Atrial Arrhythmias and Patient-Reported Outcomes in Adults with Congenital Heart Disease: an International Study

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ABSTRACT

Background: Atrial arrhythmias, i.e., intra-atrial reentrant tachycardia and atrial fibrillation, are a leading cause of morbidity and hospitalizations in adults with congenital heart disease (CHD). Little is known about their effect on quality of life and other patient-reported outcomes (PROs) in adults with CHD.

Objective: To assess the impact of atrial arrhythmias on PROs in adults with CHD and explore geographic variations.

Methods: Associations between atrial arrhythmias and PROs were assessed in a cross-sectional study of adults with CHD from 15 countries spanning 5 continents. A propensity-based matching weight analysis was performed to compare quality of life, perceived health status, psychological distress, sense of coherence, and illness perception in patients with and without atrial arrhythmias.

Results: A total of 4,028 adults with CHD were enrolled, 707 (17.6%) of whom had atrial arrhythmias. After applying matching weights, patients with and without atrial arrhythmias were comparable with regards to age (mean 40.1 versus 40.2 years), demographic variables (e.g., 52.5% versus 52.2% women), and complexity of CHD (i.e., 15.9% simple, 44.8% moderate, and 39.2% complex in both groups). Patients with atrial arrhythmias had significantly worse PRO scores with respect to quality of life, perceived health status, psychological distress (i.e., depression), and illness perception. A summary score that combines all PRO measures was significantly lower in patients with atrial arrhythmias (-3.3%, $P=0.0006$). Differences in PROs were consistent across geographic regions.

Conclusion: Atrial arrhythmias in adults with CHD are associated with an adverse impact on a broad range of PROs consistently across various geographic regions.

Keywords: Atrial fibrillation; Intra atrial reentrant tachycardia; congenital heart disease; quality of life; patient-reported outcomes

INTRODUCTION

Atrial arrhythmias are prevalent in up to 20% of adults with congenital heart disease (CHD).¹ Intra-atrial reentrant tachycardia (IART) is the most common presenting atrial arrhythmia, followed by atrial fibrillation (AF).² These arrhythmias have been associated with heart failure, thromboembolic events, and sudden death, and are a leading cause of hospitalizations in this patient population.³ Although much attention has been directed towards reducing the incidence of adverse cardiovascular events resulting from atrial arrhythmias in adults with CHD, little is known about their association with quality of life and other patient-reported outcomes (PROs). Cardiovascular societies have increasingly recognized the critical role of outcomes reported directly by patients, particularly those with chronic diseases, in assessing patient well-being and morbidity. As such, they have called for cardiovascular research to shift its focus to include PROs in comprehensive and holistic evaluations that inform decision-making.⁴

Herein, we sought to assess the impact of atrial arrhythmias in the largest study of PROs conducted in adults with CHD. The Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease - International Study (APPROACH-IS) enrolled over 4,000 patients from 15 countries spanning 5 continents.⁵ Outcomes included quality of life, perceived health status, psychological distress, sense of coherence, and illness perception. In addition, we explored potential geographic variations.

METHODS

Study population

The design and methods of APPROACH-IS have previously been reported (ClinicalTrials.gov NCT02150603).⁵ In brief, APPROACH-IS is an international cross-sectional study of 4,028 adults with CHD from 24 centers. In partnership with the

International Society for Adult Congenital Heart Disease (ISACHD), patients were enrolled between 2013 and 2015 from Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Taiwan, the Netherlands, Sweden, Switzerland, and USA. Patients were required to be diagnosed with CHD prior to adolescence, be ≥ 18 years of age, and possess physical, cognitive, and language capabilities required to complete self-report questionnaires. Those who had a cardiac transplantation were excluded. All patients enrolled in APPROACH-IS completed PROs and qualified for this substudy on atrial arrhythmias. The study was conducted in accordance with the International Council of Harmonization Tripartite Guidelines for Good Clinical Practice and adhered to the Helsinki Declaration as revised in 2013. The study was approved by the institutional review board of each participating center. All patients consented to participate.

Data collection and atrial arrhythmias

Demographic data including age, sex, education level, marital status, religion, ethnicity, and smoking status were collected from a self-reported questionnaire. Details of the medical history were extracted from patient records by site investigators. Medical history data included type of CHD, other medical conditions, cognitive impairment, cardiac implantable electronic devices (i.e., pacemakers and defibrillators), and atrial arrhythmias. Type of CHD was categorized according to complexity (i.e., simple, moderate, or complex) based on a previously defined classification scheme.⁶

The data collection form for APPROACH-IS requested that the type of arrhythmia, if present, be specified. For the purpose of the current analysis, sustained intra-atrial reentrant tachycardia (IART) and atrial fibrillation (AF) were grouped together as “atrial tachycardia”. Atrial fibrillation was diagnosed on the basis of standard definitions.⁷ The term IART encompassed all forms of rapid and regular atrial rhythms, including typical and reverse

typical atrial flutter, scar-based macroreentrant tachycardia, microreentrant atrial tachycardia, lower loop flutter, double wave reentry, and left atrial reentrant tachycardia,⁸ while excluding accessory pathway-mediated tachycardia and atrioventricular nodal reentrant tachycardia.

Patient-reported outcomes

The PROs assessed in APPROACH-IS have previously been described⁵ and are summarized in Table 1. Quality of life, which refers to the extent of satisfaction with life,⁹ was assessed by two metrics. The linear analogue scale (LAS) of quality of life is a graded vertical scale ranging from 0 (worst) to 100 (best) imaginable quality of life. The Satisfaction With Life Scale (SWLS) consists of a survey that assesses overall life satisfaction.¹⁰ Perceived health status, which captures the perceived impact of the disease on health-related quality of life, functional status, and symptoms,¹¹ was assessed by the 12-item Short-Form Health Survey version 2 (SF-12) and European Quality of Life – 5 Dimension (EQ-5D) score.¹² The SF-12 is further divided into physical (PCS) and mental (MCS) component scores. Anxiety and depression, two elements of psychological distress, were assessed by the Hospital Anxiety (HADS-Anxiety) and Depression (HADS-Depression) Scale.¹³ Sense of coherence (SOC), which refers to the extent to which one feels confident that one's environment is predictable and that demands will work out as well as could be reasonably expected,¹⁴ was assessed by the Orientation to Life Questionnaire.¹⁵ Illness perception, i.e., cognitive representations or beliefs about one's illness, was evaluated by the Brief Illness Perception Questionnaire (Brief IPQ).¹⁶ Finally, a composite score was developed by APPROACH-IS investigators (APPRtot) to assess total well-being by incorporating the various PROs.¹⁷

Statistical analyses

Categorical variables are summarized by frequency and percentage and continuous variables by mean $\pm$ standard deviation or median and interquartile range (IQR) as appropriate. A propensity-matched analysis was used to assess the impact of atrial arrhythmias on PROs. To balance patient characteristics among those with and without atrial arrhythmias, a matching weight (MW) approach was applied.¹⁸ A non-parsimonious logistic regression model with atrial arrhythmias modeled as the dependent variable was fitted to estimate propensity scores and calculate MWs based on inverse probability weighting.¹⁸ Patient-level variables included in the logistic regression model are listed in Table 2. A LOVE plot was created to compare the percentage of pooled weighted standard deviations for the values of standard differences in weighted means or weighted proportions for each covariate among patients with and without atrial arrhythmias. An absolute standardized difference <10% was considered to indicate excellent balance between groups and was obtained for all covariates.

Centers were categorized into four geographical regions: Europe (Belgium, France, Italy, Malta, Norway, Sweden, Switzerland and the Netherlands); Americas (Canada, United States of America and Argentina); Eastern region (India and Taiwan); and Pacific region (Australia and Japan). Two-sided P-values less than 0.05 were considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.2.5 (RStudio, Inc., Boston, MA).

RESULTS

Baseline characteristics

A total of 4,028 adults with CHD patients were enrolled, of whom 707 (17.6%) had atrial arrhythmias. Patient characteristics before and after application of MWs are presented in Table 2. Prior to matching, CHD patients with atrial arrhythmias were older (mean 41.4 vs

32.3 years) and were more likely to have complex forms of CHD (42.0% vs 23.5%) compared to those without atrial arrhythmias (standardized mean difference >10% for both). The proportion of women was similar between groups (52.8% vs 53.6%, standardized mean difference <10%). After matching, all patient characteristics included in the propensity-score model were well-balanced between the groups with and without atrial arrhythmias (Figure 1; standardized mean differences <5% for all variables).

Impact of atrial arrhythmias on outcomes

Patients with atrial arrhythmias had a higher hospitalization rate in the preceding year (29.7% versus 13.8%, $P<0.0001$) and more hospital admissions in adulthood [median of 2 (IQR 1, 3) versus 0 (IQR 0, 1), $P<0.0001$] when compared to those without atrial arrhythmias. Moreover, patients with arrhythmias required more frequent follow-up visits than those without (e.g., at least twice per year in 43.2% versus 24.0%, $P<0.0001$).

As summarized in Table 3, atrial arrhythmias were associated with consistently worse PROs across the spectrum of domains measured, with significantly poorer scores related to quality of life (SWLS, $P=0.002$), perceived health status (SF-12 PCS, $P<0.0001$; SF-12 MCS, $P=0.001$; EQ-5D, $P=0.019$), psychological distress (HADS-Depression, $P=0.049$), and illness perception (Brief IPQ, $P<0.0001$). The PRO scores that did not differ statistically between groups (i.e., LAS, EQ-VAS, HADS-Anxiety, and SOC) showed non-significant trends toward worse outcomes in patients with atrial arrhythmias, with P-values that ranged from 0.06 to 0.07. The PRO composite score, i.e., APPRtot, was significantly lower (i.e., indicative of poorer outcomes) in patients with atrial arrhythmias (72.4 ± 14.0 versus 74.9 ± 14.0 , $P=0.0006$).

Geographic variations in PROs in patients with and without atrial arrhythmias

As shown in Figure 2, mean differences in PRO scores in patients with and without atrial arrhythmias were generally consistent across geographic regions. Overlapping 95% confidence intervals were observed for all PROs except LAS in which scores were lower in patients with atrial arrhythmias in all geographic regions except Eastern countries. Patients with atrial arrhythmias from the Pacific region had the greatest reduction in LAS score, albeit with a wide confidence interval.

DISCUSSION

Atrial arrhythmias are frequently encountered in adults with CHD.^{1,3} The incidence of atrial arrhythmia increases with age such that the prevalence of IART or AF has been reported to be nearly 40% in adults with CHD over the age of 50 years.¹⁹ Both can be poorly tolerated and lead to an increased rate of morbidities and hospitalizations, as observed in our study.^{3,19} To our knowledge, this is the first study to comprehensively assess the impact of atrial arrhythmias on PROs in adults with CHD. Our key findings are: 1) atrial arrhythmias in CHD are associated with poor PROs including quality of life, perceived health status, psychological distress, and illness perception; and 2) differences in PROs in CHD patients with and without atrial arrhythmias are generally consistent across geographic locations.

Impact of atrial arrhythmias on PROs

In patients without CHD, AF is a well-established predictor of worse PRO scores and, hence, poorer quality of life.²⁰ The recurrent nature of these arrhythmias may lead to inherent psychological uncertainty further exacerbated by the medical regimens recommended for effective management. Medical visits, symptoms, and complications associated with AF (e.g., stroke and heart failure) appear to contribute to worse PROs.^{21,22} Consistently, alleviation of

1 symptoms^{23, 24} and the need for less frequent thromboprophylaxis monitoring with direct
2 acting oral anticoagulants^{25, 26} have been shown to improve quality of life.

3 The current study expands these findings to patients with CHD who must also endure
4 the uncertainty of their illness. In this population, atrial arrhythmias were associated with
5 poorer quality of life, lower perceived mental and physical health status, greater psychological
6 distress, and a worse perception of illness. Defining clinically meaningful changes in PROs
7 remains controversial, with antagonists who oppose the concept claiming that single threshold
8 values are misleading by virtue of conceptual problems, dependency on the distributional
9 index, and a variable meaning of change according to baseline values.²⁷ Nevertheless, to place
10 these findings in perspective, prior studies have considered a 3 to 5 point change in SF-12 to
11 be clinically important.²⁸ Differences observed in the population of adults with CHD with and
12 without arrhythmias meet this criterion. To further contextualize our findings, the between-
13 group differences in our study surpassed the statistically significant mean differences in SF-
14 12 PCS and MCS scores reported in a meta-analysis of randomized trials of catheter ablation
15 versus medical therapy for AF (i.e., 0.57 and 0.56, respectively).²⁹ It remains to be determined
16 whether arrhythmia treatment strategies and/or targeted psychoeducational interventions
17 could mitigate the adverse impact of atrial arrhythmias on PROs in patients with CHD.

19 **Effect of comorbidities on PROs in adults with CHD**

20 Little is known about the impact of comorbidities on PROs in adults with CHD. As a chronic
21 lifelong disease, CHD itself has been associated with an inconsistent reduction in quality of
22 life.^{30, 31} However, in patients with CHD, older age, severity of illness, and more advanced
23 functional class symptoms predict worse PRO scores.³¹⁻³³ Moreover, the presence of an
24 implantable cardioverter-defibrillator has been associated with a more threatening view of
25 illness in adults with CHD, with a worse quality of life in those with secondary prevention

indications.³⁴ The current study adds to the growing knowledge base by demonstrating that atrial arrhythmias should be considered among the important predictors of worse PROs, with an influence that extends across a broad spectrum of domains.

Geographic variability

With the exception of the LAS, the magnitude of reduction in PRO scores due to atrial arrhythmias was reasonably coherent across regions, regardless of variations in individual PRO scores between regions. In adults with CHD as a whole, marginal regional variations in PRO scores have been attributed to differences in standard of living and health care systems.¹⁷ The absence of marked regional variations in PROs due to atrial arrhythmias is consistent with the fact that both standard of living and health care systems remain constant in two-group comparisons within each geographical region.

There is a paucity of studies on geographic variations in PROs related to atrial arrhythmias in patients without CHD. One small study (N=129) that compared patients with AF in the USA and South Korea suggested that culture had an interactive effect on PRO scores.³⁵ Future studies are warranted to determine the association between country-specific factors on PROs in patients with atrial arrhythmias.

Limitations

Although APPROACH-IS is the largest international study of its kind in adults with CHD, its design is cross-sectional such that causality cannot be inferred. A volunteer bias (type of selection bias) may be present if study participants were more cognizant about their health or more symptomatic than the general CHD population. The MW approach is recognized as a highly effective means of creating comparable groups with regards to measured covariates but cannot directly adjust for potential confounders for which data were not collected. Given the

1 overlap and frequent coexistence of IART and AF and the fact that diagnoses were based on
2 data reported in case-report forms by site investigators without an independent adjudicating
3 committee, the impact of subtype of arrhythmia on PROs was not assessed. The study did not
4 collect data on catheter ablation or rhythm at time of the surveys, both of which could
5 potentially influence PROs.^{23, 24} The possible inclusion of patients in the atrial arrhythmia
6 group who underwent catheter ablation and/or had a low symptom burden could
7 conservatively bias results towards the null hypothesis and, hence, result in an
8 underestimation of between-group differences in PROs. Further studies are required to assess
9 the effect of these potential explanatory variables. Finally, APPROACH-IS focused on the
10 PROs applicable to a more general population of adults with CHD such that questionnaires
11 specifically tailored to patients with atrial arrhythmias (e.g., Atrial Fibrillation Effect on
12 QualiTy-of-life [AFEQT]) were not administered.

14 CONCLUSION

15 In this international study of over 4,000 adults with CHD, atrial arrhythmias were associated
16 with an adverse impact on a spectrum of PROs including metrics of quality of life, perceived
17 health status, psychological distress, and illness perception. On the whole, results were
18 consistent across various geographical regions. These findings call attention to the distressing
19 consequences of atrial arrhythmias in adults with CHD and pave the way for future studies to
20 assess the impact of therapeutic interventions on PROs

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FIGURE LEGENDS**Figure 1. LOVE plot**

The LOVE plot depicts the percentage of weighted standard deviations for the standard differences in weighted means or weighted proportions for each covariate in patients with and without atrial arrhythmias before (X) and after (O) matching. The dotted blue and red lines represent 10% and 5% cut-off values, respectively. After applying the matching weights (MW), an absolute standardized difference $<5\%$ was obtained for all covariates, indicative of excellent balance between groups.

Figure 2. Regional variations in PROs

Differences in estimated means of the various PROs between patients with and without atrial arrhythmias are plotted according to geographical region (Eastern, Europe, Americas, and Pacific). SF-12 denotes 12-item Short-Form Health Survey version 2; EQ-5D, European Quality of Life – 5 Dimension Score; EQ-Scale, European Quality of Life Scale; HADS, Hospital Anxiety and Depression Scale; SOC, Sense of Coherence score – orientation to life questionnaire; Brief IPQ, Brief Illness Perception Questionnaire; LAS, Quality of life Linear Analogue Scale; SWLS, Satisfaction with Life Scale

TABLES

Table 1. Summary of patient-reported outcomes (PROs)

Questionnaire	Scale	Description
Quality of life		
Linear analogue scale (LAS)	0-100	Vertical line: higher score reflects better quality of life
Satisfaction with life scale (SWLS)	5-35	5 statements with scores from 1 to 7; higher score reflects better quality of life
Perceived health status		
12-item Short-Form Health Survey version 2 (SF-12); divided into physical (PCS) and mental (MCS) component scores	0-100 for both PCS and MCS	Higher score reflects better perceived health status 8 health domains: <ul style="list-style-type: none"> • PCS: 1) Physical functioning; 2) Role participation with physical health problems; 3) Bodily pain; 4) General health • MCS: 5) Vitality; 6) Social functioning; 7) Emotional health; 8) Mental health
European Quality of Life – 5 Dimension Score (EQ-5D)	5-15	Higher score reflects lower perceived health status <ul style="list-style-type: none"> • 5 dimensions: 1) Mobility; 2) Self-care; 3) Usual activities; 4) Pain and discomfort; 5) Anxiety and depression
European Quality of Life – Visual Analogue Scale (EQ-VAS)	0-100	Vertical line: higher score reflects better global assessment of health
Psychological distress		
Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale	0-21 for anxiety and depression	Higher score reflects greater psychological distress
Sense of coherence		
Sense of coherence score – orientation to life questionnaire (SOC)	13-91	Higher score reflects higher sense of coherence <ul style="list-style-type: none"> • 3 components: 1) Comprehensibility; 2) Manageability; 3) Meaningfulness
Illness perception		
Brief illness perception questionnaire (Brief IPQ)	0-80	Higher score reflects worse illness perception <ul style="list-style-type: none"> • 9 items: 1) Consequences; 2) Timeline; 3) Personal control; 4) Treatment control; 5) Identity; 6) Coherence; 7) Concern; 8) Emotional response; 9) Perceived causes
Overall well-being		
APPROACH-IS total score (APPRtot)	0-100	Higher score reflects better state of well-being Composite of all PROs listed above

Adapted with permission from Apers S et al. *Int J Cardiol* 2015;179:334-42⁵.

Table 2. Patient characteristics before and after match weighting

	Before match weighting		After match weighting	
	Atrial arrhythmia (N=707)	No atrial arrhythmia (N=3,321)	Atrial arrhythmia (N=707)	No atrial arrhythmia (N=3,321)
Age (years)	41.4±14.2	32.3±11.4	40.1±13.7	40.2±14.3
Female sex (%)	52.8	53.5	52.5	52.2
<i>Ethnicity (%)</i>				
Middle-Eastern/Arabic	0.9	1.3	1.0	1.0
Asian	15.1	24.1	16.3	16.5
African	1.6	1.0	1.7	1.7
Hispanic	3.3	3.4	3.2	3.1
Caucasian	78.5	69.6	77.0	76.7
Other	0.7	0.6	0.8	1.0
<i>Education level (%)</i>				
Less than high school	6.3	4.7	6.1	6.0
High school	44.1	42.6	44.6	45.3
College	23.4	23.6	22.4	22.0
University	26.2	29.1	26.9	26.8
<i>Marital status (%)</i>				
Unmarried/never married	6.0	48.6	17.7	35.5
Separated, divorced or widowed	1.3	4.0	3.5	7.4
Married or with partner	10.4	47.2	28.8	57.2
Tobacco use (%)	11.1	12.2	11.3	11.4
Cognitive impairment (%)	1.4	1.0	1.4	1.3
<i>Complexity of congenital heart disease (%)</i>				
Simple	14.9	26.1	15.9	15.9
Moderate	43.1	50.4	44.8	44.8
Complex	42.0	23.5	39.2	39.2
<i>Cardiac implantable electronic device (%)</i>				
Pacemaker	8.2	2.5	7.6	17.2
Defibrillator	22.7	4.8	17.2	17.5

Table 3. Comparison of PROs in matched patients with and without atrial arrhythmias

PRO	Atrial arrhythmia (N=707)	No atrial arrhythmia (N=3,321)	Relative difference (%)	P-value
<i>Quality of life</i>				
LAS	74.9±17.1	76.5±17.9	-2.2	0.060
SWLS	23.8±6.9	24.9±6.7	-4.1	0.002
<i>Perceived health status</i>				
SF-12 PCS	69.4±21.7	73.9±22.2	-6.0	<0.0001
SF-12 MCS	67.9±19.9	71.0±18.9	-4.4	0.001
EQ-5D	1.4±1.5	1.2±1.5	14.1	0.019
EQ-VAS	73.4±17.6	75.0±18.0	-2.1	0.070
<i>Psychological distress</i>				
HADS-Anxiety	6.1±3.9	5.8±4.0	6.1	0.067
HADS-Depression	3.8±3.6	3.4±3.3	9.9	0.049
<i>Sense of coherence</i>				
SOC	64.0±13.5	65.2±13.3	-1.9	0.060
<i>Illness perception</i>				
Brief IPQ	36.4±13.0	32.9±13.5	10.8	<0.0001
<i>Summary score</i>				
APPRtot	72.4±14.0	74.9±14.0	-3.3	0.0006

LAS denotes Linear Analog Scale; SWLS, Satisfaction with Life Scale; SF-12, Short-Form Health Survey; PCS, Physical Component Score; MCS, Mental Component Score; EQ-5D, European Quality of Life – 5 Dimensions; EQ-VAS, European Quality of Life – Visual Analog Scale; HADS, Hospital Anxiety and Depression Scale; SOC, Sense of Coherence Orientation to Life Questionnaire; IPQ, Illness Perception Questionnaire; APPRtot, summary score of all PRO measures

	Eastern	Europe	Americas	Pacific
Number of patients with atrial arrhythmias	421	1447	1126	320
Number of patients without atrial arrhythmias	29	289	329	69