Atrial arrhythmias and patient-reported outcomes in adults with congenital heart disease: An international study

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BACKGROUND Atrial arrhythmias (ie, intra-atrial reentrant tachycardia and atrial fibrillation) are a leading cause of morbidity and hospitalization 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 The purpose of this study was 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 those without atrial arrhythmias.

RESULTS A total of 4028 adults with CHD were enrolled, 707 (17.6%) of whom had atrial arrhythmias. After applying matching weights, patients with and those without atrial arrhythmias were comparable with regard to age (mean 40.1 vs 40.2 years), demographic variables (52.5% vs 52.2% women), and complexity of CHD (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 (ie, depression), and illness perception. A summary score that combines all PRO measures was significantly lower in patients with atrial arrhythmias (−3.3%; $P = .0006$). 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; Congenital heart disease; Intra-atrial reentrant tachycardia; Patient-reported outcomes; Quality of life

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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 they are a leading cause of hospitalizations in this patient population.[3] Although much attention has been directed toward 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]

In this study, 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 >4000 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 Identifier: NCT02150603).[5] In brief, APPROACH-IS is an international cross-sectional study of 4028 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 the United States. Patients were required to be diagnosed with CHD before 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 (eg, pacemakers and defibrillators), and atrial arrhythmias. Type of CHD was categorized according to complexity (ie, 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 IART and AF were grouped together as "atrial tachycardia." AF was diagnosed based on standard definitions.[7] 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] but excluded accessory pathway-mediated tachycardia and atrioventricular nodal reentrant tachycardia.

PROs

The PROs assessed in APPROACH-IS have previously been described[5] and are summarized in Table 1. Quality of life, which refers to the extent of satisfaction with life,[9] was assessed by 2 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, 2 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 (ie, 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 analysis

Categorical variables are summarized by frequency and percentage and continuous variables by mean ± SD or median [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 those without atrial arrhythmias, a matching weight (MW) approach was applied.[18] A nonparsimonious 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 SDs 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 4 geographic regions: Europe (Belgium, France, Italy, Malta, Norway, Sweden, Switzerland and the Netherlands); Americas (Canada, United States, and Argentina); Eastern region (India and Taiwan); and Pacific region (Australia and Japan). Two-sided $P < .05$ was considered significant. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) and R Version 3.2.5 (RStudio, Inc., Boston, MA).

Results

Baseline characteristics

A total of 4028 adults with CHD patients were enrolled, of whom 707 (17.6%) had atrial arrhythmias. Patient characteristics before and after application of MWs are listed in Table 2. Before 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 (standardized mean differences <5% for all variables) (Figure 1).

Impact of atrial arrhythmias on outcomes

Patients with atrial arrhythmias had a higher hospitalization rate in the preceding year (29.7% vs 13.8%; $P < .0001$) and more hospital admissions in adulthood [2 (1–3) vs 0 (0–1); $P < .0001$] compared to those without atrial arrhythmias. Moreover, patients with arrhythmias required more frequent follow-up visits than those without (at least twice per year in 43.2% vs 24.0%; $P < .0001$).

Atrial arrhythmias were associated with consistently worse PROs across the spectrum of domains measured, with significantly poorer scores related to quality of life (SWLS: $P = .002$), perceived health status (SF-12 PCS: $P < .0001$; SF-12 MCS: $P = .001$; EQ-5D: $P = .019$),

Table 1 Summary of 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	Five statements with scores from 1–7; 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 Eight health domains: • 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 Five 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 Three components: (1) comprehensibility; (2) manageability; (3) meaningfulness
Illness perception		
Brief Illness Perception Questionnaire (Brief IPQ)	0–80	Higher score reflects worse illness perception Nine 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

PRO = patient-reported outcome.
Adapted with permission from Apers et al.[5]

psychological distress (HADS-Depression: $P = .049$), and illness perception (Brief IPQ: $P < .0001$) (Table 3). The PRO scores that did not differ statistically between groups (LAS, EQ-VAS [European Quality of Life–Visual Analogue Scale], HADS-Anxiety, and SOC) showed nonsignificant trends toward worse outcomes in patients with atrial arrhythmias ($P = .06$–$.07$). The PRO composite score (ie, APPRtot) was significantly lower (ie, indicative of poorer outcomes) in patients with atrial arrhythmias (72.4 ± 14.0 vs 74.9 ± 14.0; $P = .0006$).

Geographic variations in PROs in patients with and those without atrial arrhythmias

Mean differences in PRO scores in patients with and those without atrial arrhythmias were generally consistent across geographic regions (Figure 2). 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

Table 2 Patient characteristics before and after match weighting

	Before match weighting		After match weighting	
	Atrial arrhythmia (N = 707)	No atrial arrhythmia (N = 3321)	Atrial arrhythmia (N = 707)	No atrial arrhythmia (N = 3321)
Age (y)	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
Ethnicity				
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
Education level				
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
Marital status				
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
Complexity of congenital heart disease				
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
Cardiac implantable electronic device				
Pacemaker	8.2	2.5	7.6	17.2
Defibrillator	22.7	4.8	17.2	17.5

Values are given as mean ± SD or percent.

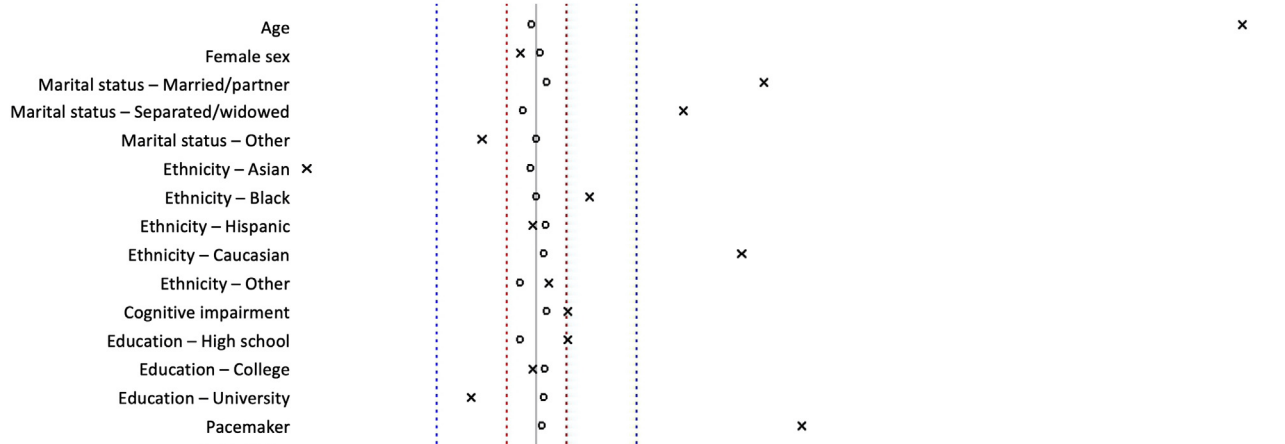


Figure 1 LOVE plot depicting the percentage of weighted standard deviations for the standard differences in weighted means or weighted proportions for each covariate in patients with and those without atrial arrhythmias before (X) and after (O) matching. *Dotted blue lines* represent 10% cutoff values; *dotted red lines* represent 5% cutoff values. After applying the matching weights (MW), an absolute standardized difference <5% was obtained for all covariates, indicative of excellent balance between groups.

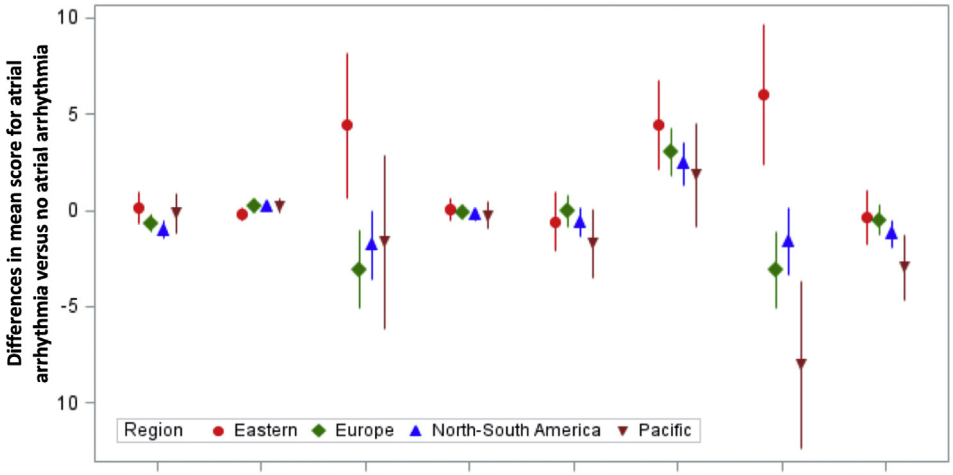
Table 3 Comparison of PROs in matched patients with and those without atrial arrhythmias

PRO	Atrial arrhythmia (N = 707)	No atrial arrhythmia (N = 3321)	Relative difference (%)	*P* value
Quality of life				
LAS	74.9 ± 17.1	76.5 ± 17.9	−2.2	.060
SWLS	23.8 ± 6.9	24.9 ± 6.7	−4.1	.002
Perceived health status				
SF-12 PCS	69.4 ± 21.7	73.9 ± 22.2	−6.0	<.0001
SF-12 MCS	67.9 ± 19.9	71.0 ± 18.9	−4.4	.001
EQ-5D	1.4 ± 1.5	1.2 ± 1.5	14.1	.019
EQ-VAS	73.4 ± 17.6	75.0 ± 18.0	−2.1	.070
Psychological distress				
HADS-Anxiety	6.1 ± 3.9	5.8 ± 4.0	6.1	.067
HADS-Depression	3.8 ± 3.6	3.4 ± 3.3	9.9	.049
Sense of coherence				
SOC	64.0 ± 13.5	65.2 ± 13.3	−1.9	.060
Illness perception				
Brief IPQ	36.4 ± 13.0	32.9 ± 13.5	10.8	<.0001
Summary score				
APPRtot	72.4 ± 14.0	74.9 ± 14.0	−3.3	.0006

Values are given as mean ± SD unless otherwise indicated.

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

age such that the prevalence of IART or AF has been reported to be nearly 40% in adults with CHD aged >50 years.[19] Both can be poorly tolerated and lead to increased rates 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 that (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 those without atrial arrhythmias are generally consistent across geographic locations.



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

Figure 2 Regional variations in patient-reported outcomes (PROs). Differences in estimated means of various PROs between patients with and those without atrial arrhythmias are plotted according to geographic region (Eastern, Europe, Americas, and Pacific). From left to right: SF-12 = 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.

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 (eg, stroke and heart failure) seem to contribute to worse PROs.[21,22] Consistently, alleviation of symptoms[23,24] and the need for less frequent thromboprophylactic monitoring with direct-acting oral anticoagulants[25,26] have been shown to improve quality of life.

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

Effect of comorbidities on PROs in adults with CHD

Little is known about the impact of comorbidities on PROs in adults with CHD. As a chronic lifelong disease, CHD itself has been associated with an inconsistent reduction in quality of life.[30,31] However, in patients with CHD, older age, severity of illness, and more advanced functional class symptoms predict worse PRO scores.[31–33] Moreover, the presence of an implantable cardioverter-defibrillator has been associated with a more threatening view of 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 2-group comparisons within each geographic 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 United States 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.

Study 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 regard to measured covariates but cannot directly adjust for potential confounders for which data were not collected. Given the overlap and frequent coexistence of IART and AF and the fact that diagnoses were based on data reported in case report forms by site investigators without an independent adjudicating committee, the impact of subtype of arrhythmia on PROs was not assessed. The study did not collect data on catheter ablation or rhythm at time of the surveys, both of which could potentially influence PROs.[23,24] The possible inclusion of patients in the atrial arrhythmia group who underwent catheter ablation and/or had a low symptom burden could conservatively bias results toward the null hypothesis and, hence, result in an underestimation of between-group differences in PROs. Further studies are required to assess the effect of these potential explanatory variables. Finally, APPROACH-IS focused on the PROs applicable to a more general population of adults with CHD, such that questionnaires specifically tailored to patients with atrial arrhythmias (eg, Atrial Fibrillation Effect on QualiTy-of-life [AFEQT]) were not administered.

Conclusion

In this international study of more than 4000 adults with CHD, atrial arrhythmias were associated with an adverse impact on a spectrum of PROs, including metrics of quality of life, perceived health status, psychological distress, and illness perception. On the whole, results were consistent across various geographic regions. These findings call attention to the distressing consequences of atrial arrhythmias

in adults with CHD and pave the way for future studies to assess the impact of therapeutic interventions on PROs.

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