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Oral anticoagulant therapy in adults with congenital heart disease and atrial arrhythmias: Implementation of guidelines

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ABSTRACT

Background: Current guidelines on oral anticoagulation (OAC) in adults with congenital heart disease (ACHD) and atrial arrhythmias (AA) consist of heterogeneous and divergent recommendations with limited level of evidence, possibly leading to diverse OAC management and different outcomes. Therefore, we aimed to evaluate real-world implementation and outcome of three guidelines on OAC management in ACHD patients with AA.
Methods: The ESC GUCH 2010, PACES/HRS 2014 and ESC atrial fibrillation (AF) 2016 guidelines were assessed for implementation. ACHD patients with recurrent or sustained non-valvular AA from 5 tertiary centers were identified using a national ACHD registry. After two years of prospective follow-up, thromboembolism, major bleeding and death were assessed.
Results: In total, 225 adults (mean age 54 ± 15 years, 55% male) with various defects (simple 43%; moderate 37%; complex 20%) and AA were included. Following the most strict indication (OAC is recommended in all three guidelines), one should treat a mere 37% of ACHD patients with AA, whereas following the least strict indication (OAC is recommended in any one of the three guidelines), one should treat 98% of patients. The various guidelines were implemented in 54–80% of patients. From all recommendations, Fontan circulation, CHA2DS2-VASc ≥ 1 and AF were independently associated with OAC prescription. Superiority of any guideline in identifying outcome (n = 15) could not be demonstrated.
Conclusions: The implementation of current guidelines on OAC management in ACHD patients with AA is low, probably due to substantial heterogeneity among guidelines. OAC prescription in daily practice was most consistent in patients with AF and CHA2DS2-VASc ≥ 1 or Fontan circulation.

1. Introduction

Atrial arrhythmias (AA) affect up to 15% of adults with congenital heart disease (ACHD) and are associated with thromboembolic complications [1,2]. Oral anticoagulant therapy (OAC) is the cornerstone of thromboembolic prevention [3]. In the general population with AA, OAC is recommended based on the CHA2DS2-VASc score [4,5]. For ACHD patients with AA, indications for OAC are less clear with three different guidelines on the thromboembolic prevention in AA, published since 2010 [6,7,5]. Remarkably, these guidelines differ from the general AA guidelines, as well as from each other, and are based on limited level of evidence. Not only do guidelines differ in their usage of the CHA2DS2-VASc score, designed for the estimation of thromboembolic risk in the general population with non-valvular atrial fibrillation (AF) as the basis for OAC recommendations in ACHD patients, they also importantly differ in their selection of specific patient groups (i.e. mild vs. moderate and severe, or specific lesions) [5] [6,7]. The heterogeneity in recommendations can lead to a similar heterogeneity in their application. This could cause important differences in OAC prescription for a single lesion, dependent on the treating physician, thereby causing disparity in risk of thrombo-embolic and/or bleeding events in ACHD patients with AA.

Substantial heterogeneity among the ACHD guidelines could induce various interpretations. However, it is currently unknown to what

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extent the guidelines on OAC in ACHD with AA patients are being implemented in real-world practice. Moreover, as there is hardly any evidence to support any of the three guidelines, it is similarly uncertain whether the implementation of these guidelines actually results in better outcome.

Therefore, we aimed to evaluate the implementation of the contemporary OAC recommendations and outcomes of such implementation in ACHD patients with AA.

2. Methods

We performed a prospective observational study of patients identified from the CONCOR registry, a national database of congenital heart disease (CHD) patients [8]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by all participating institutions' human research committee. All included patients provided informed consent.

2.1. Study cohort and data collection

All ACHD (≥18 years) patients from five participating tertiary referral centers, diagnosed with supraventricular tachycardia (SVT) in the CONCOR registry (April 2014), were eligible for inclusion. Patients were included in case of documented recurrent or sustained non-valvular AF, atrial flutter or intra atrial re-entry tachycardia (IART). Patients with other types of SVT, including atrial tachycardia, were excluded. Non-valvular AA was defined as atrial arrhythmias in the absence of severe atrioventricular (AV) stenosis or previous mechanical valve surgery, consistent with the definition in patients without congenital heart disease [9].

Baseline characteristics and follow-up data at 2 years were collected from medical charts or by telephone contact with patients. Severity of CHD was defined according to the classification (simple, moderate or complex) outlined by Task Force 1 of the 23rd Bethesda Conference [10]. Criteria for two risk scores, CHA2DS2-VASc and HASBLED are listed in the supplementary appendix [11,12].

Adverse events were defined as death, thromboembolic events (ischemic cerebrovascular accident (iCVA), transient ischemic attack (TIA), systemic or pulmonary embolism or intracardiac thrombosis) and major bleedings (significant bleeding necessitating hospitalization/interventions/≥2 units of packed 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 International Society on Thrombosis and Haemostasis criteria [13].

2.2. The guidelines

The three most recent and available AA guidelines with OAC recommendations for ACHD patients with AA were used for assessment of implementation: the ESC GUCH 2010, the PACES/HRS 2014, and the ESC AF 2016 guidelines [6,7,5]. The ESC GUCH 2010 recommends OAC in various defect groups with AA without the reference of CHA2DS2-VASc score [6]. The PACES/HRS 2014 makes a distinction between moderate or complex CHD versus simple CHD in using the CHA2DS2-VASc score [7]. The most recent ESC AF 2016 recommends OAC in specified defect subgroups whereas the rest should receive OAC based on their CHA2DS2-VASc score [5]. Table 1 shows an overview of these recommendations per guideline.

The PACES/HRS 2014 guideline states intracardiac repair as a risk factor, but does not define intracardiac repair. Therefore, we defined it as a history of any intracardiac repair of the original defect, including any valve repair, and excluding extracardiac repair (i.e. stenting of aortic coarctation) or procedures related to arrhythmias (i.e. pacemaker or implantable cardioverter defibrillator). If class of recommendation was specified in the guidelines, we considered class 1, 2a and 2b as an indication for OAC. All other patients were considered not to have an indication for treatment with OAC.

2.3. Implementation of guidelines criteria

We considered the guidelines as implemented if the patient was treated according to any of the three guidelines. If patients were not treated with OAC despite having risk factors according to the guidelines or if patients were treated with OAC without having any risk factors according to the guidelines, we considered the guidelines to be not implemented.

2.4. Statistical analysis

Differences between the baseline characteristics were analyzed using unpaired t-tests, chi-square test or Mann–Whitney U test as appropriate and reported as mean with standard deviation (±), median with interquartile range (IQR) or frequencies in percentage (%). Implementation rates were calculated by dividing the number of cases treated according to the guideline by the total number of cases in this study. Survival free from adverse events was calculated as the complement Kaplan Meier estimator. Patient time was accrued until the occurrence of the first event or censored at the time of receiving a mechanical heart valve. Adverse event rates were calculated by dividing the amount of all adverse events by the sum of all patients. In order to determine the variables, associated with the OAC treatment, we constructed a stepwise backward multivariate logistic regression model using the variables with an association of a $p < 0.10$ in the univariate analysis. Analyses were performed with SPSS version 24.0 (IBM Corp., Armonk, NY, USA). A p-value below 0.05 was considered statistically significant.

3. Results

3.1. Study cohort

From the CONCOR registry, a total of 225 ACHD patients (mean age 54 ± 15 years, male 55%) with a recurrent or sustained non-valvular AA (AF 50%, AFL/IART 23%, multiple types 27%) were included. Twenty percent of patients had a complex defect; 82% had previous intracardiac repair. The most common defects were ASD (n = 80, 36%), tetralogy of Fallot (n = 25, 11%), transposition of great arteries (n = 20, 9%), Fontan circulation (n = 19, 8%), ventricular septal defect (n = 18, 8%), coarctation of aorta (n = 14, 6%), and bicuspid aortic valve (n = 11, 5%). The median CHA2DS2-VASc was 1 [IQR 0–3] with 59% (n = 132) of the

Table 1
ACHD patients indicated for oral anticoagulants for non-valvular atrial arrhythmias according to the guidelines.

Guidelines	Indication for OAC		Number of patients (% of total cohort)	On OAC, n (% of subgroup)	Level of evidence
ESC GUCH 2010	Yes	ASD	80 (36%)	53 (66%)	NA
		Ebstein	10 (4%)	6 (60%)	
		Fontan	19 (8%)	18 (95%)	
		Eisenmenger syndrome/severe PAH	2 (1%)	1 (50%)	
		Cyanosis	6 (3%)	5 (83%)	
	No	The rest of ACHD patients	113 (50%)	70 (62%)	NA
PACES/HRS 2014	Yes (1, 2a)[a]	Moderate CHD	83 (37%)	51 (61%)	C
		Complex CHD	46 (20%)	33 (72%)	B
	May be considered (2b)[a]	Simple CHD with CHADSVASC ≥ 2	51 (23%)	45 (88%)	B
	No	Simple CHD with CHADSVASC < 2	46 (20%)	21 (46%)	NA
ESC AF 2016	Yes (2a)[a]	Intracardiac repair	186 (83%)	122 (66%)	C
		Cyanosis	6 (3%)	5 (83%)	
		Fontan	19 (8%)	18 (95%)	
		Systemic right ventricle	34 (15%)	23 (68%)	
		All other CHD with CHADSVASC ≥ 1	24 (11%)	20 (83%)	
	No	All other CHD with CHADSVASC = 0	16 (7%)	8 (50%)	NA

Abbreviations: ACHD = adult congenital heart disease, OAC = oral anticoagulant, ASD = atrial septal defect, PAH = pulmonary arterial hypertension, CHD = congenital heart disease, NA = not applicable. ESC GUCH 2010 refers to the 2010 European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease. PACES/HRS 2014 refers to the 2014 Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) recognition and management of arrhythmias in adult congenital heart disease. ESC AF 2016 refers to the 2016 ESC guidelines for the management of atrial fibrillation. CHA_2DS_2-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.
Data are presented as n(%) as the percentage of the total study cohort. Class, level stands for class of recommendation and level of evidence.
[a] Class of recommendation.

patients having a CHA2DS2-VASc score of 1 or higher. At baseline, 149 (66%) patients used OAC, 20 (9%) aspirin and 56 (25%) patients did not use any antithrombotic therapy. Baseline characteristics are presented in Table 2.

3.2. Application of guideline recommendations in real-world cohort

Table 1 and Fig. 1a show the number of patients per cohort with an OAC indication according to the three different guidelines. Since the ESC GUCH 2010 guideline uses only lesion-based recommendations without the reference of CHA2DS2-VASc score, it was the most restrictive guideline for OAC indications. The PACES/HRS 2014 guideline was more liberal in OAC indication (80%, n = 179), recommending OAC to all moderate or complex CHD lesions (57%, n = 129) and simple CHD with CHA2DS2-VASc ≥ 2 (23%, n = 51). The most liberal guideline in OAC indication was the ESC AF 2016 (93%, n = 209). That guideline recommends OAC in all patients with intracardiac repair (83%, n = 142) or CHA2DS2-VASc ≥ 1(11%, n = 24), and also in specified lesions (Fontan, cyanosis, systematic right ventricle) (Table 1). Of all the recommendations from the three guidelines, only two recommendation criteria, i.e. Fontan circulation and cyanosis, were consistent in all three guidelines.

Of a total of 225 included patients with recurrent or sustained AA, the majority of patients (n = 222, 98%) had an indication for OAC according to any recommendation from the three guidelines [6,7,5]. In contrast, only 37% (n = 84) of this cohort was indicated unequivocally according to all three guidelines (Fig. 1a).

3.3. Implementation of guidelines in daily practice

Table 1 and Fig. 1b show the pattern of OAC treatment in this cohort according to each guideline. Overall, implementation of the guidelines ranged from 54% to 80%.

If all guidelines are regarded separately, implementation of OAC recommendation was the highest according to the PACES/HRS 2014 (68%, n = 153). In adherence to this guideline, 72% (n = 128) of 179 patients were treated with OAC, whereas 46% (n = 21) of 46 patients having no indication according to this guideline, were treated with OAC.

The ESC AF 2016 guideline recommendations were implemented in 66% of the patients (n = 149). Only 68% (n = 141) of 209 patients with

Table 2
Baseline characteristics and factors associated with oral anticoagulant prescription in ACHD patients and atrial arrhythmias.

	All (n = 225)	OAC (n = 149)	No OAC (n = 76)	p-Value	Univariable OR	p-Value	Multivariable OR	95%CI	p-Value
Age at inclusion, y	54.3 ± 15.4	57.0 ± 15.7	49.0 ± 13.5	<0.001	1.04	<0.001			
Male, n(%)	129 (57.3)	82 (55.0)	47 (61.8)	0.329					
Atrial arrhythmia type									
Atrial flutter/IART	52 (23.1)	19 (12.8)	33 (43.4)	<0.001	1	…			
Atrial fibrillation	112 (49.8)	87 (58.4)	25 (32.9)	<0.001	5.21	<0.001	3.56	1.63–7.80	0.001
All types	60 (26.7)	42 (28.2)	18 (23.7)	0.409					
Guideline indication, n(%)									
ESC GUCH 2010	112 (49.8)	79 (53.0)	33 (43.4)	0.173					
PACES/HRS 2014	179 (79.6)	128 (85.9)	51 (67.1)	0.001	2.99	0.001			
ESC AF 2016	209 (92.9)	141 (94.6)	68 (89.5)	0.155					
Severity of congenital heart defect, n (%)									
Simple	97 (43.1)	66 (44.3)	31 (40.8)	0.616					
Moderate	83 (36.9)	51 (34.2)	32 (42.1)	0.247					
Complex	45 (20.0)	32 (21.5)	13 (17.1)	0.438					
Intracardiac repair	186 (82.7)	122 (81.9)	64 (84.2)	0.662					
Systematic right ventricle	34 (15.1)	23 (15.4)	11 (14.5)	0.831					
Fontan circulation	19 (8.4)	18 (12.1)	1 (1.3)	0.006	10.31	0.025	20.44	2.40–174.35	0.006
Pulmonary hypertension	29 (12.9)	21 (14.1)	8 (10.5)	0.323					
Cyanosis	6 (2.7)	5 (3.4)	1 (1.3)	0.126					
Median CHA_2DS_2-VASc	1 (IQR 0–3)	2 (IQR 0–3)	0 (IQR 0–1)	<0.001					
0	93 (41.3)	41 (27.5)	52 (68.4)	<0.001					
1	32 (14.2)	20 (13.4)	12 (15.8)	0.631	3.32	<0.001	3.70	1.84–7.41	<0.001
≥2	100 (44.4)	88 (59.1)	12 (15.8)	<0.001					
Median HASBLED	0 (IQR 0–1)	0 (IQR 0–1)	0 (IQR 0–0)	<0.001					
0	139 (61.8)	79 (53.0)	60 (78.9)	<0.001					
1	64 (28.4)	49 (32.9)	15 (19.7)	0.039	3.32	<0.001			
≥2	22 (9.8)	21 (14.1)	1 (1.3)	0.002					
Cardiovascular history, n(%)									
Thromboembolism	29 (12.9)	28 (18.8)	1 (1.3)	<0.001					
Major bleeding	11 (4.9)	8 (5.4)	3 (3.9)	0.640					
Heart failure[a]	54 (24.0)	48 (32.2)	6 (7.9)	<0.001					
Hypertension	61 (27.1)	48 (32.2)	13 (17.1)	0.016					
Diabetes mellitus	15 (6.7)	14 (9.4)	1 (1.3)	0.022					
Vascular disease	11 (4.9)	9 (6.0)	2 (2.6)	0.194					
Renal insufficiency	10 (4.4)	10 (6.7)	0	0.021					
Liver insufficiency	3 (1.3)	3 (2.0)	0	0.213					

Values are presented as median (IQR) or counts(%). Odds ratio estimates for oral anticoagulant prescription derived from univariate and multivariate analyses. Odds ratios with p-values are demonstrated.

Abbreviations: AA = atrial arrhythmias, ACHD = adult congenital heart disease, CHD = congenital heart disease, IART = intra atrial re-entry tachycardia, OR = odds ratio, CI = confidence interval. ESC GUCH 2010 refers to the 2010 European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease. PACES/HRS 2014 refers to the 2014 Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) recognition and management of arrhythmias in adult congenital heart disease. ESC AF 2016 refers to the 2016 ESC guidelines for the management of atrial fibrillation. CHA_2DS_2-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.

[a] 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.

an indication for OAC was treated accordingly, and 50% (n = 8) of 16 patients without indication were treated with OAC.

As the least implemented guideline, the ESC GUCH 2010 recommendations were implemented in 54% (n = 122) of the patients. Of 112 patients indicated for OAC according to the ESC GUCH 2010 guidelines, only 71% (n = 79) was actually treated with OAC while 62% (*n* = 70) of 113 patients without indication was treated.

Considering treatment based on recommendation with consensus in any of the three guidelines, we observed the highest percentage of OAC implementation (80%, n = 67 out of 84). Eighty-one percent (n = 65) of 80 patients was treated with OAC accordingly, and two of four patients without OAC indication were treated with OAC.

3.4. Factors associated with OAC prescription

Among the patients indicated for OAC according to any of the three guidelines (n = 221, 98%), only 148 (67%) patients were on OAC treatment. OAC prescription was recommended by the guidelines either according to their CHA2DS2-VASc score or CHD lesion. Regarding the use of CHA2DS2-VASc score, the OAC prescription rates were high in simple CHD patients with a CHA2DS2-VASc score ≥ 2 (88% on OAC) and in CHD patients with CHA2DS2-VASc score ≥ 1 in general (83% on OAC). Although aspirin could be considered in simple CHD patients with AA and CHA2DS2-VASc = 1 (PACES/HRS 2014 guidelines), it was only given to patients without an OAC indication (n = 20).

Regarding the lesion-based recommendations, OAC prescription was the highest in patients with cyanosis (83% on OAC) and Fontan circulation (95% on OAC) as recommended by all three guidelines. In contrast, OAC prescription was poor in patients with Eisenmenger syndrome/severe pulmonary arterial hypertension (50% on OAC), Ebstein's anomaly (60% on OAC), ASD (66% on OAC), intracardiac repair (66% on OAC), systemic right ventricle (68% on OAC) and moderate (61% on OAC) and complex CHD patients (72% on OAC).

Furthermore, patients, who were not using OAC (n = 76, 34%) were younger ($p < 0.001$) and more likely to have atrial flutter/IART than AF ($p < 0.001$) compared with the patients, treated with OAC. Moreover, they had significantly lower CHA2DS2-VASc ($p < 0.001$) and HASBLED scores ($p = 0.001$) with less often a history of thromboembolism ($p < 0.001$), heart failure ($p < 0.001$), hypertension ($p = 0.016$) and diabetes mellitus ($p = 0.022$).

From all potential factors associated with OAC prescription in ACHD patients with AA, age, CHA2DS2-VASc score ≥ 1, HASBLED ≥ 1, presence of a Fontan circulation, AF (including multiple types) and indication for OAC according to the PACES/HRS 2014 guideline were univariably

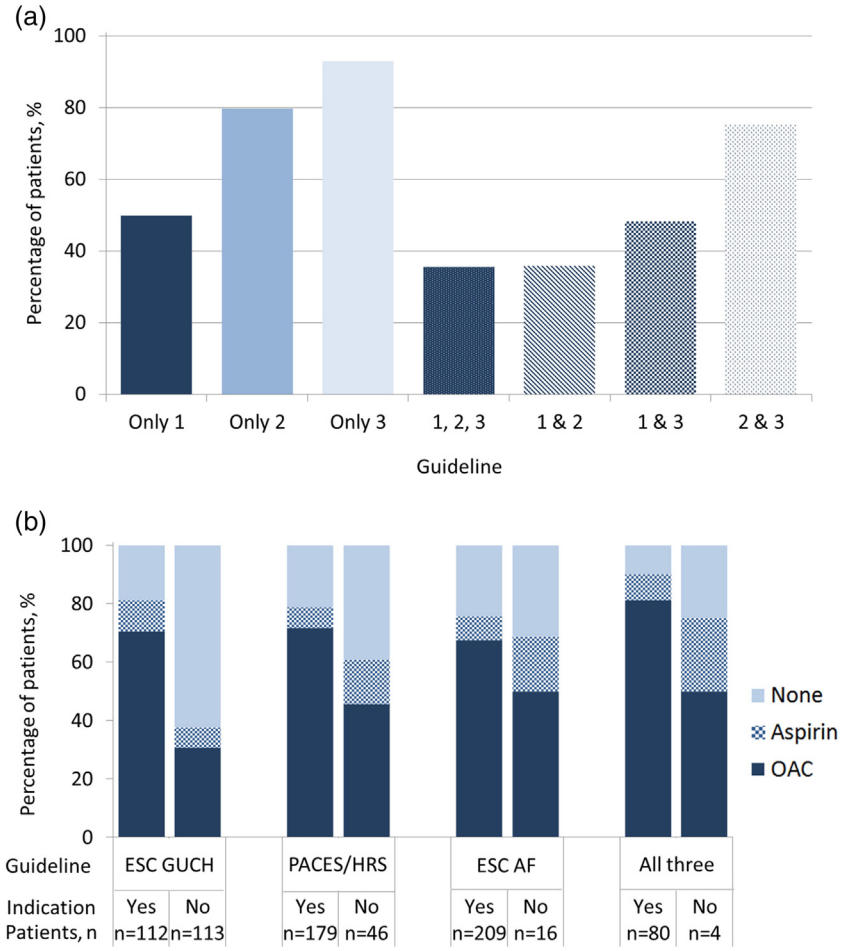

Fig. 1. a. Percentage of ACHD patients with atrial arrhythmias and an indication for oral anticoagulant. Percentage of patients, who were indicated for oral anticoagulant according to (combination of) each guideline. Guideline 1 = 2010 European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease (ESC GUCH). Guideline 2 = 2014 Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) recognition and management of arrhythmias in adult congenital heart disease (PACES/HRS). Guideline 3 = 2016 ESC guidelines for the management of atrial fibrillation (ESC AF). Abbreviations: ACHD = adult congenital heart disease b. Percentage of oral anticoagulant prescription in ACHD patients with atrial arrhythmias. Percentages of patients with anti-thrombotic therapy (oral anticoagulant, aspirin or none) are illustrated by whether the patients were indicated for oral anticoagulant according to the guidelines. Abbreviations: ESC GUCH = 2010 European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease, PACES/HRS = 2014 Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) recognition and management of arrhythmias in adult congenital heart disease (PACES/HRS), ESC AF = 2016 ESC guidelines for the management of atrial fibrillation.

associated with OAC treatment. In multivariate analysis, CHA2DS2-VASc score ≥ 1, AF and Fontan circulation remained independently associated with OAC treatment (Table 2).

3.5. Outcome

During a median follow-up of 2.0 [IQR 2.0–2.0] years, in total, 7 deaths, 4 thromboembolisms and 3 major bleedings occurred in patients treated with OAC, and one thromboembolism in patients not treated with OAC. The patient, who experienced an ischemic stroke, while not being treated with OAC, had an indication for OAC according to the PACES/HRS 2014 and the ESC AF 2016 guidelines. Causes of death were heart failure (n = 3), cardiogenic shock (n = 1), out of hospital cardiac arrest (n = 1), septic shock (n = 1), and multiple organ failure following surgery (n = 1), and seemed unrelated to OAC treatment. Fig. 2a shows freedom from any first adverse event per OAC treatment. Although most adverse events occurred in patients using OAC, they were older ($p < 0.001$), and had higher CHA2DS2-VASc (<0.001) and HASBLED scores (<0.001) than patients not using OAC (Table 2). Fig. 2b shows the adverse event rate per implementation of various guidelines. Patients treated according to the PACSE/HRS 2014 guidelines seemed to have the best outcome based on the lowest adverse event rate under implementation and the highest rate when not treated according to the guideline. However, the number of events was too small to draw any conclusion on superiority of any guideline.

4. Discussion

This is the first study to provide insight into the clinical practice of OAC management and implementation of contemporary OAC guidelines in ACHD patients with AA. Almost all patients with recurrent or sustained AA included in this study (98%) had an indication for OAC treatment according to at least one of the three guidelines. Remarkably, only 37% of the patients had indication for OAC according to all three guidelines. Furthermore, implementation of the guidelines ranged from 54% to 80%, depending on which guideline was used. OAC prescription in daily practice was most consistent in patients with AF and CHA2DS2-VASc score ≥ 1, or Fontan circulation.

4.1. Implementation of OAC guidelines

Low implementation rates of the current recommendations in ACHD patients with AA are not surprising, since they are very heterogenic. Dependent on the interpretation of the guidelines, between 37% and 98% of the patients should be treated with OAC. These discrepancies between guidelines are best illustrated by the large differences in implementation rate. Considering treatment based on recommendation with

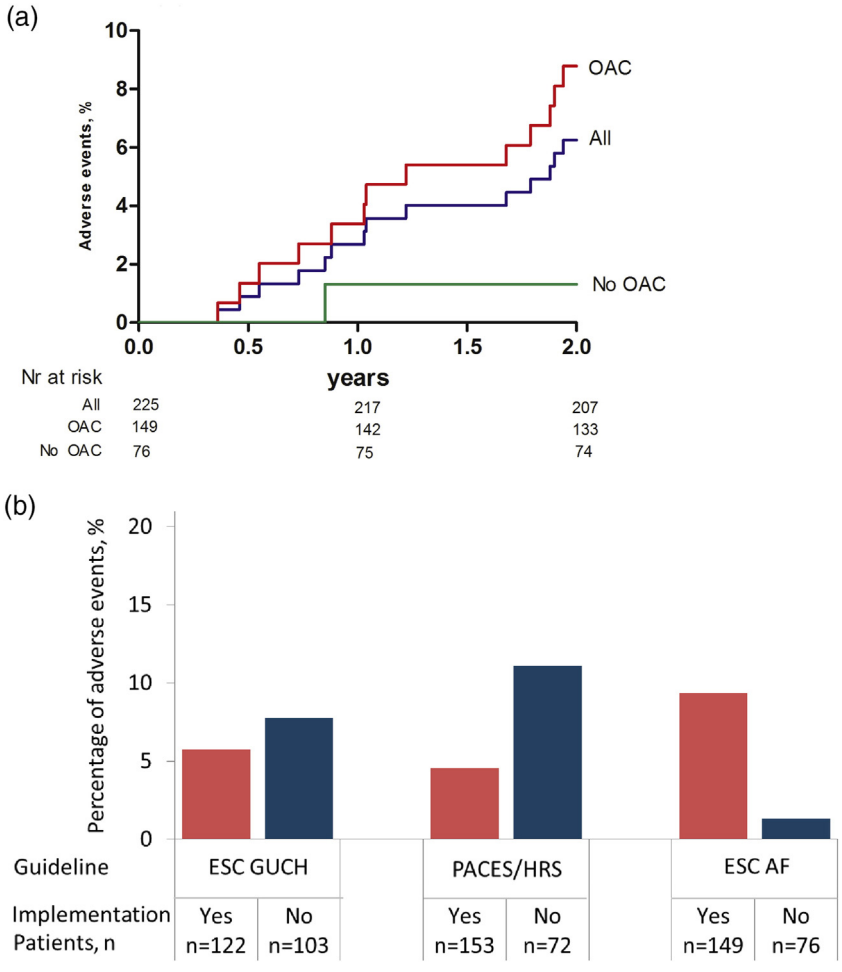

Fig. 2. a. Kaplan-Meier estimates of any adverse events in ACHD patients with atrial arrhythmias. Any adverse events were defined by death, thromboembolism and major bleeding. Adverse events are analyzed according to whether the patients were using oral anticoagulants. Abbreviations: ACHD = adult congenital heart disease, OAC = oral anticoagulants b. Percentage of adverse events in ACHD patients with atrial arrhythmias. Percentages of adverse events are illustrated according to whether the guidelines were implemented or not. Abbreviations: ESC GUCH = 2010 European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease, PACES/HRS = 2014 Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) recognition and management of arrhythmias in adult congenital heart disease (PACES/HRS), ESC AF = 2016 ESC guidelines for the management of atrial fibrillation.

consensus in any of the three guidelines, 80% of patients were treated conform recommendation, whereas considering treatment based on each individual guideline, only 54 to 68% of the patients were treated accordingly. Only in a few subgroups (Fontan circulation, cyanosis), guidelines were uniform in their recommendation and high implementation of these recommendations was observed. This may be due to the fact that these patients have clear predisposing pathophysiology to develop thromboembolism [14], although there are no robust studies of OAC in these subgroups (level of evidence C) [5].

Another important factor for increased implementation of the guidelines was the CHA2DS2-VASc score. To illustrate, a large majority of patients with a CHA2DS2-VASc score ≥ 1 in general (83%) and patients with simple lesions and a CHA2DS2-VASc score ≥ 2 (88%) were treated conforming to the guidelines. Recommendations on using CHA2DS2-VASc score to stratify thromboembolic risk are adopted in the PACES/HRS 2014 and the ESC AF 2016 guidelines (Table 1). Since the combination of these two guidelines showed the highest consensus among all guideline combinations (Fig. 1a), this may be the reason why these subgroups showed high implementation rate. Moreover, we expect most physicians to regard the risk of thromboembolism in ACHD patients similar to that of the general population. As they are used to the CHA2DS2-VASc score to stratify risk, they are likely to implement the score to their ACHD population. However, one has to bear in mind that CHA2DS2-VASc score has not been prospectively validated in ACHD patients with AA with only a few retrospective studies showing contradicting results. Whereas Heidendael et al. demonstrated that CHA2DS2-VASc with a cut-off of 2 predicted thromboembolic events, Khairy et al. could not demonstrate any difference in CHA2DS2-VASc score among patients with and without events [15,16].

Interestingly, implementation of the OAC guidelines was low in patients with Eisenmenger syndrome/severe pulmonary arterial hypertension (50%), Ebstein's anomaly (60%), ASD (66%), intracardiac repair (66%), systemic right ventricle (68%), and moderate (61%) and complex defects (72%). Such low implementation rates may be due to the lack of uniformity, and completeness in current guidelines. To illustrate, all the aforementioned patient groups are only specifically mentioned in one of the three guidelines. Also, the class and level of evidence for recommendations in patients with Eisenmenger syndrome/severe pulmonary arterial hypertension, Ebstein's anomaly and ASD are not cited in the guidelines [6]. Even if the class and level of evidence were cited in other guidelines (PACES/HRS 2014, ESC AF 2016), level of evidence would remain very limited (B—C) to most recommendations (Table 1). This may put into doubts whether guideline implementation would be effective and safe, possibly causing deviation from the guidelines.

The implementation rate of guidelines on the use of OAC in AA in ACHD is similar to the implementation rate in the general AF population [17,18,19]. Although the AA guidelines for the general population are considerably consistent compared with the AA guidelines for the ACHD patients, implementation rate of 100% is apparently difficult to achieve. Several reasons such as comorbidities for increased bleeding risk, inertia in practice patterns, and external barrier such as patient-refusal may underlie this behavior as demonstrated by two systematic reviews [20,21].

Based on our findings, we suggest using the CHA2DS2-VASc score as the primary thromboembolic risk calculator in ACHD patients with AA. Although there is currently no hard evidence to back up the CHA2DS2-VASc score in this specific patient population, we found that it is currently the most used, and the best implemented risk score. The only patient subgroup in whom OAC was used irrespective of CHA2DS2-VASs, was the Fontan population, which seems only logical considering their overall high thromboembolic risk, irrespective of the presence of arrhythmias. Clear guidelines on OAC treatment in ACHD patients in general, and for specific subgroups are warranted, as we found that physicians in general are hesitant to give long-term OAC to this relatively young group of patients with a CHA2DS2-VASc of 0.

4.2. Outcome per OAC treatment

Our findings show that adverse events mostly occurred in patients treated with OAC. This is probably due to the fact that patients treated with OAC had more often, other risk factors for adverse events compared with patients without OAC such as older age, higher CHA2DS2-VASc and HASBLED scores. Based on the percentage of adverse events per given OAC according to the guidelines, following the PACES/HRS 2014 guideline seems to result in the best outcome(Fig. 2b). Unfortunately, we were unable to demonstrate the superiority of any guideline implementation due to the low number of events. However, we speculate that although several CHD lesions with a CHA2DS2-VASc score of 0 have an indication for OAC according to the guidelines (i.e. ASD, all moderate lesions, lesions treated with intracardiac repair), they may not represent a high-risk group for thromboembolism after all. Further research is needed to verify the benefit of using OAC in all groups indicated by the contemporary guidelines.

4.3. Implications

Research in ACHD patients is often limited by small patient numbers. Accordingly, current guidelines are primarily based on small, retrospective studies and expert opinions. Therefore, it is important to investigate the implementation of current guidelines on OAC in ACHD patients with AA, and to reveal discrepancies between them, therewith evaluating the possibility of enhancement and unification of them.

Our study makes important observations, 1) the current guidelines are discrepant and confusing. They need more uniformity, 2) implementation of OAC guidelines for AA in ACHD patients seems random and suboptimal. Therefore, integration of the three existing guidelines and research on a better risk stratification for thromboembolism in ACHD patients with AA are needed to unify and strengthen the current OAC recommendations. This will lead to improved implementation of the guidelines in the future, resulting in more effective prevention of thromboembolism in ACHD patients with AA.

4.4. Study limitations

Our study carries the inherent limitation of a cohort study such as confounding by indication. Unfortunately, the confounders could not be corrected for outcome due to the low number of events, limited sample size and follow-up. Therefore, we could not demonstrate whether implementation of guidelines leads to better outcome. Furthermore, since all patients were included before the publication of the ESC AF 2016 guidelines, physicians could not have been aware of these guidelines. This may have contributed to the higher rate of non-implementation of these guidelines in this cohort. However, there was little change of OAC management during the 2 year follow-up (8 patients started OAC), which shows that this effect was limited. Of note, there are no specific recommendations in the ESC AF 2010 guidelines nor in the 2012 focused update version [6,22]. Also, as intracardiac repair lacked specified definition in their reference, our own definition may have misclassified patients with indication for OAC. At last, since this cohort is only from the tertiary referral centers in the Netherlands, treated under the Dutch health care system, our results may not represent clinical practice in other type of centers or countries.

5. Conclusions

The implementation of current guidelines on treatment with OAC in ACHD patients with AA is low. This could well be due to substantial heterogeneity and discrepancy among the guidelines. Only CHA2DS2-VASc, the presence of Fontan circulation and AF were associated with the prescription of OAC in daily practice. Therefore, efforts are needed to unify, simplify, and strengthen the current OAC recommendations in ACHD patients with AA.

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Disclosures

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Appendix A

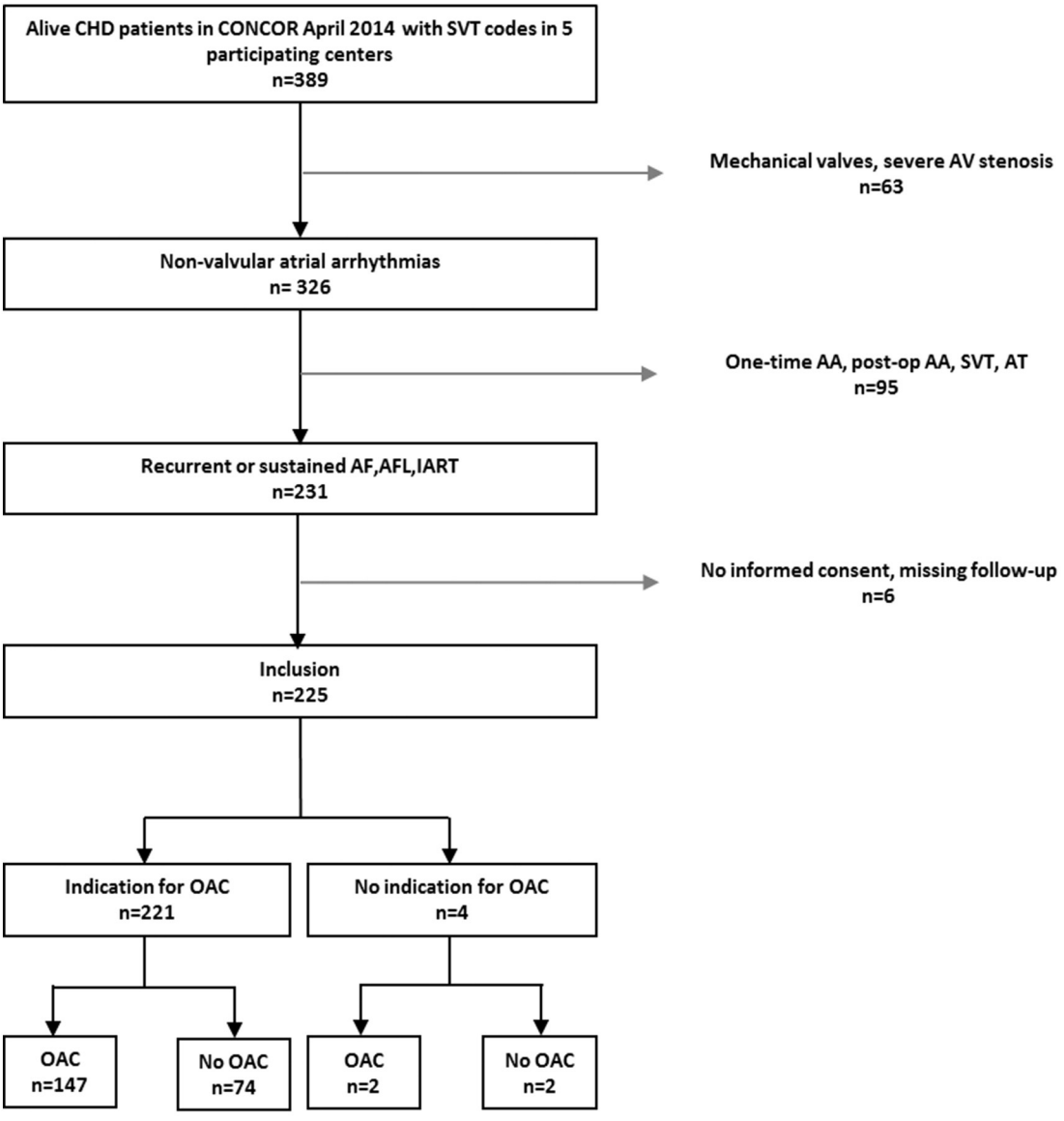

Fig. S1. Flow-chart of included study cohort. From 2014 to 2015, 225 patients with non-valvular atrial arrhythmias were included from 389 adult CHD patients in 5 tertiary centers. Abbreviations: AA = atrial arrhythmias, AF = atrial fibrillation, AFL = atrial flutter, AT = atrial tachycardia, AV = atrioventricular, IART = intra atrial re-entry tachycardia, CHD = congenital heart disease, CONCOR = CONgenital CORvitia registry, SVT = supraventricular tachycardia, OAC = oral anticoagulants.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.12.038.

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