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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.