in a rTOF cohort.

Methods: Retrospective cohort study of all adult patients age >18 years with rTOF followed at a single ACHD tertiary care center. AA of interest were atrial fibrillation (AF) and atrial flutter (AFL).

Results: Data from 260 patients were identified, mean age 37.6 SD 13.3 years, followed over 5108 patient-years (mean 16.6 SD 8.2 years). 43 patients had AF and/or AFL, and 30 patients had thromboembolic events, of which 19 patients had stroke/TIA. The event rate for any thromboembolism was 3.39 per 100 patient-years follow-up in patients with AA, compared to 1.80 in patients without ($P = .07$). In univariate analysis, older age and diabetes were associated with thromboembolic events. In multivariate analysis, only older age was associated with thromboembolic events.

Conclusions: In our relatively young cohort of adults with rTOF, there was a high prevalence of AA, associated with nearly double the rate of thromboembolic events compared to patients without AA. Older age alone is independently associated with thromboembolic events. Further studies into assessment of silent AA are required, and routine assessments should be considered at an earlier age.

KEYWORDS
atrial arrhythmia, congenital heart disease, tetralogy of Fallot, thromboembolic events

1 | INTRODUCTION

Tetralogy of Fallot (TOF) is one of the most common complex heart defects, accounting for 7%-10% of all congenital cardiac malformations.[1] With surgical and medical advances in the last few decades, more children with repaired TOF (rTOF) are surviving into adulthood, adding to a growing cohort of individuals at lifelong risk of cardiac and non-cardiac complications. A recent study showed by age 50 years, only 56% of adults with rTOF have not had an significant adverse event.[2] In the long term follow up, heart failure and arrhythmia are the primary cause of mortality in rTOF patients.[3,4] The overall prevalence of atrial arrhythmias in adults with congenital heart disease (ACHD) is 15%, with 20-year risk of developing arrhythmias starting at 7% for patients as young as age 20.[5] AA are associated with nearly 50% increase mortality risk, and double the risk of morbidity, such as stroke and heart failure.[5–7] In rTOF, the prevalence of atrial and ventricular arrhythmias rise after the age of 45 years, with up to a third developing symptomatic atrial tachycardias by adulthood.[1,8]

AA in patients with rTOF are associated with adverse events like heart failure, ventricular dysfunction, ventricular arrhythmias, stroke, and death.[2] In the general population, AF and AFL are directly linked to increased risk of stroke, which applies to ACHD patients.[5,9] However, there is a paucity of data on predictors for stroke, TIA, and other thromboembolic events in rTOF. The objectives of our study were to identify the prevalence of AA and event rate of systemic thromboembolic events, including stroke and TIA, and identify associated factors for thromboembolic events in adults with rTOF.

2 | METHODS

2.1 | Study population

This was a single-center, retrospective observational cohort study of all adults aged 18 years or older with rTOF, with at least 1 year of follow-up at the Pacific Adult Congenital Heart (PACH) Clinic in St. Paul's Hospital in Vancouver, British Columbia (BC), Canada. The PACH clinic is the designated advanced care provider for ACHD in BC, serving a population of 4.6 million people. Inclusion criteria for our study were: age >18 years, follow-up ≥1 year after entry into the PACH clinic, and previous surgical correction of TOF.

2.2 | Consent and ethics

Consent for inclusion of demographic and clinical data for research purposes was documented on charts included in the review. Approval from the Institutional Research and Ethics Board was obtained prior to initiation of the study.

2.3 | Data collection

Data collected from identified case charts included basic demographics, history of cardiac procedures, arrhythmias, thromboembolic events, oral anticoagulant therapy, and comorbidities such as diabetes mellitus, hypertension, heart failure, and peripheral vascular disease, which we define as peripheral blood vessel obstruction secondary to atherosclerotic disease. These diagnoses were taken from clinician documentation and supporting investigations, including electrocardiograms (ECG), computed tomography (CT) scans, and most recent cardiac imaging, including magnetic resonance imaging (MRI) and transthoracic echocardiograms (TTE). Ventricular function was evaluated at baseline from cardiac MRI if available, and if unavailable, most recent TTE or cardiac CT.

Atrial arrhythmias of interest were AF and AFL. These were recorded based on diagnoses clinically adjudicated by treating cardiologists with confirmation from ECG, Holter, pacemaker/defibrillator intracardiac electrograms and electrophysiology studies, and counted if there were pre-existing diagnoses before entry into the PACH clinic or after a single episode lasting more than 30 seconds duration after entry. If a patient had both arrhythmias, the patient was considered to have an arrhythmia based on age at first diagnosis, with the first arrhythmia considered the dominant, and each arrhythmia was counted on its own and included in arrhythmia totals.

Thromboembolic events were defined as ischemic stroke, TIA, intracardiac thrombus, peripheral embolus, and pulmonary embolism. Although less common than left atrial thrombus, right atrial thrombus has been associated with AF/AFL so we have included pulmonary embolism in this list, as thromboembolic complications from both right and left atria can pose serious consequences.[10] Thromboembolic events were documented in diagnostic coding, clinical data, and neuroimaging (e.g., CT head and/or MRI). The diagnosis of stroke and TIA was confirmed by neurology opinion. In patients with more than one thromboembolic event, each event was counted on its own and included in event totals. Event rates were calculated by dividing the number of thromboembolic events by the total number of patient-years in follow-up, which was counted from the time of patient enrollment in the PACH clinic to time of data collection.

Atrial arrhythmias and thromboembolic events were recorded separately during data collection with dates of first known occurrence. Patients with thromboembolic events that occurred before documentation of AA were excluded from statistical analyses seeking to identify associated factors for thromboembolism.

As many clinical events occurred remotely from the study inception, it was not possible to have secondary adjudication due to lack of several forms of source data.

2.4 | Statistical analysis

Patient characteristics, comorbidities, and ventricular function parameters were described using simple descriptive statistics (e.g., means and proportions). Patients with atrial arrhythmias were

compared to those who did not. For this comparison, a two-sample t-test for continuous variables, chi-squared or fisher's exact test (when expected counts less than 5) for categorical variables were used. The incidence of thrombotic events were then counted for the entire TOF cohort, stratified by patients with and without atrial arrhythmias, and further stratified by type of atrial arrhythmia (AF or AFL).

For the regression analysis, the two outcomes were grouped as (a) any thromboembolic events and (b) stroke and TIA events only. Both of these outcomes were compared against patients without any thromboembolic events. We first performed a univariable analysis of each variable and its effect on these outcomes using logistic regression models. Any variables that were found to have *P*-values below the a priori defined cut-off ($P < .25$) in univariable testing or those with a strong a priori hypotheses based on established knowledge (age, AF, and AFL) were added to the final multivariable model to identify predictors of the thromboembolic events and stroke/TIA. We checked the area under the curve, *c*-index likelihood ratio test, and Hosmer-Lemeshow test to ensure the model fits the data.

Kaplan-Meier curves were computed to estimate the overall "thromboembolism-free" survival probability and stratified by any AA status. Thromboembolism-free survival was calculated from date of birth to date of first thrombotic event. If a thrombotic event did not occur, the patient was censored at their last known status date (December 31, 2015). "AA-free" survival probabilities were also calculated from date of birth to date of AA diagnosis. If an AA did not occur, the patient was censored at their last known status date (December 31, 2015). The regression standardization method was used to derive adjusted probabilities rather than odds ratios, to demonstrate the effect of age specifically on risk of stroke/TIA and any thromboembolic event.

The level of significance was set at $P < .05$ for all statistical analyses, and all reported *P*-values reflect two-tailed tests. All analyses were conducted using R 3.5.2 statistical programming.[11]

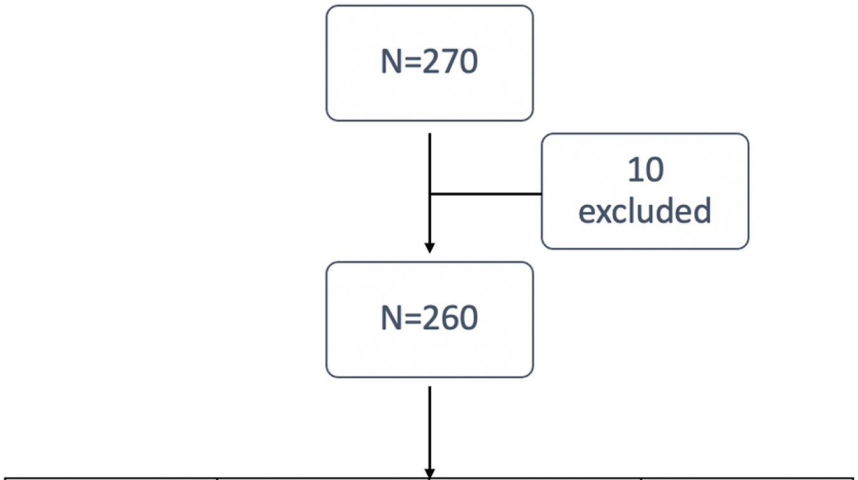
3 | RESULTS

3.1 | Cohort demographics

Two hundred seventy patients with TOF were identified in the database that formed the study group. We excluded 10 patients for insufficient follow-up data. The process of patient selection and exclusion is summarized in Figure 1. The cohort's mean age was 37.6 ± 13.3 years, 42.7% female, and the average age at repair of TOF was 5.07 ± 5.82 years. Cohort characteristics are summarized in Table 1. Patients were followed for a total of 5108 patient-years, mean follow-up 16.6 ± 8.2 years.

3.2 | Prevalence of atrial arrhythmia

Forty-three patients (16.5%) had atrial arrhythmias, 20 patients with AF and AFL, 3 with only AF, and 18 with only AFL. Patients with any atrial arrhythmia were on average older than those without, with a mean age of 49.9 ± 14.9 years compared to 35.2 ± 11.6 years ($P < .001$). The mean age at onset of first atrial arrhythmia was 45.6 ± 10.6 years. 46.5% of patients with first atrial arrhythmia went on to develop a second arrhythmia. Patients with any atrial arrhythmia were on average older at the age of repair, 9.14 ± 7.33 years compared to 4.24 ± 5.09 years ($P < .001$). For years free of any atrial arrhythmia, Kaplan-Meier



	Any AA	No AA	Total
Any TE	12	18	30
No TE	31	199	230
Total	43	217	

FIGURE 1 Process of patient selection and breakdown of patients by presence of atrial arrhythmia and thromboembolic event. Abbreviations: AA, atrial arrhythmia; TE, thromboembolic event

TABLE 1 Overall baseline patient characteristics and stratified by presence or absence of any trial arrhythmias (AF and AFL)

Characteristic	Overall (N = 260)	No AA (N = 217)	AA (N = 43)	*P*-value
Age (year)	37.7 ± 13.3	35.2 ± 11.6	49.9 ± 14.9	<.001
Female, n (%)	111 (43)	81 (41.1)	30 (47.6)	.96
Weight (kg)	75.5 ± 18.4	74.6 ± 18.2	78.1 ± 19.0	.16
Height (cm)	168.6 ± 11.6	168.6 ± 11.9	168.6 ± 10.8	.37
BMI (kg/m^2)	26.4 ± 5.3	26.1 ± 4.8	27.4 ± 6.4	.24
Age at repair (year)	5.07 ± 5.82	4.24 ± 5.09	9.14 ± 7.33	<.001
BT shunt, n (%)	99 (38.1)	78 (35.9)	21 (48.8)	.156
Hypertension, n (%)	28 (10.8)	17 (7.83)	11 (25.6)	.002
Diabetes, n (%)	21 (8.08)	11 (5.07)	10 (23.3)	<.001
PVD, n (%)	11 (4.23)	5 (2.3)	6 (14)	.004
LVEF (%)	58.1% ± 5.68%	58.4% ± 5.31%	56.6% ± 7.13%	.135
VEF (%)	40% ± 8.64	40.1% ± 8.49%	38.8% ± 9.60%	.557
Mild PR, n (%)	52 (20)	44 (20.3)	8 (18.6)	.471
Moderate PR, n (%)	55 (21.2)	43 (19.8)	12 (27.6)	
Severe PR, n (%)	76 (29.2)	67 (30.9)	9 (20.9)	
Mild TR, n (%)	112 (43)	96 (44.2)	16 (37.2)	<.001
Moderate TR, n (%)	35 (13.5)	21 (9.68)	14 (32.6)	
Severe TR, n (%)	6 (2.31)	3 (1.38)	9 (20.9)	
Prosthetic valve, n (%)	121 (46.5)	97 (44.7)	24 (55.8)	.243

Numeric summaries are mean (standard deviation) and categorical summaries are n (%).

Abbreviations: AA, Atrial Arrhythmia; BMI, Body Mass Index; BT, Blalock-Taussig; LVEF, left ventricular ejection fraction; PR, pulmonary regurgitation; PVD, peripheral vascular disease; RVEF, right ventricular ejection fraction; TR, tricuspid regurgitation.

analysis showed that at age 60 years, atrial arrhythmia-free survival probability was reduced to 59.8% (95% CI 48.1%-74.4%) (Figure 2).

3.3 | Thromboembolism event rates

Thirty patients had thromboembolic events. Two patients had two embolic events, one with TIA and PE, and TIA and peripheral embolus. The event rate for any thromboembolic event in patients with any atrial arrhythmia was 3.39 per 100 patient-years follow-up, compared to 1.80 per 100 patient-years in patients without ($P = .07$).

Eleven patients had a thromboembolic stroke, confirmed with brain imaging and neurology opinion. One patient was excluded due to the lack of confirmatory imaging. Nine patients had TIA confirmed with neurology opinion. In total, 19 patients had stroke/TIA; six patients had preceding atrial arrhythmia. Specifically, one patient with stroke had AF, 1 had AFL, and 1 had both. Two patients with TIA had AFL, and one patient had both. The stroke/TIA annual event rate was 0.47 per 100 patient-years among patients with any atrial arrhythmia, compared with 0.35 per 100 patient-years follow-up in patients without ($P = .26$).

Of the six patients with stroke/TIA and any atrial arrhythmia, four had documented atrial arrhythmias before stroke/TIA, with the remaining two having had events that pre-dated the formal diagnosis of atrial arrhythmia. Excluding these two patients, the average amount of time before the onset of atrial arrhythmia and stroke/TIA was 4 ± 1.82 years.

One patient had intra-cardiac thrombus, 9 had a peripheral embolism, and three patients had PE. The patient with intra-cardiac thrombus had AF and AFL, and three patients with peripheral embolism and two patients with pulmonary embolism had atrial arrhythmia. Overall events and breakdown according to the presence or absence of arrhythmia and type of arrhythmia are summarized in Table 2.

Kaplan-Meier analysis for years thromboembolism-free showed probability was reduced to 91.3% (95% CI 87.2%-95.7%) at age 40 years, and further reduced to 71.2% (95% CI 60.7%-83.5%) at age 60 years (Figure 2). Kaplan-Meier analysis for years thromboembolism-free stratified by patients with any atrial arrhythmia compared to those without showed no difference in thromboembolism-free survival between these two groups ($P = .83$). In patients with any AA, the thromboembolism-free probability was reduced to 96.6% (95% CI 90.1%-100%) at age 40 years and reduced to 78.3% (95% CI 62.9%-97.5%) at age 60 years (Figure 3).

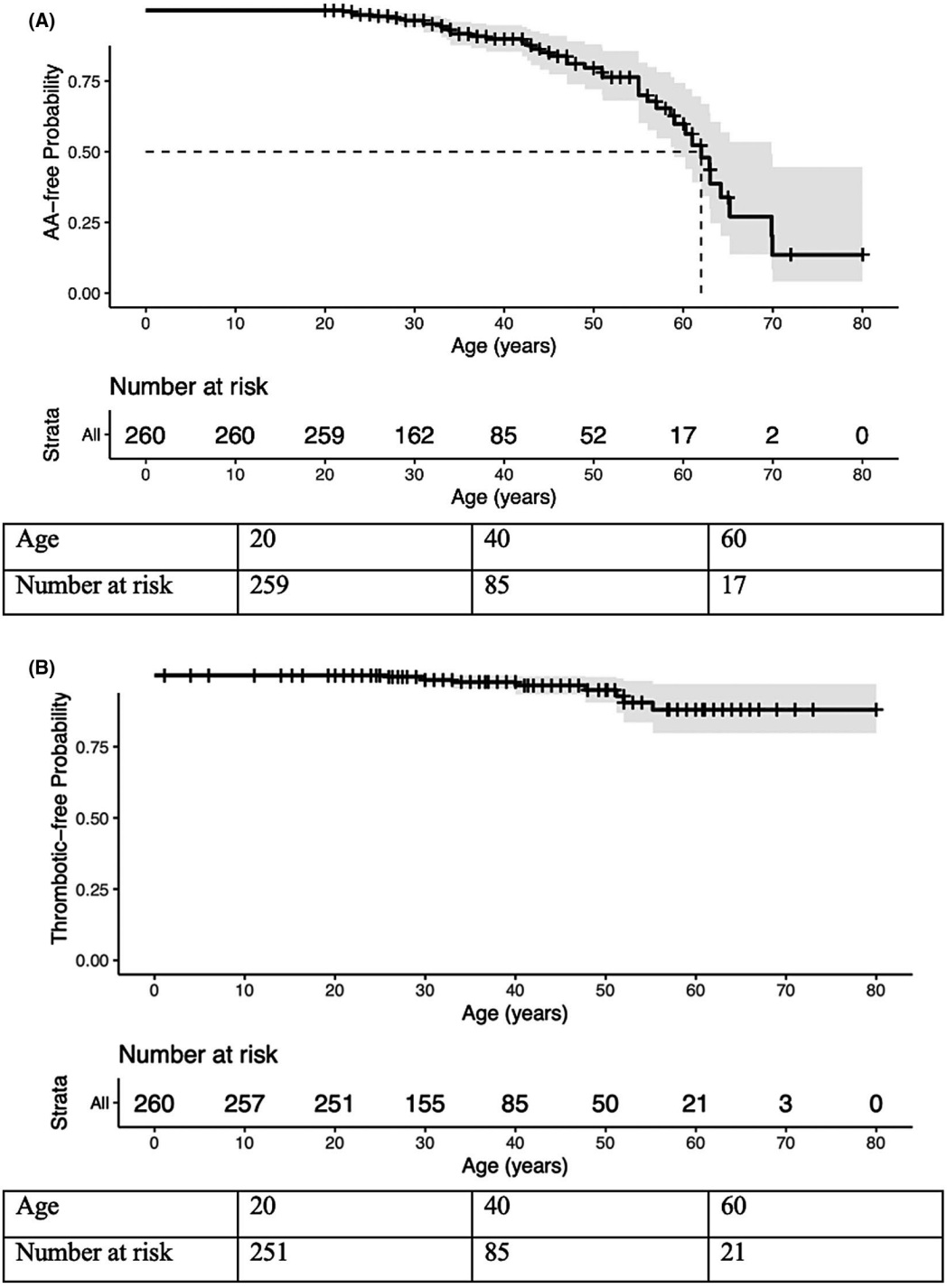


FIGURE 2 Kaplan-Meier curve for (A) years atrial fibrillation and atrial flutter-free, and (B) for years thromboembolism-free

3.4 | Oral anticoagulant therapy

Thirty-eight patients were on oral anticoagulant therapy, and of those 33 were on warfarin, and 5 were on a direct oral anticoagulant (DOAC). All 38 patients were anticoagulated in the context of AF and/or AFL. Among the 19 patients with thromboembolic stroke or TIA, 5 of the 6 patients with a preceding atrial arrhythmia were notably not anticoagulated and were initiated on oral anticoagulant after the thromboembolic event.

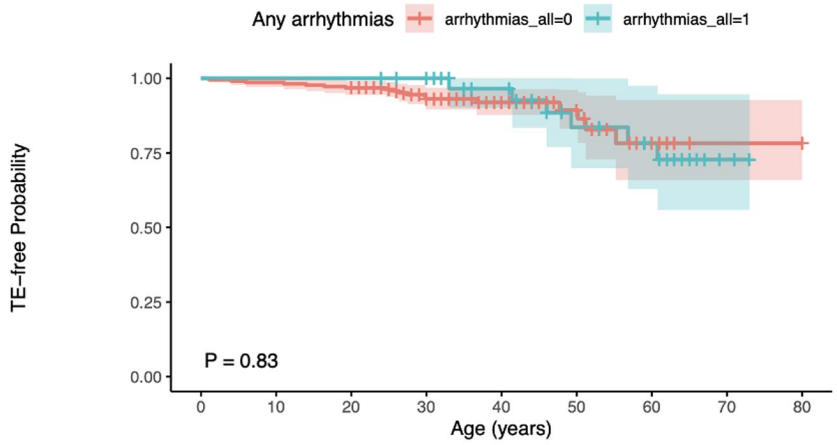
3.5 | Associated factors for thromboembolic events

In univariate analysis, older age (OR 1.06, 95% CI 1.02-1.11) and diabetes mellitus (OR 3.15, 95% CI 0.45-13.8) were associated with stroke/TIA, and these factors were subsequently selected for multivariable modeling. In multivariate analysis, only age (OR 1.07, 95% CI 1.01-1.13) was statistically significantly associated with stroke/TIA (P = .015). These results are summarized in Table 3.

TABLE 2 Thromboembolic events in cohort (n = 30 patients), note 2 patients had two events that were counted in event totals, and 5 patients had both AF and AFL. Numbers indicate events; *P*-value compares no AA group to AA group

Thromboembolic event	Total (n = 30)	No AA (n = 18)	AA (n = 12)		*P*-value
			Atrial fibrillation	Atrial flutter	
Stroke	10	7	2	2	.69
TIA	9	6	1	2	1.00
Intracardiac thrombus	1	0	1	1	.38
Peripheral thrombus	9	6	2	3	1.00
Pulmonary embolism	3	1	1	2	.54

FIGURE 3 Kaplan-Meier curve for years thromboembolism-free in patients with any atrial arrhythmia and those without



Number at risk

arrhythmias_all=0	217	214	209	118	55	30	7	1	0
arrhythmias_all=1	38	38	38	33	26	17	14	2	0

Age	20	40	60
Number at risk, with AA	38	26	14
Number at risk, without AA	209	55	7

TABLE 3 Univariable and multivariable analysis for predictors of stroke and TIA vs no thromboembolic event (n = 249 and n = 19 events)

Characteristics	Univariable ORs (95% CI)	*P*-value	Multivariable ORs (95% CI)	*P*-value
Age, per 1-year increase	1.06 (1.02, 1.11)[a]	.005	1.07 (1.01, 1.13)[b]	.015
Female (ref: male)	0.48 (0.12, 1.73)	.3	0.63 (0.14, 2.58)	.52
Diabetes	3.15 (0.45, 13.8)[a]	.2	3.30 (0.23, 27.8)	.34
Hypertension	2.50 (0.36, 10.8)	.3	0.79 (0.09, 4.64)	.81
Smoking	0.53 (0.08, 2.77)	.5	—	—
Peripheral vascular disease	3.10 (0.16, 19.8)	.4	1.45 (0.04, 23.6)	.81
Heart failure	2.46 (013, 15.1)	.5	—	—
Atrial fibrillation	2.79 (0.40, 12.1)	.3	0.99 (0.07, 11.8)	.99
Atrial flutter	1.81 (0.26, 7.69)	.5	0.62 (0.05, 4.70)	.67

[a]Statistically significant at a level = .25 for univariable testing.
[b]Statistically significant at a level = .05 for multivariable testing.

In univariate analysis with regard to any thromboembolic events, older age (OR 1.05, 95% CI 1.02-1.08), hypertension (OR 3.18, 95% CI 1.15-8.07), AF (OR 3.55, 95% CI 1.27-9.11), and AFL (OR 3.82, 95% CI 1.57-8.92) were statistically associated with any thromboembolic event. Multivariate analysis showed only age (OR 1.04, 95% CI 1.01-1.08) was significantly associated with

TABLE 4 Univariable and multivariable analysis for predictors of any thromboembolic event vs no thromboembolic event (n = 230 and n = 30 events)

Characteristics	Univariable ORs (95% CI)	*P*-value	Multivariable ORs (95% CI)	*P*-value
Age, per 1-year increase	1.05 (1.02, 1.08)[a]	<.001	1.04 (1.01, 1.08)	.021
Female (ref: male)	0.78 (0.36, 1.70)	.5	—	—
Diabetes	2.01 (0.55, 5.97)	.3	—	—
Hypertension	3.18 (1.15, 8.07)[a]	.027	1.27 (0.37, 4.03)	.69
Smoking	0.94 (0.30, 2.42)	.9	—	—
Peripheral vascular disease	3.22 (0.67, 11.9)[a]	.13	1.85 (0.32, 9.18)	.47
Heart failure	2.55 (0.55, 8.98)[a]	.2	0.97 (0.18, 4.20)	.97
Atrial fibrillation	3.55 (1.27, 9.11)[a]	.017	1.07 (0.26, 4.21)	.93
Atrial flutter	3.82 (1.57, 8.92)[a]	.004	2.26 (0.68, 7.03)	.18

[a]Statistically significant at a level = .25 for univariable testing.

any thrombotic event ($P = .021$). These results are summarized in Table 4.

Notably, traditional risk factors such as hypertension, diabetes, and heart failure were not associated with stroke/TIA in the rTOF population. On average, the CHA2DS2-VaSC score for the whole rTOF cohort was 0.8 ± 1.11. The average CHA2DS2-VaSC score before stroke/TIA for the 19 patients who developed stroke/TIA were 1.3 ± 1.31, not statistically significant from the rest of the cohort ($P = .07$). The average CHA2DS2-VaSC score for all patients with any thromboembolic event was 1.07 ± 1.14, also not statistically significant from those without ($P = .06$).

4 | DISCUSSION

In our relatively young cohort, 16.5% had AF and/or AFL. Annual event rates for any thromboembolic event, including stroke and TIA, were nearly double in patients with AF and/or AFL, compared to those without any atrial arrhythmia. Univariate analysis showed higher age, AF, AFL, and hypertension were associated with any thromboembolic event. Higher age and diabetes were associated with stroke/TIA in univariate analysis. In multivariate analysis, only higher age was associated with any thromboembolic event and also stroke/TIA.

Previous rTOF studies have showed a wide range of AA, from 2.5% to 54%.[2] An rTOF study found a prevalence of 17% of atrial arrhythmia in their cohort,[2] similar to our finding of 16.5%. Our data showed that AA-free probability was reduced to 90% (CI 85.4%-92.8%) at age 40 years and further reduced to 59.8% (CI 48.1%-74.4%) at age 60 years, suggesting that the probability of developing atrial arrhythmias is higher at a younger age in rTOF. In ACHD, one study found more than 50% of patients reaching age 18 years developed atrial arrhythmias by age 65.[5] In another rTOF study, the mean age at time of first episode of atrial arrhythmia was 46 ± 12 years, similar to our finding of 45.6 ± 10.6 years.[12] These observations highlight the need for early screening for atrial arrhythmia in rTOF, starting before age 50. We did not pursue univariate and multivariate analyses for predicting atrial arrhythmia in our cohort, as that is beyond the scope of this study.

Prior studies that investigated ACHD as a whole found AA were associated with multiple complications, as well as complications from thrombotic events.[13–15] Our study is among the first to show that rTOF patients who have been diagnosed with AF and/or AFL are at higher risk of thromboembolic events. This observation suggests that there may be a higher than appreciated burden of clinically silent AA in adults with rTOF, with an associated higher burden of morbidity and mortality downstream.[7] While the prevalence of stroke is considered low in ACHD, it is up to 100 times higher than expected to control comparable age populations.[14] This observation is highly concerning, as ACHD cohorts tend to be young and the incidence is likely to increase as they age.[14] In our cohort, the adjusted risk of stroke/TIA is 11% (CI 0.05-0.16) at age 50, and even higher past that age. Notably, the six patients in our cohort with stroke and TIA who had preceding atrial arrhythmia were not on oral anticoagulant therapy until after the thromboembolic event, highlighting the importance of early screening for risk factors like AA for stroke/TIA prevention.

Expanding beyond stroke to include any thromboembolic event, in our young cohort we found that any thromboembolic event-free probability is reduced to 91.3% (95% CI 87.2%-95.7%) by age 40 years, and projected to be further reduced to 71.2% (95% CI 60.7%-83.5%) by age 60 years. This observation has not been previously reported before, as prior rTOF studies investigated adverse events as a combination of mortality, heart transplant, ventricular arrhythmia, heart failure, endocarditis, AA, and need for pacemaker or defibrillator.[2] In those studies, by age 50 years, only 56% was free of any adverse event, and among those who had an adverse event, AA was considered a poor prognostic sign as it was associated with serious adverse events and mortality.[2] Our findings support that AA is a poor prognostic sign in adults with rTOF, as a thromboembolic event at a relatively young age has more health, economic, and social "cost" for the individual and the healthcare system.

In our univariate analysis, other than diabetes, traditional risk factors were not associated with thromboembolic events. Moreover, CHA2DS2-VaSC scores for the cohort were low. There was no significant difference between the CHA2DS2-VaSC scores for the 19

patients who had stroke/TIA or the 30 patients who had any thromboembolism compared to those who did not. This finding is supported in studies that have used CHADS2 or CHA2DS2-VaSC as risk stratification tools in ACHD. One study found that a dichotomized model using a cut-off of ≥2 points best predicted thromboembolic events due to poor correlation between events and scores ≤2, suggesting that these models do not reliably predict stroke risk for this population.[13,15]

In the most recent American Heart Association update regarding congenital heart disease in older adults, recommendations for diagnosis and treatment of arrhythmias included consideration for anticoagulation with warfarin among "older" ACHD patients with sustained AF, regardless of the presence of traditional risk factors or risk as determined by tools like CHADS2 and CHA2DS2-VaSC.[16] Our study's results support this recommendation, and further, the starting age for screening could be at 50 years of age.

4.1 | Limitations

Our study has several limitations, related in part to the small size of the study and retrospective design. Endpoints in this study are clinical and may have been underestimated. However, the clinical diagnoses are supported by invasive diagnostic testing or imaging, and all our data comes from the only tertiary center caring for ACHD in the province. There were fewer thromboembolic events than expected, leading to a large standard error that requires cautious interpretation. In one study with 191 included ACHD patients, 13 patients had thrombotic events, and in another cohort of 458 ACHD patients, there was a 2% incidence of stroke, an event rate of about 0.05% per patient-year.[13,14] We also note that 38 patients of the 43 patients with atrial arrhythmia were on oral anticoagulant therapy, which may have reduced the number of thrombotic events. However, our retrospective cohort study was not designed to collect data regarding medication adherence, and other details such as the temporary holding of medication for other medical reasons was not consistently captured.

Some patients had thromboembolic events before documentation of atrial arrhythmia; to avoid the presumption that all thromboembolic events resulted from undetected atrial arrhythmia, wherever applicable, we excluded those patients from analysis. We presented events per patient-year to compare patients with and without arrhythmia, but we note that this assumes a consistent rate per unit of time, which is useful in identifying a trend but likely not representative of clinical situations patient-by-patient basis. We were also limited in our assessment of left ventricular or right ventricular systolic function at the time of index arrhythmia, as imaging was not consistently available across all patient charts, so in an attempt to standardize data collection, we used the most recent cardiac imaging available.

5 | CONCLUSION

In our relatively young cohort of adults with rTOF, patients with AF and AFL had nearly double the event rates for any thromboembolic event, compared to those without. By age 60, the probability of arrhythmia-free survival drops to 60%, and the probability of thromboembolism-free survival drops to 71%. The CHA2DS2-VaSC score was not able to discriminate patients for stroke/TIA prevention in rTOF. These findings emphasize the need for early screening of clinically silent atrial arrhythmia in adults with rTOF and early consideration for anticoagulation if present, starting as early as 50 years of age.

5.1 | Future directions

Future directions may include a multicenter prospective study following adults with rTOF for the occurrence of AF and thromboembolic events to build on the findings in this study. To date, there is no prospective study yet published on the relationship between ACHD, AF, and thromboembolic events. Future studies involving a larger cohort of ACHD could also investigate if atrial arrhythmia burden is related to thromboembolic events. Finally, the factors associated with atrial arrhythmia and thromboembolic events identified in this study can generate hypotheses for future studies to construct a risk stratification score for ACHD. This score can be a valuable clinical tool to identify ACHD patients at higher risk for developing atrial arrhythmia and thromboembolic events.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Sameer Desai for his statistical analyses and contribution to the Methods section of this manuscript.

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How to cite this article: Tsui C, Wan D, Grewal J, Kiess M, Barlow A, Human D, et al. Increasing age and atrial arrhythmias are associated with increased thromboembolic events in a young cohort of adults with repaired tetralogy of Fallot. J Arrhythmia. 2021;37:1546–1554. https://doi.org/10.1002/joa3.12630