Implantable Cardioverter-Defibrillators and Patient-Reported Outcomes in Adults with Congenital Heart Disease: an International Study

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ABSTRACT

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

Objective—We assessed and compared 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 3,188 patients were included: 107 with ICDs and 3,081 weight-matched controls without ICDs. ICD recipients averaged 40.1±12.4 years of age, with >95% having 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 behaviours did not differ significantly in patients with and without ICDs. However, ICD recipients had a more threatening view of their illness (relative % difference 8.56, P=0.011). Those with secondary compared to primary prevention indications had a significantly lower quality of life score (linear analogue scale 72.0±23.1 versus 79.2±13.0, P=0.047). 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 (versus controls) from Switzerland, Argentina, Taiwan, and USA.

Conclusions—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.

Key words: adult congenital heart disease; implantable cardioverter-defibrillator; quality of life; patient-reported outcomes; sudden cardiac death

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] While most patients appear to adjust well to this therapy, considerable psychosocial issues have been reported in the general population with implantable cardioverter-defibrillators (ICDs).[2] Nevertheless, there is a paucity of data that specifically addresses 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 life-long 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]

We, therefore, sought to assess the impact of ICDs in the largest study of PROs in adults with CHD, i.e., Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease - International Study (APPROACH-IS), which enrolled over 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 behaviours.

METHODS

Patient selection

Design and methods of APPROACH-IS have previously been described (ClinicalTrials.gov NCT02150603).[5] In short, the study included adults (≥18 years of age) diagnosed with CHD before 10 years of age 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, Norway, Taiwan, the Netherlands, Sweden, Switzerland and USA. All patients enrolled in APPROACH-IS with complete data regarding ICD history and PROs were retained. In order to assess geographic variations, participating countries were analyzed individually and divided into the following four 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 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.

Patient-reported outcomes

A series of questionnaires were 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 behaviours. Quality of life, conceptually

4

defined as the degree of overall satisfaction with life,[7] was assessed by means of 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 judgement 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 (PCS) and mental (MCS) component scores, along with the European Quality of Life–5 Dimension (EQ-5D) score.[10] Two categories of psychological distress were assessed, i.e., anxiety and depression, by means of the Hospital Anxiety (HADS-Anxiety) and Depression (HADS-Depression) Scale.[11] Sense of coherence refers to the individual's generalized view that stimuli are structured and predictable, resources are available to meet associated demands, and that addressing these demands is worthy of investment.[12] It was evaluated using the 13-item Orientation to Life Questionnaire (SOC).[13] Illness perception, defined as cognitive representations and beliefs about one's illness, was assessed using the Brief Illness Perception Questionnaire (Brief IPQ).[14] The Health-Behaviour Scale-Congenital Heart Disease (HBS-CHD) questionnaire targets behaviours related to substance abuse, dental hygiene, and physical activity.[15] Finally, a composite score developed by APPROACH-IS investigators (APPRtot) 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 summarized as mean ± standard deviation and categorical variables by frequency and percentage. The impact of ICDs on PROs was assessed using propensity-matched analyses. Propensity scores were estimated from a non-parsimonious multivariable logistic

regression model in which ICD therapy was modelled as the dependent variable and patient-level variables listed in 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 standard deviations 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 two exposure groups were assessed according to four geographical regions. Two-sided P-values <0.05 were considered statistically significant. No adjustments were made for multiple comparisons considering the exploratory nature of the study. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.2.5.

RESULTS

Study population

A total of 3,188 patients met inclusion criteria for the APPROACH-IS ICD study: 107 with ICDs and 3,081 weight-matched controls without ICDs. Patients with ICDs were distributed according to the following countries of domicile: Argentina N=3, Australia N=2, Belgium N=10, Canada N=16, Italy N=1, Japan N=3, Norway N=12, Sweden N=1, Switzerland N=6, Taiwan N=3, the Netherlands N=10, and USA N=40. Characteristics of the two 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 versus 40.2±14.1 years (P=0.462). Overall,

50.5% and 50.4% of the matched cohorts with and without ICDs were female (P=0.985). In both groups, over 95% of patients had moderate or complex CHD.

From the 107 patients with ICDs, 41 (38.3%) were implanted for primary and 66 (61.7%) for secondary prevention. Applying the MW approach to the ICD population, 104 of 107 (97.2%) patients were retained for predefined secondary analyses comparing PROs in those with primary versus secondary prevention indications. As shown in Table 3, there were no significant differences in characteristics between matched cohorts. On average, ICDs were implanted 7.3±8.1 versus 7.6±7.1 years prior to the assessment of PROs in patients with primary versus secondary prevention indications (P=0.852).

Impact of ICDs on PROs

Comparisons of PROs in matched cohorts with and without an ICD and in those with primary versus secondary prevention indications are presented in Table 4. No differences in quality of life, perceived health status, psychological distress, sense of coherence, health behaviours, 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 versus 34.7±13.8, relative % difference 8.56, P=0.011). Moreover, ICD recipients exhibited a non-significant trend towards having a worse perceived physical health status score (SF-12 PCS 66.5±22.6 versus 70.2±23.3, relative % difference -5.26, P=0.081).

PROs with primary versus secondary prevention ICDs

As shown in Table 4, patients with secondary prevention ICDs had a lower quality of life score as assessed by LAS when compared to those with primary prevention indications (i.e. 72.0±23.1 versus 79.2±13.0, relative % difference 9.01, P=0.047). There were no significant differences in

perceived health status, psychological distress, sense of coherence, illness perception, health

behaviours, and overall composite score.

Geographic variations in PROs

Geographic variations in mean differences of the PROs for patients with and without ICDs are

portrayed in Figure 2. Panels A and B include 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 Panels A

and B, 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 behaviours (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 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 behaviours (HBS-CHD).

Differences in the APPROACH-IS summary score (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, USA, and Taiwan had

significantly lower summary scores, with non-significantly 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 behaviours are comparable in patients with and without ICDs, and

in those with primary versus 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

non-significant trend towards a higher degree of perceived physical limitations in ICD recipients

noted in the current study could potentially contribute to a less favourable illness perception. It

remains to be determined whether targeted psychoeducational interventions[19] could improve

psychological outcomes following ICD implantation in adults with CHD.

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

9

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 post-traumatic stress disorder following 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 versus primary prevention indications. The difference in point estimates for anxiety scores (HADS-Anxiety), albeit higher in patients with secondary prevention indications (6.9±4.0 versus 6.2±3.5), did not reach statistical significance. Moreover, information on ICD shocks was not collected in APPROACH-IS. In a prior study of 180 adults with CHD and ICDs, a high degree of shock-related anxiety was observed, with fears related to consequences of shocks (e.g., creating a scene) and potential triggers (e.g., 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 healthcare 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, with fewer symptoms of depression, and less risky health behaviours.[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 and

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

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 regards to characteristics through propensity score weight-matching, the analyses could not adjust for unknown or unmeasured potential confounders. The APPROACH-IS study collected comprehensive information regarding ICD implantation dates and indications. However, 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. While this issue has implications regarding generalizability, it should not impact internal validity since 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 non-responders could potentially impact PRO scores. Nevertheless, if such a measurement error is present, it is most likely non-differential and not a threat to the validity of two-group comparisons. Furthermore, patients from all continents except Africa were included. Future studies are required to assess the impact of ICDs on PROs in countries not represented.

CONCLUSION

In conclusion, in a large international study of PROs in adults with CHD, perceived health status, psychological distress, sense of coherence, and health behaviours 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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FIGURE LEGENDS

Figure 1. LOVE plot

A LOVE plot depicts 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. The dotted blue and red lines represent 10% and 5% cut-off values, respectively.

CHF denotes congestive heart failure; CHD, congenital heart disease

Figure 2. Regional variations in PROs

Differences in estimated means of the various PROs between patients with and without ICDs are plotted according to geographical region (Eastern, Europe, North and South America, and Pacific). Panel A includes PROs for which a higher score indicates a better outcome, whereas Panel B captures PROs for which a lower score reflects a worse outcome. See Table 1 for abbreviations of the various PROs.

Figure 3. Difference in summary score for PROs in patients with and without ICDs according to country

Differences in cumulative APPRtot scores between patients with and without ICDs are plotted according to country and are color-coded by region. Participating countries with at least three ICD recipients are included in the graph.

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: • 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 • 5 dimensions: 1) Mobility; 2) Self-care; 3) Usual activities; 4) Pain and discomfort; 5) Anxiety and depression
Psychological distress		
Hospital Anxiety (HADS-Anxiety) and Depression (HADS-Depression) Scale	0-21 for depression and anxiety	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 • 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

Table 2. Characteristics in matched cohorts with and without ICDs

	ICD N=107	No ICD N=3,081	P-value
Age (years)	40.1±12.4	40.2±14.1	0.462
Female sex (%)	50.5	50.4	0.985
Ethnicity (%)			1.000
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 (%)			0.919
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 (%)			0.987
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	0.829
Cognitive impairment (%)	1.9	1.7	0.686
Complexity of congenital heart disease (%)			0.381
Simple	4.7	4.5	
Moderate	54.2	52.0	
Complex	41.1	43.6	
Congestive heart failure (CHF) (%)			0.826
No history of CHF	58.9	58.0	
Past history of CHF	18.7	18.7	
Current CHF	22.4	23.3	

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

	Primary prevention N=41	Secondary prevention N=63	P-value
Age (years)	40.0±12.1	40.2±12.6	0.929
Female sex (%)	55.1	54.7	0.964
Time since ICD implantation (years)	7.3±8.1	7.6±7.1	0.852
Ethnicity (%)			0.999
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 (%)			0.991
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 (%)			0.999
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	0.939
Cognitive impairment (%)	1.3	1.3	0.998
Complexity of congenital heart disease (%)			0.967
Simple	3.3	4.3	
Moderate	51.7	51.2	
Complex	45.0	44.5	
Congestive heart failure (CHF) (%)			0.995
No history of CHF	59.2	56.6	
Past history of CHF	14.8	16.7	
Current CHF	26.1	26.7	

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

PRO	ICD versus no ICD				Primary versus secondary prevention ICD			
	ICD N=107	No ICD N=3,081	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	0.880	79.2±13.0	72.0±23.1	-9.01	0.047
SWLS	24.0±7.1	24.6±7.0	-2.62	0.341	24.6±7.0	23.1±7.3	-5.98	0.280
Perceived health status								
SF-12 PCS	66.5±22.6	70.2±24.3	-5.26	0.081	65.2±20.1	67.0±26.1	2.77	0.693
SF-12 MCS	68.5±18.0	69.5±20.2	-1.49	0.573	70.9±18.1	67.2±19.4	-5.10	0.363
EQ-5D	1.5±1.4	1.4±1.6	6.53	0.504	1.3±1.4	1.7±1.5	28.76	0.166
Psychological distress								
HADS-Anxiety	6.4±3.9	5.8±3.8	10.05	0.130	6.2±3.5	6.9±4.0	10.47	0.397
HADS-Depression	3.6±3.3	3.5±3.5	2.41	0.788	3.5±3.0	3.8±3.4	10.27	0.556
Sense of coherence								
SOC	65.7±13.3	65.6±13.2	0.09	0.961	67.7±12.7	64.2±14.0	-5.22	0.172
Illness perception								
Brief IPQ	37.7±12.1	34.7±13.8	8.56	0.011	36.1±9.6	38.7±14.6	5.75	0.392
Health behaviours								
HBS-CHD	1.7±1.2	1.6±1.2	4.26	0.528	1.8±1.2	1.6±1.2	-6.83	0.569
Summary score								
APPRtot	72.0±14.1	73.4±15.2	-1.85	0.348	73.2±10.9	70.2±16.9	-4.13	0.287

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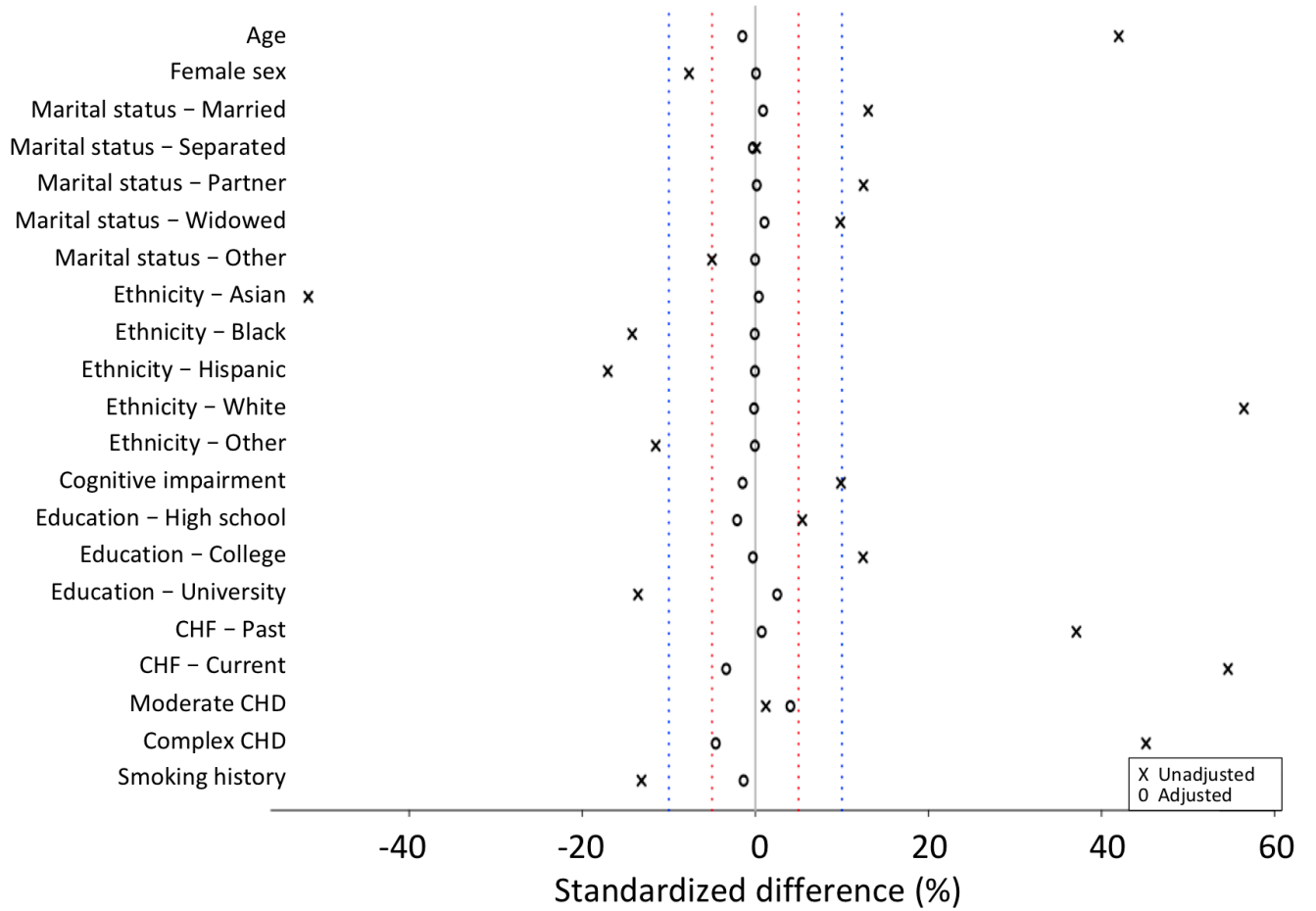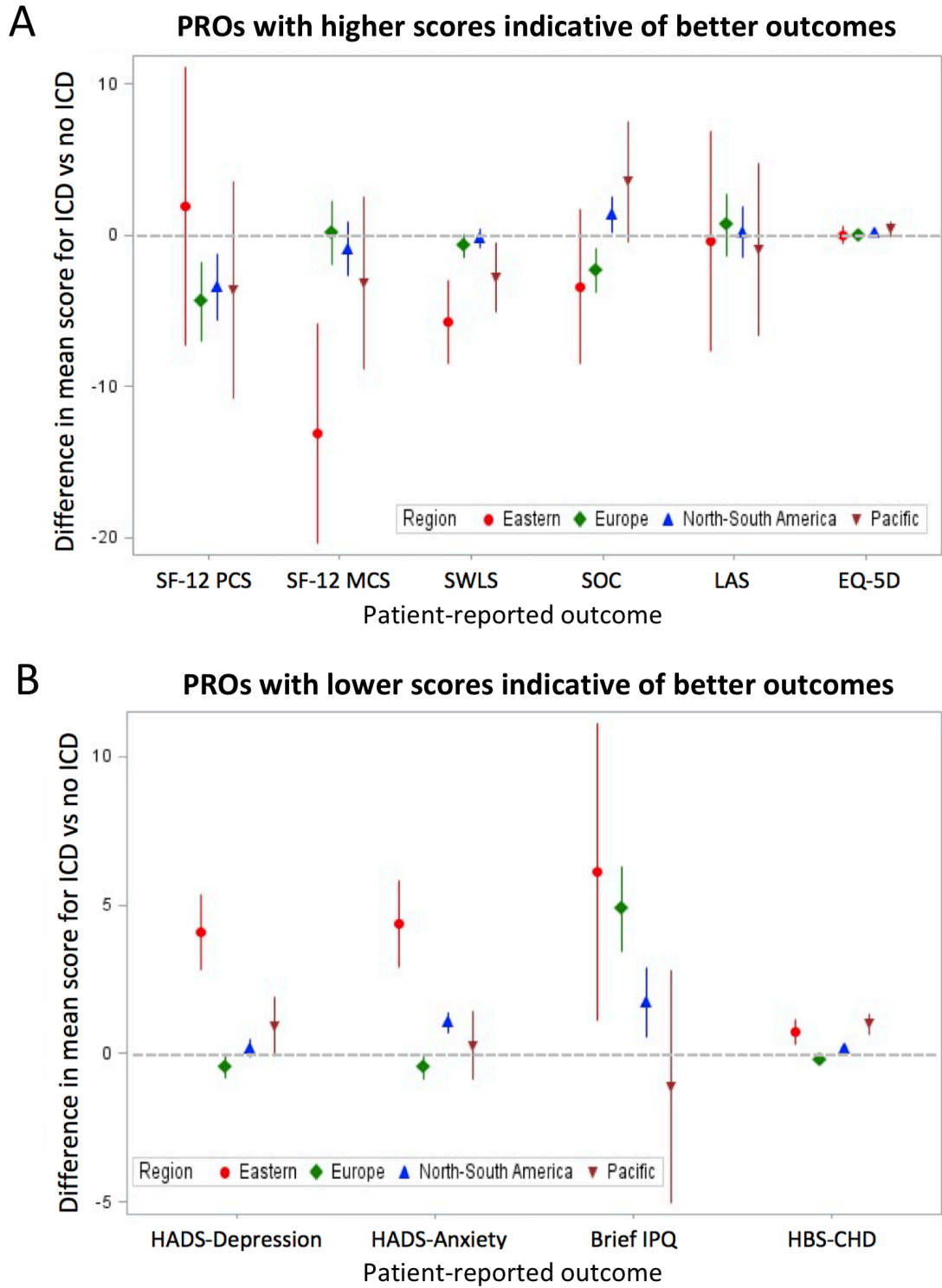
Figure 1

Figure 2

A   **PROs with higher scores indicative of better outcomes**

B   **PROs with lower scores indicative of better outcomes**

Figure 3