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# Weighing the risks: Thrombotic and bleeding events in adults with atrial arrhythmias and congenital heart disease

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ABSTRACT

*Introduction:* Atrial arrhythmias are associated to thromboembolism and anticoagulant treatment is installed according to risk profile. This study aimed to assess the rate of thrombotic events and major bleedings in adults with congenital heart disease (CHD) and atrial arrhythmias, as well as to determine the predictive value of specific clinical features and two risk scores for thromboembolism and bleeding.

*Methods and results:* In this retrospective study, a total of 229 adult CHD patients with atrial arrhythmias, were included. Incidence and risk factors of thromboembolism were assessed in patients without a mechanical valve (n = 191), whereas bleeding incidence and risk factors were studied in patients receiving vitamin K antagonists (n = 164). In 13 patients without a mechanical valve thrombotic events occurred, the first thrombotic event rate per year being 1.4%. A total of 29 patients on vitamin K antagonists suffered from major bleedings, at an annual first event rate of 4.4%. $CHA_2DS_2$-VASc score and HAS-BLED score predicted thromboembolic and bleeding risk best in a dichotomized form. At a cut-off of ≥2 for high risk the rate of thrombotic events was 3.0% per year compared to 0.7% for a score of <2 (HR 3.7; 95%-CI 1.2–11.5; p = 0.021). A major bleeding rate of 10.8% per year was found in patients on vitamin K antagonists for HAS-BLED ≥ 2 as opposed to 3.5% with a score of <2 (HR 2.6; 95%-CI: 1.1–6.6; 0.017).

*Conclusion:* In adult CHD patients, thrombotic events and major bleedings are important complications of atrial arrhythmias and anticoagulant treatment. Assessment of thromboembolic and bleeding risk in this patients group can be performed with dichotomized $CHA_2DS_2$-VASc and HAS-BLED scores respectively.



## 1. Introduction

Atrial arrhythmias occur in 15% of adult patients with congenital heart disease (CHD) [1,2]. Most common are atrial fibrillation and intra-atrial reentry tachycardia (IART), a flutter-type arrhythmia often arising from post-incisional reentry [3,4]. Thromboembolic prevention in atrial arrhythmias has been a subject of debate for decades and much effort has been put in the development of accurate risk assessment for thromboembolism and bleeding in non-CHD patients, for example with the $CHA_2DS_2$-VASc [5,6] and the HAS-BLED score [7,8] respectively. These risk scores enable a balanced decision to install long-term anticoagulant treatment. Where reliable data are widely available for acquired heart disease, only a few studies have addressed the issue of thromboembolic risk in atrial arrhythmias in CHD patients. These studies demonstrated a higher risk of stroke in atrial arrhythmias (HR 1.6) [1], a higher prevalence of stroke in patients without sinus rhythm versus the entire population (4% vs. 2%) [9], and the presence of intra-atrial thrombi assessed with transesophageal echocardiography in less than half of CHD patients with IART [10]. Data on the incidence of thromboembolism are limited. Since the adult CHD population differs in various factors from the general population with atrial arrhythmias, such as a younger age and obviously the presence of a structural heart defect, it is uncertain whether the established thromboembolic and bleeding risk scores are reliable in CHD patients. Therefore, the decision to start long-term anticoagulant treatment in CHD patients remains a piercing question, calling for clarification.

This study aimed to provide insights in the rate of thrombotic events and major bleedings in adult patients with CHD and atrial arrhythmias. Secondly, we assessed the predictive value of specific clinical features and two established risk scores for thromboembolism and bleeding.

## 2. Methods

We performed a retrospective, observational cohort study, between 2002 and 2014. Patients were selected from the CONCOR registry, a national database of CHD patients that comprises most of the CHD population under regular medical care in the Netherlands since 2002 [11]. The records of all registered adult (≥18 years) CHD patients in one

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tertiary reference center with diagnostic codes for supraventricular tachycardia (SVT) in the CONCOR registry, were screened. Patients were included in case of a documented diagnosis of atrial fibrillation, IART (including atrial flutter), or atrial tachycardia. Patients with SVTs other than atrial arrhythmias were excluded. Baseline was set at first registration in CONCOR or at first diagnosis of atrial arrhythmia thereafter. We stratified for this difference of either pre-existing or new-onset atrial arrhythmias at baseline. The flowchart in Fig. 1 displays the inclusion process.

Baseline characteristics and follow-up data were collected from medical charts up to the latest record before January 2014. Primary endpoints were thrombotic events and major bleedings. Thrombotic events were defined as ischemic cerebrovascular accident (iCVA), transient ischemic attack (TIA), pulmonary embolism, systemic embolism and intracardiac thrombosis. Major bleedings were defined as intracranial hemorrhage, fatal bleeding, or any symptomatic bleeding leading to a drop of hemoglobin of ≥2 g/dL, the need for ≥2 packed cells, an intervention or hospitalization, according to the International Society of Thrombosis and Hemostasis criteria [12]. At baseline the following definitions applied. Complexity of CHD was defined according to the proposed classification by Warnes et al. in 2001 [13]. Artificial intracardiac materials consisted of patch, conduit, annuloplasty, septal occlusion device and pacemaker lead. Heart failure was defined as the presence of symptoms of congestive heart failure and/or moderately to severely abnormal left or right ventricle function in the echocardiography report or as left or right ventricle ejection fraction < 40% on MRI. Echocardiographic assessment of biventricular function was performed according to the latest guidelines, during the study timeline [14,15]. Ventricular function was assessed at baseline. Vascular disease was defined as acquired coronary or peripheral artery disease. Impaired renal function was registered at a cut off of creatinine ≥ 200 mmol/l [7]. Impaired liver function was defined as transaminases (AST/ALT) or alkaline phosphatase 3× upper limit of normal (ULN), bilirubin 2× ULN or cirrhosis [7]. Alcohol usage was defined as the documentation of ≥8 units of alcohol consumption per week [7]. Two risk scores for thromboembolism and bleeding were evaluated: the $CHA_2DS_2$-VASc score, composed of heart failure, hypertension, advanced age, diabetes mellitus, prior TE, vascular disease and female gender [5,6] and the HAS-BLED score consisting of hypertension, liver- and renal dysfunction, prior stroke, prior bleeding, labile INR's advanced age (≥65 years) and use of non-steroidal drugs, antiplatelet or alcohol [7,8]. INR measurements and data on alcohol consumption were only available in a few patients. If no information was available, no points were assigned to these items in the HAS-BLED score.

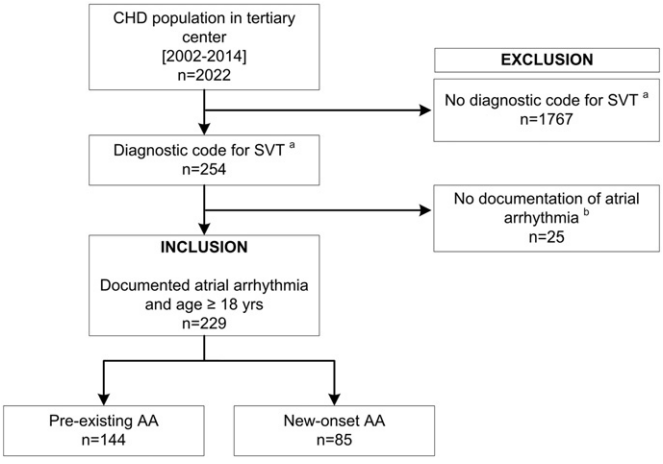


**Fig. 1.** Flowchart of inclusion of study population. [a]All diagnostic codes for SVT used in Concor registry: Supraventricular rhythm disturbances, supraventricular tachycardia, ectopic (automatic) atrial tachycardia, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia. [b]AV (nodal) rhythm disturbance (5), sinus nodal dysfunction (3), no documentation of SVT (15) and lost to follow-up (2). CHD, congenital heart disease; SVT, supraventricular tachycardia; AA, atrial arrhythmia.

### 2.1. Statistical analysis

Baseline characteristics were presented as absolute numbers (%), or median (interquartile range). Differences between the two baseline cohorts were evaluated using $Chi^2$ statistic or Mann–Whitney U test as appropriate. Significance was defined as $p < 0.05$ (2-sided). For the primary endpoints, time to event curves and cumulative incidences with standard error (±SE) were calculated as the complement of the Kaplan–Meier estimator with Log-rank test for comparison. First event rates were calculated by dividing the amount of all first events by the sum of all patients-years up to first event. The effects of putative risk factors for thromboembolism and bleeding were tested in a stepwise backward Cox-regression model and hazard ratios at a significance level of $p \leq 0.1$ were presented with 95% confidence intervals (95%-CI) in a table. Because of the low number of events we decided not to perform multivariate analysis. The strength of the risk scores and best cut-off for age were assessed with a receiver operator characteristic curve.

Thrombotic event rate and risk factors were assessed in patients without a mechanical valve (n = 191), to obtain a study population with nonvalvular atrial arrhythmias. Ten patients received a mechanical valve during follow-up. These patients were censored at time of valve implantation. For comparison of patients with and without mechanical valves, all events that occurred after valve implantation were analyzed in the population with mechanical valves. Bleeding incidence and risk factors were studied in patients receiving vitamin K antagonists (n = 164). For these analyses the follow-up time on vitamin K antagonists was used, and the time without anticoagulation was not taken into account. Separate analyses were performed in patients with univentricular heart physiology (UVH).

## 3. Results

### 3.1. Patient cohort

A total of 229 patients were included in the study. Baseline characteristics are presented in Table 1. Median age was 42 years (32–57) and gender was evenly distributed. Overall, 37% of patients had mild CHD, 41% moderate CHD, and 23% severe CHD. Valvular surgery had been performed in 39%, and 17% had a mechanical valve. Atrial fibrillation was diagnosed in 65% of patients, IART (including atrial flutter) in 33% and atrial tachycardia in 10%; 17 patients had more than one type of atrial arrhythmia. Heart failure and hypertension were the most common cardiovascular risk factors (21% and 19% respectively).

Baseline variables between new onset (n = 85, 37%) and pre-existing atrial arrhythmia (n = 144, 63%) were similar, except for a higher age in pre-existing atrial arrhythmia, a slightly different distribution of CHD type and more concomitant vitamin K antagonists and antiplatelet (APT) usage in patients with new-onset atrial arrhythmia.

### 3.2. Time to event analyses of thrombotic events and major bleedings

During a median follow-up of 6 years (IQR 2–9) 27 thrombotic events occurred in 20 patients, of whom 7 patients had a mechanical valve. A total of 36 major bleedings occurred in 32 patients, of whom 29 patients were receiving vitamin K antagonists. The thrombotic events consisted of 11 iCVAs, 9 TIAs, one pulmonary embolism, 2 systemic embolisms and 4 intracardiac thromboses. Only one intracardiac thrombosis occurred as a first event in the population without mechanical valves. Three intracranial hemorrhages occurred. Most other major bleeding events were gastro-intestinal (n = 9), post-operative (n = 7) and intramuscular (n = 6) bleedings, 4 of which were fatal (Supplementary Table 1). Cumulative incidences of TE in patients without a mechanical valve and major bleeding in patients on vitamin K