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Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study

Yang, H ; Bouma, B J ; Dimopoulos, K ; Khairy, P ; Ladouceur, M ; Niwa, K ; Greutmann, M ; et al

Abstract: **BACKGROUND** Current guidelines consider vitamin K antagonists (VKA) the oral anticoagulant agents of choice in adults with atrial arrhythmias (AA) and moderate or complex forms of congenital heart disease, significant valvular lesions, or bioprosthetic valves, pending safety data on non-VKA oral anticoagulants (NOACs). Therefore, the international NOTE registry was initiated to assess safety, change in adherence and quality of life (QoL) associated with NOACs in adults with congenital heart disease (ACHD). **METHODS** An international multicenter prospective study of NOACs in ACHD was established. Follow-up occurred at 6 months and yearly thereafter. Primary endpoints were thromboembolism and major bleeding. Secondary endpoints included minor bleeding, change in therapy adherence (80% medication refill rate, 6 out of 8 on Morisky-8 questionnaire) and QoL (SF-36 questionnaire). **RESULTS** In total, 530 ACHD patients (mean age 47 SD 15 years; 55% male) with predominantly moderate or complex defects (85%), significant valvular lesions (46%) and/or bioprosthetic valves (11%) using NOACs (rivaroxaban 43%; apixaban 39%; dabigatran 12%; edoxaban 7%) were enrolled. The most common indication was AA (91%). Over a median follow-up of 1.0 [IQR 0.0-2.0] year, thromboembolic event rate was 1.0% [95%CI 0.4-2.0] (n = 6) per year, with 1.1% [95%CI 0.5-2.2] (n = 7) annualized rate of major bleeding and 6.3% [95%CI 4.5-8.5] (n = 37) annualized rate of minor bleeding. Adherence was sufficient during 2 years follow-up in 80-93% of patients. At 1-year follow-up, among the subset of previous VKA-users who completed the survey (n = 33), QoL improved in 6 out of 8 domains (p = 0.05). **CONCLUSIONS** Initial results from our worldwide prospective study suggest that NOACs are safe and may be effective for thromboembolic prevention in adults with heterogeneous forms of congenital heart disease.

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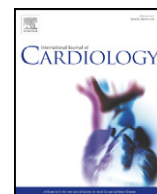
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Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study☆

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ABSTRACT

Background: Current guidelines consider vitamin K antagonists (VKA) the oral anticoagulant agents of choice in adults with atrial arrhythmias (AA) and moderate or complex forms of congenital heart disease, significant valvular lesions, or bioprosthetic valves, pending safety data on non-VKA oral anticoagulants (NOACs). Therefore,

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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the international NOTE registry was initiated to assess safety, change in adherence and quality of life (QoL) associated with NOACs in adults with congenital heart disease (ACHD).

Methods: An international multicenter prospective study of NOACs in ACHD was established. Follow-up occurred at 6 months and yearly thereafter. Primary endpoints were thromboembolism and major bleeding. Secondary endpoints included minor bleeding, change in therapy adherence ($\geq 80\%$ medication refill rate, ≥ 6 out of 8 on Morisky-8 questionnaire) and QoL (SF-36 questionnaire).

Results: In total, 530 ACHD patients (mean age 47 SD 15 years; 55% male) with predominantly moderate or complex defects (85%), significant valvular lesions (46%) and/or bioprosthetic valves (11%) using NOACs (rivaroxaban 43%; apixaban 39%; dabigatran 12%; edoxaban 7%) were enrolled. The most common indication was AA (91%). Over a median follow-up of 1.0 [IQR 0.0–2.0] year, thromboembolic event rate was 1.0% [95%CI 0.4–2.0] ($n = 6$) per year, with 1.1% [95%CI 0.5–2.2] ($n = 7$) annualized rate of major bleeding and 6.3% [95%CI 4.5–8.5] ($n = 37$) annualized rate of minor bleeding. Adherence was sufficient during 2 years follow-up in 80–93% of patients. At 1-year follow-up, among the subset of previous VKA-users who completed the survey ($n = 33$), QoL improved in 6 out of 8 domains ($p < 0.05$).

Conclusions: Initial results from our worldwide prospective study suggest that NOACs are safe and may be effective for thromboembolic prevention in adults with heterogeneous forms of congenital heart disease.

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1. Introduction

Despite improved survival, adults with congenital heart disease (ACHD) are at risk for thromboembolic complications including significantly increased stroke rates compared to age- and sex-matched controls [1–3]. The causes for this increased risk of stroke are multifactorial, including high incidence rates of atrial arrhythmias, residual valvular heart disease, residual intracardiac shunts, presence of cyanosis, myocardial scarring and ventricular dysfunction, and use of prosthetic materials for intracardiac repair [4–6]. Consequently, appropriate use of oral antithrombotic drugs to prevent thromboembolism is of paramount importance in this vulnerable patient group.

In Ruff meta-analysis, non-vitamin K antagonist oral anticoagulants (NOACs) had a favourable risk–benefit profile in patients with non-valvular atrial fibrillation, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for vitamin K antagonists (VKA), but increased gastro-intestinal bleeding [7]. Furthermore, NOACs offer an attractive alternatives to VKAs in the young and active ACHD population in whom regular monitoring of the international normalized ratio, dose adjustments, and dietary consistency could adversely impact quality of life and adherence.

However, it is uncertain whether results from other populations are applicable in ACHD patients considering the differences in structural heart disease and pathophysiology for thromboembolic complications [5]. To date, clinical data on the rates of thromboembolism and major bleeding associated with NOACs in ACHD has been scarce, and the available studies are hampered by limited sample sizes and short follow-up periods [8–10]. Therefore, in the absence of large-scale data specific to patients with congenital heart disease, current guidelines for ACHD patients caution against generalizing the results of NOAC trials to the ACHD population beyond those with simple lesions (without bioprosthetic valves or significant valve disease), atrial arrhythmias, and a CHA₂DS₂-VASc score ≥ 2 [11].

In order to address a major knowledge gap regarding the safety and efficacy of NOACs in the ACHD population, we initiated the worldwide prospective NOTE registry (non-vitamin K antagonist oral anticoagulants for thromboembolic prevention in patients with congenital heart disease registry; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02928133) registration NCT02928133) through the International Society for Adult Congenital Heart Disease (ISACHD).

2. Methods

2.1. Study design and participants

Initiated in April 2014, the NOTE registry is an open international prospective observational study with longitudinal follow-up in ACHD patients prescribed NOACs for thromboprophylaxis. Any ACHD patient using NOACs (with an indication to continue for

at least 3 months) was included with the exception of patients with mechanical prosthetic valves or significant mitral stenosis.

2.2. Medical ethics committee and informed consent

The NOTE registry protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee of all participating medical centres. All individual participants provided informed consent in accordance with national and local regulations. Through collaboration ISACHD, patients were recruited from 35 centres in 13 countries (Belgium, Canada, France, Israel, Italy, Japan, Lithuania, Netherlands, Poland, Sweden, Switzerland, United Kingdom, United States of America).

2.3. Inclusion and follow-up

Patients were identified at the participating institutions during clinical counter or by means of national registries. The severity of their cardiac defect was classified according to the classification (simple, moderate or complex) outlined by Task Force 1 of the 23rd Bethesda Conference [12]. The choice of NOAC agent was at the discretion of the treating cardiologist with no protocol-specific recommendation. The inception of the cohort was triggered by prescription of NOACs or the time of first visit or telephone call if the patients were already on NOACs. At inclusion, demographics, pre-defined clinical data including history of anti-thrombotic medication use, history of thromboembolism and bleeding, factors associated with thromboembolism or bleeding, and details on prescription of NOACs were collected. Prior use of VKAs was noted (VKA group), with data collected regarding transitioning to NOAC. Those who did not transition from VKA to NOAC were defined as a VKA-naïve group. Significant valvular abnormalities were defined as any valvular disease classified as moderate or severe. The first follow-up was at 6 months or 1 year and yearly thereafter, coinciding with routine outpatient clinical visits or telephone contacts. At each follow-up, data on the pre-defined end points were conducted and adjudicated by a trained investigator or a site coordinator.

2.4. Data management

We collected patient data in an electronic case report form (eCRF) submitted through a secure website, which is certified for Good Clinical Practice. We assigned all patients with a unique study identifier so that personal identifiable data could be removed at the hospital source, ensuring anonymity and protecting confidentiality. The principle registry coordinator and each site coordinator examined the completeness and accuracy of the eCRFs. The principle registry coordinator as an author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

2.5. Endpoints

The primary efficacy endpoints were thromboembolism (ischemic cerebrovascular accident; iCVA, transient ischemic attack; TIA, systemic or pulmonary embolism or intracardiac thrombus formation). The primary safety endpoint was major bleeding (significant bleeding necessitating hospitalization/interventions ≥ 2 units of packed red blood cells, and/or with a haemoglobin drop ≥ 1.24 mmol/L and/or bleeding that was fatal or occurred in the following critical sites: intra-cranial, intra-spinal, intra-ocular, pericardial, intra-articular, intra-muscular with compartment syndrome) according to the criteria from the International Society on Thrombosis and Haemostasis [13].

Secondary endpoints included minor bleeding events (any bleeding not classified as major bleeding), side-effects, therapy persistence, therapy adherence, quality of life (QoL), and all-cause mortality. Therapy adherence was assessed yearly during follow-up, using a questionnaire (Morisky 8) and interrogation from pharmacists regarding the

quantity of medication collected by the patient during a defined time frame. In accordance with the Morisky 8 questionnaire criteria, sufficient adherence was defined as a score of 6 or higher (range 1 to 8; 8 corresponding to the highest adherence). Using the pharmacy interrogation data, medication refill adherence (MRA) was calculated by dividing the total days for which NOACs were supplied by the number of days of study participation. This value was multiplied by 100 to obtain a percentage adherence rate [14]. We defined sufficient adherence as $\geq 80\%$. QoL in patients was assessed yearly during follow-up by means of the SF-36 questionnaire, with a focus on general functioning in daily life.

2.6. Sample size calculation

To estimate non-inferiority of NOACs compared with VKAs, we performed a sample size estimate based on previously published event rates in ACHD patients with atrial arrhythmias on VKAs, along with the risk ratio associated with NOACs versus VKAs in the general population with atrial arrhythmias [15–17]. The non-inferiority margin for thrombotic events and stroke or systemic embolism was set at +1.5% per year (annual event rate 3.1%) and major bleeding at +2.0% per year (annual event rate 5.9%). The sample size estimation was performed with a power of 0.8 and a one-sided significance level of 0.05. As a result, an estimated 400 patient-years were required to assess the non-inferiority of NOACs compared to VKAs.

2.7. Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Kaplan-Meier survival curves were created to determine event-free survival. For comparison between the NOAC group and the VKA group with the Kaplan-Meier survival curves, we censored the patients at 4 years follow-up in the VKA group, which was the maximum follow-up period of the NOAC group. Incidence rates of the outcomes were calculated using Poisson regression. For time-to-event analyses, subjects who discontinued NOACs or were lost to follow-up were censored at the time of last known NOACs use. In case of a change in QoL or therapy adherence over time, differences were analysed by a Wilcoxon signed rank test or a chi-square test. Results are presented as mean with standard deviation (SD), median with interquartile range (IQR) and incidence rates with 95% confidence intervals (95% CIs). A *p*-value below 0.05 was considered statistically significant. Analyses were performed using R version 3.2.4 (R core team) and SPSS version 23 (IBM).

3. Results

3.1. Baseline characteristics

In total, 530 ACHD using NOACs (rivaroxaban 43%; apixaban 39%; dabigatran 12%; edoxaban 7%) were recruited between April 2014 and August 2018 (mean age 47 SD 15 years; 55% male, Table 1) from 13 countries distributed over Europe, North-America and Asia. The cohort consisted of patients with heterogeneous forms of congenital heart disease classified as complex in 40%, moderate in 45%, and simple in 15% (Fig. 1). At baseline, 56% of patients were not on any anti-thrombotic therapy, 15% were on aspirin, 1% on NOACs, and 28% on VKA (14 with concomitant aspirin use). The large majority of patients (91%, $n = 481$) started NOACs for thromboembolic prophylaxis in the context of atrial arrhythmias (Appendix I). Other indications were primary (3%, $n = 17$) and secondary (6%, $n = 32$) prevention of thromboembolism in the absence of atrial arrhythmias. In all, 54% and 95% of patients had CHA₂DS₂-VASC and HAS-BLED scores ≤ 2 , respectively (per indication, see Appendix I). Overall, 11% had a bioprosthetic valve(s) (aortic valve $n = 6$, pulmonary valve $n = 46$, mitral valve $n = 1$, tricuspid valve $n = 1$, pulmonary and tricuspid valves $n = 3$), 46% had significant valvular abnormalities (pulmonic regurgitation $n = 48$, pulmonic stenosis $n = 17$, aortic regurgitation $n = 43$, aortic stenosis $n = 7$, mitral regurgitation $n = 114$, tricuspid regurgitation $n = 171$, tricuspid stenosis $n = 4$), 8% had pulmonary hypertension and 31% had a history of heart failure defined by clinical signs or low systolic systemic ventricular function by imaging (Table 1). Seventy-four patients (14%) had a Fontan circulation (atriopulmonary connection, $n = 26$; total cavopulmonary connection, $n = 48$) with the following indications for NOACs: 69% atrial arrhythmias, 16% primary and 15% secondary prevention of thromboembolism.

3.2. Prescription pattern of NOACs

Reasons for selecting a specific agent and for prescribing a NOAC over a VKA were reported by 262 physicians. Most physicians selected

NOACs instead of VKAs due to the absence of need for laboratory monitoring of anticoagulation (45%). Other reasons for selection of NOACs over VKA were labile international normalized ratio (INR) (7%), physician preference (6%), potentially reduced risk of intracranial bleeding (3%), bleeding complication under VKA (2%), intolerance of VKA (1%) and unknown (36%). Reasons for physicians to choose a specific type of NOAC ($n = 53$) were once daily regimen (22%), physician preference (19%), reported lowest bleeding risk (15%), gastro-intestinal symptoms (13%) and side-effects with other NOAC (11%).

3.3. Primary endpoints in NOAC cohort

The total duration of follow-up was 613 patient-years with a median duration of 1.0 [IQR 0.0–2.0] year. During follow-up, 6 patients (1.1%) experienced thromboembolic events (pulmonary embolism $n = 2$; intracardiac thrombus $n = 2$; deep vein thrombosis $n = 1$; ischemic stroke $n = 1$) and 7 patients (1.3%) had major bleeding events (menorrhagia $n = 4$; gastro-intestinal bleeding $n = 2$; hematuria $n = 1$) (Fig. 2a). The rate of thromboembolic events ($n = 6$) was 1.0% [95%CI 0.4–2.0] per year. The rate of major bleeding ($n = 7$) was 1.1% [95%CI 0.5–2.2] per year. None of these events was related to interventional or surgical procedures and all were observed in patients with moderate to complex defects (Table 2). Out of 6 patients with thromboembolic events, 4 patients switched to VKA and 2 remained on the same NOACs. In 7 patients with major bleeding, 5 patients were switched to VKA, 1 switched to another NOAC and 1 remained on the same NOAC. In total, 37 patients experienced minor bleeds translating into an annual rate of 6.3% [95%CI 4.5–8.5] per year (Appendix II). A total of 57 patients

Table 1

Baseline characteristics of ACHD patients using NOACs.

	All ($n = 530$)	Previous VKA ($n = 150$)
Age at inclusion, y	47 SD15	47 SD16
Male, n (%)	289 (55)	74 (49)
Severity of congenital heart defect, n (%)		
Simple	79 (15)	22 (15)
Moderate	239 (45)	58 (39)
Complex	212 (40)	70 (47)
Defect repaired, n (%)	421 (79)	125 (87)
Fontan circulation, n (%)	74 (14)	37 (25)
Bioprosthetic valves, n (%)	57 (11)	14 (9)
Significant valvular lesion, n (%)	243 (46)	65 (43)
Median CHA ₂ DS ₂ -VASC	1 [1–3]	2 [1–3]
Cardiovascular history, n (%)		
Stroke or TIA	54 (10)	17 (11)
Pulmonary embolism	22 (4)	10 (7)
Deep venous thrombosis	9 (2)	2 (1)
Intracardiac thrombus	11 (2)	4 (3)
Systemic embolism	9 (2)	3 (2)
Myocardial infarction	2 (0.5)	1 (1)
Other type of thrombus	4 (1)	2 (1)
Heart failure*	163 (31)	63 (42)
Hypertension	121 (23)	36 (24)
Diabetes mellitus	49 (9)	14 (9)
Median HASBLED	0 [0–1]	0 [0–1]
History of major bleeding, n (%)	17 (3)	11 (7)

Values are presented as mean (standard deviation, SD), median (interquartile range, IQR) or counts (%).

Abbreviations: VKA, vitamin K antagonist; CHA₂DS₂-VASC, stroke risk factor scoring system in which 1 point is given for heart failure, hypertension, age 64–74 years, diabetes mellitus, history of vascular disease, female sex and 2 points are given for age ≥ 75 years, history of stroke/TIA/thromboembolism; HASBLED, bleeding risk factor scoring system in which 1 point is given for uncontrolled hypertension, abnormal renal or liver function, history of stroke or bleeding, labile international normalized ratio, age ≥ 65 years, use of nonsteroidal anti-inflammatory drug or antiplatelet agents or alcohol; TIA, transient ischemic attack; ASA, aspirin or ascal.

* Heart failure is defined as the presence of signs and symptoms of either right (elevated central venous pressure, hepatomegaly, dependent oedema) or left ventricular failure (exertional dyspnoea, cough, fatigue, orthopnoea, paroxysmal nocturnal dyspnoea, cardiac enlargement, crackles, gallop rhythm, pulmonary venous congestion) or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction.

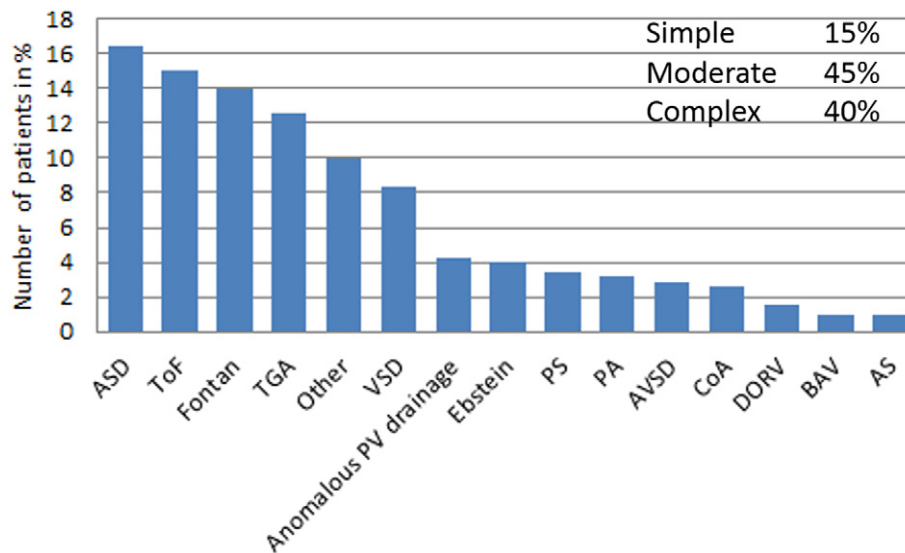


Fig. 1. Congenital heart defect distribution of ACHD patients using NOACs ($n = 530$). Abbreviations: ToF—tetralogy of Fallot; TGA—transposition of great arteries; ASD—atrial septal defect; PS—pulmonary stenosis; TA—tricuspid atresia; Anomalous PV drainage—anomalous pulmonary venous drainage; PA—pulmonary atresia; AVSD—atrioventricular septal defect; CoA—coarctation of aorta; DORV—double outlet right ventricle; VSD—ventricle septal defect; Other—congenital defects with $n < 5$ (tricuspid atresia, hypertrophic cardiomyopathy, Marfan syndrome, congenitally corrected transposition of the great arteries, dextrocardia, atrial septum abnormality, mitral valvar abnormality, tricuspid valvar abnormality, cor triatriatum, coronary sinus abnormality, double chambered right ventricle, double outlet left ventricle, double inlet left ventricle, Holt Oran syndrome, patent arterial duct, subaortic membrane, truncus arteriosus, White-Bland-Garland syndrome).

(10.7%) permanently ceased NOACs during follow-up. Reasons for cessation are illustrated in Appendix III.

3.4. Primary endpoints in historical VKA cohort

Among the 530 patients, 28% ($n = 150$) were previously on VKA before starting the NOACs. These patients served as a historical control group. Complication rates of these patients, while treated with VKA, were analysed retrospectively. The mean follow-up time under treatment with VKA was 3.8 [IQR 1.1–8.6] years. During the period under VKA, 12 patients experienced thromboembolic events, accounting for 1.2% per year [95%CI 0.6–2.1] (Fig. 2b) and 9 had major bleeding events, accounting for 1.1% per year [95%CI 0.5–1.9] (Fig. 2c).

3.5. Secondary endpoints in NOAC cohort

Using pharmacy interrogation data, adherence was sufficient ($\geq 80\%$ of the pills received) at 1- and 2-year follow-up in 95% ($n = 41$) and 93% ($n = 28$) of patients, respectively. Based on the Morisky-8 questionnaire, adherence was sufficient ($= \text{score} \geq 5$) in 80% ($n = 69$) and 91% ($n = 49$) of patients at 1 and 2 years of follow-up, respectively. There was no appreciable difference between 1- and 2-year follow-up rates of adherence using pharmacy interrogation ($p = 0.500$) or Morisky-8 questionnaire ($p = 0.453$).

QoL questionnaire was completed by 72 patients at baseline and at 1 year follow-up (Appendix IV), 33 of whom had received a VKA prior to the NOAC. In the VKA subgroup ($n = 33$), QoL was improved in 6 out of 8 domains (social functioning $p = 0.027$, mental health $p = 0.003$, role emotional $p = 0.027$, vitality $p = 0.022$) following transition to a NOAC. In VKA-naïve group ($n = 39$), no domain of QoL declined over 1 year.

4. Discussion

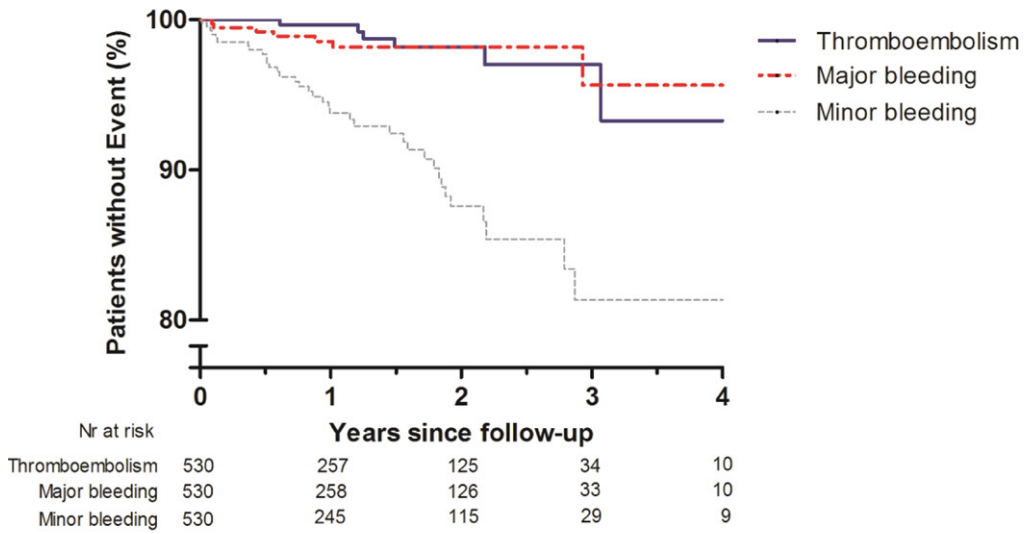
This is the largest prospective cohort study to assess the safety and short-term efficacy of NOACs in ACHD. Our results show low rates of thromboembolic complication (1.0% [95%CI 0.4–2.0] per year) and major bleeding complications (1.1% [95%CI 0.5–2.2] per year). Comparisons to historical cohorts suggest that NOACs have non-inferior safety

and short-term efficacy profiles when compared to VKAs in ACHD patients. Furthermore, adherence to NOACs was stable and sufficient during 2 years of follow-up and QoL at 1 year of follow-up improved in 6 out of 8 domains in patients who previously used VKAs and transitioned to NOACs.

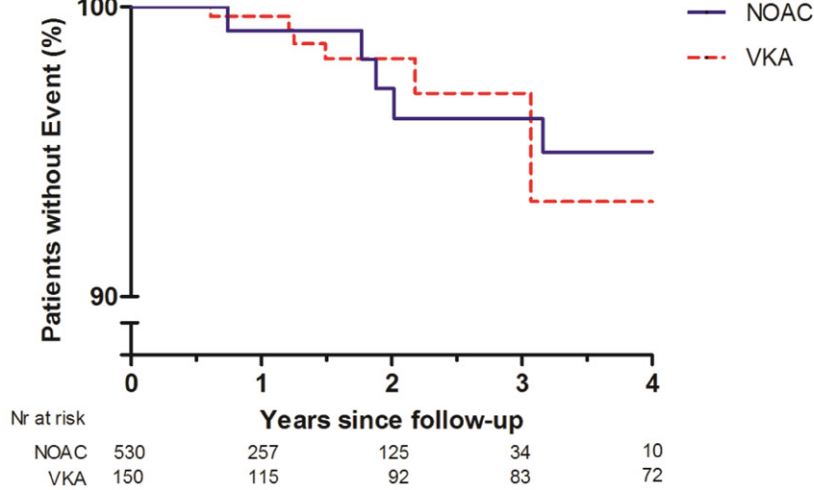
Previously, two retrospective studies evaluated the rates of thromboembolic- and major bleeding events in ACHD patients with atrial arrhythmias on VKAs, antiplatelet therapy, or no thromboprophylaxis [15,18]. Heidendael et al. followed 229 ACHD patients with atrial arrhythmias for a median follow-up of 6 years and reported an annualized thromboembolic event rate of 1.4% in 191 patients (using VKAs, antiplatelet therapy or both, along with an annualized major bleeding rate of 4.4% in 164 VKA users [15]. Khairy et al. reported an annualized thromboembolic event rate of 1.14% in 482 ACHD patients (38% antiplatelet therapy, 54% OAC including $\gg 90\%$ VKAs, 8% neither) and an annualized major bleeding rate of 0.77% in 262 VKA users during a median follow-up of 5.9 years [18]. Direct comparisons to patients in the NOTE registry are obscured by the various thromboprophylaxis treatment regimens, inclusion of patients with contraindications to NOACs such as mechanical valves, and differing indications for anticoagulation (e.g. limited to atrial arrhythmias in the two cohort studies but not the NOTE registry). Nevertheless, the reported thromboembolic and major bleeding rates of 1.1–1.3% and 0.8–4.4% per year are similar to the rates observed with NOACs in the NOTE registry. Furthermore, the results of this study are consistent with a previous smaller study of 75 ACHD on NOACs that reported neither thromboembolic nor major bleeding event during 1 year of follow-up [9]. In this cohort, only 16 (21%) had complex congenital heart disease, thereby precluding firm conclusions as to the merits of NOACs in this patient population.

In the absence of data, the most recent 2018 AHA/ACC guideline for the management of adults with congenital heart disease set a high-impact research question as which patients with ACHD can use NOAC instead of warfarin [19]. Furthermore, the 2014 PACES/HRS expert consensus statement on the management of arrhythmias in ACHD issued a weak recommendation (Class IIb, level of evidence C) stating that in adults with simple forms of congenital heart disease and no prosthetic heart valve or hemodynamically significant valve disease, a NOAC may be a reasonable alternative to a VKA when anticoagulation is indicated.

a) Kaplan-Meier curves for survival free from thromboembolic event, major bleeding and minor bleeding under NOACs.



b) Kaplan-Meier curves for survival free from thromboembolic event according to use of NOACs and previous VKA use.



c) Kaplan-Meier curves for survival free from major bleeding according to use of NOACs and previous VKA use.

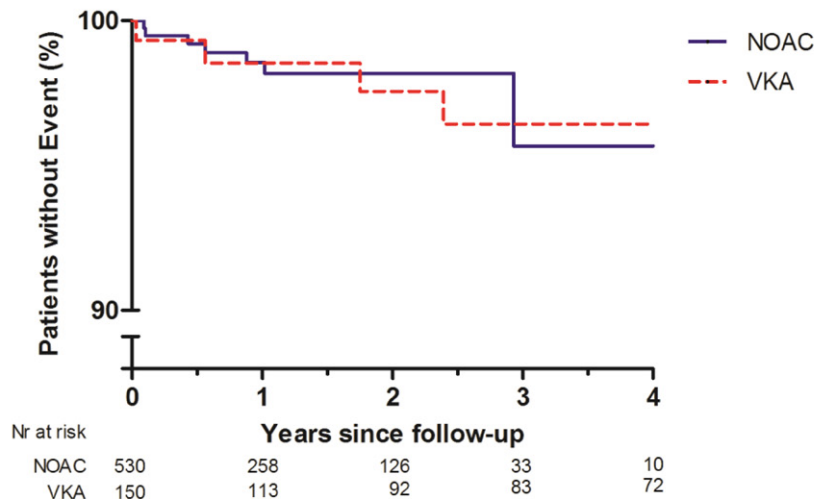


Fig. 2. a) Kaplan-Meier curves for survival free from thromboembolic event, major bleeding and minor bleeding under NOACs. b) Kaplan-Meier curves for survival free from thromboembolic event according to use of NOACs and previous VKA use. c) Kaplan-Meier curves for survival free from major bleeding according to use of NOACs and previous VKA use. Abbreviations: NOAC-non vitamin-K antagonist oral anticoagulant; VKA-vitamin K antagonist.

Table 2
Patients with thromboembolic or major bleeding event.

Thromboembolism											
Patient	Age (yr)	Sex	CHD	TE location	NOAC	Indication	CHA ₂ DS ₂ -VASc	HASBLED	Bioprosthetic valves	Significant valvular lesions	
1	30	♂	Coronary AV fistula	Deep vein thrombosis	Dabigatran	Atrial arrhythmia	3	2	No	TR	
2	42	♂	Fontan	Pulmonary embolism	Apixaban	Atrial arrhythmia	0	3	No	No	
3	25	♂	Fontan	Intracardiac thrombus	Rivaroxaban	Atrial arrhythmia	2	1	No	No	
4	44	♂	ToF	Pulmonary embolism	Apixaban	Atrial arrhythmia	1	1	No	No	
5	23	♂	Fontan	Ischemic stroke	Apixaban	Atrial arrhythmia	1	0	No	No	
6	25	♀	TGA	Intracardiac thrombus	Apixaban	Atrial arrhythmia	4	0	No	TR	
Major bleeding											
Patient	Age (yr)	Sex	CHD	Bleeding location	NOAC	Indication	CHA ₂ DS ₂ -VASc	HASBLED	Bioprosthetic valves	Significant valvular lesions	
1	56	♀	Fontan	GI-bleeding	Apixaban	Atrial arrhythmia	2	1	No	MR	
2	71	♀	PAPVC	GI-bleeding	Rivaroxaban	Atrial arrhythmia	3	1	No	TR	
3	23	♀	CoA	Menorrhagia	Rivaroxaban	Atrial arrhythmia	2	0	Aortic & pulmonary	No	
4	42	♀	Eisenmenger	Menorrhagia	Rivaroxaban	Secondary prevention of pulmonary embolism	3	2	No	No	
5	41	♀	Fontan	Menorrhagia	Apixaban	Atrial arrhythmia	4	0	No	MR	
6	80	♂	ToF	Hematuria	Apixaban	Atrial arrhythmia	4	1	No	PS	
7	67	♀	Fontan	Menorrhagia	Rivaroxaban	Atrial arrhythmia	2	2	No	No	

Abbreviations: CHD = congenital heart disease; TE = thromboembolism; NOAC = non-vitamin K antagonist oral anticoagulant; CHA₂DS₂-VASc, stroke risk factor scoring system in which 1 point is given for heart failure, hypertension, age 64–74 years, diabetes mellitus, history of vascular disease, female sex and 2 points are given for age ≥ 75 years, history of stroke/TIA/thromboembolism; HASBLED, bleeding risk factor scoring system in which 1 point is given for uncontrolled hypertension, abnormal renal or liver function, history of stroke or bleeding, labile international normalized ratio, age >> 65 years, use of nonsteroidal anti-inflammatory drug or antiplatelet agents or alcohol; Coronary AV fistula = coronary arteriovenous fistula; ToF = tetralogy of Fallot; TGA = transposition of great arteries; PAPVC = partial anomalous pulmonary venous connection; CoA = coarctation of the aorta; GI-bleeding = gastro-intestinal bleeding; MR = mitral valve regurgitation; TR = tricuspid valve regurgitation; PS = pulmonary stenosis.

The panel concluded that there was insufficient safety and efficacy data to recommend NOACs in those with moderate or complex forms of congenital heart disease [20]. Our study addresses this knowledge gap and provides reassuring safety data in a cohort with predominantly moderate and complex forms of congenital heart disease (85%), including a Fontan circulation (14%). So far, only one study previously evaluated the safety of NOACs in Fontan patients (n = 21) who are prone to thrombus formation and bleeds [21,22], and reported 1 thromboembolic event and no major bleeding event during a median follow-up of 13 months [10]. However, in our study, 50% of thromboembolic events and major bleeds occurred in Fontan patients, each in 3 of 74 patients (4.1%), confirming their vulnerability for these events. Fontan patients, therefore, remain an important subgroup in whom further data are required to draw definitive conclusions regarding the safety of efficacy of NOACs.

Our reassuring thromboembolic and major bleeding rates overall may reflect, in part, the low median CHA₂DS₂-VASc and HAS-BLED scores observed in this young cohort. Previous studies showed mixed results regarding the applicability of CHA₂DS₂-VASc and HAS-BLED scores in ACHD patients with atrial arrhythmias [15,18,23]. Although patients with thromboembolic events in the NOTE registry seemed to have low CHA₂DS₂-VASc scores and those with major bleeding events had low HAS-BLED scores (Table 2), correlations could not be assessed given the limited number of events. Furthermore, factors beyond those included in the CHA₂DS₂-VASc score may be associated with thromboembolic events in ACHD patients. For example, studies have shown that, rather than traditional atherosclerotic risk factors, complexity of congenital heart disease, heart failure, previous shunt operations, residual/unclosed septal defects and cyanosis (Eisenmenger syndrome) were associated with thromboembolism in ACHD patients [2,3,18,24,25].

In 2014, the PACES/HRS expert consensus statement did not recommend prescribing NOACs to ACHD patients with prosthetic valves or hemodynamically significant valve disease [20]. What constitutes significant valve disease with contraindication to NOAC use was later clarified in 2015 European and Canadian guidelines to include mechanical prosthetic valves, any degree of rheumatic mitral stenosis, and moderate or severe non-rheumatic mitral stenosis [26,27]. Although controversial, NOAC use in patients with bioprosthetic valves is thought to be reasonable, particularly for valves in the aortic position. Three major studies (two meta-analyses and post-hoc analysis of randomised controlled trial of edoxaban) have consistently shown that the overall efficacy and safety of NOACs were not affected by the presence of valvular diseases (other than moderate/severe mitral stenosis or mechanical heart valves) nor prior valve surgery (bioprosthetic replacement, valve repair, valvuloplasty) in patients with atrial fibrillation [28–30]. In half of the NOTE registry cohort, valve disease was prevalent with 11% of patients having bioprosthetic valves (none of them used NOACs for the indication of bioprosthetic valves) but none having a mechanical valve or mitral stenosis. Reassuringly, no thromboembolic event and only one major bleed occurred in patients with bioprosthetic valves. Hence, we conclude that when anticoagulation is indicated, it appears reasonable to consider NOACs in ACHD patients with bioprosthetic valves or valvular heart disease, except mitral valve stenosis or mechanical valves.

Adherence to long-term anticoagulation is a concern that is amplified by the lack of blood testing monitoring for patients on NOACs. Although there is no adherence data on VKA use in ACHD patients for comparison, our data showed higher rates of NOAC adherence compared with previous studies of NOAC adherence in the general population (e.g. with pharmacy interrogation, 93–95% vs. 67–88% [31,32]). This could be due to a greater awareness among ACHD patients regarding their heart disease, more intense monitoring and education by

physicians, and/or a Hawthorn effect due to participation in a registry [33]. Interestingly, knowledge of oral anticoagulants appears to be similar among ACHD patients and those with acquired heart disease and thus does not seem to be a likely explanation [34]. Despite the reassuring data, given the prospect of long term use of thromboprophylaxis in these patients and the small number of participants, prescribers should always be aware of the risk of non-persistence and adverse effects of therapy and evaluate these issues on a regular basis. In patients, who used VKA at baseline, the overall QoL improved after using NOACs for 1 year. These improvements could be due to freedom from repeat monitoring and dose adjustments based on food/drug interactions [35].

5. Limitations

This study is limited by the heterogeneity of the ACHD population, low event rates and the observational design. Therefore, the data should be interpreted with caution pending longer follow-up and validation in other cohorts with a different mix of congenital defects and defect-specific indications for anticoagulation. Furthermore, it should be taken into consideration that unavoidably, some patients may have been switched to a NOAC in order to be included in this registry. Although we analysed the historical data of VKA users at baseline for completeness, these patients may not be representative of the typical VKA users owing to the fact that the VKA was switched to a NOAC for a reason that could have included a complication associated with VKA such as bleeding or thromboembolic event. The small number of events precluded exploratory regression analyses to determine factors associated with thromboembolic and bleeding events. Finally, results should not be extrapolated to the distant future considering the relatively short follow-up period (average follow-up 1 year). We expect to address many of these limitations in the future with ongoing recruitment into the global registry and longer-term follow-up. However, if feasible, a head-to-head comparison of NOACs and VKAs by randomised controlled trial in this group would be ideal to establish efficacy of NOACs.

In the largest study to date on NOAC use in ACHD patients across 13 countries, NOACs appeared to be safe and effective in the short term for thromboprophylaxis in patients with predominantly moderate and complex forms of congenital heart disease, including those with various forms of valve disease and bioprosthetic valves. Future recommendations on anticoagulation in ACHD should consider this international experience. Larger studies with longer-term follow-up are required to determine factors associated with thromboembolic and bleeding events in NOAC users and to assess safety and efficacy in higher risk subgroups, such as those with Fontan palliation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.06.014>.

References

- [1] J. Lanz, J.M. Brophy, J. Therrien, M. Kaouache, L. Guo, A.J. Marelli, Stroke in adults with congenital heart disease clinical perspective, *Circulation* 132 (2015) 2385–2394.
- [2] Z. Mandalenakis, A. Rosengren, G. Lappas, P. Eriksson, P. Hansson, M. Dellborg, Ischemic stroke in children and young adults with congenital heart disease, *J. Am. Heart Assoc.* 5 (2016), e003071. <https://doi.org/10.1161/JAHA.115.003071>.
- [3] A. Hoffmann, P. Chockalingam, O.H. Balint, A. Dadashev, K. Dimopoulos, R. Engel, M. Schmid, M. Schwerzmann, M.A. Gatzoulis, B. Mulder, E. Oechslin, Cerebrovascular accidents in adult patients with congenital heart disease, *Heart* 96 (2010) 1223–1226.
- [4] J. Bouchardy, J. Therrien, L. Pilote, R. Ionescu-Ittu, G. Martucci, N. Bottega, A.J. Marelli, Atrial arrhythmias in adults with congenital heart disease, *Circulation* 120 (2009) 1679–1686.
- [5] P. Khairy, Thrombosis in congenital heart disease, *Expert. Rev. Cardiovasc. Ther.* 11 (2013) 1579–1582.
- [6] P. Monagle, Thrombosis: congenital heart disease and thrombosis: what do we know? *Nat. Rev. Cardiol.* 11 (2014) 132–134.
- [7] C.T. Ruff, R.P. Giugliano, E. Braunwald, E.B. Hoffman, N. Deenadayalu, M.D. Ezekowitz, A.J. Camm, J.I. Weitz, B.S. Lewis, A. Parkhomenko, T. Yamashita, E.M. Antman, Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, *Lancet* 383 (2014) 955–962.
- [8] H. Yang, B.J. Bouma, B.J.M. Mulder, J.F. Heidendael, G. Veen, T.C. Konings, G.T.J. Sieswerda, F.J. Meijboom, M.C. Post, A. van Dijk, W. Budts, M. Morissens, M. Ladouceur, D. Tobler, M. Schwerzmann, T. Rutz, J. Bouchardy, M. Grewtman, G. Scognamiglio, K. Skoglund, C. Christersson, L. Gumbiene, M. Laukyte, P. Khairy, J. Aboulhosn, G. Veldtman, G. Webb, C.S. Broberg, A.R. Opatowsky, K. Shafer, S.F. Tsai, T. Moe, K. Niwa, A. Mizuno, Is initiating NOACs for atrial arrhythmias safe in adults with congenital heart disease? *Cardiovasc. Drugs Ther.* 31 (2017) 413–417.
- [9] C. Pujol, A.-C. Niesert, A. Engelhardt, P. Schoen, E. Kusmenkov, D. Pittrow, P. Ewert, H. Kaemmerer, Usefulness of direct oral anticoagulants in adult congenital heart disease, *Am. J. Cardiol.* 117 (2016) 450–455.
- [10] J. Georgekutty, A. Kazerouninia, Y. Wang, P.R. Ermis, D.R. Parekh, W.J. Franklin, W.W. Lam, Novel oral anticoagulant use in adult Fontan patients: a single center experience, *Congenit. Heart Dis.* (2018) 3–7.
- [11] P. Khairy, G.F. Van Hare, S. Balaji, C.I. Berul, F. Cecchin, M.I. Cohen, C.J. Daniels, B.J. Deal, J.A. Dearani, N. de Groot, A.M. Dubin, L. Harris, J. Janousek, R.J. Kanter, P.P. Karpawich, J.C. Perry, S.P. Seslar, M.J. Shah, M.J. Silka, J.K. Triedman, E.P. Walsh, C.A. Warnes, PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease, *Hear. Rhythm.* 11 (2014) e102–e165.
- [12] C. a Warnes, R. Liberthson, G.K. Danielson, L. Harris a Dore, J.I. Hoffman, J. Somerville, R.G. Williams, G.D. Webb, Task force 1: the changing profile of congenital heart disease in adult life, *J. Am. Coll. Cardiol.* 37 (2001) 1170–1175.
- [13] F. Rodeghiero, A. Tosetto, T. Abshire, D.M. Arnold, B. Coller, P. James, C. Neunert, D. Lillicrap, ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders, *J. Thromb. Haemost.* 8 (2010) 2063–2065.
- [14] L.M. Hess, Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures, *Ann. Pharmacother.* 40 (2006) 1280–1288.
- [15] J.F. Heidendael, J.P. Bokma, J.R. De Groot, D.R. Koolbergen, B.J.M. Mulder, B.J. Bouma, Weighing the risks: thrombotic and bleeding events in adults with atrial arrhythmias and congenital heart disease, *Int. J. Cardiol.* 186 (2015) 315–320.
- [16] C.T. Ruff, R.P. Giugliano, E. Braunwald, E.B. Hoffman, N. Deenadayalu, M.D. Ezekowitz, a J. Camm, J.I. Weitz, B.S. Lewis, A. Parkhomenko, T. Yamashita, E.M. Antman, Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, *Lancet* 383 (2014) 955–62.
- [17] K. Viele, S. Berry, B. Neunschwander, B. Amzal, F. Chen, N. Enas, B. Hobbs, J.G. Ibrahim, N. Kinnersley, S. Lindborg, S. Micallef, S. Roychowdhury, L. Thompson, Use of historical control data for assessing treatment effects in clinical trials, *Pharm. Stat.* 13 (2014) 41–54.
- [18] P. Khairy, J. Aboulhosn, C.S. Broberg, S. Cohen, S. Cook, A. Dore, S.M. Fernandes, A. Fournier, J. Kay, S. Levesque, L. Macle, F. Marcotte, B. Mond?sert, F.P. Mongeon, A.R. Opatowsky, A. Proietti, L. Rivard, J. Ting, B. Thibault, A. Zaidi, R. Hamilton, Thromboprophylaxis for atrial arrhythmias in congenital heart disease: a multicenter study, *Int. J. Cardiol.* 223 (2016) 729–735.

- [19] K. Stout, C. Daniels, J. Aboulhosn, B. Bozkurt, C. Broberg, J. Colman, S. Crumb, J. Dearani, S. Fuller, M. Gurvitz, P. Khairy, M. Landzberg, A. Saidi, A. Valente, G. Van Hare, *AHA/ACC Guideline for the Management of Adults with Congenital Heart Disease a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines*, 2018 2018.
- [20] P. Khairy, G.F. Van Hare, S. Balaji, C.I. Berul, F. Cecchin, M.I. Cohen, C.J. Daniels, B.J. Deal, J.A. Dearani, N. De Groot, A.M. Dubin, L. Harris, J. Janousek, R.J. Kanter, P.P. Karpawich, J.C. Perry, S.P. Seslar, M.J. Shah, M.J. Silka, J.K. Triedman, E.P. Walsh, C.A. Warnes, *PACES/HRS Expert Consensus Statement on the Recognition and management of arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS)*. Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD), *Can. J. Cardiol.* 11 (2014) e102–e165.
- [21] K.C. Odegard, F.X. McGowan, D. Zurakowski, J.A. DiNardo, R.A. Castro, P.J. Del Nido, P.C. Laussen, *Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis*, *J. Thorac. Cardiovasc. Surg.* 125 (2003) 1260–1267.
- [22] K.C. Odegard, F.X. McGowan, D. Zurakowski, J.A. DiNardo, R.A. Castro, P.J. Del Nido, P.C. Laussen, *Coagulation factor abnormalities in patients with single-ventricle physiology immediately prior to the Fontan procedure*, *Ann. Thorac. Surg.* 73 (2002) 1770–1777.
- [23] K. Masuda, T. Ishizu, K. Niwa, F. Takechi, S. Tateno, H. Horigome, K. Aonuma, *Increased risk of thromboembolic events in adult congenital heart disease patients with atrial tachyarrhythmias*, *Int. J. Cardiol.* 234 (2017) 69–75.
- [24] J.P. Bokma, I. Zegstroom, J.M. Kuijpers, T.C. Konings, R.R.J. van Kimmenade, J.P. van Melle, P. Kiës, B.J.M. Mulder, B.J. Bouma, *Factors associated with coronary artery disease and stroke in adults with congenital heart disease*, *Heart* (2017) <https://doi.org/10.1136/heartjnl-2017-311620> heartjnl-2017-311620.
- [25] J. Lanz, J.M. Brophy, J. Therrien, M. Kaouache, L. Guo, A.J. Marelli, *Stroke in adults with congenital heart disease clinical perspective*, *Circulation* 132 (2015) 2385–2394.
- [26] H. Heidbuchel, P. Verhamme, M. Alings, M. Antz, H.-C. Diener, W. Hacke, J. Oldgren, P. Sinnaeve, A.J. Camm, P. Kirchhof, *Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation*, *Europace*. (2015) euv309.
- [27] L. Macle, J.A. Cairns, J.G. Andrade, L.B. Mitchell, S. Nattel, A. Verma, A. Verma, L. Macle, J. Andrade, C. Atzema, A. Bell, J.A. Cairns, S. Connolly, J.L. Cox, P. Dorian, D. Gladstone, J. Healey, K. Leblanc, L.B. Mitchell, S. Nattel, R. Parkash, L. Pilote, M. Sharma, A. Skanes, M. Talajic, T. Tsang, S. Verma, D. Bewick, V. Essebag, P. Guerra, B. Heilbron, C. Kerr, B. Kiaii, G. Klein, S. Kouz, M.S. McMurtry, D. Ngui, P. Page, P.T. Pollak, J. Surkes, D.G. Wyse, *The 2014 atrial fibrillation guidelines companion: a practical approach to the use of the Canadian Cardiovascular Society guidelines*, *Can. J. Cardiol.* 31 (2015) 1207–1218.
- [28] A.P. Carnicelli, E.M. Antman, F. Nordio, R.P. Giugliano, G. Renda, C.T. Ruff, E. Braunwald, R. De Caterina, M. Trevisan, M.F. Mercuri, *Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial*, *J. Am. Coll. Cardiol.* 69 (2017) 1372–1382.
- [29] F.J. Pinto, D. Caldeira, J.J. Ferreira, J. Costa, C. David, *Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis*, *Eur. Hear. J. Cardiovasc. Pharmacother.* 4 (2017) 111–118.
- [30] G. Renda, F. Ricci, R.P. Giugliano, R. De Caterina, *Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease*, *J. Am. Coll. Cardiol.* 69 (2017) 1363–1371.
- [31] C.A. McHorney, C. Crivera, F. Laliberté, W.W. Nelson, G. Germain, B. Bookhart, S. Martin, J. Schein, P. Lefebvre, S. Deitelzweig, *Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure*, *Curr. Med. Res. Opin.* 31 (2015) 2167–2173.
- [32] J.M. van den Heuvel, A.M. Hövels, H.R. Büller, A.K. Mantel-Teeuwisse, A. de Boer, A.H. Maitland-van der Zee, *NOACs replace VKA as preferred oral anticoagulant among new patients: a drug utilization study in 560 pharmacies in The Netherlands*, *Thromb. J.* 16 (2018) 1–10.
- [33] J. Billett, M.R. Cowie, M.A. Gatzoulis, I.F. Vonder Muhll, A. Majeed, *Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis*, *Heart* 94 (2008) 1194–1199.
- [34] S. Van Damme, K. Van Deyk, W. Budts, P. Verhamme, P. Moons, *Patient knowledge of and adherence to oral anticoagulation therapy after mechanical heart-valve replacement for congenital or acquired valve defects*, *Hear. Lung J. Acute Crit. Care* 40 (2011) 139–146.
- [35] T. Wilke, S. Bauer, S. Mueller, T. Kohlmann, R. Bauersachs, *Patient preferences for oral anticoagulation therapy in atrial fibrillation: a systematic literature review*, *Patient* 10 (2017) 17–37.