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ORIGINAL ARTICLE

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Novel oral anticoagulant use in adult Fontan patients: A single center experience

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Abstract

Objective: Adult Fontan patients are at increased risk for thrombosis and thromboembolic complications leading to increased morbidity and mortality. Most are prescribed antiplatelet or anticoagulant therapy for thromboprophylaxis; novel oral anticoagulants (NOACs) are uncommonly used given lack of data on their use in this population and generalized concerns regarding Fontan patients' abnormal coagulation. We report the largest single-center experience with the use of NOACs for treatment and prophylaxis of thrombosis and thromboembolism in adult Fontan patients.

Results: A retrospective chart review identified 21 patients (11 female, 10 male), median age 33 years (18-50) at first initiation, who were prescribed a NOAC on 27 different occasions. The main indications for anticoagulation were arrhythmia (N = 12), thrombosis (N = 8), and persistent right to left shunts (N = 2); one patient was initially on anticoagulation for arrhythmia but restarted for thrombosis. The most common indications for initiation of a NOAC over warfarin were patient/provider preference (N = 11), labile international normalized ratio (INR) (N = 5), initiation of therapy elsewhere (N = 3), and history of poor clinical follow-up (N = 2). Over a cumulative 316 months of patient therapy, one new thrombotic event was noted. No major or nonmajor bleeding events occurred, and 10 patients experienced minor bleeding that did not require the cessation of therapy. One patient died from multiorgan system failure following an unwitnessed, out of hospital arrest. At present, 10 patients remain on NOAC therapy in the setting of ongoing arrhythmia (N = 4), history of stroke (N = 2), history of pulmonary embolism (N = 2), history of deep vein thrombosis (N = 1), and history of right ventricle thrombus (N = 1).

Conclusions: While our study is limited by size, our results suggest that NOACs may be a noninferior alternative to traditional anticoagulation and that further study is warranted.

KEYWORDS

arrhythmia, Fontan, novel oral anticoagulant, thrombosis

1 | INTRODUCTION

It is well established that Fontan patients are at risk for thrombosis and thromboembolism due to factors including impaired blood flow in a nonpulsatile circuit, presence of prosthetic material, right to left shunts, blind cul-de-sacs, atrial arrhythmias, and altered coagulation.[1] The 2014 PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease recommended long term oral antiplatelet or anticoagulation thromboprophylaxis for congenital heart disease patients when atrial arrhythmias are present.[2] Most Fontan patients are prescribed antiplatelet (aspirin, clopidogrel) or anticoagulant (warfarin) agents for thromboprophylaxis. Because of conflicting efficacy evidence, prescribing practice is largely based on prescriber preference.[1,3–7]

Novel oral anticoagulants (NOACs), which include the direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, rivaroxaban), have gained acceptance as first line agents in noncongenital patients who meet indications for anticoagulation.[8,9] In clinical trials comparing each NOAC against warfarin in noncongenital patients with atrial fibrillation, NOACs have been shown to be at least noninferior in reducing stroke or systemic embolization, and superior with regard to intracranial hemorrhage.[10–13] NOACs are also indicated for the treatment and prevention of deep vein thrombosis (DVT) and/or pulmonary embolism in selected patients.[14] NOACs have fewer drug–drug interactions, do not require dietary modification, and have pharmacodynamic properties obviating the need for routine lab monitoring of drug effect thereby making them an appealing alternative to warfarin.[15]

However, the experience with NOACs in patients with congenital heart disease is limited, particularly in adult Fontan patients.[16–21] Recognizing this, the 2014 PACES/HRS Expert Consensus Statement guidelines made a Class III, Level of Evidence C, recommendation against the use of NOACs in adult Fontan patients due in part to the lack of safety, efficacy, pharmacokinetic, and pharmacodynamic data, along with concerns regarding abnormal Fontan coagulation.[2,22,23]

While not well studied in adult Fontan patients specifically, the pharmacokinetic and pharmacodynamics properties of NOACs have been well established in the tens of thousands of patients who received them during clinical trials and even greater numbers since they have become popularized after gaining American and European guideline approval.[8–13] Bioavailability, time to peak concentration, half-life, drug–drug interactions, and mechanisms of NOAC excretion have been well established, as has dose adjustment or avoidance based on renal function.[8–11] To begin the process of addressing safety and efficacy, we report our experience with the use of NOACs for the prevention and treatment of thrombosis and thromboembolic complications in adult Fontan patients.

2 | METHODS

We identified adult Fontan patients (≥18 years old) on NOAC therapy (dabigatran, apixaban, rivaroxaban, or edoxaban) by review of our electronic medical record. Basic demographic information, underlying anatomy, Fontan type, indication(s) for therapy, NOAC prescribed, thrombotic events, bleeding events, and duration of therapy were recorded. New York Heart Association functional classification (NYHA class), CHA_2DS_2-VASc, and HAS-BLED scores were calculated at the time of each NOAC initiation.[8]

Thrombotic events on therapy were defined as new stroke, transient ischemic attack (TIA), DVT, pulmonary embolism, Fontan circuit thrombus, or intracardiac thrombus identified on imaging that was obtained at the discretion of the provider. Arrhythmia warranting anticoagulation included atrial fibrillation and/or atrial flutter/intraatrial reentrant tachycardia (IART) as determined by the clinical provider. Persistent arrhythmia was defined as continuous arrhythmia lasting more than 7 days and included patients receiving cardioversion (electrical or chemical). Arrhythmia procedure was defined as either catheter or surgical based modified Maze or Cox Maze III procedure.

Bleeding events were separated into three categories: major, nonmajor, and minor, derived from previously reported definitions.[24,25] Major bleeding was defined as an acute clinical bleed requiring cessation of therapy and a hemoglobin drop of ≥2 g/dL in 24 hours, transfusion of blood products, or bleeding into a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal). Bleeding events not meeting major bleeding criteria but requiring cessation of therapy were defined as nonmajor bleeding. Bleeding events not meeting major or nonmajor criteria and not requiring cessation of therapy were defined as minor bleeding.

Duration of therapy was determined by the start and stop date in the patient's medical record. If a patient was lost to follow-up (>6 months without any communication), the stop date was recorded as the last date of communication or when medication supply would have run out.

The study was approved through the Institutional Review Board of Baylor College of Medicine.

3 | RESULTS

Twenty-one adult Fontan patients (11 female, 10 male) were identified as being on NOAC therapy at a median age of 33 years (18–50) at first initiation (Table 1). The median duration of NOAC therapy was 13 months (1–42 months) with a total of 316 cumulative patient months on NOAC therapy. Underlying anatomy included double inlet left ventricle (N = 6), hypoplastic right ventricle (N = 5), tricuspid atresia (N = 6), unbalanced atrioventricular septal defect (N = 2), hypoplastic left heart syndrome (N = 1), and straddling tricuspid valve (N = 1). An extracardiac conduit (N = 10) was the most common Fontan type followed by lateral tunnel (N = 6), atriopulmonary (N = 4), and other (N = 1).

The most common indications were arrhythmia (N = 12), thrombosis (N = 8), and persistent right to left shunt (N = 2); one patient was initially on anticoagulation for arrhythmia but continued for thrombosis (Table 2). The most common reason for initiation of, or switch to, a NOAC over warfarin was patient/provider preference (N = 11), followed by labile INR on warfarin (N = 5), initiation elsewhere (N = 3), and history of poor clinical follow-up (N = 2). Of the 21 patients started on NOACs, 4 were stopped then restarted and 1 was stopped and restarted twice, leading to 27 unique NOAC initiation events. CHA_2DS_2-VASc scores were: 0 (N = 6), 1 (N = 6), 2 (N = 6), 3 (N = 6), 4 (N = 1), and 5 (N = 2). HAS-BLED scores were: 0 (N = 10), 1 (N = 10), and 2 (N = 7). NYHA class distribution was: I (N = 12), II (N = 13), and III (N = 2).

One new thrombotic event occurred during the study period in a 21-year-old patient on dabigatran for persistent right to left shunting through a fenestration created to palliate failing Fontan physiology with protein losing enteropathy: he presented with a DVT after 12.6 months on NOAC therapy. While he reported compliance with

TABLE 1 Demographics

Total number of patients	21 patients
Gender	11 female, 10 male
Median age at therapy initiation (years)	33 (18–50)
Median duration of therapy (months)	13 (1–42)
Total cumulative months of therapy (months)	316
Events during therapy	
Thrombotic or thromboembolic events	1 event
Bleeding events	11 events
Major	0
Nonmajor	0
Minor	11 (experienced by 10 patients; 1 patient experienced 2 unique bleeding events)
Anatomy before therapy initiation	
Double inlet left ventricle	6 patients
Tricuspid atresia	6
Hypoplastic right ventricle	5
Unbalanced atrioventricular septal defect	2
Hypoplastic left heart syndrome	1
Straddling tricuspid valve	1
Fontan type before therapy initiation	
Extracardiac conduit	10 patients
Lateral tunnel	6
Atriopulmonary	4
Other	1
Indication for anticoagulation[a]	
Active arrhythmia	12 patients
Thrombosis	8
Persistent right to left shunt	2
NOAC prescribed[b]	
Apixaban	17 patients
Rivaroxaban	5
Dabigatran	5
Edoxaban	0

CHA_2DS_2-VASc score[b]		HAS-BLED score		NYHA functional classification	
0	6 NIs	0	10 NIs	I	12 NIs
1	6	1	10	II	13
2	6	2	7	III	2
3	6			IV	0
4	1				
5	2				

[a]$N = 22$ because 1 patient was initially on anticoagulation for arrhythmia but continued for thrombosis.
[b]$N = 27$ because 4 patients were stopped and restarted on a NOAC, and 1 patient was stopped and restarted twice, resulting in 27 distinct NOAC Initiations [NIs] across 21 patients.

dabigatran, his PTT was 29.1 seconds (reference range 24.8–34.4 seconds) at the time of diagnosis. At the time of initiation of dabigatran, his CHA_2DS_2-VASc was 1, his HAS-BLED score was 0, and his NYHA class was II. Another patient had progression of Fontan circuit and left atrial thrombus while on therapy with apixaban with a therapeutic anti-Xa level (Anti Xa-Unfractionated Heparin >1.10 units/mL, reference range 0.30-0.70 units/mL). Aspirin was started to help stabilize the clot, but then held 10 days later due to dark, tarry stools. Apixaban was continued and a repeat CT abdomen/pelvis performed a month later suggested resolution of the thrombus, but did not image enough of the heart to definitively rule it out; a transthoracic echocardiogram 2 months later at an outside facility did not document the thrombus. At the time of initiation, his CHA_2DS_2-VASc score was 3 (for congestive heart failure history and thrombosis), his HAS-BLED was 2, and his NYHA class was II. Two additional patients were on concomitant NOAC and aspirin therapy.

TABLE 2 Detailed demographics

	Age at start (years)	Sex	Total time on NOAC (mos.)	Anatomy before Fontan	Fontan type	Indication for anticoagulation	NOAC	Why NOAC stopped/continued?	CHA_2DS_2-VASc	NYHA class	HAS-BLED	Events
1	24	F	1.9	TA	AP	Arrhythmia	Apixaban	Stopped: No arrhythmia recurrence	1	I	1	None
2	33	F	32.0	TA	ECC	Thrombosis	Apixaban	Continued: Stroke history	3	I	1	minBleed
3	38	F	1.0	RVAVC	Other	Arrhythmia	Apixaban	Stopped: No arrhythmia recurrence	4	II	2	None
4	39	F	15.6	TA	ECC	Arrhythmia	Rivaroxaban	Continued: Arrhythmia	1	I	0	None
5	20	M	12.6	HLHS	LT	R to L shunt	Dabigatran*	Stopped: Switch to warfarin (DVT)	1	II	0	minBleed, DVT
6	35[1]	M	2.0	DILV	ECC	Arrhythmia	Apixaban	See footnote 1	0	I	0	None
7	32	M	21.4	DILV	AP	Thrombosis	Apixaban	Continued: PE history	3	II	2	None
8	20	M	1.0	HypoRV	LT	Arrhythmia	Apixaban	Stopped: No arrhythmia recurrence	0	I	0	None
9	50[2]	M	21.8	TA	ECC	Arrhythmia	Apixaban†	See footnote 2	0	I	1	None
10	28	F	1.4	DILV	ECC	Arrhythmia	Apixaban	Stopped: No arrhythmia recurrence ‡	2	II	1	minBleed
11	27	F	6.4	StrdgTV	ECC	Arrhythmia	Apixaban	Stopped: No arrhythmia recurrence	2	II	1	minBleed
12	33[3]	F	30.4	DILV	LT	R to L shunt	Mixed[3]	See footnote 3	2	II	2	minBleed
13	45[4]	F	41.0	DILV	AP	Arrhythmia	Mixed[4]*	See footnote 4	2	III	2	minBleed
14	28	F	41.1	HypoRV	ECC	Thrombosis	Dabigatran	Continued: DVT history	5	II	0	minBleed
15	45	M	1.0	HypoRV	AP	Arrhythmia	Apixaban*	Stopped: Lost to follow-up	1	II	0	None
16	18	F	14.8	HypoRV	ECC	Thrombosis	Rivaroxaban*†	Continued: RV thrombus history	3	I	0	minBleed
17	28[5]	M	42.3	TA	LT	Mixed[5]	Mixed[5]	See footnote 5	1	II	0	minBleed
18	28	M	19.1	DILV	ECC	Thrombosis	Rivaroxaban	Continued: Arrhythmia	5	II	1	None
19	36	M	1.7	HypoRV	ECC	Thrombosis	Apixaban†	Stopped: Unable to afford NOAC	3	II	2	minBleed
20	35	M	5.5	Lg I/O VSD	LT	Arrhythmia	Rivaroxaban	Stopped: Therapy complete	0	I	1	None
21	34	F	1.6	TA	LT	Thrombosis	Apixaban	Continued: PE history	1	I	0	None

Abbreviations: TA, tricuspid atresia; RVAVC, right ventricle dominant atrioventricular canal defect; HLHS, hypoplastic left heart syndrome; DILV, double inlet left ventricle; HypoRV, hypoplastic right ventricle; StrdgTV, straddling tricuspid valve; Lg I/O VSD, large inlet/outlet ventricular septal defect; AP, atriopulmonary; ECC, extracardiac conduit; LT, lateral tunnel; R to L, right to left; PE, pulmonary embolism; DVT, deep vein thrombosis; RV, right ventricle; minBleed, minor bleed.

[1]Initiated on apixaban for thromboprophylaxis following cardioversion for IART twice. Arrhythmia was infrequent, so switched to aspirin both times.

[2]Initiated on apixaban for thromboprophylaxis following cardioversion for IART twice. Due to IART frequency, remained on apixaban after second cardioversion.

[3]Initially on coumadin for history of a right to left shunt; switched to dabigatran for labile INR. Changed to apixaban after complaints of bruising. Died after out of hospital cardiac arrest.

[4]Initially on coumadin for frequent IART; switched to dabigatran for labile INR. Switched to reduced dose apixaban due to AKI.

[5]Initially on dabigatran for thromboprophylaxis following cardioversion for IART. Switched to aspirin once therapy was completed. He later had a stroke and was initially on rivaroxaban, but switched to apixaban.

*Nonstandard (reduced) dose.

†Cotreated with aspirin 81 mg daily.

‡Stopped because of pregnancy, not restarted because arrhythmia had not recurred frequently enough postpartum.

There were no major or nonmajor bleeding events, but 10 patients experienced minor bleeding events with 1 patient experiencing 2 episodes of minor bleeding, for a total of 11 unique minor bleeding events. The bleeding events were intermittent, rare hemorrhoid bleeding (N = 3), easy bruising (N = 3), gastrointestinal bleeding related to a site of biliary tree stenting (N = 1), heavy menses (N = 1), and gum bleeding (N = 1). An additional patient had minor bleeding during two different episodes. The final minor bleed patient was initiated on NOAC therapy twice: she complained of one episode of "spitting up blood" during her first round of therapy, then subsequently complained of intermittent melena during her second round of therapy. Esophagoduodenoscopy and colonoscopy showed Grade I esophageal varices, moderate portal hypertensive gastropathy, and a tubular adenoma.

Using a logistic regression model, the odds ratio for patients with an elevated HAS-BLED score (≥1) having a bleed compared with patients with a HAS-BLED score of 0 was 1.05 (95% CI: 0.21–5.16). By contrast, using the same analysis, the odds ratio for patients with an elevated NYHA class (≥II) having a bleed was significantly higher than patients with a NYHA class of I (OR = 7.5, 95% CI: 1.20–47.04).

One death occurred during the study period. A 35-year-old female with a fenestrated lateral tunnel Fontan and failing Fontan physiology with protein losing enteropathy suffered irreversible multiorgan system failure following an unwitnessed, out of hospital arrest. Her original indication for anticoagulation was right to left shunting across her fenestration. She had labile INRs and preferred NOAC therapy. She was on dabigatran for 30 months prior to her death, during which time she reported easy bruising which improved after switching to apixaban. Autopsy was not performed.

Ten patients remain on active NOAC therapy due to ongoing arrhythmia (N = 4), a history of stroke (N = 2), history of pulmonary embolism (N = 2), history of DVT (N = 1), and history of right ventricle thrombus (N = 1). An eleventh patient with ongoing arrhythmia was lost to follow-up.

4 | DISCUSSION

This study reports the largest single center experience in current literature of NOAC therapy in adult Fontan patients. The next largest studies are three prospective, observational studies: one that includes 11 Fontan patients, a second with 5 Fontan patients, and the last with 3 Fontan patients.[16,17,21] A search of pubmed.gov only identified two additional case reports on the topic.[20,26] In aggregate, only one of the 21 patients experienced an adverse bleeding event and only 1 patient, in the case report by Pinto et al, experienced a lateral tunnel thrombus on appropriate dosing of apixaban following ablation of an atrial arrhythmia. In our study, 21 patients over a total of 316 cumulative months tolerated NOAC therapy with 1 new thrombotic event, no major or nonmajor bleeding events, and 10 patients experiencing 11 unique minor bleeding events.

Notably, one patient started on NOAC therapy for treatment of a clot experienced clot expansion within 2 weeks of NOAC initiation, though imaging ultimately showed resolution in the following months. We would typically expect the thrombus to decrease in size within 2 weeks, based on case reports showing that intraatrial thrombi, in the setting of atrial fibrillation, can resolve within 2–3 weeks following apixaban initiation.[27,28] However, as many as 4% of patients can have left atrial thrombus even after 4 weeks of NOAC therapy. Similar rates exist even with warfarin therapy.[29] Thus, we do not consider the initial expansion an incidence of treatment failure.

The CHA_2DS_2-VASc score in our group was low; this score is recommended to assess annual stroke risk and guide the antiplatelet versus anticoagulation therapy decision in noncongenital patients with atrial fibrillation and/or atrial flutter.[8,9] This likely reflects the fact that, in general, adult Fontan patients are younger and have a lower incidence of systemic hypertension, peripheral vascular disease, and/or diabetes. However, in considering the need for anticoagulation in adult Fontan patients, it is important to keep in mind that in patients with congenital heart disease, the thromboembolic risk is estimated to be 10–100 times higher than aged matched controls.[30] As others have suggested, the incorporation of congenital heart disease severity into a risk assessment tool may better help guide the decision about therapy in the congenital population.[21,31]

The overall HAS-BLED score was also low. This score helps identify noncongenital patients with atrial fibrillation/atrial flutter at risk for bleeding on warfarin[32] or NOACs.[33] It also helps identify modifiable risk factors to mitigate bleeding risk. In contrast to the CHA_2DS_2-VASc score, this score considers issues common in adult Fontan patients including renal disease, liver disease, and lability of the INR. In patients with congenital heart disease and atrial arrhythmia, the HAS-BLED score has been independently associated with major bleeding.[31] In our study, HAS-BLED scores were not predictive of minor bleeding events.

Worse NYHA class was associated with a higher risk of minor bleeding in our patient population, with a statistically significant *P* value; however, the broad 95% confidence interval diminishes the ability to draw a confident conclusion. Nevertheless, this would suggest that in the adult Fontan population, functional measure of cardiac function can help identify patients at risk for bleeding, and may serve as a reasonable addition to a risk assessment tool. This finding may be due to liver and/or spleen dysfunction secondary to heart failure in a single ventricle circulation, or it may simply be due to polypharmacy.

Notably, two patients were on NOAC therapy after undergoing surgery or procedure. One patient was on apixaban for 2 months following Fontan conversion surgery including a surgical Maze procedure, and had no evidence of pericardial effusion on predischarge or subsequent serial echocardiograms during pregnancy. Another patient tolerated 1 month of apixaban therapy following ablation of IART facilitated by trans-Fontan baffle puncture. Neither patient suffered major bleeding in the pericardial space, a risk suggested in the RE-ALIGN study in which non-CHD patients who underwent mechanical valve replacement experienced major bleeding in the pericardial space more commonly if on dabigatran versus warfarin.[34,35] While this is encouraging, further work is needed to establish if NOAC therapy is advisable specifically in the postsurgical or postablative state.

The findings in this study suggest that NOACs, in the short term, may be a viable alternative to warfarin or aspirin for the prevention or

treatment of thrombosis and thromboembolism in adult Fontan patients. Our work is limited by the retrospective nature of our study as well as the smaller patient population. Additionally, we do not typically screen asymptomatic patients for thrombus and so our rate of "silent" thrombosis may be higher. The study period is relatively short term, and so we cannot make any conclusions regarding the use of NOACs lifelong. Finally, we do not routinely use either laboratory tests or questionnaires to assess the compliance of the patients with NOAC therapy. Further work with a larger number of patients and longer follow up is necessary; such work is forthcoming with ongoing studies such as the International Society for Adult Congenital Heart Disease's NOTE registry.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors contributed to analysis, drafting, revision, and approval.
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