

Outcomes of Anticoagulation Therapy in Adults With Tetralogy of Fallot

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Background—Available outcomes data for anticoagulation therapy in adults with congenital heart disease (CHD) provide assessment of global risk of this therapy for CHD patients (a heterogeneous population), but the risk of complications for the different CHD diagnoses is unknown. The purpose of the study was to describe the indications for anticoagulation, and the incidence and risk factors for major bleeding complication in adults with tetralogy of Fallot.

Methods and Results—We queried Mayo Adult Congenital Heart Disease (MACHD) database for tetralogy of Fallot patients (aged ≥ 18 years) that received anticoagulation, 1990–2017. Of 130 patients (42 ± 14 years, 75 men [58%]), warfarin and direct oral anticoagulants were used in 125 (96%) and 5 (4%), respectively because atrial arrhythmias ($n=109$), mechanical prosthetic valve ($n=29$), intracardiac thrombus ($n=4$), pulmonary embolism ($n=6$), stroke ($n=3$), and perioperative anticoagulation ($n=44$). The median hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use score for the entire cohort was 1 (0–2) and 27 (21%) had hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use score ≥ 2 . There were 14 minor bleeding events (1.6% per year) and 11 major bleeding events (1.3% per year) in 8 patients during median follow-up of 74 months (856 patient-years). Mechanical prosthesis (hazard ratio 1.78, CI 1.29–3.77, $P=0.021$) and hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use score ≥ 2 (hazard ratio 1.41, CI 1.03–3.88, $P=0.046$) were risk factors for major bleeding events. All-cause mortality was higher in patients with major bleeding events ($n=6$, 75%) compared with patients without major bleeding events ($n=25$, 21%), $P=0.001$.

Conclusions—Considering the heterogeneity of the CHD population, data from the current study may be better suited for clinical decision-making in tetralogy of Fallot patients. (*J Am Heart Assoc.* 2019;8:e011474. DOI: 10.1161/JAHA.118.011474.)

Key Words: anticoagulation • bleeding • stroke • tetralogy of Fallot • thromboembolism

The guidelines for management of adults with congenital heart disease (CHD) recommend anticoagulation with warfarin for patients with risk factors for thromboembolism such as atrial arrhythmia, mechanical valve prosthesis, and prior history of thromboembolism.^{1–3} In addition to these standard thromboembolic risk factors, the risk for thromboembolism also varies with certain CHD diagnoses and underlying physiology.^{4–6} Even within a specific diagnosis such as tetralogy of Fallot (TOF), the risk for thromboembolism will

change over time as the patients become older and develop more comorbidities such as atrial arrhythmia, renal failure, ventricular dysfunction, and need for prosthetic valves.^{7,8} There are limited data about outcomes of anticoagulation in adults with CHD,^{9–12} and there are no studies specifically looking at outcomes of anticoagulation in adults with TOF. The purpose of the study was to describe the indications for anticoagulation and the incidence and risk factors for major bleeding complication in adults with TOF.

Methods

Patient Selection and Data Collection

The authors will make their data, analytic methods, and study materials available to other researchers on request.

The Mayo Adult Congenital Heart Disease (MACHD) database was queried for patients (aged ≥ 18 years) with repaired TOF that received anticoagulation therapy at Mayo Clinic Rochester, Minnesota from January 1, 1990 through

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Clinical Perspective

What Is New?

- The incidence rate of major bleeding complication is 1.3% per year in patients with tetralogy of Fallot.
- In patients with tetralogy of Fallot, having a mechanical prosthesis or a hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use score ≥ 2 is a risk factor for major bleeding complications.
- Having a major bleeding complication is associated with all-cause mortality.

What Are the Clinical Implications?

- Patients with tetralogy of Fallot who have risk factors for bleeding complications should have meticulous monitoring to prevent bleeding events and potentially reduce all-cause mortality.

December 31, 2017. The patients with pulmonary atresia were excluded. The Mayo Clinic institutional review board approved this study and waived informed consent for patients who provided research authorization. The electronic health records were extensively reviewed in these patients.

Study Terminologies

A major bleeding event was defined as intracranial bleeding, intra-thoracic or intra-abdominal hematoma requiring drainage or arterial embolization, any bleeding event leading to a decrease in hemoglobin >2 g/dL and/or requiring transfusion of blood products.^{9,13,14} A minor bleeding event was defined as cutaneous bleeding, epistaxis, gastrointestinal bleeding, or any bleeding event that did not meet the criteria for major bleeding event. Hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio [INR]; elderly [>65 years]; drug or alcohol use (HAS-BLED) score was calculated for all patients as previously described.¹³

Statistical Analysis

Data were presented as mean \pm SD, median (interquartile range) or counts (%). Unpaired *t* test, Wilcoxon rank sum test, χ^2 or Fisher exact test (as appropriate) were used to compare between-group differences. Freedom from major bleeding event was assessed using the Kaplan–Meier method, and the time of initiation of anticoagulation (or first presentation to Mayo Clinic for patients who were already on an anticoagulant) was used as “time zero”. In patients with >1 bleeding

event, the first bleeding event was used as the index event in the assessment of time-to-event end point. Comparisons in between-group freedom from major bleeding events were performed using the Wilcoxon test. Univariate and multivariate Cox proportional hazard models were constructed to determine the risk factors for major bleeding events, and association between variables and outcomes were expressed as hazard ratio and 95% CI. The variables included in the univariate model were chosen a priori on the basis of their previously demonstrated association with bleeding complications,^{9,13} and only the variables with significant association with major bleeding complication in the univariate model (pre-defined as $P<0.20$) were incorporated into the multivariate model. HAS-BLED score showed significant association with major bleeding complications in the univariate model both as continuous variable and as categorical variable. We only used HAS-BLED score as categorical variable (HAS-BLED score <2 versus ≥ 2) in the multivariate model to avoid collinearity. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC) and $P<0.05$ (apart from the pre-defined entry criterion for the multivariable model) was considered statistically significant.

Results

Baseline Characteristics

Out of 465 TOF patients in the MACHD database, we selected 130 (28%) patients who met the study inclusion criteria. The average age at the beginning of the study was 42 ± 14 years, the age at the time of TOF repair was 8 (5–18) years, and 75 (58%) were men. Table 1 shows the baseline clinical and echocardiographic data of the study cohort.

The indications for anticoagulation were atrial arrhythmia ($n=109$), mechanical prosthetic valve ($n=29$), intracardiac thrombus ($n=4$), pulmonary embolism ($n=6$), stroke ($n=3$), and perioperative anticoagulation for valve surgery and/or maze procedure ($n=44$). Of the 4 patients who had intracardiac thrombi, 3 patients had thrombi attached to pacemaker/defibrillator leads while 1 patient had a left atrial thrombus that was identified during transesophageal echocardiogram before direct current cardioversion. Among the 109 patients who receive anticoagulation because of atrial arrhythmia, the average CHA₂DS₂-VASc score was 2 ± 1 and 74 (68%) had CHA₂DS₂-VASc score ≥ 2 . The median HAS-BLED score for the entire cohort was 1 (0–2) and 27 (21%) had HAS-BLED score ≥ 2 .

Out of the 130 patients in the study, 26 (20%) patients were already on anticoagulation at the time of their first presentation to Mayo Clinic while anticoagulation was initiated in the other 104 (80%) patients in the course of follow-up. Warfarin was used in 125 (96%) patients; direct oral

Table 1. Baseline Characteristics

	All (N=130)	Major Bleeding (n=8)	No Major Bleeding (n=122)	P Value
Age, y	42±14	37±19	43±14	0.456
Male	75 (58%)	5 (53%)	70 (57%)	0.776
Body mass index, kg/m ²	27±6	27±6	27±5	0.843
Body surface area, m ²	1.9±0.3	1.9±0.2	1.9±0.3	0.632
Age at TOF repair, y	8 (5–18)	11 (6–33)	8 (4–19)	0.437
Prior palliative shunt	61 (47%)	4 (50%)	57 (47%)	0.857
Mechanical valve prosthesis	29 (22%)	3 (38%)	26 (21%)	0.090
Antiplatelet therapy	49 (38%)	2 (25%)	47 (39%)	0.444
% time in therapeutic range	84%	91%	82%	0.318
Comorbidities				
Atrial arrhythmia	109 (84%)	5 (63%)	104 (85%)	0.090
Hypertension	56 (43%)	1 (13%)	55 (45%)	0.071
Hyperlipidemia	75 (58%)	4 (50%)	71 (58%)	0.651
Coronary artery disease	32 (25%)	4 (50%)	28 (23%)	0.083
Current or prior smoker	32 (25%)	2 (25%)	30 (25%)	0.979
Diabetes mellitus	26 (20%)	2 (25%)	24 (20%)	0.715
Sleep apnea	54 (42%)	4 (50%)	50 (41%)	0.616
NYHA III/IV	32 (25%)	3 (38%)	29 (24%)	0.243
HAS-BLED score	1 (0–2)	2 (1–2)	1 (0–2)	0.064
Elevated ALT and/or AST*	1 (0.7%)	0	1 (0.8%)	...
Laboratory tests				
Hemoglobin, g/dL	14.1±1.8	14.3±1.3	14.0±14.9	0.627
Creatinine, mg/dL	1.1±0.4	1.1±0.3	1.1±0.4	0.732
Echocardiography				
≥Moderate RV enlargement [†]	95 (73%)	7 (88%)	88 (72%)	0.307
≥Moderate RV systolic dysfunction [†]	55 (42%)	6 (75%)	49 (40%)	0.053
≥Moderate RA enlargement [†]	92 (11%)	7 (88%)	85 (70%)	0.423
≥Moderate LA enlargement [†]	76 (59%)	4 (50%)	72 (59%)	0.266
Lateral E/e'	7±3	8±2	7±3	0.656
LV ejection fraction, %	55±10	57±6	55±10	0.379

HAS-BLED indicates hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use; LA, left atrium; LV, left ventricle; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; RA, right atrium; RAAS, renin angiotensin aldosterone system; RV, right ventricle; TOF, tetralogy of Fallot; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*Elevated ALT and/or AST defined as a level of alanine aminotransferase and/or aspartate aminotransferase >3 times the upper limit of normal.

[†]Qualitative assessment of chamber size and/or function.

anticoagulant was used in 5 (4%) patients, and 4 of the 5 patients who received direct oral anticoagulant had bioprosthetic pulmonary valves. Concomitant anti-platelet therapy was used in 49 (38%) patients. Of the 125 patients who received warfarin, the target INR was 2.0 to 3.0 in 108 (83%) patients, 2.5 to 3.5 in 17 (13%) patients with mechanical mitral, tricuspid, or pulmonary valves. The average number of INR results reviewed was 11±7 per patient, and time within therapeutic range was 84% for the entire cohort.

Bleeding Complications

The median duration of follow-up was 74 months (21–98) months, and the cumulative follow-up for the entire cohort was 856 patient-years. There were 14 minor bleeding events (1.6% per year [16 events per 1000 patient-years]), and these events were epistaxis (n=5), gastrointestinal bleeding (n=8), and menorrhagia (n=1). Anticoagulation was discontinued in 2 of these patients because of the bleeding complication.

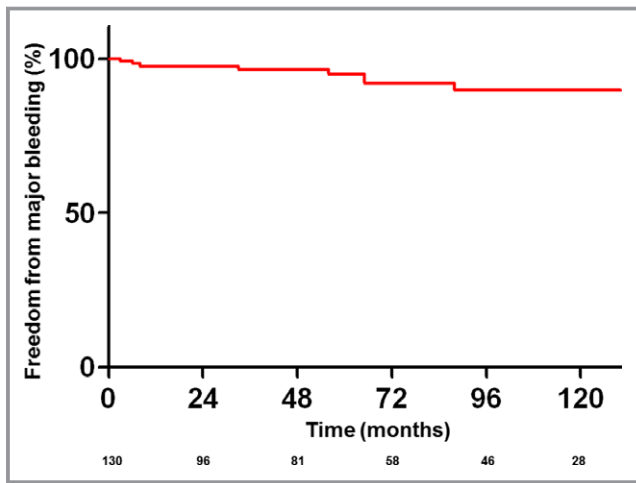


Figure 1. Kaplan–Meier curve showing the freedom from major bleeding complication.

There were 11 major bleeding events (1.3% per year [13 events per 1000 patient-years]), in 8 patients. The mean INR at the time of major bleeding event was 3.2 ± 0.9 , and 2 of these events occurred in the setting of INR above the therapeutic range for the indication. The freedom from major bleeding event was 89% in 10 years. There was no difference in the incidence of bleeding events, between the early era (1990–2003) and the late era (2004–2017); 1.3% versus 1.1%, $P=0.788$.

Of the 11 major bleeding events, 2 events (retroperitoneal hemorrhage after catheter ablation and intracranial hemorrhage after a motor vehicle accident) were provoked. Excluding these 2 provoked events, major bleeding event rate was 0.9% per year (9 events per 1000 patient-years). The freedom from

major bleeding event was 93% at 10 years (Figure 1), and was significantly different in patients with HAS-BLED scores ≥ 2 versus < 2 (88% versus 96% at 10 years, $P=0.038$), and in patients with mechanical prostheses versus no mechanical prosthesis (83% versus 94% at 10 years, $P=0.007$), Figure 2.

The multivariate risk factors for major bleeding event were mechanical prosthesis (hazard ratio 1.78, CI 1.29–3.77, $P=0.021$) and HAS-BLED score ≥ 2 (hazard ratio 1.41, CI 1.03–3.88, $P=0.046$), Table 2. A subgroup analysis showed that major bleeding event rate in patients with mechanical valve prosthesis ($n=29$) was 2.1% per year (21 events per 1000 patient-years), while major bleeding event rate in patients without mechanical valve prosthesis ($n=101$) was 0.9% per year (9 events per 1000 patient-years). There were 31 deaths (all-cause mortality), death was more common in patients with major bleeding events ($n=6$, 75%) compared with patients without major bleeding events ($n=25$, 21%), $P=0.001$. In addition to the 9 patients with embolic events before the initiation of anticoagulation (6 patients with history of pulmonary embolism and 3 patients with history of ischemic stroke), and 1 patient with a prior history of pulmonary embolism had another pulmonary embolism in the setting subtherapeutic INR of 1.3.

The clinical profiles of the 8 patients with major bleeding events are as follows:

Patient #1: A male, aged 49 years, with Down syndrome and mechanical mitral valve prosthesis who was on warfarin and aspirin and had spontaneous subdural hematoma that was managed conservatively. He subsequently had a large hematoma in the right thigh (requiring percutaneous drainage) secondary to a mechanical fall at

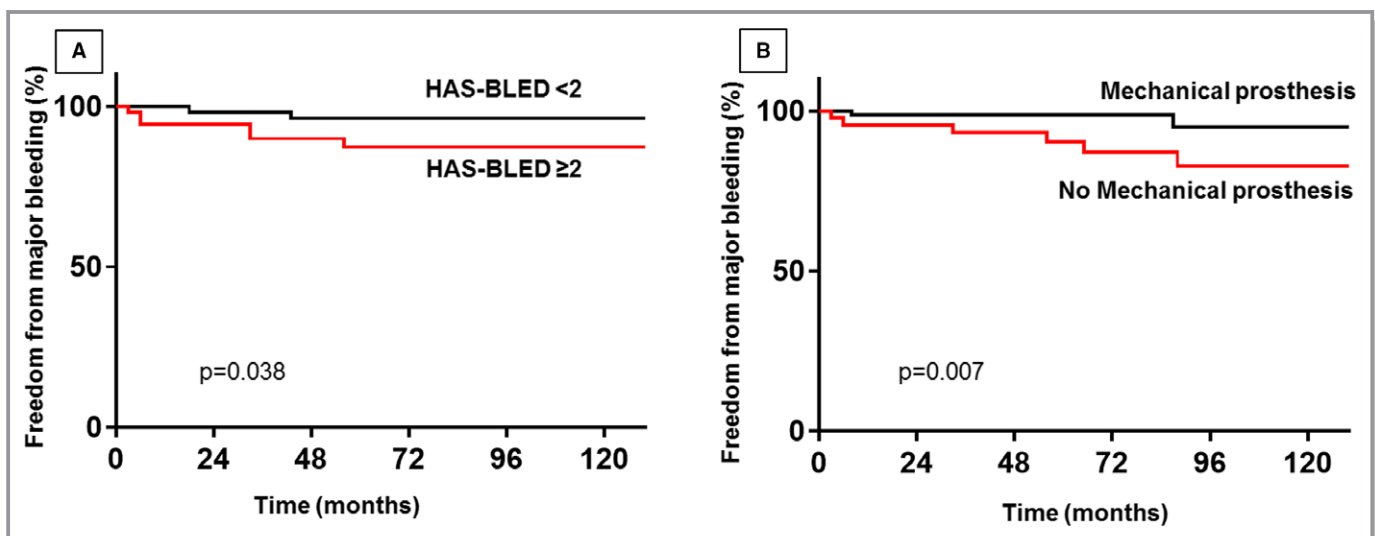


Figure 2. Kaplan–Meier curve comparing the freedom from major bleeding complication between patients with HAS-BLED scores ≥ 2 vs < 2 (A), and between patients with mechanical prostheses vs no mechanical prosthesis (B). HAS-BLED indicates hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (> 65 years); drug or alcohol use.

Table 2. Risk Factors for Major Bleeding Complications

Bleeding Complications	Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, y	0.92 (0.61–2.04)	0.105	1.25 (0.21–3.14)	0.611
Male sex	1.01 (0.22–4.12)	0.872		
Percentage of time within therapeutic range	0.86 (0.26–2.11)	0.286		
Antiplatelet therapy	1.34 (0.76–2.15)	0.352		
HAS-BLED score	1.76 (0.98–3.06)	0.076		
HAS-BLED score ≥ 2	1.85 (1.08–3.17)	0.038	1.41 (1.03–3.88)	0.046
Mechanical prosthesis	2.14 (1.85–3.34)	0.007	1.78 (1.29–3.77)	0.021
Direct oral anticoagulants	1.71 (0.63–5.18)	0.674		

HAS-BLED indicates hypertension, abnormal renal or liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly (>65 years); drug or alcohol use; HR, hazard ratio.

the age of 57 years. The patient died within 12 months from end-stage heart failure.

Patient #2: A male patient, aged 43 years, with mechanical aortic valve prosthesis who was on warfarin (without aspirin), and had iliopsoas hematoma (requiring surgical drainage) and a subsequent episode of massive gastrointestinal bleeding requiring multiple blood transfusions 3 months later.

Patient #3: A male patient, aged 43 years, with mechanical aortic valve prosthesis that was on warfarin (without aspirin). He had an episode of massive gastrointestinal bleeding requiring multiple blood transfusions and died 3 days later from presumed sudden cardiac death.

Patient #4: A female patient, aged 46 years, who was on warfarin (without aspirin) for atrial fibrillation/flutter. She had an episode of subarachnoid hemorrhage related to multiple intracranial aneurysms and required a neurosurgical intervention. Anticoagulation was discontinued after this event. The patient was followed for another 31 months after discontinuation of anticoagulation, and there were no other bleeding or embolic complications.

Patient #5: A female, aged 63 years, who was on warfarin (without aspirin) for atrial flutter and left atrial thrombus. She had retroperitoneal bleeding after catheter ablation while anticoagulated. This was managed conservatively with multiple blood transfusions and discontinuation of anticoagulation. She died at the age of 72 years from end-stage heart failure.

Patient #6: A male, aged 86 years, who was on warfarin (and aspirin) for persistent atrial fibrillation and had gastrointestinal bleeding requiring blood transfusions. Aspirin was discontinued and anticoagulation was switched from warfarin to a direct oral anticoagulant (dabigatran). The patient had another gastrointestinal bleeding 10 months later, and anticoagulation was discontinued completely. He died at the age of 91 years from a malignancy.

Patient #7: A male, aged 43 years, with history of cirrhosis, renal failure, and prior banding of esophageal varices. He was on warfarin (without aspirin) for persistent atrial fibrillation and died from massive gastrointestinal bleeding.

Patient #8: A male, aged 53 years, on warfarin for atrial flutter and pulmonary embolism. He died from bilateral subarachnoid and subdural hemorrhage after a motorcycle accident.

Discussion

In this review of the indications and outcomes of anticoagulation therapy in 130 adult TOF patients, the most common indications for anticoagulation were atrial arrhythmias, perioperative anticoagulation, and mechanical prosthetic valves. The annual risk of all major bleeding complications and unprovoked major bleeding complications was 1.2% and 0.9%, respectively, and mechanical valve prostheses and HAS-BLED score ≥ 2 were risk factors for major bleeding complications.

Anticoagulation with warfarin is routinely recommended in adults with CHD who have thromboembolic risk factors such as atrial arrhythmia, mechanical valve prosthesis, and history of thrombosis or thromboembolism.^{1–3} These anticoagulation indications are similar to those suggested for patients with acquired heart disease. We did not identify any additional indications for anticoagulation in our patient population.

The HAS-BLED score was derived and validated in large cohorts of patients with acquired heart disease,^{13,15} and prognostic data of the HAS-BLED score in adults with CHD are limited.^{11,12} The current study shows an association between HAS-BLED score and annual bleeding risk in TOF patients, and this is consistent with the limited data from studies of other CHD patients.^{11,12} Since the components of the HAS-BLED score are based on information from history, physical exam, and routine laboratory blood tests, it can be assessed in all patients, and taken into account when deciding on anticoagulation therapy in the CHD population.

In contrast to patients with acquired heart disease where there are robust data to guide anticoagulation management,^{16,17} outcomes data for anticoagulation in adults with CHD are limited.^{8–12} In a multicenter study of 229 adults with CHD from the CONCOR (Congenital Corvita) registry, the

annual risk of bleeding was 4.4%, and HAS-BLED score was associated with major bleeding events.¹² The annual bleeding risk from the CONCOR registry was much higher than reported in the current study, and we speculate that this difference may be related to the heterogeneous CHD diagnoses of the patients in the CONCOR registry. Of the 229 patients in the CONCOR study, patients with Fontan palliation and unrepaired single ventricle made up 12% of the cohort, and both of these diagnoses are known to have high bleeding risk,^{9,10,18,19} while TOF patients only comprised 13% (30 of 220 patients) of that study. Since the current study was based entirely on TOF patients, we anticipate that the results of our study will be more applicable and generalizable to the adult TOF population.

In another multicenter study of outcomes of thromboprophylaxis for atrial arrhythmia in 482 adults with CHD, the annual risk of bleeding was 1.8%, and HAS-BLED score was associated with a major bleeding event.¹¹ The specific CHD diagnoses of the patients in the multicenter study were not specified, and thus diagnosis-specific risk of bleeding complications could not be assessed. Prior data have demonstrated that certain CHD patient populations demonstrate excess bleeding risk on anticoagulation.^{9,10,18,19} Despite the heterogeneity of CHD diagnosis in the multicenter study, the findings are consistent with our results. Our study provides outcomes data of anticoagulation in TOF patients, thereby bridging the knowledge gap of disease-specific risk for the TOF population. The CHD patient populations, comorbid conditions, level and indications for anticoagulation vary between the 2 multicenter studies which likely accounts for the marked difference in bleeding risk.

Apart from patients with mechanical prosthetic valves in whom anticoagulation is mandatory, the decision to initiate anticoagulation therapy is based on a careful analysis of thromboembolic risk versus bleeding risk. Anticoagulation therapy, whether short-term or long-term, is indicated when thrombotic risk without anticoagulation exceeds bleeding risk with anticoagulation. While the current study did not perform a comparative analysis of thromboembolic events in TOF patients with and without anticoagulation, it provides important data about bleeding risk and factors that influence bleeding risk in patients on anticoagulation; this information will be helpful for risk stratification in clinical practice.

All-cause mortality was higher in patients with major bleeding complications compared with the rest of the cohort even though there were no significant differences in the baseline clinical characteristics of both subgroups. Although the association between major bleeding events and mortality may be because of other confounders that the study was not powered to adjust for, this finding is consistent with prior data showing a relationship between bleeding complications and

mortality in patients with acquired heart disease.^{20–22} If indeed such an association does exist, then meticulous risk stratification before initiating anticoagulation and clearly defining the duration and level of anticoagulation become even more important in the CHD population.

Direct oral anticoagulant is now the preferred anticoagulation therapy for non-valvular atrial fibrillation in selected patients with acquired heart disease because of a lower risk of bleeding compared with warfarin.^{16,17,23} Unfortunately there are limited data about safety and efficacy of direct oral anticoagulants in patients with CHD.²⁴ Only 6 patients received direct oral anticoagulants in the current study, thereby limiting our ability to perform any meaningful comparative analysis of bleeding risk in this subgroup. This is an important knowledge gap that should be addressed as we strive towards improving long-term outcomes of adults with CHD.

The current study was limited by the retrospective study design, referral bias, and small sample size. However, it provides data about the incidence and risk factors for bleeding complications in TOF patients. In contrast to previous studies that reported outcomes of anticoagulation in adults with CHD (a heterogeneous population), data from the current study may be better suited for clinical decision-making in TOF patients. In addition to being a retrospective single center study, another limitation of the current study is the difference in the demographics of the patients included in this study and previously published TOF cohorts from other studies. Our patients were older (median age 42 years) and underwent TOF repair at an older age (median age 8 years). This will potentially affect the generalizability of the results.

In summary, the current study reported a 1.2% annual risk of major bleeding complication (0.9% annual risk of unprovoked major bleeding complication), identified mechanical valve prostheses and HAS-BLED score as risk factors for major bleeding complications, and highlighted a potential association between major bleeding complications and all-cause mortality. This information is important for the risk stratification of TOF patients being considered for anticoagulation therapy. Additionally, it provides preliminary data to support future studies to further assess the relationship between bleeding complications and mortality, and the potential role of direct oral anticoagulants as a strategy to reduce bleeding complications.

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Disclosures

None.

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