Implantable cardioverter-defibrillators and patient-reported outcomes in adults with congenital heart disease: An international study

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BACKGROUND Implantable cardioverter-defibrillators (ICDs) are increasingly being used to prevent sudden death in the growing population of adults with congenital heart disease (CHD). However, little is known about their impact on patient-reported outcomes (PROs).

OBJECTIVE The purpose of this study was to assess and compare PROs in adults with CHD with and without ICDs.

METHODS A propensity-based matching weight analysis was conducted to evaluate PROs in an international cross-sectional study of adults with CHD from 15 countries across 5 continents.

RESULTS A total of 3188 patients were included: 107 with ICDs and 3081 weight-matched controls without ICDs. ICD recipients were an average age of 40.1 ± 12.4 years, and >95% had moderate or complex CHD. Defibrillators were implanted for primary and secondary prevention in 38.3% and 61.7%, respectively. Perceived health status, psychological distress, sense of coherence, and health behaviors did not differ significantly among patients with and without ICDs. However, ICD recipients had a more threatening view of their illness (relative % difference 8.56; $P = .011$). Those with secondary compared to primary prevention indications had a significantly lower quality-of-life score (Linear Analogue Scale 72.0 ± 23.1 vs 79.2 ± 13.0; $P = .047$). Marked geographic variations were observed. Overall sense of well-being, assessed by a summary score that combines various PROs, was significantly lower in ICD recipients (vs controls) from Switzerland, Argentina, Taiwan, and the United States.

CONCLUSION In an international cohort of adults with CHD, ICDs were associated with a more threatening illness perception, with a lower quality of life in those with secondary compared to primary prevention indications. However, marked geographic variability in PROs was observed.

KEYWORDS Adult congenital heart disease; Implantable cardioverter-defibrillator; Patient-reported outcomes; Quality of life; Sudden cardiac death

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Introduction

Sudden cardiac death is a leading cause of mortality in adults with congenital heart disease (CHD) such that defibrillators are increasingly implanted in this growing population.[1] Although most patients seem to adjust well to this therapy, considerable psychosocial issues have been reported in the general population with an implantable cardioverter-defibrillator (ICD).[2] Nevertheless, there is a paucity of data that specifically address the impact of ICDs on quality of life and other patient-reported outcomes (PROs) in adults with CHD. Understanding the influence of ICDs on PROs is of particular importance considering the high baseline prevalence of psychosocial concerns in adults with CHD, including generalized anxiety, depression, and difficulties coping with a lifelong medical condition.[3] Indeed, targeted therapy to reduce psychological distress has been recognized as an important component of comprehensive care for adults with CHD.[4]

Therefore, we sought to assess the impact of ICDs in the largest study of PROs in adults with CHD, the Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease–International Study (APPROACH-IS), which enrolled >4000 patients from 15 countries across 5 continents.[5] Outcomes of interest included quality of life, perceived health status, psychological distress, sense of coherence, illness perception, and health behaviors.

Methods
Patient selection

Design and methods of APPROACH-IS have previously been described (ClinicalTrials.gov Identifier NCT02150603).[5] In brief, the study included adults (age ≥18 years) diagnosed with CHD before age 10 years with the physical, cognitive, and language capabilities required to complete self-reported questionnaires. A total of 4028 patients from 24 centers were recruited from the following countries via the International Society for Adult Congenital Heart Disease (ISACHD): Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, the Netherlands, Norway, Taiwan, Sweden, Switzerland, and the United States. All patients enrolled in APPROACH-IS with complete data on ICD history and PROs were retained. In order to assess geographic variations, participating countries were analyzed individually and divided into the following 4 regions: Americas (Canada, USA, and Argentina), Europe (Belgium, France, Italy, Malta, Norway, Sweden, Switzerland, and the Netherlands), Eastern (Taiwan and India), and Pacific (Australia and Japan).

Data collection and ICDs

Demographic data including age, sex, ethnicity, educational level, and marital status were collected using a self-reported

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	5 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 PCS and MCS	0–100 for both PCS and MCS	Higher score reflects better perceived health status 8 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 (EQ-5D) score	5–15	Higher score reflects lower perceived health status 5 dimensions: (1) mobility; (2) self-care; (3) usual activities; (4) pain and discomfort; (5) anxiety and depression
Psychological distress		
Hospital Anxiety and Depression Scale (HADS)-Anxiety, HADS-Depression	0–21 for depression and anxiety	Higher score reflects greater psychological distress
Sense of coherence		
Sense of Coherence (SOC) score–orientation to life questionnaire	13–91	Higher score reflects higher sense of coherence 3 components: (1) comprehensibility; (2) manageability; (3) meaningfulness
Illness perception		
Brief Illness Perception Questionnaire (Brief IPQ)	0–80	Higher score reflects worse illness perception 9 items: (1) consequences; (2) timeline; (3) personal control; (4) treatment control; (5) identity; (6) coherence; (7) concern; (8) emotional response; (9) perceived causes
Health behaviors		
Health Behavior Scale–Congenital Heart Disease (HBS-CHD)	0–7	Higher score reflects greater health risk 3 items: (1) substance abuse; (2) physical activity; (3) dental hygiene
Overall well-being		
APPROACH-IS total score (APPRtot)	0–100	Higher score reflects better state of well-being Composite of all PROs listed above

APPROACH-IS = Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease–International Study; MCS = mental component score; PCS = physical component score; PRO = patient-reported outcome.

questionnaire. Type and complexity of CHD, history of congestive heart failure, and details regarding ICDs were extracted from medical records by site investigators. Complexity of CHD was categorized as simple, moderate, or complex according to a previously defined classification scheme.[6] The presence or absence of an ICD was noted, along with date of surgery and whether the device was implanted for primary or secondary prevention against sudden cardiac death. All subjects provided written informed consent to participate. The study was approved by the local institutional review board of each participating center and was conducted in accordance with the International Council of Harmonization Tripartite Guidelines for Good Clinical Practice.

PROs
A series of questionnaires was administered in the patient's language to assess the following PROs summarized in Table 1: quality of life, perceived health status, psychological distress, sense of coherence, illness perception, and health behaviors. Quality of life, conceptually defined as the degree of overall satisfaction with life,[7] was assessed using a linear analogue scale (LAS) and the Satisfaction With Life Scale (SWLS). The LAS consists of a vertical graded line that ranges from worst (0) to best (100) imaginable quality of life. The SWLS is a 5-question survey that assesses the individual's global judgment of life satisfaction.[8] Perceived health status was defined as the patient's perception of the impact of the disease on symptoms, functional status, and health-related quality of life.[9] It was assessed by the 12-item Short-Form Health Survey version 2 (SF-12), which is divided into physical component score (PCS) and mental component score (MCS), along with the European Quality of Life–5 Dimension (EQ-5D) score.[10] Two categories of psychological distress were assessed by means of the Hospital Anxiety and Depression Scale (HADS): anxiety (HADS-Anxiety) and depression (HADS-Depression).[11] Sense of coherence refers to the individual's generalized view that stimuli are structured and predictable, that resources are available to meet associated demands, and that addressing those demands is worthy of investment.[12] It was evaluated using a 13-item orientation to life questionnaire (Sense of Coherence [SOC] score).[13] Illness perception, defined as cognitive representations and beliefs about one's illness,

Table 2 Characteristics in matched cohorts with and without ICDs

	ICD (N = 107)	No ICD (N = 3081)	P value
Age (y)	40.1 ± 12.4	40.2 ± 14.1	.462
Female sex	50.5	50.4	.985
Ethnicity			1
Middle-Eastern/Arabic	0.9	0.9	
Asian	5.6	5.5	
African	0.0	0.0	
Hispanic	0.9	0.9	
White	92.5	92.6	
Educational level			.919
Less than high school	4.7	4.6	
High school	42.1	42.4	
College	29.9	30.6	
University	23.4	23.4	
Marital status			.987
Unmarried/never married	35.5	36.0	
Separated, divorced or widowed	5.6	5.8	
Married or with partner	58.9	58.2	
Tobacco use	8.4	8.6	.829
Cognitive impairment	1.9	1.7	.686
Complexity of congenital heart disease			.381
Simple	4.7	4.5	
Moderate	54.2	52.0	
Complex	41.1	43.6	
CHF			.826
No history of CHF	58.9	58.0	
Past history of CHF	18.7	18.7	
Current CHF	22.4	23.3	

Values are given as mean ± SD or % unless otherwise indicated.

CHF = congestive heart failure; ICD = implantable cardioverter-defibrillator.

was assessed using the Brief Illness Perception Questionnaire (Brief IPQ).[14] The Health Behavior Scale–Congenital Heart Disease (HBS-CHD) questionnaire targets behaviors related to substance abuse, dental hygiene, and physical activity.[15] Finally, APPRtot, a composite score developed by APPROACH-IS Investigators, was used as a summary measure to capture the various PROs.[16] A higher composite score indicates a superior state of well-being.

Statistical analysis

Continuous variables are given as mean ± SD and categorical variables as frequency and percentage. The impact of ICDs on PROs was assessed using propensity-matched analyses. Propensity scores were estimated from a nonparsimonious multivariable logistic regression model in which ICD therapy was modeled as the dependent variable and patient-level variables (Table 2) were included as covariates. Covariates were limited to variables with a low proportion of missing values (<5%).

A matching weight (MW) approach was used, which is an extension of inverse probability of treatment weighting that reweights both treatment groups to render them as comparable as possible.[17] In Figure 1, a LOVE plot depicts the percentage of pooled weighted SDs for the values of standard differences in weighted means or weighted proportions for each covariate across exposure groups. After applying MWs, an absolute standard difference <10% was obtained for all covariates, indicating excellent balance between groups. To assess regional variations, differences in weighted means of PROs among the 2 exposure groups were assessed according to 4 geographic regions. Two-sided $\underline{P}$ <.05 was considered significant. No adjustments were made for
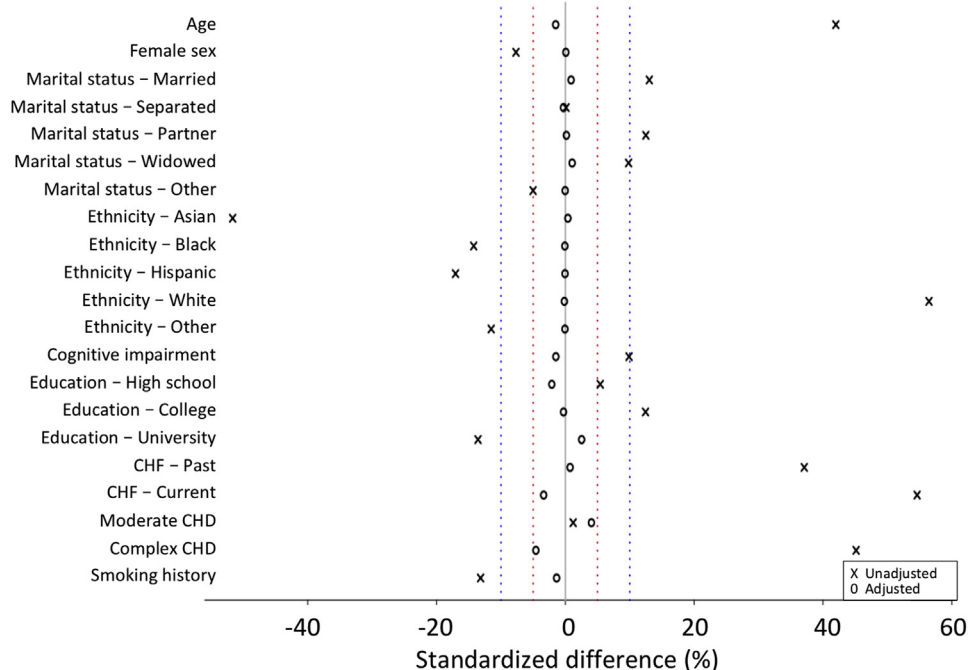

Figure 1 LOVE plot depicting the percentage of pooled weighted standard deviations for the standard differences in weighted means or weighted proportions for each covariate across exposure groups before (X) and after (O) matching. *Dotted blue* and *red lines* represent 10% and 5% cutoff values, respectively. CHD = congenital heart disease; CHF = congestive heart failure.

Table 3   Characteristics in matched cohorts with primary and secondary prevention ICDs

	Primary prevention (N = 41)	Secondary prevention (N = 63)	P value
Age (y)	40.0 ± 12.1	40.2 ± 12.6	.929
Female sex	55.1	54.7	.964
Time since ICD implantation (y)	7.3 ± 8.1	7.6 ± 7.1	.852
Ethnicity			.999
Middle-Eastern/Arabic	0.0	0.0	
Asian	5.9	5.5	
African	0.0	0.0	
Hispanic	0.0	0.0	
White	94.1	94.5	
Educational level			.991
Less than high school	4.0	5.1	
High school	46.9	44.6	
College	26.3	26.6	
University	22.8	23.8	
Marital status			.999
Unmarried/never married	35.5	35.8	
Separated, divorced or widowed	5.9	5.8	
Married or with partner	58.6	58.4	
Tobacco use	5.9	5.6	.939
Cognitive impairment	1.3	1.3	.998
Complexity of congenital heart disease			.967
Simple	3.3	4.3	
Moderate	51.7	51.2	
Complex	45.0	44.5	
CHF			.995
No history of CHF	59.2	56.6	
Past history of CHF	14.8	16.7	
Current CHF	26.1	26.7	

Values are given as mean ± SD or % unless otherwise indicated.

CHF = congestive heart failure; ICD = implantable cardioverter-defibrillator.

multiple comparisons considering the exploratory nature of the study. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and R version 3.2.5.

Results
Study population
A total of 3188 patients met inclusion criteria for the APPROACH-IS ICD study: 107 with ICDs and 3081 weight-matched controls without ICDs. Patients with ICDs were distributed according to the following countries of domicile: Argentina 3, Australia 2, Belgium 10, Canada 16, Italy 1, Japan 3, Norway 12, Sweden 1, Switzerland 6, Taiwan 3, the Netherlands 10, and the United States 40. Characteristics of the 2 matched groups are summarized in Table 2. No statistically significant difference was observed for any characteristic. The average age of patients with and without ICDs was 40.1 ± 12.4 years and 40.2 ± 14.1 years, respectively (P = .462). Overall, 50.5% and 50.4% of the matched cohorts with and without ICDs were female

(P = .985). In both groups, >95% of patients had moderate or complex CHD.

Among the 107 patients with ICDs, 41 (38.3%) were implanted for primary prevention and 66 (61.7%) for secondary prevention. Applying the MW approach to the ICD population, 104 of 107 patients (97.2%) were retained for predefined secondary analyses comparing PROs in those with primary vs secondary prevention indications. No significant differences in characteristics between matched cohorts were found (Table 3). On average, ICDs were implanted 7.3 ± 8.1 years vs 7.6 ± 7.1 years before the assessment of PROs in patients with primary vs secondary prevention indications, respectively (P = .852).

Impact of ICDs on PROs
Comparisons of PROs in matched cohorts with and without an ICD and in those with primary vs secondary prevention indications are given in Table 4. No differences in quality of life, perceived health status, psychological distress, sense of coherence, health behaviors, or composite summary score were noted in adults with CHD with and without ICDs. However, patients with ICDs had a significantly more threatening view of their illness (Brief IPQ score 37.7 ± 12.1 vs 34.7 ± 13.8, relative % difference 8.56; P = .011). Moreover, ICD recipients exhibited a nonsignificant trend toward having a worse perceived physical health status score (SF-12 PCS 66.5 ± 22.6 vs 70.2 ± 23.3, relative % difference –5.26; P = .081).

PROs with primary vs secondary prevention ICDs
Patients with secondary prevention ICDs had a lower quality-of-life score as assessed by LAS compared to those with primary prevention indications (72.0 ± 23.1 vs 79.2 ± 13.0, relative % difference 9.01; P = .047) (Table 4). There were no significant differences in perceived health status, psychological distress, sense of coherence, illness perception, health behaviors, and overall composite score.

Geographic variations in PROs
Geographic variations in mean differences of PROs for patients with and without ICDs are shown in Figure 2. Figures 2A and 2B show PROs for which higher scores indicate better and worse reported outcomes, respectively. On visual inspection, mean differences in PROs, along with their 95% confidence intervals, tended to cluster below and above the 0 value in Figures 2A and 2B, respectively, indicative of worse reported outcomes in patients with ICDs. However, notable regional variations were observed. For example, in the Eastern region, patients with ICDs had significantly worse reported outcomes with respect to satisfaction with life (SWLS), perceived mental health status (SF-12 MCS), psychological distress (HADS), illness perception (Brief IPQ), and health behaviors (HBS-CHD). In Europe and the Americas, ICD recipients reported worse outcomes in physical perceived health status (SF-12 PCS) and illness perception (Brief IPQ). In addition, Europeans with ICDs had a

Table 4 Comparisons of PROs in matched cohorts with an ICD vs no ICD and in those with primary vs secondary prevention indications

	ICD vs no ICD				Primary vs secondary prevention ICD			
PRO	ICD (N = 107)	No ICD (N = 3081)	Relative difference (%)	P value	Primary prevention (N = 41)	Secondary prevention (N = 63)	Relative difference (%)	P value
Quality of life								
LAS	75.7 ± 18.8	75.4 ± 18.5	0.36	.880	79.2 ± 13.0	72.0 ± 23.1	−9.01	.047
SWLS	24.0 ± 7.1	24.6 ± 7.0	−2.62	.341	24.6 ± 7.0	23.1 ± 7.3	−5.98	.280
Perceived health status								
SF-12 PCS	66.5 ± 22.6	70.2 ± 24.3	−5.26	.081	65.2 ± 20.1	67.0 ± 26.1	2.77	.693
SF-12 MCS	68.5 ± 18.0	69.5 ± 20.2	−1.49	.573	70.9 ± 18.1	67.2 ± 19.4	−5.10	.363
EQ-5D	1.5 ± 1.4	1.4 ± 1.6	6.53	.504	1.3 ± 1.4	1.7 ± 1.5	28.76	.166
Psychological distress								
HADS-Anxiety	6.4 ± 3.9	5.8 ± 3.8	10.05	.130	6.2 ± 3.5	6.9 ± 4.0	10.47	.397
HADS-Depression	3.6 ± 3.3	3.5 ± 3.5	2.41	.788	3.5 ± 3.0	3.8 ± 3.4	10.27	.556
Sense of coherence								
SOC	65.7 ± 13.3	65.6 ± 13.2	0.09	.961	67.7 ± 12.7	64.2 ± 14.0	−5.22	.172
Illness perception								
Brief IPQ	37.7 ± 12.1	34.7 ± 13.8	8.56	.011	36.1 ± 9.6	38.7 ± 14.6	5.75	.392
Health behaviors								
HBS-CHD	1.7 ± 1.2	1.6 ± 1.2	4.26	.528	1.8 ± 1.2	1.6 ± 1.2	−6.83	.569
Summary score								
APPRtot	72.0 ± 14.1	73.4 ± 15.2	−1.85	.348	73.2 ± 10.9	70.2 ± 16.9	−4.13	.287

Values are given as mean ± SD unless otherwise indicated.

ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

significantly worse sense of coherence (SOC), and those from the Americas had higher anxiety scores (HADS-Anxiety). Finally, ICD recipients from the Pacific region had significantly worse scores for satisfaction with life (SWLS) and health behaviors (HBS-CHD).

Differences in APPRtot in patients with and without ICDs are plotted in Figure 3. Marked variability in overall sense of well-being was observed across the various countries. Patients with ICDs in Switzerland, Argentina, the United States, and Taiwan had significantly lower summary scores, with nonsignificantly lower point estimates also observed for the Netherlands and Canada. In contrast, ICD recipients in Belgium had a significantly higher cumulative score.

Discussion

To our knowledge, this is the largest study to assess the impact of ICDs on PROs in adults with CHD. Main findings include the following: (1) perceived health status, psychological distress, sense of coherence, and health behaviors are comparable in patients with and without ICDs, and in those with primary vs secondary prevention indications; (2) ICD recipients perceive their illness as more threatening than matched controls without ICDs; (3) the quality-of-life score (LAS) is significantly lower in those with secondary compared to primary prevention ICD indications; and (4) marked geographic variations are observed in PROs, with a significantly lower overall sense of well-being in ICD recipients in some but not all countries studied.

The psychological impact and adaptive response to an ICD is complex and multifactorial. Psychological distress and concerns regarding ICDs have been reported in approximately 20% of the general population with ICDs.[18] Our observation that ICD recipients with CHD perceive their illness as more threatening is, therefore, compatible with these findings. This perception might not be unrealistic given that patients who require an ICD may objectively have a more threatening condition than those who do not. Determinants of a more threatening illness perception, which remain speculative, may include factors such as fear of sudden death and one's ability to cope, social support, intensity of medical follow-up, apprehension about possible shocks, and concerns surrounding the ICD, including complications, malfunction, and costs. The nonsignificant trend toward a higher degree of perceived physical limitations in ICD recipients noted in the current study could potentially contribute to a less favorable illness perception. Whether targeted psychoeducational interventions[19] could improve psychological outcomes after ICD implantation in adults with CHD remains to be determined.

Among the factors that influence the psychological response of individuals to an ICD are the circumstances surrounding the implant.[20] Our findings show that adults with CHD who had a resuscitated cardiac arrest or sustained ventricular arrhythmia have a significantly worse quality-of-life score compared to matched patients with primary prevention indications. Individuals with an ICD implanted for a near-miss sudden death may have a lower perceived level of control,[21] be at greater risk for posttraumatic stress disorder after a cardiac arrest,[22] and experience a higher rate of appropriate shocks during follow-up.[23] Our study could not confirm whether these factors influenced the lower quality-of-life score in patients with secondary vs primary prevention indications. The difference in point estimates for anxiety scores (HADS-Anxiety), albeit higher in patients with secondary
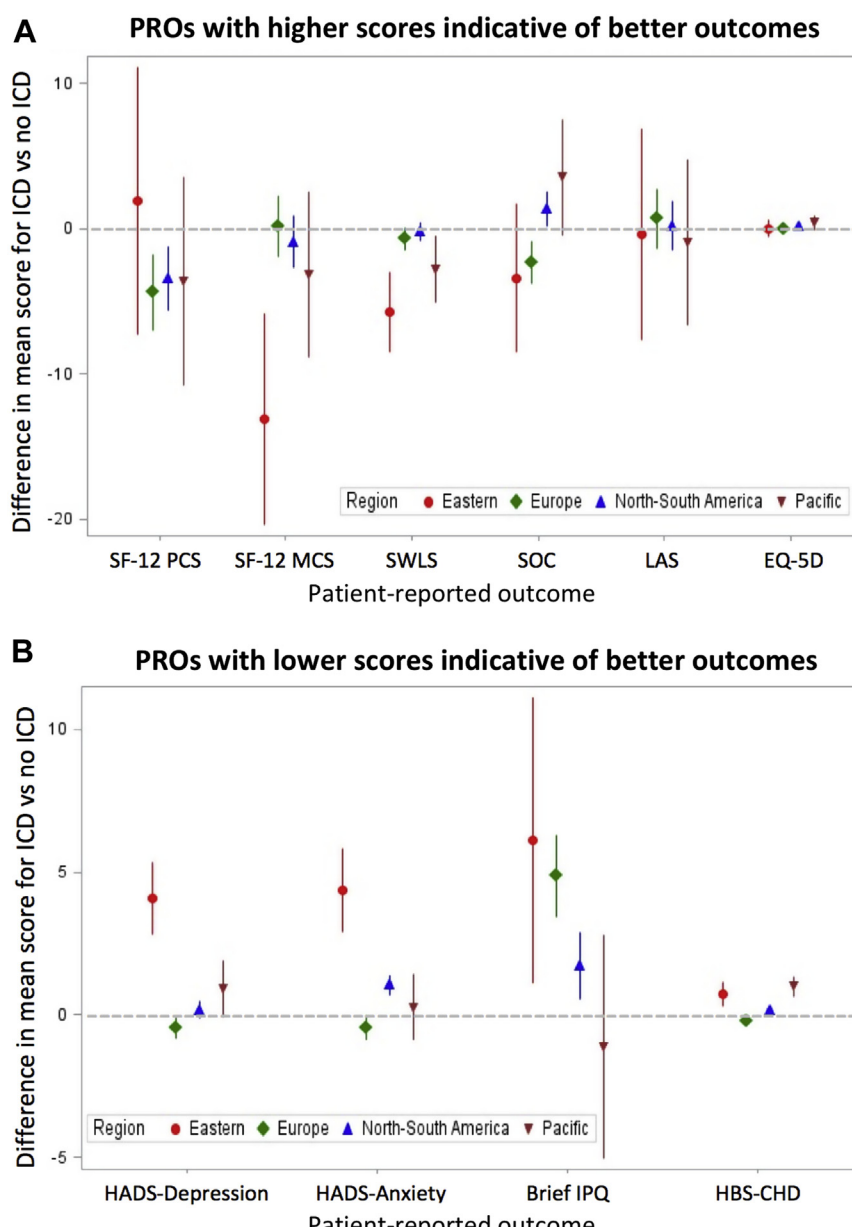
Figure 2 Regional variations in patient-reported outcomes (PROs). Differences in estimated means of the various PROs between patients with and without implantable cardioverter-defibrillators (ICDs) are plotted according to geographic region (Eastern, Europe, North and South America, and Pacific). **A:** PROs for which a higher score indicates a better outcome. **B:** PROs for which a lower score reflects a worse outcome. Brief IPQ = Brief Illness Perception Questionnaire; EQ-5D = European Quality of Life–5 Dimension score; HADS = Hospital Anxiety and Depression Scale; HBS-CHD = Health Behavior Scale–Congenital Heart Disease; LAS = Linear Analogue Scale; MCS = mental component score; PCS = physical component score; SF-12 = 12-Item Short-Form Health Survey; SWLS = Satisfaction With Life Scale; SOC = Sense of Coherence score.

prevention indications (6.9 ± 4.0 vs 6.2 ± 3.5), did not reach statistical significance. Moreover, information on ICD shocks was not collected in APPROACH-IS. In a previous study of 180 adults with CHD and ICDs, a high degree of shock-related anxiety was observed, with fears related to consequences of shocks (eg, creating a scene) and potential triggers (eg, sexual activity and exercise).[24]

The marked geographic variations observed in the current analysis are compatible with results reported in adults with CHD at large.[16] Indeed, standard of living and health care system factors were previously found to impact PROs above and beyond clinical factors. More specifically, patients from

countries with a higher standard of living had a higher composite APPROACH-IS score, fewer symptoms of depression, and less risky health behaviors.[16] Such geographic variations may contribute, in part, to inconsistencies in the general literature regarding the impact of ICDs on PROs.[25] In the current analysis, the ICD population in Eastern countries had worse PROs compared to those without an ICD for all outcomes except physical perceived health status (PCS). Interestingly, ICD recipients in North and South America and Eastern countries but not Europe had significantly higher anxiety scores compared to those without ICDs. However, such subgroup analyses should be considered hypothesis-generating
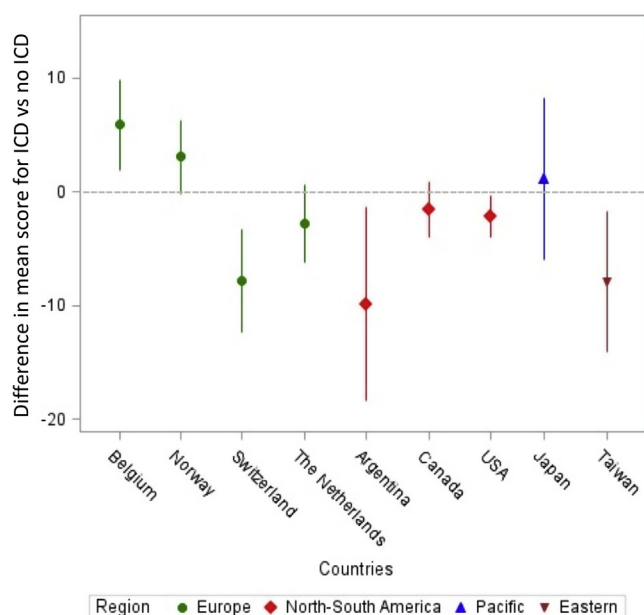
Figure 3   Differences in cumulative Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease–International Study total scores between patients with and without implantable cardioverter-defibrillators (ICDs) plotted according to country and color-coded by region. Participating countries with at least 3 ICD recipients are included in the graph. **Q7**

and be interpreted with caution in the context of limited sample sizes with multiple testing that may yield spurious associations.

Study limitations

This exploratory study is cross-sectional in nature and subject to associated limitations, including the inability to infer causality. Although every effort was made to produce balanced groups with regard to characteristics through propensity score weight-matching, the analyses could not adjust for unknown or unmeasured potential confounders. APPROACH-IS collected comprehensive information regarding ICD implantation dates and indications. However, data on procedure-related complications and shocks were not assessed. These potential explanatory variables could have shed further light on the impact of ICDs on PROs. Most subjects were recruited in clinic, which may result in a referral bias, as reflected by the low proportion of enrolled patients with simple forms of CHD. Although this issue has implications regarding generalizability, it should not impact internal validity because the groups compared were well balanced with respect to CHD complexity. The response rate and characteristics of patients who did not return questionnaires were unknown for most countries. Systematic differences in PROs between responders and nonresponders could potentially impact PRO scores. Nevertheless, if such a measurement error is present, it is most likely nondifferential and not a threat to the validity of 2-group comparisons. Furthermore, patients from all continents except Africa were included. Further studies are required to assess the impact of ICDs on PROs in countries not represented.

Conclusion

In a large international study of PROs in adults with CHD, perceived health status, psychological distress, sense of coherence, and health behaviors were comparable in those with and without ICDs. However, ICDs were associated with a more threatening perception of illness. Patients with ICDs implanted for secondary prevention reported a worse quality-of-life score than their counterparts with primary prevention indications despite adjusting for complexity of CHD, heart failure, and other comorbidities. Importantly, marked geographic variations in PROs were observed, reflecting the importance of cultural and socioeconomic factors on reported outcomes. These findings call attention to the need to address psychological concerns in ICD recipients with CHD and pave the way for future studies to assess targeted interventions.

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