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REVIEW

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Non-vitamin K antagonist oral anticoagulants in adults with congenital heart disease

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Abstract

Despite an improved survival rate, cardiovascular accidents including thromboembolic events are a common cause of death in adults with congenital heart disease (CHD). Therefore, many adult patients with CHD require long-term oral anticoagulants depending on disease complexity, atrial tachyarrhythmia, residual intracardiac shunt, ventricular dysfunction, and the presence of a prosthetic valve. Although prevention of stroke and pulmonary embolism has traditionally been managed with vitamin K antagonists (VKA), recent guidelines suggest the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with adult CHD presenting with atrial fibrillation (AF), stroke, or pulmonary embolism. NOACs are an efficient alternative to VKA with reduced bleeding propensity, relatively low dietary and drug interactions, and the potential to eliminate the need for international normalized ratio monitoring in patients with nonvalvular AF. Recently, several multicenter studies reported the indication for thromboprophylaxis and the potential role of NOACs in adult CHD patients. In this review, we aim to assess the efficacy and safety of NOACs in adult CHD patients and to pursue adequate anticoagulation strategies in this special population.

Keywords: Anticoagulants, Adult congenital heart disease

Introduction

With improvements in surgical techniques and perioperative care, mortality rates of adult patients with congenital heart disease (CHD) have been constantly declining. Despite an improved survival, adult patients with CHD are at a higher risk for thromboembolic complications, such as stroke, than the general population [1–3].

The cause of thromboembolic events is multifactorial and associated with the complexity of CHD, high incidence rates of atrial tachyarrhythmias, residual intracardiac shunt, valvular steno-insufficiency, ventricular dysfunction, and the presence of prosthetic valves and materials [3–6]. The estimated risk of atrial fibrillation (AF) in CHD is 22 times higher than that in the general population, and patients with conotruncal defects are at the highest risk [7]. Although prevention of stroke and pulmonary embolism has traditionally been managed with vitamin K antagonists (VKA), such as warfarin, recent guidelines suggest the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with adult CHD presenting with AF, stroke, or pulmonary embolism [8, 9]. NOACs are an efficient alternative to VKA with reduced bleeding propensity, relatively low dietary and drug interactions and the potential to eliminate the need for international normalized ratio (INR) monitoring in patients with nonvalvular AF. Recently, several multicenter studies reported the indication for thromboprophylaxis and the potential role of NOACs in adult patients with CHD [10–14]. The aim of this review was to assess the efficacy and safety of NOAC in adult CHD

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and to pursue adequate anticoagulation strategies in this special population.

Action mechanism of NOAC

The coagulation cascade of NOAC is initiated from tissue factor/factor VIIa and propagated with factor IX, X, II and finally completed with fibrin formation. NOAC binds directly to the key proteins of the clotting cascade, leading to the inhibition of fibrin formation. Rivaroxaban, apixaban, and edoxaban prevent the conversion of prothrombin to thrombin (factor IIa) by inhibiting coagulation factor Xa. Dabigatran prevents the conversion of fibrinogen to fibrin by inhibiting factor IIa (thrombin) [15].

Indications for anticoagulation in adult CHD

Specific indications for anticoagulation in adult CHD are summarized in Table 1.

The common atrial arrhythmia in adult patients with CHD is intra-atrial reentrant tachycardia (IART) or AF. Among adults with CHD, those with atrial tachyarrhythmias have a twofold higher risk of stroke [3]. Previously, there was limited evidence for the use of anticoagulation in adult CHD. The Pediatric and Congenital Electrophysiology Society and Heart Rhythm Society (PACES/HRS) Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adults with Congenital Heart Disease recommended long-term anticoagulation in patients with recurrent or sustained IART, or AF in the presence of moderate or complex CHD [8].

Anticoagulation has consistently been recommended for Fontan patients with atrial arrhythmias, fenestration, atrial thrombus, or a previous thromboembolic event [16]. Many patients who had an atriopulmonary Fontan operation with atrial flow stasis have an increased thrombotic risk that might support long-term anticoagulation (class IIb, level of evidence C) [17].

Patients with Eisenmenger physiology need a complex clinical decision regarding the choice of anticoagulants. The mechanism of increased thromboembolic risk is not clear, but it might be related to ventricular dysfunction and decreased pulmonary blood flow [18]. Although this population has a significantly increased risk of pulmonary hypertension and pulmonary artery thrombosis, patients also have a potential risk of pulmonary hemorrhage and hemoptysis.

Intracardiac shunt closure is generally recommended before intracardiac lead or other material implantation. However, if the shunt is not closed, oral anticoagulation therapy should be considered with respect to the increased thromboembolic risk. Although a NOACs are not considered and contraindicated in this setting, VKAs are mostly applied in the current experience [19].

Adult CHD patients might have prostatic valve replacement. In the presence of a mechanical heart valve, cardiovascular thromboembolic events can develop because of abnormal intracardiac blood flow conditions. Therefore, lifelong anticoagulation with VKAs is required in this setting.

Pregnancy is a relatively hypercoagulable state, increasing the risk of thromboembolic complications in the adults with CHD. In patients with mechanical valve, a low molecular weight heparin (LMWH) with strict factor Xa monitoring during the first trimester is usually recommended. LMWH is generally considered to be safe in pregnancy. Before delivery, switching to intravenous unfractionated heparin is recommended with a mechanical heart valve in a hospital setting.

Table 1 Indication for anticoagulation in adult congenital heart disease

Atrial tachyarrhythmia
Fontan physiology
Eisenmenger syndrome
Intracardiac right to left shunt
History of thromboembolic event
Prostatic heart valve, especially mechanical valve
Pregnancy
Moderate/ complex congenital heart disease
CHA2-DS2-VASc score ≥ 2

Risk stratification for thromboembolic prophylaxis

Regarding anticoagulation for thromboembolic prophylaxis in the general population, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65–74 years), and **S**ex (Female) (CHA2DS2-VASc) scoring system help guide clinical risk stratification. And **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), and **D**rugs/Alcohol Concomitantly (HAS-BLED) scores were used for predicting major bleeding events. However, there has been no specific validation of the CHA2DS2-VASc scores and HAS-BLED scores in the adult CHD population. The first data of NOACs in adult CHD demonstrated that sixty-nine percent of patients had CHA2DS2-VASc scores of 0 or 1, and no patients suffered from thromboembolic events or major bleeding during the follow-up period [10]. Thus, NOACs might be a safe alternative to VKA in low risk adult CHD.

According to several recent multicenter studies, NOAC therapy in adult patients with CHD was also assessed according to the CHA2DS2-VASc score regardless of AF or atrial flutter [12–14]. Adult patients with CHD have

many heterogeneous conditions that can lead to stroke in addition to AF, so the CHA2DS2-VASc score was used to evaluate the indications for oral anticoagulant therapy. To date, there are no clear guidelines. However, it should be considered that adult patients with moderate or complex forms of CHD may be predisposed to thromboembolic conditions even in the absence of atrial tachyarrhythmias; thus, selected patients might benefit from NOAC therapy to prevent stroke events [8, 9].

Evidence of NOAC related to adult CHD

Pujol et al. [10] initially reported the use of NOACs in 75 patients with adult CHD. The most common CHD was mild CHD, such as pre-tricuspid shunts ($n=31$, 41%), and 16 patients (21%) had complex CHD including 3 Fontan patients. The CHA2DS2-VASc score was ≥ 2 in 23 (31%) patients, and 9 (12%) had a HAS-BLED score ≥ 2. The administered NOACs were rivaroxaban in 55 patients, apixaban in 13 and dabigatran in 7 patients. The indications for NOACs were thromboembolic prophylaxis in atrial arrhythmias ($n=57$), stroke/transient ischemic attacks ($n=11$), deep vein thrombosis ($n=4$), pulmonary embolism ($n=1$), and atrial thrombi ($n=3$). They reported neither thrombotic or major bleeding events nor major side effects in this first NOAC study.

Prospective databases, such as the non-vitamin K antagonist oral anticoagulants for thromboembolic prevention (NOTE) registry (prospective international registry of efficacy and safety of non-vitamin K antagonist oral anticoagulants for thromboembolic prevention in patients with CHD) have been established since 2014 to pursue understanding of NOACs in the adult patients with CHD. Based on the NOTE registry, Yang et al. [11] reported the prospective data of NOACs for atrial arrhythmias. Among a total of 99 patients, 54 patients transitioned from VKA to NOACs. The moderate and severe forms of CHD were 55% and 29%, respectively. The most commonly prescribed NOAC was apixaban (62%). Regarding safety during the first 30-day follow-up after the initiation of NOACs, 8 minor adverse events (5 minor bleeding events, 3 side-effects, and 1 drop-out due to minor bleeding) occurred within 30 days after the transition. There was no thromboembolic event nor major bleeding in both groups during the first 30 days. Recently, several multicenter studies of NOACs in adult patients with CHD have been published. Table 2 shows the characteristics of the included studies of NOACs vs. VKA in adult CHD.

Pujol et al. [12] retrospectively reported the use of NOACs in 215 adult CHD patients. The mean age was 48.4 ± 15.4 years and the mean follow up was 15.8 ± 15.8 months. In this study, 44% of the patients had complex CHD, including 12 patients (5.6%) who underwent a Fontan operation. Among the total patients, 49.3% had a CHA2DS2 –VASc score ≥ 2, and 87.5% had a HAS–BLED score ≤ 2. The most commonly used NOAC was rivaroxaban (54.2%), followed by apixaban (32.2%), dabigatran (9.3%), and edoxaban (3.7%). In 67% of the patients ($n=143$), the primary indication for anticoagulation was atrial arrhythmias (AF 45%, atrial flutter 21%), 43% received a NOAC for secondary thromboprophylaxis and 5.6% for primary thromboprophylaxis in Fontan circulation. During follow-up, major events were reported in 11 patients (9 major bleeding events, 2 thromboembolic events). The annual risks for major bleeding and thromboembolic events were 3.1% and 0.7%/patient/year, respectively. In the multivariate analysis, renal disease was an independent predictor for major bleeding (HR 6.13, 95% CI 1.04–36.27, $p<0.05$).

Yang et al. [13] reported the first international multicenter prospective cohort study based on the NOTE registry assessing the safety and efficacy of NOACs (rivaroxaban 43%; apixaban 39%; dabigatran 12%; edoxaban 7%) in adult CHD patients**.** In a total of 530 patients, the mean age was 47 ± 15 years, and moderate (45%) or complex defects (40%) were predominant. Seventy-four (14%) patients had a Fontan circulation. A CHA2DS2 -VASc sore ≥ 2 was present in 46% and an HAS-BLED score ≤ 2 in 95%. Indications for NOACs included atrial arrhythmias (91%, $n=481$; AF 58%, atrial flutter 40% and atrial tachycardia 2%), primary (3%, $n=17$), and secondary thromboprophylaxis (6%, $n=32$). Among a total of 530 patients, 150 patients (28%) were previously on VKA therapy. Over a median follow-up of 1.0 [IQR 0.0–2.0] year, the thromboembolic event rate was 1.0% [95% CI 0.4–2.0] ($n=6$) per year, with a 1.1% [95% CI 0.5–2.2] ($n=7$) annualized rate of major bleeding. All thromboembolic events occurred in patients with moderate or severe forms of CHD, and 50% ($n=3$) were in Fontan patients. Among patients with major bleeding, 43% ($n=3$) occurred in Fontan circulation.

While treated with VKA ($n=150$), 12 patients experienced thromboembolic events, accounting for 1.2% per year [95% CI 0.6–2.1], and 9 had major bleeding events, accounting for 1.1% per year [95% CI 0.5–1.9]) during a mean follow-up of 3.8 [IQR 1.1–8.6] years.

Freisinger et al. [14] retrospectively evaluated clinical outcomes in unselected adult patients with CHD on anticoagulation treatment and the long-term safety and effectiveness of NOACs compared with VKA in Germany. Among a total of 6504 adult patients with CHD with a first anticoagulation prescription between 2010 and 2016, 4,851 were initially prescribed VKA, and 1,653 initially received NOACs. The median age of NOACs was 70 years (range, 57–78 years). In the NOAC prescription group, rivaroxaban (59.9%) was most commonly

Table 2 Summary of the use of NOACs versus VKA in adult congenital heart disease

Author	Total patients, *n*	Age, years Mean ± SD	Severity of CHD, %			Indication for anticoagulation, %			Thromboembolic events, % per year	Bleeding events, % per year
			Simple	Moderate	Complex	AA	Primary TP	Secondary TP		
NOACs therapy										
Pujol et al. [10]										
NOACs	75	50 ± 13	45	34	21	76	0	24	0	0
Pujol et al. [12]										
NOACs	215	48.4 ± 15.4	32.1	23.7	44.2	66.8	5.6	42.9	0.7	3.1
NOACs vs. VKA										
Yang et al. [11]										
NOACs	54	47.3 (38–61)	15	52	33	NA	NA	23	NA	NA
VKA	45	52.0 (37–61)	16	60	24	NA	NA	17	NA	NA
Yang et al. [13]										
NOACs	530	47.0 ± 15.0	14.9	45.1	40.0	90.8	3.2	6.0	1.0	1.1
VKA	150	47.0 ± 16.0	14.6	38.6	46.6	NA	NA	NA	1.2	1.1
Freisnger et al. [14]										
NOACs	1653	Median 70 (range 57–78)	68.3	24.2	7.5	72.7	NA	NA	2.8	11.7
VKA	4851	Median 69 (range 54–76)	63.8	23.1	12.9	63.2	NA	NA	3.7	6.7

AA, atrial arrhythmias; *CHD*, congenital heart disease; *NOACs*, non-vitamin K antagonist oral anticoagulants; *TP*, thromboprophylaxis; *VKA*, vitamin K antagonist

used, followed by apixaban (23.2%), dabigatran (14.2%), and edoxaban (2.7%). The severity of CHD was 68% simple lesions, 24% moderate complexity, and 8% complex lesions. The median CHA2DS2-VASc score was 4 (range 2–5) in both groups.

In this nationwide analysis, the result was disappointing compared to two previous multicenter studies. NOACs had higher thromboembolic (3.8% vs. 2.8%), major adverse cardiovascular (7.8% vs. 6.0%), bleeding (11.7% vs. 9.0%), and all-cause mortality (4.0% vs. 2.8%; all $P < 0.05$) rates after 1 year of therapy than VKA. This might be due to the relatively older age group and higher CHA2DS2-VASc score compared to other studies. Adult patients with CHD taking oral anticoagulant therapy are relatively younger than the general population. Therefore, there were insufficient safety and efficacy data in a young cohort with a lower CHA2DS2-VASc score.

As several studies have shown, the predominant indication for NOACs in adult patients with CHD remains atrial arrhythmias. IART and AF are the most common presenting tachyarrhythmias. In adult CHD patients, AF is associated with considerable morbidity over the age of 50 [9, 20–22]. NOACs can be prescribed in patients with simple defects**.** In addition, their use may also be considered in moderate or complex CHD patients [12–14].

NOAC in Fontan physiology

Georgekutty et al. [23] reported the first retrospective data of NOACs in Fontan patients in a single center study**.** In a total of 21 patients, 76% had a total cavopulmonary connection**.** The Fontan patients were prescribed a NOAC either for primary or secondary thromboprophylaxis (apixaban 63%, dabigatran 18.5%, rivaroxaban 18.5%). The indications for NOAC were atrial arrhythmias (57%, $n = 12$), previous thrombotic events (33%, $n = 8$), and intracardiac right to left shunts (9.7%, $n = 2$). CHA2DS2-VASc score ≥ 2 was present in 43% of patients, while all patients had a HAS-BLED score ≤ 2. All patients were treated with warfarin before NOAC initiation. The main reasons for the change to NOACs were either patient/provider preference ($n = 11$), labile INR ($n = 5$), initiation of therapy elsewhere ($n = 3$), and history of poor clinical follow-up ($n = 2$). During a cumulative 316 months of therapy, one new thrombotic event occurred in a failing Fontan patient. No major bleeding events occurred, but 10 patients experienced minor bleeding. One patient died from multiorgan failure out of hospital.

Yang et al. [24] reported the prospective NOAC data in Fontan patients using the NOTE registry. In this study, 74 patients with a Fontan circulation using NOACs (anabaptist, $n = 27$; dabigatran, $n = 7$; edoxaban, $n = 4$; rivaroxaban, $n = 36$) were included. The mean age was 32 ± 10 years. The CHA2DS2-VASc score was ≥ 1 in 49 patients (66%) and only 2 patients had a high HAS-BLED score. During a median follow-up of 1.2 years, 3 thromboembolic events and 3 major bleeding events occurred in five atriopulmonary Fontan and one total cavopulmonary connection Fontan patients. Fifteen patients experienced minor bleeding**.** In Fontan patients with VKA ($n = 37$) prior to NOAC use, the annual incidence of thromboembolic events and major bleeding were 2.4% (95% CI 0.4- 7.4) ($n = 2$) and 1.2% (95% CI 0.7–5.1) ($n = 1$), respectively.

Special considerations in NOAC use

Of the two types of prosthetic valves, the mechanical heart valve is more durable and is thus preferentially implanted in patients with a long life expectancy. However, mechanical valves are much more thrombogenic than bioprostheses, requiring lifelong anticoagulation with VKA to avoid subclinical thrombosis. In contrast, bioprosthetic heart valves do not require lifelong anticoagulation with VKA [25, 26]. Oral anticoagulation using a VKA should be considered for the first 3 months after surgical implantation of a bioprosthetic valve in the absence of AF, venous thromboembolism, hypercoagulable state or, with a lesser degree of evidence, severely impaired LV dysfunction (ejection fraction < 35%) [25]. In adult CHD with a bioprostatic valve, lifelong VKA therapy is not considered in the absence of risk factors related to the stroke event. However, repeated replacement of the bioprosthetic valve may be necessary due to valve degeneration and the need for additional surgical procedure. Therefore, single antiplatelet therapy or oral anticoagulation therapy could be considered. The recent results showed that NOACs could be safely used in bioprosthetic heart valves with adult patients with CHD during short-term follow-up [13].

NOAC has a contraindication during pregnancy and is not allowed to be used [27–29]. Women of reproductive age with CHD taking a NOAC should be counseled about the need for effective contraception. If pregnancy is planned, an anticoagulation strategy should replace the NOAC with LMWH. LMWH does not cross the placenta and is therefore not associated with embryopathy. However, LMWH is associated with higher rates of thromboembolic complications in pregnant women, especially with mechanical valves. Therefore, close monitoring of anti-Xa levels is necessary.

NOAC application and drug interactions

All NOACs are partially eliminated by the kidney (dabigatran 80%, edoxaban 50%, rivaroxaban 35%, apixaban 27%) and should be dose adjusted. In practical use of NOAC, the dose of rivaroxaban, edoxaban, and

apixaban should be adjusted to creatinine clearance. A large retrospective study of patients with AF who were receiving dialysis suggests that apixaban might be associated with fewer major bleeds and a similar risk of stroke or systemic embolism compared with VKA [30].

Low body weight (< 60 kg) patients taking NOACs have a fourfold higher risk of major bleeding than normal weight patients. The doses of apixaban and edoxaban should be adjusted to body weight [21].

Potential drug interactions with NOACs must be considered. In patients taking amiodarone, phenytoin, and fluconazole in combination with a NOAC, the major bleeding risk is increased [31]. Amiodarone, verapamil, and diltiazem increase the serum concentrations of dabigatran, apixaban and edoxaban, via P glycoprotein competition**.** In addition, verapamil and diltiazem are cytochrome P450 3A4 (CYP3A4) inhibitors, resulting in a substantial increase in NOAC levels [27]. Regarding drug interaction with NOACs, careful consideration is especially required when using antiepileptic drugs.

Conclusion

Recent international multicenter studies demonstrated that NOACs might be considered in selected indications for adult patients with CHD. However, these patients are a heterogeneous population, with often complex pathophysiology. NOAC treatment decisions have to be based on the individual specific factors as well the individual risk of stroke and bleeding, especially in patients with cyanotic CHD and single ventricles in Fontan physiology.

Therefore, further data and specifically prospective research will be needed in this population.

Abbreviations

AF: Atrial fibrillation; CHD: Congenital heart disease; NOACs: Non-vitamin K antagonist oral anticoagulants; VKA: Vitamin K antagonists; INR: International normalized ratio; IART: Intra-atrial reentrant tachycardia; LMWH: Low molecular weight heparin.

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Author carried out literature search and analysis, drafted the manuscript and critically revised the manuscript. Author read and approved the final manuscript.

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