Title: The use of HeartQoL in patients with coronary heart disease: Association with risk factors and European reference values

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Abstract

Background: Lately, the assessment of health-related quality of life (HRQL) has gained on importance. HeartQoL is a recently developed core HRQL instrument in patients with coronary heart disease (CHD) for making between-diagnosis comparisons possible and to assess the change in HRQL after treatment.

Aim: The current study has the aim to provide reference values for patients with CHD across Europe and to investigate the association with their coronary risk profile.

Method: Analyses are based on the cross-sectional EUROASPIRE IV (EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events) survey. Patients with a diagnosis of coronary heart disease were examined and interviewed 6 months to 3 years after their coronary event. Mean and median age and gender specific HeartQoL values were calculated. Furthermore the 10^{th}, 25^{th}, 75^{th} and 90^{th} percentiles and the ceiling percentage are reported. To assess the association with the risk profile, multilevel analyses were used.

Results: The HeartQoL instrument was completed by 7449 CHD patients. Significantly worse outcomes were observed in higher risk patient groups, with lower scores in females, older patients and lower educated patients. Metabolic risk factors such as diabetes, obesity and central obesity as well as behavioural risk factors such as smoking and insufficient physical activity were also associated with worse HeartQoL outcomes. A closer look at the number of risk factors indicated worse HeartQoL scores as the number of risk factors increases. Mean reference values for Global HeartQoL amounted to 2.25 (0.64); 2.29 (0.61) and 2.19 (0.64) for males <60years; between 60 and 69 years and ≥70 years respectively. Likewise in females the global HeartQoL reference values amounted to 2.02 (0.66); 2.01 (0.65) and 1.84 (0.70) respectively. The ceiling effect in males amounted to 11.0%, 10.2% and 7.3% for the 3 age classes respectively, whereas in females the ceiling effect was 5.2%; 3.4%; and 1.9% in those <60years; between 60 and 69 years and ≥70 years respectively.

Discussion: Similar to other instruments, HeartQoL scores were associated with the patients' coronary risk profile. The reference values can help other researchers in to interpret HeartQoL scores and to assess whether their study population scores rather low or high on the HeartQoL instrument. Further research should focus on the MID in order to evaluate the effect of therapies and lifestyle changes.

Introduction

Coronary heart disease (CHD) is associated with a substantial physical and mental burden (1). Patients are likely to have an impaired health-related quality of life (HRQL) due to pain, anxiety, functional, and social limitations. During the latest decades, the assessment of patient reported outcomes has become increasingly important as highlighted by the Institute of Medicine, the European Medicines Agency, and the UK National Health Service (2-4). Successful therapies are not only assessed by their impact on longevity but also on their impact regarding HRQL, aiming at similar HRQL outcomes to healthy individuals (1).

Various instruments, such as generic instruments, which can be used across different patient groups and disease-specific instruments, for use in a particular diagnostic groups, are available to assess HRQL. The most well-known generic tools are the SF-36 (36-items Short form), SF-12 (12-items short form) and EQ-5D (EuroQoL 5-dimensions) questionnaire (5-7). Both types of measures cover multiple areas such as social functioning, physical functioning and mental functioning; generic instruments are applicable in any given population (healthy individuals as well as patients with specific pathologies) whereas disease-specific instruments are only applicable in a particular patient group, do not allow for across patient group comparisons, and tend to be more sensitive to small changes. The HeartQoL is a recently developed core HRQL instrument in patients with CHD for making between-diagnosis comparisons possible and to assess the change in HRQL after treatment and has been validated in patients with angina, myocardial infarction (MI) and ischaemic heart failure (8;9). It has the advantage above other existing CHD tools (like Seattle Angina Questionnaire (SAQ) for angina patients; Minnesota Living with Heart Failure (MLHF) questionnaire for patients with heart failure) to allow for between diagnosis comparisons of HRQoL (10;11).

HRQL outcomes are known to be associated with the patients' characteristics, their coronary risk profile and their long-term cardiovascular prognosis (12-14). The aim of this study was to establish HeartQoL reference values for patients with CHD across Europe and to investigate the association with their coronary risk profile using information from the EUROASPIRE IV (EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events) survey.

Methods

Study population and data collection

Analyses are based on the EUROASPIRE IV study (2012-2013). This is a cross-sectional survey initiated to evaluate whether the guidelines on cardiovascular prevention are being followed in everyday clinical practice (15). More detailed information of the study has been reported previously (REF kotseva). Patients eligible for inclusion were men or women, aged ≥18 years and <80 years at the time of identification who were interviewed 6 months to 3 years following the recruiting event which was hospitalization for a first or recurrent coronary event. The event(s) included elective or emergency coronary artery bypass graft surgery (CABG); elective or emergency percutaneous coronary intervention (PCI); first or recurrent acute MI; acute myocardial ischemia. Patients were retrospectively identified from diagnostic registers, hospital discharge lists or other sources at 78 different hospital centres in 24 European countries: Belgium, Bosnia Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Ireland, Latvia, Lithuania, Netherlands, Poland, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, Turkey, Ukraine and the United Kingdom. Data collection was done in a standardized way by trained research staff. Personal and demographic details as well as medical and cardiovascular history, and reported lifestyle and risk factor management regarding smoking, exercise, blood pressure, lipids, glucose and medication use were gathered. Furthermore, a physical examination assessing weight, height, waist circumference, blood pressure, heart rate, breath carbon monoxide, serum total cholesterol, HDL-cholesterol, tryglycerides, plasma glucose and HbA1c was performed.

Physical activity levels were assessed using the validated International Physical Activity Questionnaires (IPAQ) (16). In addition, a single question on physical activity levels was included in the questionnaire. Patients were also asked to complete the validated HeartQoL questionnaire (8), comprising 14 items with 4 answer categories ranging from 'not bothered by' to 'bothered a lot by'. Both a global (all items), physical (10 items) and emotional (4 items) score, calculated as the mean of the item scores, can be computed with scores ranging between 0 (lowest HRQL) and 3 (best HRQL). The HeartQoL questionnaire can be found in Figure 1. The psychometric characteristics of the HeartQoL tool have been previously assessed with good reliability and validity (8)+REF De Smedt HQ1.

The most recent European guidelines on cardiovascular prevention were used to set the risk factor targets (15). Risk factor targets include the following: blood pressure ≥140/90mmHg (≥140/80mmHg in patients with diabetes); LDL-cholesterol ≥1.8mmol/; and HbA1c <7% in diabetes patients. As no targets for total cholesterol and fasting glucose were set in the current guidelines, we used the following targets based on the previous guidelines: total cholesterol <4.5mmol/L and fasting glucose ≥6.1mmol/L (17). Central obesity was defined as a waist circumference >102cm and >88cm for men and women, respectively; and overweight and obesity were defined as a BMI ≥25kg/m² and ≥30kg/m², respectively.

Statistical analyses

Descriptive analyses for males and females were reported separately. To calculate the reference values, HeartQoL scores were stratified by gender, age group (<60 years; ≥60 years <70 years; ≥70 years) diabetes and educational level (primary education: primary school or less; secondary education: secondary school completed, high school completed or intermediate between secondary level completed; high education: university/college degree or equivalent). Mean (SD) and median (interquartile range) values were calculated and the 10^{th} and 90^{th} percentiles and the ceiling percentage are reported. One half a standard deviation has been shown to be representative of the minimal

important difference (MID) in several HRQL instruments (18). The MID can be seen as the smallest difference in score of importance to patients and clinicians.

To assess the association with the risk profile, generalized linear mixed models were used in order to account for clustering of patients within countries. Baseline adjustments for age, gender, and educational level were performed. Additional adjustment for recruiting diagnosis, diabetes, history of stroke, and coronary recurring events was done. Statistical significance was defined as $p<0.05$. All analyses were performed with IBM SPSS statistical software (version 21.0).

Results

Patient characteristics

From the 7998 patients interviewed and examined at least 6 months and not later than 3 years following their recruiting event, 7449 patients completed the HeartQoL instrument. Patient characteristics are provided in Table 1. The mean age was 64.0 (SD=9.6) years; 76.0% were male; 16.6% had a low education and 22.8% was highly educated; and 15.5% were current smokers. Self-reported diabetes was seen in 26.8% of the patients, with 47.6% having an uncontrolled HbA1c; raised total cholesterol was observed in 38.6% of the patients, a LDL-cholesterol ≥2.5mmol/L in 41.7% and ≥1.8mmol/L in 80.1% of the patients; and an elevated blood pressure was seen in 42% of the patients. Lipid lowering medication use was reported by 87.3% and blood pressure lowering medication use by 95.3% of patients. Central obesity was observed in 58.2% of patients with 44.6% being overweight and 37.7% obese at the time of the interview. Furthermore 19.2% of patients had a low IPAQ and 42.2% had a high IPAQ. The distribution of leisure time physical activity based on one single question was as follows: 8.0% indicated no physical activity, 50.7% indicated only light physical activity in most weeks, 21.0% indicated vigorous physical activity >20 min once or twice/week, and 20.3% reported >20 min vigorous physical activity ≥ three times/week.

HeartQoL scores

The mean global HeartQoL score amounted to 2.2 (SD=0.66), the mean physical and emotional subscale scores were 2.1 (SD=0.72) and 2.3 (SD=0.72), respectively. The HeartQoL global scale and subscale scores followed a typical HRQL distribution with global scale and both subscale scores skewed to the left. The mean country-specific HeartQoL global scores, adjusted for age and gender, are shown in Figure 2; with scores of >2.4 in Spain and Greece and mean scores <1.9 in Croatia, Poland, Bulgaria, Bosnia Herzegovina, and Lithuania. With a mean standard deviation of 0.66 on the global scale and 0.72 on the subscales, the MID is around 0.35 points on the 4-point HeartQoL scale. The difference between the five countries with the worst global score (Lithuania, Bosnia Herzegovina, Bulgaria, Poland, Croatia) and the top five countries (Spain, Greece, Latvia, Sweden, Netherlands) with the best global score exceeded the MID.

HeartQoL reference data

Reference values are given for CHD patients stratified by gender and age in Table 2. In addition to mean and median values, the 10^{th} and 90^{th} percentiles as well as the floor and ceiling effects on the global scale and the subscales are shown. No floor effect was observed, whereas a ceiling effect was seen on both the global scale as well as on both subscales. Better scores are seen in males and younger patients, resulting in higher ceiling effects. The difference in mean global (2.25 and 1.94) and physical score (2.21 and 1.88) between males and females approached the MID. Particularly in the 60-69 years age group, the MID was reached between males and females on both the global scale as well as on the subscales.

HeartQoL scores were further stratified by diabetes and educational level. Patients with diabetes scores worse than those without diabetes, however the MID was not reached. Within diabetes patients however, the MID was reached between males and females on all three scales.

Likewise, lower educated patients scored worse than highly educated patients, however again, the MID was not reached. In lower educated patients, the MID between males and females was well exceeded on all scales. The same was true for the global scale in high educated patients.

Furthermore, mean items scores are provided with the highest mean found on Item 1 in both males (2.7) and females (2.5) and the lowest mean found on item 5 again both in males (2.0) and females (1.7). Four items (n°2, 3, 4 and 5) exceeded the MID between males and females. Amongst males, only item n°5 had a mean score <2.0; whereas among females, nine items had mean scores <2.0 (item n°2, 3, 4, 5, 7, 8, 12, 13, 14)

HeartQoL scores and coronary risk

Generalized linear mixed models analyses indicated differences in scores between different patient groups, with significantly worse outcomes in higher risk patient groups (Table 4).

A. Non modifiable risk factors: Significantly lower scores were observed in females, older patients, and primary education level patients. However, with the exception of gender (global and physical HeartQoL), none of the age or education level differences met or exceeded the MID.
B. Metabolic risk factors: Diabetes, obesity and central obesity were associated with worse HeartQoL outcomes whereas no association could be found of HeartQoL with raised HbA1c in diabetes patients, nor with raised blood pressure or raised cholesterol in medically treated patients after full correction of the model. None of the metabolic risk factor differences met or exceeded the MID.
C. Behavioural risk factors: HeartQoL scores were associated with better outcomes in prior smokers, in those who report higher physical activity levels, and those who have attempted to increase their physical activity level. The latter two seem to reinforce one another with the best outcome in highly active patients who have made an attempt to increase their physical activity,

and the worst outcome in insufficiently active patients who did not make any attempt to increase their physical activity. Finally, weight change was not associated with HeartQoL scores. The physical activity variables (both the single question, as well as the IPAQ and the combination of physical activity changes and IPAQ) met or exceeded the MID, with the lower physical activity categories having clinically relevant worse global and physical HeartQoL scores compared to the higher activity levels.

D. Number of risk factors: Worse HeartQoL scores were seen as the number of risk factors increased with the lowest HeartQoL scores in patients with ≥3 risk factors; the difference between the global and physical scores in patients with 0 or 1 risk factor and ≥3 risk factors exceeded the MID (Table 3).

Discussion

The aim of this study was to establish HeartQoL reference values for patients with CHD across Europe and to investigate the association with their coronary risk profile using data from the EUROASPIRE IV study which included HeartQoL information from 7449 European patients with CHD. Patients included in the study had a typical coronary profile and, similar to the EUROASPIRE III survey, a worse risk factor profile was associated with poor HRQL values with an increase in number of risk factors being associated with worse HeartQoL outcomes (13;14). In general, behavioral changes were associated with favourable HeartQoL outcomes.

This study is the first to provide HeartQoL reference values. These values can be useful for other researchers in order to interpret HeartQoL scores and to assess whether their study population scores rather low or high on the HeartQoL instrument. Reference values were generated, stratifying by gender, age group, educational level, and diabetes status since these variables are known to be associated with HRQL. Clinically relevant differences between males and females were found in the complete sample, as

well as in the diabetes patients and the lower educated patients. Relevant differences mainly occurred on the global and physical scale and in the 60-69 years age class.

Next, the association between the coronary risk profile and HeartQoL scores was assessed. First, HeartQoL was associated with non-modifiable demographic risk factors such as gender, age and educational level. Substantiating previously reported findings in the general population as well as in CHD patients, worse HeartQoL outcomes were found in female patients (14;19;20). Several underlying causes have been suggested; some suggest women tend to over report their problems during interviews because women verbalize better than men (21); others argue that women perceive symptoms in a different way (22;23); also, higher depression rates (which has also been seen in the EUROAPSIRE III and IV surveys), lower sense of coherence (i.e., experiencing the world as comprehensible, meaningful and manageable) and social status (continuing demand in home environment) are referred to as reasons for worse HRQL outcomes in females (24-26). Similar to the general population, worse HeartQoL scores were seen with increasing age due to the aging process which is associated with a deterioration of both physical and mental abilities (27). A lower educational level was also associated with worse outcomes. Educational level, which has a direct relation to the expected income level, its associated with health habits, comorbidities, access to health care facilities and a more adverse cardiovascular risk factor profile (28-31) which might explain a lower self-perceived health status as seen in this study. Importantly, the gender was most pronounced between males and females in the lowest age class.

Consistent with previous studies, patients with adverse metabolic risk factors such as diabetes, obesity and central obesity also performed worse on the HeartQoL instrument although, as in the EUROASPIRE III study, no association was seen with the emotional component for weight or waist circumference (20;32;33). Finally, behavioural risk factors such as smoking and low physical activity were associated with worse outcomes (34-40). All physical activity variables showed clinically relevant differences

between lower and higher physical activity levels. Furthermore, whereas BMI was associated with HeartQoL, no such association was seen with weight changes. In CHD and other chronic disease patients, weight changes can occur for different reasons. Sometimes reduction in weight is a result of well thought lifestyle changes which can result in better HRQL outcomes, however often patients lose weight unintentionally as a result of their disease not resulting in improved HRQL scores.

In summary, these HeartQoL reference values can be used in clinical practice across Europe. Similar to other instruments, HeartQoL scores were associated with the patients' coronary risk profile. Clinically relevant differences were seen between males and females, especially in diabetes patients and lower educated patients, and between higher and lower physical activity levels. Also the number of risk factors showed important differences in HeartQoL scores0 Further research should however focus on the HeartQoL MID, since current MID values are based on other HRQL instruments. This will help to evaluate the effect of therapies and lifestyle changes on HeartQoL scores.

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