Novel Oral Anticoagulant Use in Adults With Congenital Heart Disease: a Single-center Experience

Daniel Samarai (samaraidaniel@gmail.com)
Lund University Faculty of Medicine: Lunds universitet Medicinska fakulteten https://orcid.org/0000-0001-6423-1105
Nazim Isma
Lund University: Lunds Universitet
Sandra Lindstedt
Lund University: Lunds Universitet
Joanna Hlebowicz
Lund University: Lunds Universitet

Research

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Abstract

Introduction

Adults with congenital heart disease (ACHD) are a group with an increased risk of thromboembolic complications and arrhythmias. Vitamin K antagonists (VKA) are the most commonly used thromboprophylaxis therapy in this population. Studies on the efficacy and safety of novel oral anticoagulants (NOAC) are scare, but emerging together with their increasing use.

Methods

ACHD patients taking NOAC treatment were identified in AuriculA, a Swedish national quality register for atrial fibrillation and anticoagulation. Data on duration of treatment and patient characteristics were provided by the Register. CHA_2DS_2-VASc and HAS-BLED scores for atrial fibrillation were calculated. CHD severity was determined according to guidelines. Thromboembolic and major bleeding events were provided by AuriculA.

Results

30 patients who had been taking NOAC treatment for a minimum of 3 months were included. Their median age was 55 years (SD 17 years) and 57% were male. Median follow-up was 17 months (IQR: 10-41). Apixaban was the most commonly used NOAC (47%). Median CHA_2DS_2-VASc score was 2 (IQR: 0-3) and HAS-BLED was 1 (IQR: 0-2). Complex CHD was prevalent in 27% of the patients. No thromboembolic events were recorded; however, one major bleeding, unspecified, was reported during the total cumulative patient follow-up time of 64 years.

Conclusion

The results of our study, although limited in size, suggest NOAC to be a non-inferior alternative to VKA in a heterogenic study group with a balanced inclusion of CHD severity defects. Further and larger studies on VKA and NOAC in ACHD patients are warranted.

Introduction

Adults with congenital heart disease (ACHD) are a patient group with an increased risk of thromboembolic complications and arrhythmias (1, 2). The patient group is often anatomically heterogenic, attributing the increased risk of thromboembolism to multiple factors. A sufficient anticoagulant therapy for thrombophylaxis indication is, therefore, a fundamental and essential treatment. NOAC, non-vitamin K oral anticoagulants, including the direct thrombin inhibitor dabigatran and factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) are emerging clinically in the general population; however, they are used in a restricted manner in adults with CHD due to limited data on safety and efficacy. Vitamin K antagonists (VKA) are therefore the treatment of choice in these patients. The quality of VKA treatment can vary over time, being influenced by the intensity of the treatment, measured

as time in therapeutic range (TTR) and also the variability of the international normalized ratio (INR). A suboptimal treatment, specifically with a low TTR and high INR variability, has been shown to increase the risk of adverse events (3). In a Swedish study of ACHD patients with an average VKA treatment of good quality, the incidence of thromboembolism and major bleeding was low (4). In ACHD patients treated with NOAC, a systemic review reported a low annual rate of thromboembolic and major bleeding events (5). AuriculA, created in 2006, is a Swedish national quality register for atrial fibrillation and anticoagulation, which includes patient characteristics, indications and complications. As data on safety and efficacy are scarce and of value in this patient group, our aim was to report our experience of NOAC in ACHD patients, including the incidence of thromboembolism and major bleeding events.

Methods

SWEDCON, the Swedish National Quality Registry for Congenital Heart Disease was used to identify retrospectively all ACHD patients in the South Region of Sweden (Region Skåne) who had a registered use of oral anticoagulation (n = 424). AuriculA was used in the next stage to identify all patients who had taken NOAC therapy (n = 33). A minimal therapy of 3 months was set as an inclusion criterion; one patient was excluded. Two patients were excluded for being duplicates.

Gender, age, treatment indication, type of anticoagulant, data on thromboembolic events and major bleeding events, and dates of starting and finishing anticoagulation were provided by AuriculA. SWEDCON provided the main congenital heart defect diagnosis, comorbidities and interventions. Medical records of the patients were also reviewed for diagnoses and events. CHA_2DS_2-VASc and HAS-BLED scores for the calculation of atrial fibrillation stroke risk were calculated at the time of each NOAC initiation. Start and stop date of anticoagulation therapy in the patient's medical record also determined the duration of therapy. Congenital heart defects were classified into simple, moderate and complex according to guidelines (6).

Complications registered by AuriculA were according to ISTH (International Society on Thrombosis and Haemostasis) definitions for major bleeding and clinically verified arterial or venous thrombosis (7, 8). Minor bleedings were not searched for due to unreliable accessibility in medical journals.

Descriptive statistics were used to summarize characteristics. Results were presented as median with SD or interquartile range (IQR), percentages and 95% confidence intervals (CI). Calculations and analyses were performed using SPSS Statistics Version 25 and Microsoft Excel Version 15.41. The study was approved by the Regional Ethical Review Board in Lund.

Results

Thirty adults with congenital heart disease were identified with NOAC as the anticoagulation therapy. The median age was 55 years (SD 17 years) with a slight male predominance (57%). The predominant indication was atrial arrhythmia (87%) with five patients also having bioprosthetic valves.

Apixaban was the most commonly used NOAC (47%) followed by rivaroxaban (30%) and dabigatran (23%). Severity of the defects was predominantly simple-moderate (67%) with 27% being complex. Hypertension was the most common comorbidity (30%).

Median CHA_2DS_2-VASc was 2 points (IQR: 0–3) with 12 patients (40%) having a score higher than the median. The median HAS-BLED score was 1 point (IQR: 0–2), with 57% having a score lower than 2 points. In a total cumulative duration of 63 years of follow up, no thromboembolic events were noted. One major bleeding event was recorded, described as “other”, not intracranial or gastric, giving an annual rate of 1.58 (95% CI: 0.08–7.78). The patient concerned was a female, 46 years of age, with Fallot’s tetralogy (moderate CHD) who was treated with rivaroxaban. She had a CHA_2DS_2-VASc score of 1 and HAS-BLED 0. The bleeding occurred after 19 months of treatment.

The most common cause of discontinued treatment was according to plan (16.7%), followed by a new indication (6.7%) and change to another anticoagulation (6.7%).

Discussion

This retrospective study reports a single-center experience of NOAC use in ACHD patients and found no thromboembolic and major bleeding events during a median duration of 17 months of therapy.

Studies of NOAC use in ACHD patients are emerging, but limited. A systemic review of NOAC use in ACHD patients included three studies with a total number of 766 patients. The annual rate of thromboembolic and major bleeding events was 0.98% (95% CI: 0.51–1.86) and 1.74% (95% CI: 0.86–3.49), respectively. One study included Fontan patients only, reporting a higher annual rate of both events, confirming the increased risk of thromboembolism in ACHD patients of complex severity (9). The two largest studies included 530 and 215 patients, not Fontan-exclusive (10, 11). In these studies, the rate of complex severity of ACHD was 40% and 44.2% and six and two thromboembolic events were registered, respectively. The total patient-years of follow-up was 896.3 years. Compared to our total patient-years of follow-up of 63.7 years, the low incidence of adverse events in our studies is plausible. However, compared to the largest included study of 530 patients, the median follow-up was 1 year, compared to 17 months in ours (10). Furthermore, the prevalence of complex ACHD severity, which is a major risk factor for thromboembolism (12), was only 27%. CHA_2DS_2-VASc > 2 was between 46.4–49.3% comparable to 40% in our study. For HAS-BLED, however, the scoring differed, with our study having 57% <2 points and the other two studies reporting a higher 87.5–95% <2 points (10, 11). The risk of bleeding could thus be described to be higher in our study group, but the thromboembolic risk was lower with regard to the prevalence of complex severity defects and CHA_2DS_2-VASc scores. The above-mentioned factors together with the lower patient-years of follow-up could be an explanation for the low rates of thromboembolism and bleeding.

The incidence of thromboembolism and major bleeding events in ACHD with good quality VKA therapy was reported in a Swedish study with 213 patients from the same center: 1.0 (95%CI: 0.6–1.6) and 1.4

(95%CI: 0.9–2.2), respectively. In this study, the median duration of therapy was 6.6 years (± 3.3 years) (13). The follow-up time was longer and could, in our study, be a reason for an underestimated incidence of events. Risk factors, such as female gender, lower age, heart failure and history of thromboembolism, for poor anticoagulation and complications (thromboembolism and major bleeding) in ACHD patients with VKA therapy could be reasons to consider NOAC as an alternative(13). As heart failure is one of the strongest predictors for stroke, an increased risk of renal failure in these patients may make VKAs a more plausible choice (1). NOAC was mostly discontinued according to plan, a new indication and change to another anticoagulant. Bleeding, other diseases and poor compliance were other less common causes for stopping NOAC therapy. As ACHD patients interact with health care at a younger age, compliance has been problematic. NOAC therapy can be an advantage in this patient group, especially for younger patients with normal heart and kidney function. NOAC can also be advantageous in patients on polypharmacy, which can interact with VKA. The benefits of NOAC, such as less regular blood tests, changing of dosing and consideration of food intake, could possibly appeal to younger patients and replace a potentially low compliance VKA therapy with its increased risk of thromboembolic events.

When comparing effectiveness and safety of NOAC to VKA for atrial fibrillation and venous thromboembolism, a systemic review and meta-analyses concluded NOAC to be comparable or superior to VKA in a non-ACHD population. The study suggested individualizing the choice of anticoagulation therapy based on the benefit and safety patient profiles and characteristics (14). Use of NOAC in ACHD patients is emerging with data showing effectiveness and safety, although with caution as studies are rather small and study populations are typically heterogenic. NOAC may thus seem like a practical anticoagulation alternative when patient profiles and characteristics are associated with poor anticoagulation and complications.

Conclusion

The results of our study, although limited in size, suggest NOAC to be a non-inferior alternative to VKA in a heterogenic study group with a balanced inclusion of CHD severity defects. Further and larger studies on VKA and NOAC in ACHD patients are of interest.

Limitations

Small population. Unable to perform multivariate analysis for potential risk factors. Adherence is unknown and difficult to evaluate. The follow-up was not long. Heterogeneity of ACHD population. Patients predominately simple-moderate severity of defects. Retrospective study design.

Declarations

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Conflict of interest

None to declare.

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Availability of data

Data may be available on request.

Author contributions

DS, SL, NI and JH contributed to the conception or design of the work. DS, NI, SL and JH contributed to the acquisition, analysis, or interpretation of data for the work. DS drafted the manuscript. NI, SL and JH critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Tables

Table 1
Demographics, severity of CHD, comorbidities and results of CHA_2DS_2-VASc and HAS-BLED scores.

Demographics	
All patients (n)	30
Gender	17 male (57%): 13 female (43%)
Median age*	55 years (SD 17 years)
Median duration of therapy (months)	17 (Min-max: 3–71)
Total cumulative duration of therapy (months)	764
Complications	
Events during therapy	1
Thrombotic or thromboembolic events	0
Bleeding events	1
Severity of CHD*	
Simple	9
Moderate	11
Complex	8 (27%)
Unclassified	2
Defect repaired	27 (90%)
Bioprosthetic valves	5
Indication for anticoagulation	
Atrial arrhythmia	26
Venous thromboembolism	1
Other	3
Comorbidities	
Hypertension	9 (30%)
Diabetes	4 (13%)
Type of NOAC	
Apixaban	14
Rivaroxaban	9

Demographics	
Dabigatran	7
Scores	
Median CHA_2DS_2-VASc	2 (IQR: 0–3)
0	8
1	4
2	6
3	10
4	1
5	1
Median HAS-BLED	1 (IQR: 0–2)
0	13
1	4
2	12
3	1

Table 2
Causes for discontinued NOAC treatment.

Causes	**Number (n)**
According to plan	5
Due to bleeding	1
Due to other diseases	1
Due to poor compliance	1
Due to new indication	2
Change to other anticoagulation	2