Measurement properties of the HeartQoL questionnaire in patients following heart valve surgery

A methodological study

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ABSTRACT

Background: To our knowledge no disease specific instrument for measuring health related quality of life (HRQoL) is available for patients with heart valve disease or following heart valve surgery. A recently developed disease-specific core questionnaire, The Heart Quality of Life questionnaire (the HeartQoL), intends to assess HRQoL across patients with coronary heart diseases. Since heart valve disease frequently coexists with ischemic heart disease, we hypothesized that the HeartQoL questionnaire could be used for patients following heart valve surgery. The aim of this study was to evaluate the measurement properties of the HeartQoL questionnaire, Danish version, in terms of reliability and validity in a mixed sample of patients following heart valve surgery.

Designs: A cross-sectional and a test-retest reliability study.

Methods: A total of 557 patient following heart valve surgeries completed the Danish version of the HeartQoL, the Short-Form 36 and the Hospital Anxiety and Depression Scale. Internal consistency was assessed by Cronbach's α. A total of 92 patients participated in the test-retest study. Relative reliability was analysed with intraclass correlation coefficient model 2.1 and the absolute reliability with standard error of measurement (SEM) and smallest detectable change (SDC). Construct validity was assessed with a priori hypotheses together with the discriminative validity; the "known-group approach".

Results: Internal consistency was high (Cronbach's alpha ≥ 0.87). Relative reliability showed large values of ICC ≥ 0.80. For the absolute reliability SEM ranged from 0.17 to 0.26 and SDC_{95} ranged from 0.5 to 0.7 points. Construct validity: The HeartQoL showed strong correlation with hypothesized corresponding measurement and with non-corresponding measurements ($r > 0.60$). Known-group discriminative validity analysis confirm that the HeartQoL questionnaire distinguish well between patient groups. The analysis demonstrates support for 81% of all a priori hypotheses for predicted variables.

Conclusions: The HeartQoL questionnaire shows acceptable reliability regarding internal consistency and test-retest reproducibility. The questionnaire was also found to have acceptable construct validity for patients following heart valve surgery evaluated in a representative population of post-surgery patients in Denmark. It is recommended that future studies should focus on assessing the responsiveness of the HeartQoL questionnaire.

DANSK RESUMÉ

Baggrund: Så vidt vi ved findes der ingen sygdomsspecifikke helbredsrelateret livskvalitets spørgeskemaer beregnet til patienter med hjerteklap sygdom eller efter hjerteklapkirurgi. Et nyligt udviklet sygdoms specifikt måleinstrument The Heart Quality of Life spørgeskema (the HeartQoL) har til hensigt at vurdere helbredsrelaterede livskvalitet på tværs af patientgrupper med hjertekarsygdomme. Da hjerteklapsygdom ofte optræder sammen med iskæmisk hjertesygdom, antager vi, at HeartQoL vil kunne anvendes til patient efter hjerteklapkirurgi. Formålet med denne undersøgelse er at evaluere måleegenskaberne af HeartQoL spørgeskemaet, den danske version, i form af reliabilitet og validitet i en blandet population af patienter efter hjerteklap kirurgi.

Design: En tværsnitsundersøgelse og et test-retest reliabilitets studie.

Metoder: I alt 557 patient efter hjerteklap operation besvarede den danske version af HeartQoL samt spørgeskemaerne Short-Form 36 og HADS. Intern konsistens blev vurderet ved Cronbachs α. 92 patienter deltog i test-retest studie. Relativ reliabilitet blev analyseret med intraclass correlation coefficient model 2.1. Absolut reliabilitet med målefejl (SEM) og mindst målbare forskel (SDC). A priori-hypoteser blev defineret til vurdering af construct validitet med undersøgelse af konvergent og divergent validitet af HeartQoL. Diskriminativ validitet blev undersøgt ved "known-group" metoden.

Resultater: Intern konsistens var høj (Cronbachs alpha ≥ 0,87). Relativ reliabilitet viste store værdier af ICC ≥ 0.80. For absolut reliabilitet varierede SEM fra 0.17 til 0.26. SDC_{95} varierede fra 0.5 til 0.7 point. HeartQoL viste stor korrelation med associerende og ikke associerende måleinstrumenter (r> 0,60). "Known group" metoden bekræfter at HeartQoL spørgeskemaet skelner godt mellem patientgrupper vi forventede ville score forskelligt på HeartQoL spørgeskemaet, da 81 % af de opstillede præ definerede hypoteser blev bekræftet.

Konklusioner: På baggrund af dette studie har HeartQoL spørgeskemaet vist acceptabel reliabilitet med hensyn til intern konsistens og test-retest reproducerbarhed samt construct validitet for patienter efter hjerteklap kirurgi vurderet i en repræsentativ population af post-kirurgi patienter i Danmark. Det anbefales, at fremtidige studier bør fokusere på at vurdere responsivness af HeartQoL spørgeskemaet.

ACKNOWLEDGEMENT

This master study is now in the final phase and it has truly been three fantastic years. The Department of Health Sciences (Institute of Health and Society, at the University of Oslo) has composed this outstanding program: Master of Health Science. I have met exceptional teachers who have shared knowledge and experience and been a huge inspiration.

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ABBREVIATIONS

CABG	Coronary arteries bypass grafting
COSMIN	**CO**nsensus-based **S**tandards for selection of health **M**easurement **In**struments
GH	General Health perception index
HADS	Hospital and Depression Scale
HeartQoL	Heart Quality of Life questionnaire
HRQoL	Health related Quality of life
ICC	Intraclass correlation coefficient
IHD	Ischemic heart disease
LoA	Limits of agreement
MCS	Mental Component Summary score
PCS	Physical Component Summary score
PIN	Personal identification number
PROM	Patient reported outcome measure
SDC	Smallest detectable change
SEM	Standard error of measurement
SF_{36}	Short-Form 36 Health Survey

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1 INTRODUCTION

During the last decades an increasing focus on patient reported health-related quality of life (HRQoL) has evolved, using patient reported HRQoL as a complementary healthcare outcome when assessing the treatment efficacy and health status among heart patients[1-4]. HRQoL is commonly measured through patient-reported outcome measures (PROMs) collected through self-report questionnaires[5].

The Heart Quality of Life questionnaire (the HeartQoL) is a recently developed core heart disease-specific HRQoL questionnaire. It is designed to capture a broader spectrum of cardiac diseases. The core questionnaire also intends to give the possibility to make between-diagnose comparisons in subgroups across cardiac diseases.

The incidence of heart valve disease has increased worldwide over the last decades in line with increasing life expectancy and due to improved treatment options[6]. To our knowledge no disease-specific HRQoL questionnaire is developed for patients with heart valve disease or following heart valve surgery. The HeartQoL has until recently only been validated in patient populations suffering from ischaemic heart disease (IHD)[7] and before HeartQoL can be taken into use in new patient populations it is essential to evaluate if the questionnaire demonstrates acceptable methodological standards.

The purpose of this master thesis is to evaluate the measurement properties of the HeartQoL questionnaire with regard to its reliability and validity, in a sample of patients following heart valve surgery.

This master study relies on the **CO**nsensus based **S**tandards for the selection of health **M**easurement **IN**strument (COSMIN) initiative. The COSMIN initiative has proposed standards to evaluate the methodological quality and design and preferred statistical analyse of a study on measurement properties[8].

If this present master thesis supports the expectations that the HeartQoL questionnaire is a valid and reliable HRQoL measurement instrument to be used in patients following heart valve surgery, the HeartQoL questionnaire will contribute to the possibility of shedding light of HRQoL in a growing patient population. In addition it will provide the opportunity to using subjective treatment targets after cardiac surgery, assist with follow-up treatment and

rehabilitation, and permit between-diagnose comparison of HRQoL in subgroups across cardiac diseases.

This master thesis is a part study of The CopenHeart research project which was initiated in 2010. The purpose with the CopenHeart project is to establish a theoretical foundation for the rehabilitation of patients with complex cardiac diagnoses. In particular the project examines the benefit of rehabilitation in relation to physical and psychosocial functioning along with economic effects of rehabilitation. The validation part of this master study is based on data from the CopenHeart nationwide survey; a study on patients quality of life, self-rated health and cardiac rehabilitation.

This master thesis is written as an article with an initial «extended abstract». The «extended abstract» describes the theoretical background, the method applied, the data collection, brief outline of results, methodological considerations, discussion of main results and finally conclusion remarks. The article has not yet been commented by the co-authors to reflect that the work is done solely by the master student. The article will be published in a relevant peer-reviewed scientific journal.

2 AIM

The aim of this master thesis is to evaluate the measurement properties of the disease specific measuring instrument, the HeartQoL questionnaire, in terms of reliability and validity in a mixed sample of patients following heart valve surgery.

3 BACKGROUND

3.1 HEART VALVE DISEASE

3.1.1 Epidemiology of heart valve disease in Denmark

Heart valve disease is a general term for diseases involving impaired function of the heart valves. The two main causes of heart valves disease are heart valve stenosis and heart valve insufficiency. Approximately 100.000 people suffer from heart valve disease in Denmark[9] and the worldwide prevalence was estimated to 2.5% in a large American population-based study[10]. The incidences are increasing due to high age and increased survival rate of the population[6,9]. Patients develop slowly progressing symptoms such as exertional dyspnea, chest pain, abnormal fatigue, impaired functioning and syncope[11]. In addition heart valve patients often have secondary heart diseases such as ischaemic heart disease (IHD). An untreated or late diagnosed heart valve disease may also increase the risk of developing chronic heart failure. Without surgery the mortality is high. In symptomatic aortic stenosis which is one of the most common heart valve diseases, 50% will die within 1.5 to 3 years. The prognosis is worse if complicated by heart failure[12].

3.1.2 Treatment of valve disease

The treatment of heart valve disease is surgery with replacement or repair of the involved heart valve as determined by clinical guidelines and taking into account the severity of symptoms[12]. During the last 6 years there has been a 23% increase in heart valve operations in Denmark[13]. This is related to increasing life expectancy, better and more widespread diagnosis elucidation and better surgical techniques. Approximately 1800 heart valve surgeries are performed annually[13]. Blauwert and Miller have estimated that more than 280.000 heart valve surgeries are performed each year worldwide[14]. The surgical option for heart valve disease is most often the open heart procedure. But with a new gentler surgical intervention technique, known as the percutaneous procedure, an increasing number of elderly patients with a high degree of comorbidity and at risk of complications are being submitted for heart valve surgery[15,16]. In Denmark heart valve surgery is performed at the four heart centres; Rigshospitalet, Odense, Skejby and Ålborg. According to the Danish Heart Register,

heart valve surgery is performed *"in the long term to improve survival and quality of life for patients"* [13].

3.1.3 Health Related Quality of Life status and heart valve disease

Before surgery, patients may suffer deconditioning due to many years of chronic illness causing physical limitations and severe shortness of breath with little exertion. Several studies have demonstrated that patients experience impaired health related quality of life (HRQoL) before surgery[17,18]. Despite the improved quality of life after surgery some patients suffer from physical and mental challenges as anxiety and worries related to risk of readmission, reoperations and complications[18-20]. In addition, some patients are disturbed by clicking noise from mechanical valves and the complication initiated by lifelong anticoagulation treatment. Many patients experience various physical challenges due to limitations of physical function during the first 6 to 8 weeks post-operative in relation to the sternal wound healing and reduced preoperative activity level [20-26].

For some patients the physical and psychological challenges after heart valve surgery can prevent or delay the return to work and activities of daily living[27]. Ultimately, patients may be left in a vacuum where there is a risk that they will not achieve the full benefit of a very extensive surgery, neither physically nor mentally.

3.2 MEASURING PATIENT PERCEIVED HRQoL

3.2.1 Concepts and definition of Health Related Quality of Life (HRQoL)

HRQoL is being increasingly used in the medical scientific literature and has been a subject of considerable debate in terms of the concept and the way the concept is measured. The concept was introduced in the 1980's by Kaplan & Bush with the intention to delimit the quality of life concept for health and medicine. Thus it distinguishes between the broad descriptions of quality of life (physical, psychological, social and existential aspects of life) and the aspects of quality of life that is related to health. Over the years there have been several different approaches to define HRQoL but no consensus on its definition[28]. It is

though essential that HRQoL focuses on the influence of a perceived health state and the ability to live a fulfilling life.

A conceptual clarification was necessary with the growing focus on health related quality of life as a complementary health care outcome when assessing treatment efficacy and health status among patients and to become a standard outcome in many research trials and clinical studies[1-4,29]

In 2005 The European Medicine Agency (EMA) formulated a definition of HRQOL as a:

"Multi-domain concept referring to the effect of an illness and its therapy upon a patient's physical, psychological and social wellbeing, as perceived by the patients themselves" (p. 3)[2]

The approach is that this multidimensional concept can only be assessed by subjective measures through self-report thus giving information on patient's perception of their current health or disease status and their everyday functioning. Individuals may have a different perspective of which factors influence HRQoL. Different interpretations and meaning makes HRQoL a challenging concept.

HRQoL is measured commonly through patient-reported outcome measures (PROMs)[5].

3.2.2 Patient reported outcome measures (PROMs)

Patient reported outcome measures (PROMs) are used as an umbrella term for measures of subjective symptoms, HRQL and treatment satisfaction[2]. Information obtained directly from the patient is referred to as a patient-reported outcome. PRO are defined by the United Stated Food and Drug Administration as" *any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"* (p. 2)[1] and by The European Medicine Agency as "*any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s)* (p.3)[2].

PROMs provides a means of quantifying qualitative information and is typically collected through a self-administered questionnaire completed by the patient.

3.2.3 Biases in reponding

When it comes to the use of these subjective outcomes some conditions must be considered when it comes to responses. In the literature this is called response bias and refers to conditions that can affect the responses. Some respondents will answer in a way that makes them more favorable or unfavorable. And some respondents will only select the most extreme options or answers available or have a resistance to extreme scores and therefore are generally in the middle of a scale. It is obvious that the level of response bias can affect the results that are obtained[28,30].

Response shift is another phenomenon which can be seen in longitudinal studies where self-reported measurements are administered over time. Response shift is a change in patients understanding of the concept to be measured and are often a result of adaptation to change in health status. In connection with disease progression it is known that perceptions of HRQoL can change. People adapt themselves to new conditions and define new standards for their health status and quality of life. Response shift must therefore be taken into consideration when measuring HRQoL over time[5,28,29].

3.2.4 Types of measuring instruments

A large number of instruments have been developed for measuring the impact of a specific disease, treatment or condition on health related quality of life. The instruments are often classified into three main groups of questionnaire types; the generic, the specific HRQoL and core instrument.

The generic HRQoL instrument

The generic instruments are designed based on issues relevant to a broad spectrum of diseases or population samples independent of diagnose and are intended to cover a wide range of conditions. The advantage of using generic instruments is that they can be used for comparison regardless of populations or diseases and can therefore also make it possible to compare between a sick and healthy population. An example of a generic instrument is the well-known The Short-Form 36 Health Survey or SF-36. Items contained in a generic instrument are not necessarily adequate with respect to a particular patient population and

generic instruments may therefore be limiting for specific conditions and diseases. For that purpose the specific HRQoL instrument is preferred[28,29].

The specific HRQoL instrument

The specific instruments are designed for patients with either a specific disease or a specific diagnosis within a given disease. It is developed with the intention to focus on disease-related concerns/conditions particularly characteristic and relevant for the specific patient groups. The items are specifically targeting aspects the patient group typically experience and make it possible to assess HRQoL related to the specific condition. An example of HRQoL disease-specific instruments related to heart disease is the MacNew Heart Disease HRQoL Questionnaire[31], the Seattle Angina Questionnaire[32] and the Minnesota Living with Heart Failure Questionnaire[33]. The disadvantage when using a disease specific instrument is the inability to compare with the general population[28,29].

Commonly the different types of questionnaires are used together for giving the best assessment of HRQoL. For the purpose of comparing between disease-specific subgroups, a core questionnaire can be used.

Core questionnaires

With a core questionnaire the intention is to combine the benefits of the generic and the disease specific instruments. The instruments are designed to cover a range of issues relevant to a broad range of patients within a specific disease group with co-occurring conditions thus making it possible to create between-diagnose comparisons in disease specific subgroups. The core instrument must then have suitable generalizability and appropriate specificity. Core questionnaires are known from the field of cancer[34,35]. For example the EORTC Quality of Life Questionnaire Core (EORTC QLQ-C30)[34].

Selecting the most appropriate instrument

Selecting an instrument is dependent on the condition of interest, the relevance for the study population, the burden for the respondents' (e.g. length of questionnaire and the time to completion) and the administrative burden for the investigator[3,36]. And exclusively: To be

able to rely on results and consequent conclusions it is crucial the measurement properties of the instrument is evaluated and conform to the present standards.

3.3 MEASUREMENT PROPERTIES

In 2010 The COSMIN group published an international consensus report on terminology and definitions concerning measurement properties (FIGURE:1a)[8]. The group comprised of leading experts in the field. The recommendation was developed to give specifics standards and explicit criteria for developing and evaluation of health status measurement instruments. To ensure the methodological quality of this master thesis, the evaluation of the HeartQoL questionnaire is appraised using the recommendations from the COSMIN group.

The measurement properties concerns three domains: reliability, validity and responsiveness with underlying subdivisions (FIGURE:1a). Interpretability is not considered as a measurement property but is regarded as an important characteristic of a measurement instrument and therefore included in the taxonomy[8].

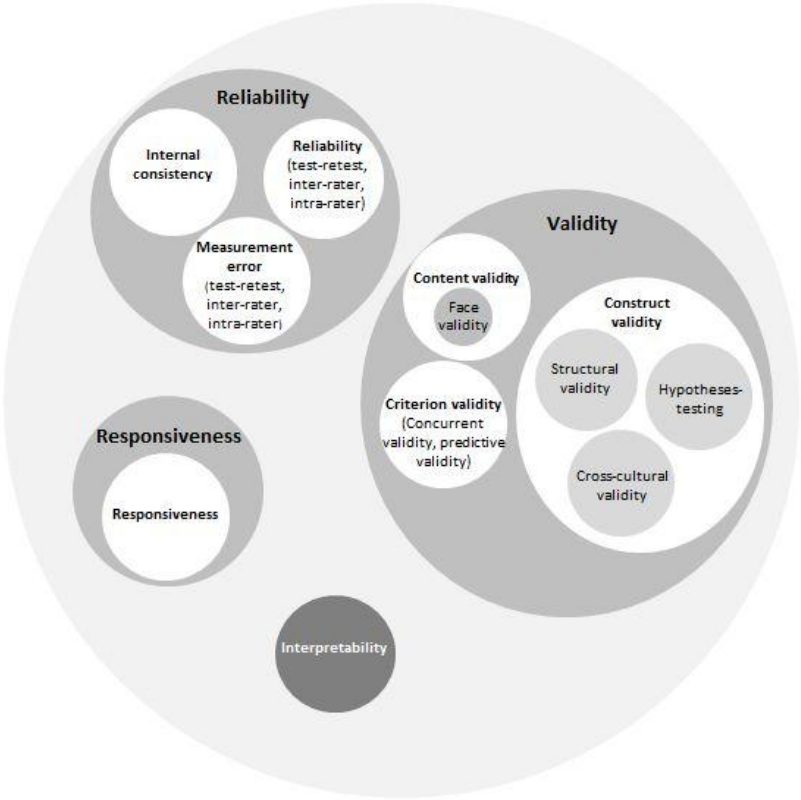

FIGURE 1a The taxonomy of measurement properties[8]. Reprinted from Mokkin et al. With permission from Elsevier.

Reliability

Reliability is defined as *"the degree to which the measurement is free of measurement error"* (p.743)[8]. It is quantified by the degree to which measurements are consistent (constant or stable) and reproducible (repeatable). Repeated measurements will always present some variations. The source of error for variation may be due to the measuring instrument itself, the respondent or the conditions in which the measurement is conducted. Another important circumstance is the time interval between the two measurements. The time gap must be considered to be short enough to ensure that the respondent measured clinical parameters has not been changed and at the same time long enough to avoid recall of previous answers[5].

Under the domain of reliability are the subcategories: internal consistency, reliability and measurement error. The last two are also termed relative and absolute reliability respectively.

Internal consistency is defined as *"the degree of interrelatedness among items"* (p.743)[8] and reflects the degree to which the various items of the instrument are associated to each other. Referring to the homogeneity of the instrument The Cronbach's alpha is considered adequate to assess the internal consistency[5]. Reliability (relative reliability) is defined as *"the proportion of the total variance in the measurement which is because of the true differences among patients"* (p.743)[8] and explores the degree of reproducibility in repeated measurements. The statistical test used to calculate the reliability depends on the types of response options. For continuous scores the intraclass correlation coefficient (ICC) is preferred. A distinction is made between the $ICC_{consistency}$ and $ICC_{agreement}$ where $ICC_{agreement}$ refers to absolute agreement between the repeated measurements and takes into account for systematic differences and the $ICC_{consistency}$ refers to the consistency between ratings[5]. For dichotomous or nominal scores the Cohen's Kappa coefficient should be used[37]. Measurement error (absolute reliability) is defined as *"the systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured"* (p.743)[8]. This refers to the differences between hypothetical "true scores" and the actual obtained scores. The measurement error for continuous measures is determined by estimating the standard error of measurement (SEM) and is expressed in the same units as the measurement. Finally the COSMIN group recommends the determination of the smallest detectable change (SDC). The SDC can be interpreted as a real change in score and not a measurement error.

Validity

Validity is defined as *"the degree to which an instrument measures the construct(s) it is purposes to measures"* (p.743)[8]. The domain is divided into three measurement properties: Content validity, criterion validity and construct validity. Content validity is defined as *"the degree to which the content of an instrument is an adequate reflection of the construct to be measured"* (p.743)[8]. The content validity is based on subjective assessments. Criterion validity is explained as*" the degree to which the scores of an instrument are an adequate reflection of a golden standard"*. For both content and criterion validity the assessment is included in the development of an instrument.

In this master thesis we illuminate the construct validity defined as *"the degree to which the scores of an instrument are consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured"* (p.743)[8]. Construct validity refers to the degree to which the scores of a measurement instrument are consistent with a hypothesis with regard to relationship with scores of other comparable instruments or to score differences between relevant groups.

To evaluate construct validity a detailed description of the construct to be measured is of great important (see section 4.2.1 The HeartQoL questionnaire) along with an appropriate description of the comparable instruments (see section 4.2.2 The Short-Form 36 health Survey and 4.2.3 The Hospital Anxiety and Depression Scale). Subsequently the construct validity is explored with a priori formulated hypotheses with regard to relationship with scores to the corresponding or non-corresponding constructs and with a priori hypotheses conceived for subgroups of responder which is expected to score differently[37].

Responsiveness

Responsiveness is explained as *"the ability of an instrument to detect change over time in the construct to be measured"* (p.743)[8]. Responsiveness can only be explored in longitudinal studies designs where changes to the construct to be measured are likely to occur. It involves at least two measurements to be taken in order to calculate change scores. The assessing of responsiveness is performed by testing hypotheses concerning the instrument and score changes in relationship between other instruments that measure similar constructs[5]. An instrument can only be responsive if it can discriminate between those respondents

performing changes in scores (improved or deteriorated) and those respondents who do not change in scores; thus to be sensitive to change when change has occurred. Responsiveness is not a part of this master thesis due to study design.

Interpretability

Interpretability is not considered a measurement property but is regarded as an important characteristic of a measurement instrument. It is defined as *"the degree to which one can assign qualitative meaning - that is clinical or commonly understood connotations - to an instrument's quantitative scores or change in scores"* (p.743)[8]. The COSMIN group suggests interpretability of an instrument contains an inspection of the scores in the target population and determination of possible floor and ceiling effect. Cut-off scores for the HRQoL instrument are clinically meaningful allowing clinicians to interpret scores more easily. As a final point the COSMIN group recommends the determination of minimal important change (MIC) defined by the COSMIN group as "*the smallest change in score in the construct to be measured which patient perceive as important"* (p.245)[5].

4 MATERIALS AND METHODS

4.1 STUDY DESIGN AND SAMPLES

4.1.1 Design

The study is divided in two parts:

1) A cross-sectional study to determine the validity of The Heart Quality of Life questionnaire (the HeartQoL) in patients following heart valve surgery, (Study I)

2) A test-retest reliability study to determine the reproducibility of The Heart Quality of Life questionnaire (the HeartQoL) in patients following heart valve surgery, (Study II)

4.1.2 Study sample for the validity study (Study I)

This study sample is based on the national CopenHeart survey. In the period from January 1st to June 30th 2011 a total of 876 patients were admitted for heart valve surgery in Denmark. Information on demographics and treatment was retrieved from the Danish National Patient Register using the unique personal identification number and the health care classification system (SKS procedure codes) for heart valve procedures. Personal data like address, civil status and mortality was obtained through the National Civil Registration System. Linkage between registers was obtained by the unique personal identification number.

In December 2011 eligible patients (n=742) were invited to participate in the nationwide postal questionnaire survey, 6-12 months post-surgery. A total of 557 patients responded by completing the three following self-reporting questionnaires: The Short-Form 36 Health Survey, The Hospital Anxiety and Depression Scale, The Heart Quality of Life questionnaire and a socio-demographic questionnaire.

Inclusion criteria were patients with a Danish PIN admitted to hospital for heart valve surgery and age ≥18. Exclusion criteria were death between surgery and survey, address/research protection and emigration. Presented in flowchart FIGURE: 2a.

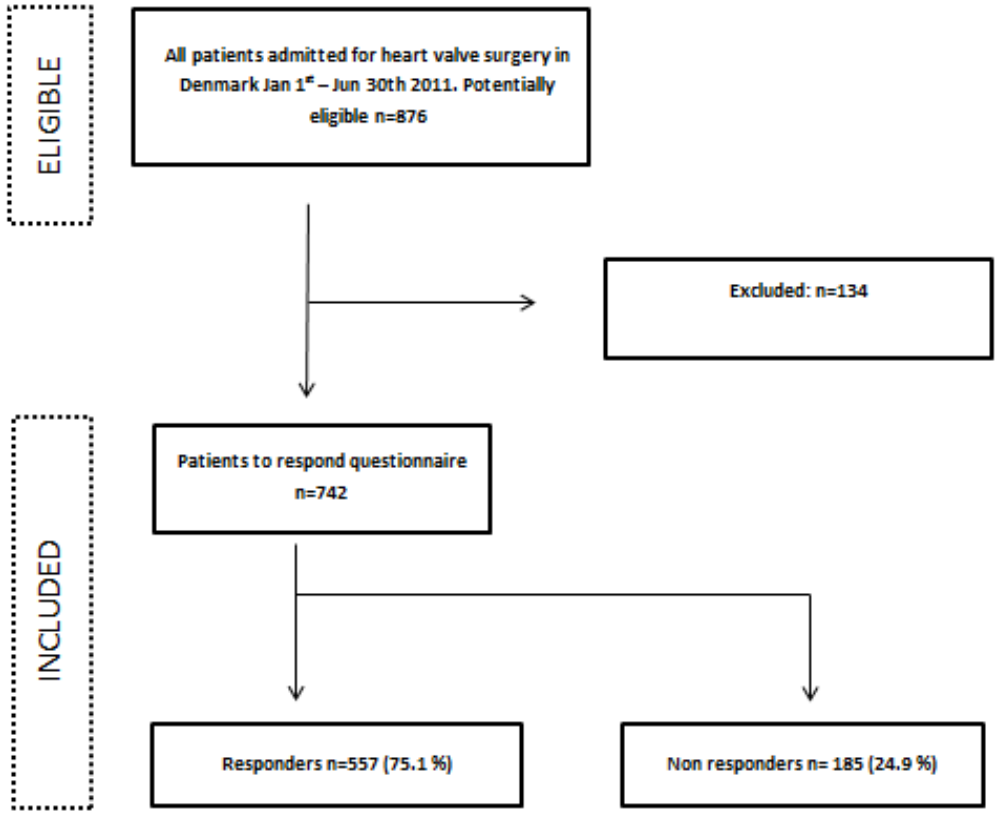

FIGURE 2a Flowchart study I

4.1.3 Sample of the test-retest study (Study II)

A total of 266 patients underwent heart valve surgery at Rigshospitalet, University Hospital Copenhagen, in the period between November 18th 2013 and 15th May 2014. The patients' data was extracted from a local hospital register (Web-PATS).

Inclusion criteria were patients admitted to hospital for heart valve surgery, age ≥18 and residence in Denmark. Exclusion criterion was death between surgery and survey. A random selected sample of 150 patients was invited to participate in the study. A total of 92 patients participated in the test-retest study by completing The HeartQoL questionnaire twice. Presented in flowchart FIGURE: 3a

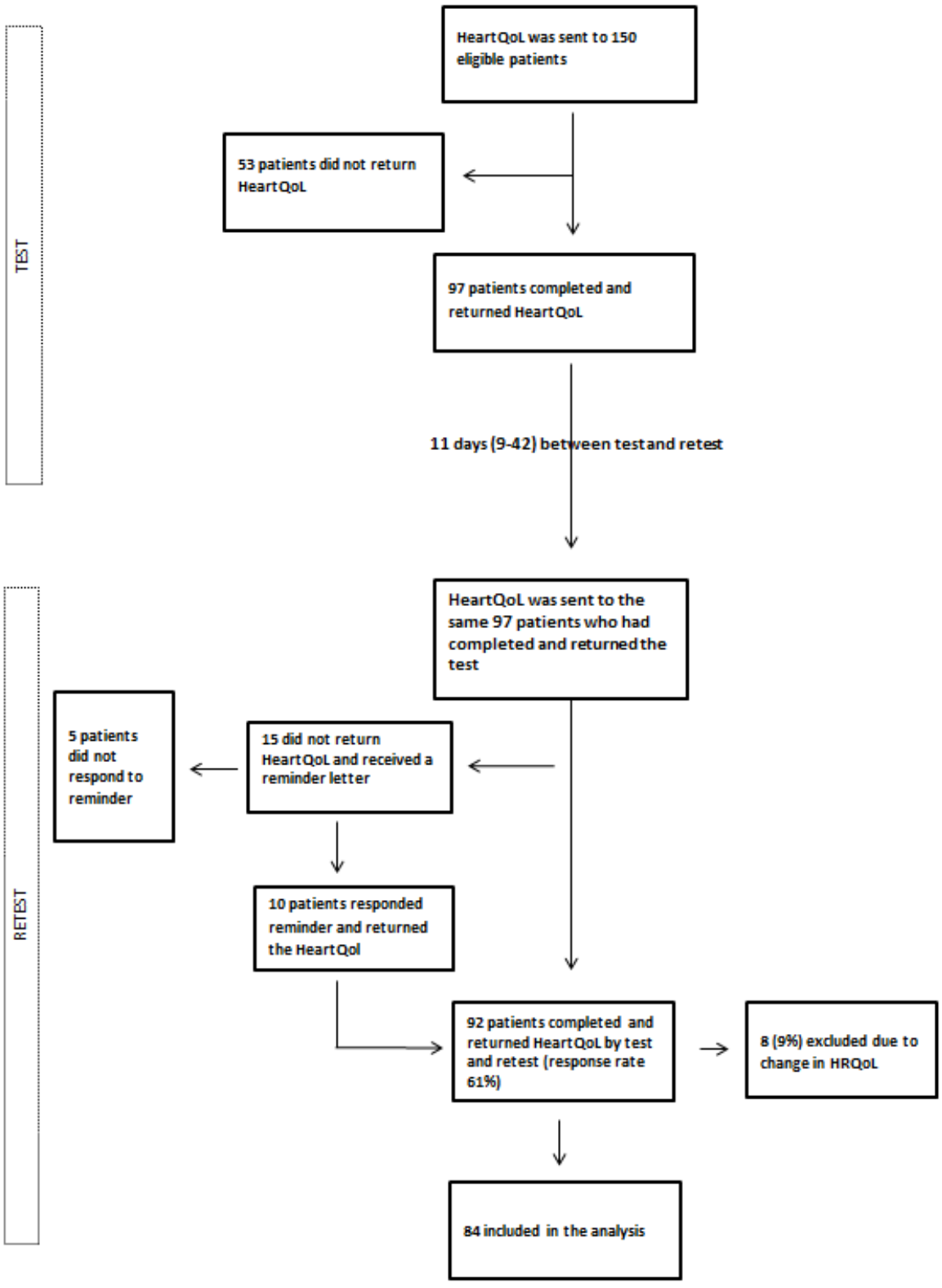

FIGURE 3a Flowchart study II

4.2 PATIENT-REPORTED DATA

The following chapter presents a description of the selected measurements for the validations study.

4.2.1 The Heart Quality of Life questionnaire (The HeartQoL)

The HeartQoL is a recently developed core heart disease-specific HRQoL questionnaire[38]. The purpose of the HeartQoL is to develop a core questionnaire designed to combine the benefits of both the generic and the disease-specific instruments by addressing heart specific questions of relevance to a broad range of heart patients. The HeartQoL then allows between-diagnose comparison of HRQoL in subgroups across cardiac diseases. The HeartQoL was designed using subjects from 3 established and validated disease-specific Health-Related Quality of Life instruments for use in patients with ischemic heart disease: The Seattle Angina Questionnaire, The Minnesota Living with heart failure and the MacNew heart disease Health-related Quality of Life Questionnaire. Item reduction was conducted using the clinical impact method where patients rate each item due to the individual's importance and by Mokken scaling analysis. The content validity of the HeartQoL instrument was established in the development of the questionnaire[39]. The HeartQoL measures patient perceived health related quality of life over the previous 4 weeks. It is a short one page questionnaire comprising 14 items covering two dimensions: a physical and a mental dimension. 10 items measure the HeartQoL physical dimension and 4 items measure the HeartQoL emotional dimension, providing a global assessment and evaluation of how patients perceives they are bothered by their heart disease. The HeartQoL items are rated on a 4 point Likert scale from 0 to 3, where a score of 3 refer to higher health-related quality of life. Scores are calculated by dividing the sum of responded items with the number of responded items. The HeartQoL scores are presented on a global scale and two subscales; a physical and an emotional subscale. The HeartQoL global score can be divided into 3 categories indicating low (≤ 2.00), moderate (2.01-2.99) and high (=3) health related quality of life[40]. The HeartQoL questionnaire was translated into Danish according to the guidelines for forward-backward translation, as a part of the international HeartQoL project[39]. Currently The HeartQoL has only been validated in patients with IHD[7]. The Danish HeartQoL questionnaire exists in two versions, the HeartQoL version 1.0 and version 2.0. Due to one ambiguous item (item 9) in version 1.0 (See article Appendix: Item properties of the HeartQoL questionnaire) the item

was rephrased to improve understanding. In this master thesis the HeartQoL version 1.0 was used in the study I and the version 2.0 was used in study II. At present no user's manual exists and the HeartQoL scores were calculated based on instruction from the authors. Only one item needs to be completed for the questionnaire to be answered in a valid way.

4.2.2 The Short-Form 36 Health Survey (SF-36)

The SF36 is a generic health survey instrument developed to evaluate general health status. It has been widely validated for use across a range of health care professions, settings and patients[41]. It consists of 36 items calculated to 8 scales. The items refer to the previous 4 weeks. The scales contain 2-10 items each and measure: physical functioning (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items) and mental health (5 items). The raw scores are calculated and transformed to a 0-100 scale; with higher values representing a better health status. Finally individual scales are combined to form The Physical Component Summary (PCS) and The Mental Component summary (MCS). In addition a single item that provides an indication of perceived change in general health status over a one year period, known as the General health transition item, is also included in the SF-36[41]. The SF36 has been validated in Danish[42]. The calculation of SF-36 scores in this study follows the "Scoring Instructions" outlined in the user manual.

4.2.3 The Hospital Anxiety and Depression Scale (HADS)

The HADS is a valid and reliable generic self-rating psychological screening instrument designed to determine levels of anxiety and depression in patients[43,44]. The observation period refer to the previous week. It has been found to take 2-5 minutes to complete[43]. The HADS includes 14 items, 7 related to anxiety (HADS-A) and 7 related to depression (HADS-D). The subscale scores are calculated separately. HADS scores are rated on a 4 point Likert scale from 0 to 3 where 3 refers to greater symptom severity. Item scores are added, giving subscale scores from 0 to 21. Commonly used cutoff scores on the HADS are HADS-A $\geq$8 and HADS-D $\geq$8. Scores of <8 indicate normal levels of anxiety and depression[43,45].

4.3 REGISTER BASED DATA

Demographic data for the validation study included age, gender, civil status, type of surgery and medical history was drawn from a number of different registers. The registers are presented below.

4.3.1 The Danish Civil Registration System (CRS)

The register was established in 1968 and includes the entire population living and residing in Denmark. The register records information's by the unique personal identification number (PIN) assigned to all Danish citizens along with name, gender, date of birth, address, marital status and citizenship[46] . Until the first of March 2014 it was possible to request for research protection in the CRS and thereby avoiding inquiries regarding scientific studies.

4.3.2 The Danish National Patient Register (NPR)

The NPR is a national health register of patients treated in Danish hospitals since 1977. It contains both administrative and clinical data, as well of other information such as hospital department, date and time of hospital stay, diagnosis, type of surgery and treatment. The register serves mainly administrative purposes and contributes to medical research[47].

4.3.3 Web-PATS

The Web-PATS is a local hospital register at Rigshospitalet which covers eastern-Denmark, Greenland and Faroe Islands. An administrative and clinical database containing information about heart surgical procedure and complications from patients hospitalized at Rigshospitalet. The database contains information on name, address, age and gender as well as type of surgery and date for intervention. The database contributes with information to The Danish Heart Register.

4.3.4 Charlson Comorbidity Index (CCI)

In our study the CCI was based on hospitalization diagnoses recorded in NPR. CCI is an internationally accepted classification of comorbidity illness severity. CCI includes 19 pre-defined diagnoses. Each diagnosis is assigned a weighted value from 0-6 indicating the

seriousness of the comorbid disease. The sum of all the weights is calculated and results in a single comorbidity index. The higher the score the higher the severity of illness[48]. In our study the CCI was calculated from 17 pre-defined diagnoses as all cancer diagnoses are merged to one. The CCI was categorized into two comorbidity levels: 0-1 indicates none or mild comorbidity or ≥ 2 indicating severe to very severe comorbidity.

4.4 DATA MANAGEMENT AND DATA COLLECTION

4.4.1 Data management

Data managers were the two supervisors at the National Institute of Public Health to ensure the data extraction and processing was accomplished in accordance with regulations from the Danish Data Protection Agency. Data was stored on a secure hard drive. A securely kept code file was stored at the National Institute of Public Health separated from other data materials.

The data for Study I was based on data from a large population-based survey, the national CopenHeart survey, conducted in 2011 which was prior this master thesis. Therefore the author of this master thesis had no influence on the data entering. However, variables from the questionnaires were checked by the author for missing data and outlying values by using frequency tables.

Data entering for the Study II was performed in EpiData, software designed for simple data entry. EpiData has the advantage that data double entered can be compared. The data entry was completed by a trained assistant instructed in handling discrepancies. Data was double-checked for typing errors by unbiased master students. Data was subsequently exported to SPSS (IBM Corporation, Armonk, NY, USA) for further analysis.

4.4.2 Data collection for study I

Data were collected before the start of this master thesis and was supplied to the master student in an encrypted format with disarming of names and the unique personal identification number in order to eliminate the identity of individuals. Confidentiality is thereby preserved.

4.4.3 Data collection for study II

The construction of a mailing list was performed by the data managers with randomly generated registration numbers. The data collection started mid-October 2014 and ended mid-January 2015. The HeartQoL questionnaire was posted, with overnight post service, with a personalized invitation letter with the participant's name and a postage-paid return envelope. In the invitation letter, the study purpose was described briefly and information on deadline for reply within 7 days was given. Contact information for the research assistant was also given. Questionnaires were sent from Holbaek Hospital for financial reasons and return envelopes were addressed to the National Institute of Public Health, University of Southern Denmark. Printing and packaging of the questionnaires for the test and retest was completed entirely by the master student. Questionnaires were returned de-identified, so that neither the name nor address of the participant appeared. Only registration numbers appeared on the questionnaires. A reminder letter was only sent to those who had not replied to retest. A new questionnaire were sent with a personal reminder letter and pre-stamped return envelope.

4.5 ETHICAL CONSIDERATIONS

Data extraction and processing was accomplished according to the Act on Processing of Personal Data which states the rules and regulations stated in the Danish law. The Danish Data Protection Agency approved this study with File number: 2013-41-1643. Before the Study II was launched The Danish Data Protection Agency was approached for an extension of the original approval (the national CopenHeart survey approval) as the data extraction in this study is based on medical record information. The approval extension was given on February 14, 2014. Afterwards, The Web-PATS Committee at Rigshospitalet approved the data extraction from Web-PATS. The study was exempted from approval by the Danish Ethical Committee as this study did not involve biological material[49].

The participants received written information as a letter of invitation. It was emphasized in the letter, that participation in the study was voluntary and lack of participation would not affect current or future healthcare treatments. The right to withdraw from the study at any time during the study period was clarified. The study purpose and design was also explained. A research assistant could be contacted if there were any questions about the study. It was specified that the answers would be kept confidential and results would be published in

anonymous form so that individuals could not be recognized. The study conforms to the principles outlined in the Declaration of Helsinki.

5 ANALYSES

5.1 STATISTIC

Data was analysed by the master student using SPSS version 22 (IBM Corporation, Armonk, NY, USA). Descriptive analysis was performed to obtain a description of the characteristic of the samples. The normality of the distribution was assessed. In case of non-normality distribution data a non-parametric test was used. Group differences were examined with Chi-square test and Fischer's exact test. Data is presented as mean and standard deviation (SD) or with a 95% confidential interval if normally distributed and median and interquartile range (25th-75th quartile) if skewed. Categorical variables are reported in number and percentage. Statistical significance was set at a 5 % level ($P< 0.05$).The pre-planned analysis for evaluate the measurement properties of the HeartQoL questionnaire are presented in TABLE 1a.

Table 1a Overview of the analysis plan

	Measurement property	Analytic method	Interpretation of results
Reliability	Internal consistency	Cronbach alpha	Values above 0.70 were considered as acceptable, above 0.80 as good, and values above 0.90 as excellent[50]
	Reliability (relative reliability) Mean difference between test and retest	The Intra-class Correlation Coefficient ($ICC_{2,1}$) calculated with a two-way random model for absolute agreement Paired t-test	A value of at least 0.70 is recommended as an acceptable reliability[5]
	Measurement error (absolute reliability)	Standard error of measurement (SEM) $SEM = SD_{DIFF} / \sqrt{2}$. $SDC_{95} = 1.96 \times \sqrt{2} \times SEM$ Bland-Altman limits of agreement (LoA) $LoA = mean_{DIFF} \pm 1.96\ SD_{DIFF}$	The measurement error should be smaller than the minimal important change (MIC)[37]
Validity	Construct validity Testing a priori formulated hypotheses: Correlation between HeartQoL and corresponding measures ($r \geq 0.4$) Correlation between HeartQoL and non-corresponding measures ($r \leq 0.4$)	The Pearson or the Spearman Rho Correlation analysis	Very weak correlation: r = 0.00 to 0.19, Weak correlation: r = 0.20 to 0.39, Moderate correlation: r = 0.40 to 0.59, Strong correlation: r = 0.60 to 0.79 and Very strong correlation r = 0.80 to 1.00[51]
	A priori hypotheses conceived for subgroups of responders expected to score differently on the HeartQoL questionnaire.	The "known-group" analysis using the student t-test or the Mann-Whitney U test	Construct validity is considered acceptable with at least 75% of the predefined hypotheses confirmed[37]
Interpretability		Floor and ceiling effects	Floor and ceiling effects occur if more than 15% of the respondents achieve the lowest or highest possible score, respectively[5]

5.2 ADDITIONAL ANALYSES FOR THE ABSOLUTE RELIABILITY

An additional analysis for the absolute reliability was performed with a Bland-Altman plot which examines the agreement between test and retest scores. The Bland-Altman plot provides visual interpretation of the degree of agreement and identifies bias and outliers. And the relationship between the mean scores and the mean difference between scores can easily be seen[5]. The 95% limit of agreement (LoA) ($mean_{DIFF} \pm 1.96SD_{DIFF}$) gives an indication of how much the scores can vary in stable individuals. LoA represent the expected 95% of the differences between repeated measurements to lie between these limits. The 95% limits of agreement depend on the assumption of normality distribution of the difference between test and retest. The Bland-Altman plot is established by calculation of the mean difference between test and retest with associated standard deviation (SD_{DIFF}).

6 RESULTS

6.1 MAIN RESULTS

Reliability and validity

The HeartQoL questionnaire shows good to excellent internal consistency with Cronbach's alpha values for the global scale and each subscale ranged from 0.87 to 0.94. With $ICC_{2,1}$ > 0.80 the relative reliability is considered good for the global and the two subscales. Absolute reliability for the global, physical and emotional scales was calculated, showing measurement error (SDC) of 0.6, 0.7 and 0.5 points, respectively. One participant was detected as outlier for the global scale and physical subscale. When omitting this participant the SDC_{95} global was then reduced to 0.4 points and SDC_{95} physical to 0.5 points.

Regarding construct validity the analysis demonstrated support for 13 of the 16 a priori hypotheses. With the result of 81% of the a priori hypotheses being confirmed, The HeartQoL questionnaire shows satisfactory construct validity.

Additional results

The statistics are presented in TABLE 3. Bland-Altman plots for the global scale and the two subscales of HeartQoL are presented in FIGURE $4a_1$, $4a_2$, $4a_3$. The normality distribution of the mean difference in scores for the HeartQoL global, physical and emotional scales between test and retest was determined with histograms and appear to follow a normal distribution.

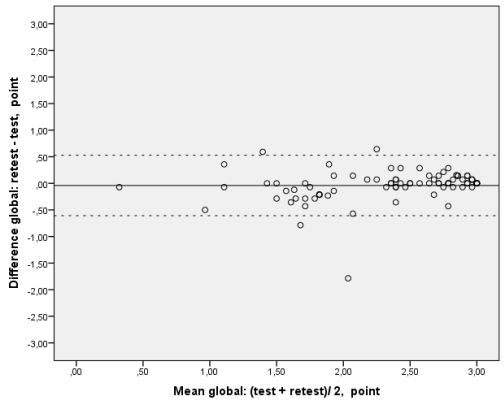

FIGURE $4a_1$ Global HeartQoL scale

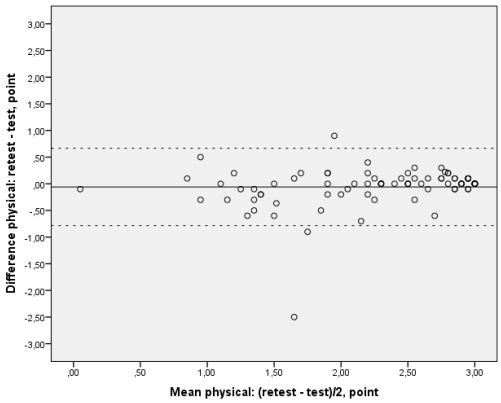

FIGURE $4a_2$ Physical HeartQoL subscale

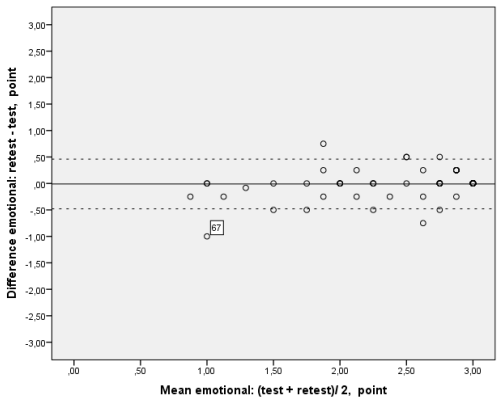

FIGURE $4a_1$, $4a_2$, $4a_3$ Bland-Altman plots for the differences between scores from test and retest against the mean of the test and retest for each responder for the HeartQoL global scale, physical and emotional subscales. The 95% limits of agreement lines are indicated by the dashed lines. The solid lines represent the mean differences scores between the repeated measurements.

FIGURE $4a_3$ Emotional HeartQoL subscale

The mean differences for HeartQoL global, physical and emotional scales were 0.04, 0.06 and 0.01 respectively. One outlier for the HeartQoL global scale (FIGURE: $4a_1$) and one outlier for the HeartQol physical subscale (FIGURE: $4a_2$) were noted, scoring at the lower end of the scale. The remaining patients all scored between 1 and 3. The limits of agreement for the HeartQoL global scale was -0.61 to 0.53; the HeartQoL physical scale: -0.79 to 0.67 and the HeartQoL emotional scale: -0.48 to 0.46. The test-retest study is based on the participation of 84 stable patients meaning the respondents clinical parameters had not changed from test to retest. The plot for the emotional scale (FIGURE: $4a_3$) would appear to visually represent fewer respondents. This is caused by several respondents sharing the same score value and the scores are therefore superimposed. Score values from retest were lower than the score values from the test for the HeartQoL global and the two subscales as the mean difference between test and retest are negative. The plots show no heteroscedasticity as there is no larger variability for higher scores and no larger variability with lower scores. No proportional bias is seen as the differences between test and retest is not linear across the data range.

7 DISCUSSION

7.1 METHODOLOGICAL CONSIDERATIONS

7.1.1 The theoretical framework

This master study is based on the theoretical principles proposed by the COSMIN group. The recommendation was developed as an international Delphi study to archive consensus on terms and definitions as well as preferred statistical analyse. The COSMIN group involves a large multidisciplinary team of experts in the field of health status measurement instruments and psychometric theory. There exists other guideline for validation of measurement instruments for example the recommendation by the Scientific Advisory Committee of the Medical Outcomes Trust (SAC) and Hays[52,53]. The COSMIN recommendation was determined to be the theoretical framework for this master thesis as the COSMIN recommendation has international acceptance and it is the most recently published.

7.1.2 Study design

A cross-sectional design was used to assess validity and a test-retest design for assessing reliability of the HeartQoL questionnaire. The time interval between assessments is important for determining test-retest reliability. Reliability studies depend on stable patients, meaning their status of HRQoL did not change during the period since they filled in the HeartQoL the first time. We asked the patients to note if they had been subjected to a major life event which could have affected their HRQoL in the time interval between test and retest (See Appendix B). The time interval was based on a presumption that the respondents did not remember the questionnaire so well that their response was based on their previous responses and that they were in a stable condition. No exact criteria exist concerning the time span[5]. We assumed that a time period of 14 days would be appropriate.

7.1.3 Study samples

This study is based on two different study samples, both admitted for heart valve surgery. The first sample consisted of patients participating in the national CopenHeart survey (Study sample I) and the second sample consisted of patients admitted to Rigshospitalet for surgery

(Study II). The time period between surgery and survey completion of 6-12 month post-surgery was identical in both samples.

In study I and study II the samples were similar according to age and gender. For study I approximately 62% were men and for study II 64%. This gender proportion is comparable to other studies in patients following heart valve surgery also when observing the age distribution with an elderly population[18,19,22,25]. In study I and study II the median age was 73 years and 70 years respectively. Regarding the underrepresentation of younger patients, heart valve disease is most common among older individuals and most individuals are in their 50's when diagnosed. With this in mind our study sample seems to resemble the total population of patients with heart valve disease.

The samples in study I was based on a large population of patients recruited from the four heart centers in Denmark. Comparing respondents with non-respondents, respondents were more often male, older and married and with no or mild comorbidity index score (Table 1). Other studies have found that the number of non-responders is larger among men than among women in self-administered surveys and unmarried are more likely to be a non-respondent than married[54,55]. We have no explanation for why women are underrepresented in our study but this condition will limit the interpretation of the HeartQoL in female heart valve patients.

7.1.4 Selection bias

The population for study I was selected using The Danish National Patient Register and comprises a complete study population of patients admitted for heart valve surgery from all of the four Heart Centers in Denmark in the defined time period. However registers may be biased due to concerns with the accuracy of data e.g. concerns regarding a possible variation in coding or lack of registration[56] .Cardiac diagnose and heart valve surgery uses well-defined diagnose and operation coding systems. Registration must be considered as valid and the risk of selection bias low.

Regarding study II we selected the study population from a local register, the web-PATS at Rigshospitalet which covers eastern-Denmark, Greenland and Faroe Islands. We are aware of that serious ill patient for example; with infective heart valve endocarditis, will be referred for surgery at Rigshospitalet. We thus presume patients undergoing heart valve surgery at Rigshospitalet to be comparable to other heart valve patients in Denmark and therefore to be a

random sample of heart valve patients. The exclusion of patients from Greenland and the Faroe Islands were of practical reasons due to the postal communication concerning those parts of the country.

7.1.5 Sample size

There are no general criteria for the required sample size in validation studies however a methodological reference for assessing validity recommends a minimum sample size of 50 patients but larger samples are preferred[5]. The sample size for the validation study (study I) is constituted by the total population of patients the first half of 2011 admitted to hospital for heart valve surgery in Denmark, and with a total of 557 patients participating in the study a large sample size for the validation study is achieved. The sample size for the test-retest reliability study (Study II) was based on a recommendation that at least 50 patients should be included in the reliability analysis[5]. We included 150 patients in the test-retest study, to account for drop-outs as the test-retest study demands the questionnaire to be completed twice. Due to self-reported change in HRQoL during the period between test and retest 8 (9%) patients were excluded as retested patients must be in a stable condition with respect to the construct to be measured. Finally, 84 patients completed the questionnaire twice and the sample size was sufficient for analyses.

7.1.6 Response rate

Different initiatives can be conducted to optimize the response rate[57]. To improve the response rate in study I a reminder was sent to non-responders 2 weeks after the initial distribution. As the Master student did not participate in the data collection in the validation part of this study the following describes considerations concerning only study II:

We formed a well-designed questionnaire with logo from Rigshospitalet, National Institute of Public Health, University of Southern Denmark and Holbaek Hospital. We applied the official logos to enhance the credibility of our study. We personalized the letter of invitation and we clearly explained the study purpose. We also informed the respondents about the expected time it would take to complete the questionnaire. In addition we provided a phone number and an email address at which a research assistant could be contacted in case the respondents had questions (See Appendix A). To further increase the response rate we sent a reminder letter (See Appendix C). We experienced that 97 responded (a response rate of 65%) to the test and

therefore we decided only to send reminders to those who did not respond to retest. If they did not respond to the reminder no further action was taken.

7.1.7 Data Collection for the test-retest study

All letters were sent by overnight mail in order to comply with the time interval between test and retest. It was clarified in the letter of invitation that patients should note the date for completion of the questionnaire. We registered the date on which each respondent had completed the HeartQoL questionnaire the first time. An attempt was made to send the second HeartQoL questionnaire 10 days after the first response for obtaining the time period between test and retest of approximately 14 days. The distribution of the second questionnaire was challenged as some patients forgot to note the date for completion. Since the questionnaires were returned to a PO Box it was not possible to label the questionnaire with date to calculate the distribution of the retest questionnaire. In the analysis of the test-retest study we included all patients with a stable HRQoL state who had responded the HeartQoL twice regardless of patients reporting date of completion or not. The test-retest analysis was performed for patients with and without date annotation but made no difference in the results. The disadvantage of inclusion of patients who have not registered the date is the possibility of recall bias. We noted, however, that the median interval between test and retest was 11 days (9-42 days) and therefore consider that risk of recall bias must be minimal.

7.1.8 The HeartQoL questionnaire

The HeartQoL consists of a few short questions and we consider it user-friendly as the median time for patients to complete the HeartQoL questionnaire was only 5 minutes. The administrative burden is minimal as it is easy to quantify by its simple structure. These conditions are of major advantage when implementing the use of HeartQoL in clinical settings as well as for research purposes.

The original layout of the Danish version 2.0 of the HeartQoL questionnaire was used in the test-retest part of this study (See Appendix A) and comprises the headline: "HeartQoL". The name HeartQoL does not make any sense in relation to the Danish language, and furthermore it is difficult to pronounce in English. In relations to the headline conferring to Danish it will thus for many individuals not be possible to understand the sense of the questionnaire.

A disadvantage with the questionnaire is that The HeartQoL has added the scores for each response alternative in the questionnaire. It must be taken into account that this may affect the patients' way to score and thereby result in response bias. Some patients might want to show themselves in a more favorable light and choose to score with the highest score possible. In our study we saw that 36% of the patient population in the validation study scored the highest score possible on the emotional subscale.

The HeartQoL questionnaire contains two dimensions of HRQoL; the physical and the emotional dimension. The social wellbeing dimension is not included in the HeartQoL when referring to the consensus definition of HRQoL outlined by the European Medicine Agency[2]. In the development process of the HeartQoL questionnaire the social domain items did fulfill the clinical impact score but were not among the 14 items determined by Mokken analysis[39]. It is well known that the lack of social relationships is a strong predictor of morbidity and mortality[58] and therefore the social well-being dimension is an essential issue regarding HRQoL. Social relations can allude to the personal relationships with others, social support and social life status. Absence of this important variable questions the HeartQoL ability to fully uncover patients' perception of their health related quality of life.

7.2 DISCUSSION OF MAIN FINDINGS

7.2.1 Relative and absolute reliability

To our knowledge, this is the first study to evaluate the reproducibility of the HeartQoL questionnaire. According to recommended limits we found the test-retest reliability to be satisfactory for the HeartQoL global scale and the two subscales. We found ICC ranges between 0.00 and 1.00, with values closer to 1.00 representing stronger reliability. In our study the ICC values were adequate for the global and the two subscales with $ICC_{2,1}$ values above 0.80 indicating a good relative test-retest reliability (TABLE 3).

The absolute reliability was evaluated through the measurement error. For the interpretation of change in scores, determination of the measurement error is necessary, as changes in scores cannot be considered to be a true or real change but is due to the measurement error. We have performed a test-retest reliability study in a stable patient sample which makes it possible to determine the measurement error. The standard error of the measurement (SEM) was calculated for the global and the two subscales and ranged from 0.17 to 0.26 points (TABLE 3). The SEM was converted into smallest detectable change (SDC_{95}) reflecting the smallest individual change in score that can be distinguished from measurement error. The SDC are expressed using the same units as the original measures which is of considerable value for clinical use. The SDC_{95} in our study ranged from 0.5 to 0.7 points which indicates that a score change on the global, physical and emotional scale of respectively 0.6, 0.7 and 0.5 points is needed to be 95% confident that a true change has occurred. Consequently score change smaller than SDC can be attributed to measurement error. In daily practice questionnaires need to have small measurement errors to make them suitable. As The HeartQoL items are rated on a scale from 0 to 3, a SDC ranging from 0.5 to 0.7 points is to be considered as relatively large measurement error.

A clear presentation of the test retest scores are presented in FIGURE 4a the Bland-Altman plots with LoA. Most of the scores are at the higher end of the scale from 1-3, which gives an indication that most of the patients in this test-retest study were only slightly affected by their heart valve diagnose in relation to HRQoL. An explanation for this could be that the patients were included in this study in a stable phase 6 to 12 month after heart valve surgery. One outlier for the HeartQoL global scale (FIGURE $4a_1$) and one outlier for the HeartQoL

physical subscale (FIGURE $4a_2$) were observed (the same individual). The scores for the outlier were checked for typing errors but found correct. It must be considered that this outlier might have experienced a life event in the time interval between test and retest even though the patient has not noted this and may not have been stable. The limits of agreement represent the range where 95% of the score differences between measurement by the test and retest will lie. In our test-retest study the range for the global scale and the two subscales was small. If the LoA are small and the mean difference is near zero then the instrument can be considered reliable. But it is to be noted that in the present study test-retest reliability in patients scoring from 0-1 are not included in this analysis of absolute reliability.

7.2.2 Validity

As stated in the scientific paper of this thesis the convergent validity of the HeartQoL questionnaire in a heart valve surgery population is confirmed with strong correlation of the two hypothesized corresponding measurements; SF36 and HADS (TABLE 4). In relation to the analysis of the divergent validity we observed higher correlation than expected between dissimilar constructs. The HeartQoL emotional subscale was correlated with the SF36 physical component scale and the HeartQoL physical subscale to the HADS-D. Same observations of correlation between physical and emotional constructions have been seen in a number of validation studies of MacNew heart disease health-related quality of life questionnaires[59-61]. Like The MacNew questionnaire some of the questions in the HeartQoL physical subscale are expressed with the word "feeling" which refers to the experience of symptoms and not to the performed physical limitation. The formulation of item 8 "feeling tired, fatigued, low on energy" on the physical scale, may lead the responders to relate to their emotional state rather than their physical condition, as was intended. Other possible explanation could be that the overall emotional function can affect the physical health status. Other studies have presented that people suffering from depression and anxiety are likely to have lower levels of physical activity[62,63].

Concerning the "known group validity" analysis between subgroups of responders who we expected to score differently on the HeartQoL questionnaire (TABLE 5), we did not a priori specify the minimally important between group differences as recommended by the COSMIN group. The statistically significant differences are not of relevance as they are related to the sample size. It is more important that the differences are as large as could be expected[8].

7.2.3 Interpretation of scores

Floor and ceiling effects were predefined as present if more than 15% of the patients reporting lowest (0) or highest (3) possible scores. In our study were found a ceiling effect for the HeartQoL emotional subscale of 36% (TABLE 3). This indicates that improvement in emotional health cannot be detected by the HeartQoL instrument in 36% of this patient population. It is to be noted that there can be a problem with the limited choice of response levels for the emotional subscale. Another consideration is the possibility that the respondents 6 to 12 months post-surgery no longer experience excessive emotional reactions and therefore have high self-reporting values on the emotional scale. According to de Vet and colleagues floor and ceiling effect often occur when an existing measurements is applied to another population than the instrument was originally developed for[5]. However the ceiling effect of the emotional subscale was already observed in the original validation study[7].

7.3 ETHICAL CONSIDERATIONS

This study was made without written informed consent from the responders. Research without consent is controversial but according to Danish law, without direct contact with the researcher, de-identified returns of questionnaires can be considered as valid consent[64].

Prior to the study II considerations were made in relation to the inconvenience for the respondents in completing the questionnaire. The inconveniences were considered acceptable as The HeartQoL questionnaire is short and the items are not of a sensitive nature. We were however aware of that the test-retest design would require time for the respondents to complete the questionnaire twice and post the forms. Regarding privacy; from 2000 to March 2014 it was possible to request research protection in the CRS register and thereby avoid inquiries regarding scientific surveys. Therefore patients with research protection were excluded in Study I. Since the protection was abolished by law the first of March 2014 it was no longer possible, in the inclusion process for Study II, to take account of patients who did not want to be contacted for scientific studies.

8 CONCLUSION AND FUTURE PERSPECTIVES

The aim of this master thesis was to evaluate the measurement properties of the disease specific measuring instrument, The HeartQoL Questionnaire, in terms of reliability and validity in a mixed sample of patients following heart valve surgery.

The result of this study concludes that the HeartQoL instrument shows acceptable reliability regarding internal consistency and relative test-retest reproducibility although the measurement error was somewhat high. The questionnaire was also found to have acceptable construct validity for patients following heart valve surgery evaluated in a representative population of post-surgery patients in Denmark.

Future research

In this study we were not able to assess responsiveness of the HeartQoL questionnaire in the heart valve surgery population due to the study design. Further investigation will be needed to establish this important part of the measurement properties evaluation of the HeartQoL questionnaire.

Clinical implications

The role of HRQoL and PROM's in clinical research and practice is expected to increase due to longer life expectancy and greater focus on shared decision making between medical staff and patients. In addition the outcome of surgery is no longer evaluated only in terms of morbidity, mortality and complications but on whether the patient can function well and participate in society with a good quality of life[3]. The HeartQoL has already been found clinically appropriate in the prediction of 5 years mortality and hospital readmissions in patients with ischemic heart disease[40]. We consider the HeartQoL questionnaire to be easy to implement in clinical settings and for research purposes; by its user-friendliness according to the quantity of questions, time spent and minimal administrative burden. The result of this study indicates that The HeartQoL core questionnaire can be proposed as a PROM instrument that can be used for clinical evaluation in cardiac diagnosis populations, after cardiac surgery and rehabilitation.

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9 ARTICLE

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The HeartQoL questionnaire is a valid and reliable core heart disease measurement instrument".

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Abstract

Background: To our knowledge no disease specific HRQoL measuring instruments exist specifically for patients with heart valve disease or following heart valve surgery. A recently developed disease-specific core questionnaire The Heart Quality of Life questionnaire (the HeartQoL) intends to assess HRQoL across patients with coronary heart disease. Since heart valve disease frequently coexists with ischemic heart disease, we hypothesized that the HeartQoL questionnaire could be used for patients following heart valve surgery. The aim of this study was to evaluate the measurement properties of the Danish version of the HeartQoL questionnaire, in terms of reliability and validity in a mixed sample of patients following heart valve surgery.

Design: A cross-sectional and a test-retest reliability study.

Methods: 557 patients following heart valve surgeries completed the Danish version of the HeartQoL, the Short-Form 36 and the Hospital Anxiety and Depression Scale. Internal consistency was assessed by Cronbach's α. A total of 92 patients participated in the test-retest study. Relative reliability was analyzed with intraclass correlation coefficient model 2.1. Absolute reliability was analyzed by standard error of measurement and smallest detectable change. Construct validity was assessed with a priori hypotheses together with the discriminative validity; the "known-group approach".

Results: Internal consistency was high (Cronbach's alpha ≥ 0.87). Relative reliability showed large values of ICC ≥ 0.80. For the absolute reliability SEM ranged from 0.17 to 0.26 and SDC_{95} ranged from 0.5 to 0.7 points. Construct validity: The HeartQoL showed strong correlation with hypothesized corresponding measurements and with non-corresponding measurements ($r > 0.60$). Known-group discriminative validity analysis confirmed that the HeartQoL questionnaire distinguishes well between patients groups. The analysis demonstrated support for all a priori hypotheses for predicted variables.

Conclusions: The HeartQoL questionnaire shows acceptable reliability regarding internal consistency, test-retest reproducibility and construct validity for patients following heart valve surgery evaluated in a representative population of post-surgery patients in Denmark. It is recommended that future studies should focus on assessing the responsiveness of the HeartQoL questionnaire.

Abstract word count: 323

Key words: Quality of life, HeartQoL questionnaire, Danish version, measurement properties, heart valve surgery

Introduction

Heart valve disease is a growing public-health problem due to high age and the increasing survival rate of the population[1]. A large American population-based study estimated the prevalence of heart valve disease to 2.5%[2]. Blauwert and Miller estimated that more than 280.000 heart valve surgeries are performed worldwide each year[3]. With the new and gentler surgical techniques, percutaneous procedure, an increasing number of elderly patients with a high degree of comorbidity and risk of postoperative complications are now submitted for heart valve surgery [4,5]. Following heart valve surgery, some patients have been found to suffer from anxiety and worries related to readmission and reoperations, postoperative complications, clicking sounds from the mechanical valve prosthesis, lifelong anticoagulant treatment and deconditioning due to many years of chronic illness [6-12]. The physical and psychological challenges after heart valve surgery with impact on quality of life can prevent or delay return to work and the usual activities of daily living[8,9]. Correspondingly new nationwide studies have showed that self-reported health status and level of activity is lower 6-12 months after heart valve surgery than in the general population[13].

The outcomes after surgery are often evaluated in terms of morbidity, mortality and complications. There is however increasingly focus on patient reported health related quality of life (HRQoL) as complementary health care endpoints when assessing treatment efficacy and health status among patients. Patients-Reported outcome measures are now prominent features in international health policy and in health research[14-17].

The tools for measuring HRQoL are typically divided in to two categories; generic or disease-specific questionnaires. The generic instruments are based on issues relevant to a broad spectrum of diseases or population samples independent of diagnose and provides information on HRQoL at a general level. The disease specific instruments are designed and developed with the intension to be clinically sensitive in relation to the types of issues particularly characteristic for the specific groups of patient. Both the generic and disease-specific instruments intend to quantify the disease influence on quality of life[18,19].

There are currently a number of disease-specific instruments assessing the HRQoL in patients with various forms of heart disease[20-22]. There is however no HRQoL measuring instrument intended for patients with heart valve disease. Recently a disease specific self-reported questionnaire, The Heart Quality of Life questionnaire (HeartQoL), was developed as a core

instrument to assess health related quality of life across patients with coronary heart disease presenting as myocardial infarction, angina and heart failure[23]. The intention with core questionnaires is the possibility to make between diagnose comparisons following interventions in disease specific subgroups i.e. cancer diseases[24,25]. The HeartQoL instrument was developed and validated in 2013 in a large patient population suffering from ischaemic heart disease (IHD) and showed good psychometric properties[26]. The HeartQoL instrument is simple and easy to administer in daily clinical practice with only 14 items. A recently published study has shown that the HeartQoL questionnaire can be used as a predictor of mortality and hospital readmission in patients suffering from IHD[27].

Since heart valve disease and IHD frequently coexist and heart valve disease can lead to heart failure, the symptoms between the patient groups (IHD, congestive heart failure and heart valve disease) are in many ways similar. We therefore hypothesize that The HeartQoL questionnaire also can be used for measuring health related quality of life in patients following heart valve surgery however, this needs to be properly evaluated.

Thus, the aim of this study is to evaluate the measurement properties of the disease specific measuring instrument; The HeartQoL Questionnaire in terms of reliability and validity in a mixed sample of patients following heart valve surgery.

Methods and materials

The study was divided in two parts:

I) A cross-sectional study to determine the validity of the HeartQoL questionnaire.

II) A test-retest reliability study to determine the reproducibility of the HeartQoL questionnaire.

For the validation study all adult patients admitted for heart valve surgery in Denmark, between January 1st to June 30th 2011 (n=879), including conventional open heart surgery for the four valves, heart valve replacement alone or combined with Coronary Artery Bypass Grafting (CABG) and percutaneous valve replacement or repair, were identified in the Danish National Patient Register. The health care classification system (SKS procedure codes) for KFG (surgery of tricuspid valve), KFK (surgery of mitral valve), KFM (surgery of aortic valve), KFJE (surgery of isolated pulmonary valve stenosis) and KFJF (implantation of

pulmonary vale prosthesis) were used and linked to the National Civil Registration System by the unique personal identification number assigned to all Danish citizens. In addition inclusion criteria was age ≥18. Exclusion criteria were death between surgery and survey, address/research protection and emigration. In December 2011 all eligible patients (n=742) were invited to participate in a nationwide postal questionnaire survey, 6-12 months post-surgery. A reminder was sent to non-responders 2 weeks after the initial distribution. A total of 557 (75.1%) patients responded by completing a booklet of self-reported questionnaires as follows: The Short-Form 36 Health Survey, The Hospital Anxiety and Depression Scale, The HeartQoL version 1.0 questionnaire and a sociodemographic questionnaire. The national survey was consigned from Department of Cardiology, The Heart Centre, Rigshospitalet, University Hospital of Copenhagen, Denmark and from The National Institute of Public Health, University of Southern Denmark.

In the test-retest reliability study the participants was extracted from the Rigshospitalet, University Hospital of Copenhagen, using the electronic patient journal system, Personnel Action Tracking System (Web-PATS), which covers eastern-Denmark, Greenland and Faroe Islands. Additional inclusion criteria were age ≥18 and residence in Denmark. The exclusion criteria was death. The study sample size was determined according to methodological recommendations from Vet suggesting a sample size of at least 50 patients for test-retest reliability studies[28]. To account for drop-outs 150 patients undergoing heart valve surgery, conventional open heart surgery for the four valves, heart valve replacement alone or combined with CABG and percutaneous heart valve replacement or repair between November 18th 2013 and 15th May 2014 were invited to participate in the study. All eligible patients received a written invitation with information about the study. Included in the letter was the first self-administered HeartQoL questionnaire version 2.0. The questionnaires were sent to the patients' home address with a pre-stamped return envelope included. It was emphasized that participation was voluntary. The time frame from test to retest was set to 2 weeks. This time interval was considered long enough to avoid recall of previous answers and yet short enough to prevent the probability of a change in the clinical parameters to occur. The second HeartQoL questionnaire was posted when the investigators had received the first filled in questionnaire. A follow-up letter was sent to the non-responders. Supplementary questions were included in the retest concerning time spent and occurrence of major life events since the initial test. Patients not reporting the occurrence of any major life event were considered stable and included in the test-retest reliability analyse.

Measurement instruments

Demographic data for the validation study included age, gender, civil status, educational level, employment status, type of surgery and medical history. The data were collected from the Danish Civil Registration System, the Danish National Patient Register and questions on socio-demographic in the CopenHeart questionnaire.

The HeartQoL questionnaire (The HeartQoL) measures patient perceived quality of life over the previous 4 weeks. It consists of 14 items, including 10-items of physical subscales and 4-items of emotional subscales that when combined provides a global scale. The HeartQoL items are rated on a 4 point Likert scale from 0 ("a lot bothered") to 3 ("not bothered"). Scores are calculated as the mean of item scores and results are presented for the global scale and the two subscales[23,26]. HeartQoL global scores can be divided in 3 categories indicating low (≤ 2.00), moderate (2.01-2.99) and high (=3) HRQoL[27]. The HeartQoL was translated into Danish as a part of the international HeartQoL project[23]. The Danish HeartQoL questionnaire exists in two versions, the HeartQoL version 1.0 and version 2.0. Due to one ambiguous item (item 9) in version 1.0 (See Appendix) the item was rephrased to improve understanding.

To investigate the validity of the HeartQoL questionnaire, we included two other measurements:

The Short-Form 36 Health Survey (SF-36) is a generic health survey instrument developed to evaluate general health status[29]. It consists of 36-items with 8 subscales measuring physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE) mental health (MH) and 2 summary scores; the Physical Component Scale (PCS) and The Mental Component Scale (MCS). The items refer to the previous 4 weeks. The raw scores are calculated and transformed to a 0-100 scale; with higher values representing better health status. The SF-36 also includes a single-item measure of global health transition. The respondents are asked to rate their general health compared to one year ago[29]. The SF-36 has been validated as a Danish version[30].

The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable self-rating psychological screening instrument designed to determine levels of anxiety and depression[31,32]. The HADS includes 14 items, 7 related to anxiety (HADS-A) and 7 related to

depression (HADS-D). The observation periods refer to the previous week. HADS scores are rated on a 4 point Likert scale from 0 to 3 where 3 refers to greater symptom severity. Anxiety and depression scores are calculated separately and patients will thus have two scores, one for each dimension. Commonly used cut off scores on the HADS are HADS-A ≥8 and HADS-D ≥8 indicating a possible or probable disorder, where scores of <8 indicate normal levels of anxiety and depression[31,33]. HADS has been proved as a useful tool for screening of heart patients[34].

Statistical analysis

Data were analysed using SPSS version 22 (IBM Corporation, Armonk, NY). Descriptive statistics have been used for the analysis of demographic variables. Data is presented by mean ± SD if normally distributed, or by median and range if skewed. The statistical level of significance was set to less than 0.05.

This study investigates the construct validity, containing convergent and divergent validity as well as known-group comparisons. The relative and absolute reliability of the HeartQoL questionnaire is also investigated. Face and content validity of the instrument have been established earlier[26].

Floor and ceiling effects of the HeartQoL questionnaire were examined. A floor and ceiling effect occurs when more than 15% of the respondents record the lowest (0) and the highest scores (3), respectively[28].

Analysis of internal consistency reliability for each domain and the global scores was performed with Cronbach's Alpha test. Values above 0.70 were considered as acceptable, above 0.80 as good, and values above 0.90 as excellent[35]. Paired-samples *t*-test was used to calculate the mean difference between test and retest. The Intra-class Correlation Coefficient ($ICC_{2,1}$) was used to consider relative reliability and calculated with a two-way random model for absolute agreement[36,28]. An ICC of at least 0.70 is recommended as an acceptable reliability[35]. Absolute reliability was expressed by standard error of measurement (SEM) and smallest detectable change (SDC). The SDC can be interpreted as a real change beyond measurement error. The SEM was calculated using the formula: $SD_{(difference)} / \sqrt{2}$. The SDC was calculated with the formula $SDC_{95} = 1.96 \times \sqrt{2} \times SEM$[28].

The construct validity was explored with a priori formulated hypotheses for convergent (measures for similar constructs) and for divergent validity (dissimilar constructs). Correlations between corresponding measurements were hypothesized to be moderate (0.4 or greater) and for correlation between non-corresponding measures it was hypothesized to be weak (0.4 or less). The Pearson or the Spearman Correlation Coefficient was used conditionally based upon of the distribution of the scores. The guidelines from Evans were used for descripting the strength of the correlation[37]. Very weak correlation: r = 0.00 to 0.19, weak correlation: r = 0.20 to 0.39, moderate correlation: r = 0.40 to 0.59, strong correlation: r = 0.60 to 0.79 and very strong correlation r = 0.80 to 1.00.

Analyses of the differences between known groups were used to determine the discriminative validity. A priori hypotheses were conceived for subgroups of responders expected to score differently on the HeartQoL questionnaire. We proposed six hypotheses that are listed in table 5. The analyses were performed for both the global scale and the two subscales.

The construct validity was considered acceptable with at least 75% of the predefined hypotheses confirmed[38].

Ethical considerations

Data extraction and processing was accomplished according to the Act on Processing of Personal Data following the rules and regulations stated in the Danish law. The Danish Data Protection Agency approved this study (File number: 2013-41-1643). The study adheres to the principles outlined in the Declaration of Helsinki.

Results

The majority of the responders were male with a median age of 73 years (range 18-95) (Table 1). At time of surgery 64% of the study population was married. A large part of the study population had aortic valve surgery (80%) and one third (28%) had concomitant CABG. No differences between responders and non-responders concerning type of surgery, medical history or time from surgery to completion of the questionnaire were found. Non-responders were more likely than responders to be women, living alone and had severe or very severe comorbidity measured by Charlson-comorbidity index (Table 1).

The scores of the different measurement instruments are presented in table 2. A total of 61 of the respondents (11%) indicated having the highest score on the HeartQoL with a score of =3 (Table 2). A ceiling effect of 36 % for the emotional subscale was observed (Table 3).

The proportion of missing values was 9.5% in item 9 "Not feeling relaxed and free of tension?" and 7.5% for item 13 "being limited in doing sports or exercise?" The remaining 12 items showed missing values between 4.5% and 6.8%. Concerning the global scale and subscales none of the scales showed more than 4.1 % missing values. Item 1 "walk indoors on level ground" presented a ceiling effect of 91.1% (See Appendix).

Cronbach's alpha values for the global scale and each subscale ranged from 0.87 to 0.94. A total of 150 patients were included in the test-retest study. 92 patients participated and completed both questionnaires with a response rate of 61%. The median time period between test and retest was 11 days (range 9-42 days). The majority of the respondents were male (64%) with a median age of 70 years (range 30-88). It took a median time of 5 minutes (0.5-30.0) to complete the HeartQoL questionnaire. Eight responders (9%) reported having suffered a major life event which substantially had affected their quality of life since the initial test and were therefore excluded in the test-retest reliability analysis. Reliability values are shown in table 3. Mean differences (± SD) between test and retest ranged from 0.01 (± 0.24) to 0.06 (± 0.29) ($p>0.05$). Relative reliability ($ICC_{2,1}$) showed values above 0.80 for all three scales of the HeartQoL. For absolute reliability SEM ranged from 0.17 to 0.26 points, while SDC_{95} ranged from 0.5 to 0.7 points (Table 3). One participant was detected as an outlier for the global scale and physical subscale. The analysis was repeated after omitting this participant and the SDC_{95} global was then reduced to 0.4 points and SDC_{95} physical to 0.5 points.

The HeartQoL physical, mental and global scales all showed strong correlation (greater than $r > 0.60$) with hypothesized corresponding measurement; SF36 (PCS, MSC, GH) and HADS-A and HADS-D. However, the HeartQoL physical and emotional scale also showed moderate correlation (greater than $r > 0.40$) and strong correlation (greater than $r > 0.60$) with non-corresponding measurements. The HeartQoL emotional subscale was associated with the SF36 physical component summary scale (PCS); ($r= 0.45$) and the HeartQoL physical subscale was associated with HADS-D; ($r= -0.66$) (Table 4). Known-group discriminative validity analysis confirmed that the HeartQoL questionnaire distinguishes well between

patients groups. The analysis demonstrate support for all a priori hypotheses for the predicted variables; gender, SF-36 health transition, comorbidity congestive heart failure and anxiety and depression, with significant differences in scores (Table 5).

Discussion

We evaluated the measurement properties of the core heart disease specific Health-related quality of life questionnaire; the HeartQoL, in patients following heart valve surgery. According to methodological recommendations for patient-reported health status questionnaires we found an acceptable reliability regarding internal consistency, test-retest reproducibility and construct validity. However, the measurement error seems somewhat large.

The results from the present study suggest that the HeartQoL questionnaire could be a suitable instrument for measuring patient-reported HRQoL in patients following heart valve surgery and usable for patients with different heart disease i.e. myocardial infarction, angina pectoris, heart failure.

In our analysis we found a high ceiling effect (36%) concerning the emotional subscale which is above the recommended limit of 15%[28]. This indicates that improvement in emotional health cannot be detected by the HeartQoL instrument in 36% of the patient population. This could indicate that HeartQoL instrument may not be suitable for measuring changes, but this should be investigated further. The ceiling effect of the emotional subscale was already observed in the original validation study[26]. It is to be noted, that there can be a problem with the limited choice of response levels for the emotional subscale. Another consideration is the possibility that the respondents had reached a stable state without excessive emotional reactions six to twelve months post-surgery and therefore had high self-reporting values on the emotional scale. According to de Vet and colleagues a floor and ceiling effect often occurs when an existing measurement is applied to another population than the instrument was originally developed for[28]. Regarding item 1 “walk indoors on level ground” we observed that 91.1 % of the respondents reported maximum scores indicating having no problem. In the original validations study of HeartQoL the item properties was not enlightened[26]. Since the HeartQoL questionnaire is designed as a core questionnaire it is intended to capture a broad spectrum of cardiac diseases. For patients six to twelve months after heart valve surgery it

could indicate that walking indoors on level ground has no influence on their physical health status.

In the validation study the Danish version 1.0 of the HeartQol questionnaire was used. We observed nearly 10% missing values in conjunction with item 9; "Not feeling relaxed and free of tension". In the Danish version 1.0 of the HeartQoL questionnaire this question may be perceived as ambiguous and more - starting with a negation. This causes the question to be unclear in the Danish language and difficult to reply to. This may be the reason why 10% of the participants omitting item 9 in the questionnaire. The question was later rephrased as "feeling relaxed" in the Danish version 2.0 of the HeartQoL used in the test-retest study. The HeartQoL item 13 "Being limited in doing sports or exercise" was not completed by approximately 8% of the patients. The missing values for the question may possibly be due to the median age of 73 in the present study as older people are generally less active.

The HeartQoL was developed as an international study with participants from 22 different countries with 15 different languages spoken. Thus a cross-cultural adaption process was taken into account in the development process[23]. The HeartQoL questionnaire was translated into Danish, following the guidelines for forward-backward translation. It was not language pre-tested for detection of comprehension of issue formulation and misleading items as otherwise recommended[39]. A language test would apparently have intercepted the comprehension problem with item 9 in the first Danish version of the HeartQoL questionnaire. Due to the manner in which the HeartQoL was developed it is assumable that measurement properties found in our validation study are similar when using the HeartQoL instrument in another language version and thus allow making international comparison of HRQoL outcomes in patients following heart valve surgery.

To our knowledge, this is the first study to evaluate the reproducibility of the HeartQoL. According to recommended limits we found the test-retest reliability to be satisfactory for the HeartQoL global scale and the two subscales. $ICC_{2,1}$ showed values for the HeartQoL questionnaire above 0.80 indicating a good test-retest reliability. We found slightly lower mean score values concerning the retest for the global scale and the two subscales but no statistical significant differences were found from test to retest. Regarding our calculation of the absolute reliability we found that one participant contributed to a big difference in the measurement error for the global and physical scales. It is worth considering that the true

value of the SDC_{95} for the global and physical scale probably would be between the two findings.

Internal consistency is defined as the degree of inter relatedness among the items in the questionnaire[28]. Internal consistency was confirmed for the HeartQoL global scale and each subscales measured good to excellent Cronbach's alpha values. This finding is identical to the original HeartQoL validation study with a population suffering from IHD[26]. It is worth noting that Cronbach's alpha values are sensitive to the amount of items on a scale and therefore can explain the lower value of the HeartQoL emotional subscale as the scale only consists of 4 items.

Convergent validity of the HeartQoL questionnaire in a heart valve surgery population was confirmed with strong correlation of all of the 2 hypothesized corresponding measurements; SF36 and HADS. However related to the divergent validity we found higher correlation than expected between dissimilar constructs. We did not expect the HeartQoL emotional subscale to be correlated with the SF36 physical component scale or the HeartQoL physical subscale to correlate with the HADS-D. Same observations of correlation between physical and emotional constructions have been seen in a number of validation studies of MacNew heart disease health-related quality of life questionnaire[40-42]. Like the MacNew questionnaire some of the questions in the HeartQoL physical subscale are expressed with the word "feeling" which refers to the experience of symptoms and not to the performed physical limitation. The formulation of item 8 "feeling tired, fatigued, low on energy" on the physical scale, may lead the responders to relate to their emotional state rather than their physical condition, as was intended. Other possible explanations could be that the overall emotional function can affect the physical health status. In other studies it has been shown that people suffering from depression and anxiety are likely to have lower levels of physical activity[43,44].

The HeartQoL show that it can significantly distinguish between groups with known differences. The difference was statistically significant. Similar findings have been seen in the original HeartQol validation study[26], underlining that the questionnaire has good discriminative validity.

The analyses of construct validity in our study demonstrate support for 13 of the 16 a priori hypotheses. With the result of 81% of the a priori hypotheses being confirmed, The HeartQoL

questionnaire showed satisfactory construct validity. The questionnaire can therefore be used as a measuring tool for evaluating quality of life in patients following heart valve surgery.

There are some limitations of the present validation study. Among the respondents there is a male predominance and an underrepresentation of patients younger than 60 years. We therefore cannot conclude that our study sample is entirely representative. However regarding underrepresentation of younger patients, heart valve disease is most common among older people and most people are in their 50's when diagnosed[1]. With this in mind our study sample seems to resemble the total population. The under-representation of women is atypical for surveys and we have no explanation for this. Another limitation in this study is that we were not able to assess responsiveness of the HeartQoL questionnaire in the heart valve surgery population. Further investigation will be needed for establishing this important part of the measurement properties evaluation of the HeartQoL questionnaire.

The strengths in our study are the large number of respondents in both our validation study and our test-retest reliability assessment. The study population for the validation study was linked using personal identification numbers, to administrative registers. This makes it possible to implement a detailed description of the non-responders.

We consider the HeartQoL questionnaire to be easy to implement in clinical settings as well as for research purposes. The questionnaire consists of a few and short questions and the administrative burden is minimal as it is easy to quantify by its simple structure. It is user-friendly as the median time for patients to complete the HeartQoL questionnaire was 5 minutes in our study. By comparison it takes an average of 10 minutes to complete the MacNew questionnaire[20].

Conclusion

The HeartQoL questionnaire shows acceptable reliability regarding internal consistency and test-retest reproducibility. It also shows acceptable construct validity for patients following heart valve surgery evaluated in a representative population of post-surgery patients in Denmark. It is recommended that future studies should focus on assessing the responsiveness of the HeartQoL questionnaire.

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Declaration of conflicting interests

The author declares no conflicts of interest concerning this manuscript.

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TABLE 1: Sociodemographic and Clinical Characteristics for the Study Population.

Patient characteristics	Total gruppe n=742	Respondents n=557 (75.1%)	Non respondents n=185 (24.9%)	P-value*
Age (years)				0.003
median, min/max	72 (18 - 95)	73 (18 - 95)	70 (18 - 95)	
Gender n (%)				0.02
Male	458 (62)	357 (64)	101 (55)	
Civil status at surgery n (%)				<0.001
Widow/Widower	164 (22)	120 (22)	44 (24)	
Single	131 (18)	83 (15)	48 (26)	
Married	447 (60)	354 (64)	93 (50)	
Time from surgery to questionnaire n (%)				0.64
6-7 months	248 (20)	191 (34)	57 (31)	
8-9 months	242 (33)	181 (32)	61 (33)	
10-12 months	252 (34)	185 (33)	67 (36)	
Education n=509 (91)				
Up to 10 years of education	-	183 (36)	-	
11-12 years of education	-	285 (56)	-	
≥ 13 years of education	-	125 (25)	-	
Employment status: n=523 (94)				
Employed	-	87 (17)	-	
Type of heart valve surgery n (%)				
Mitral valve	166 (22)	126 (23)	40 (22)	0.86
Aortic valve	587 (79)	446 (80)	141 (76)	0.31
Pulmonary valve	11 (1)	6 (1)	5 (3)	0.15
Tricuspid valve	10 (1)	7 (1)	3 (2)	0.77
Percutaneous valve surgery	75 (10)	57 (10)	18 (10)	0.96
Concomitant CABG	206 (28)	154 (28)	52 (28)	0.98
Medical history n (%)				
Previous Heart valve surgery	4 (1)	3 (1)	1 (1)	1.00
Previous PCI procedure	37 (5)	27 (5)	10 (5)	0.92
Previous CABG prucedure	37 (5)	26 (5)	11 (6)	0.77
Cronic heart failure	162 (22)	113 (20)	49 (26)	0.10
Charlson comobidity index score n (%)				0.12
No or mild comobidity (score ≤ 1)	534 (72)	409 (74)	125 (67)	
severe or very severe (score ≥ 2)	207 (28)	147 (26)	60 (32)	

Specified in number and as percentage. P-values under 0.05 was considered to be statistically significant.

Percutaneous valve surgery: valve surgery performed by percutaneous procedure. CABG: Conorary Artery Bypass Grafting. PCI: Percutaneous Coronary Intervention. Charlson comobidity score: an index score calculating the rate of co morbidity due to predefined diagnoses.

*Comparison between nonrespondents and respondents: chi-square and Fischer's Exact test

TABLE 2: Patient-reported outcome scores and porportion of missing items in the respective scales

Patient-reported instrument	Scores	% missing
HeartQoL		
Global	2.29 (1.57-2.79)	2
Physical	2.20 (1.36-2.80)	2
Emotional	2.75 (2.00 -3.00)	4
HeartQoL score in 3 groups n (%)		
Low (≤2.00)	224 (41 %)	
Moderat (2.01-2.99)	261 (48%)	
High(=3)	61 (11%)	
SF-36		
PCS	44.5 (±10.6)	24
MCS	51.9 (±10.4)	24
GH	65.4 (±22.0)	10
HADS		
HADS-Anxiety	3.5 (±3.6)	10
% anxiousΔ	13.6%	
HADS-Depression	3.3 (±3.5)	7
% depressedΔ	13.8%	

HeartQoL: Health relatede Quality of life Questionnaire for Heart Patients; global og subscales. Data are presented as median and interquartile range (25th-75th quartile) for continuous variables and for categorical varables as number(percentage). 0.0-3.0, 3 = best scores.

SF-36: Short - Form Health Survey; physical (PCS), mental (MCS) component summary scale and general health (GH) perceptions index. Data is presented as mean value (±SD) 0-100, 100 = best

HADS: The Hospital Anxiety and Depression Scale; Δ HADS score ≥ 8; 0-21, 0 = best score

TABLE 3: Reliability parameters of the HeartQoL scales

	HeartQoL Global	HeartQoL Physical	HeartQoL Emotional
Internal Consistency (n = 557)			
Cronbach's α	0.94	0.93	0.87
Floor effect (%)	8.42	13.55	5.61
Ceiling effect (%)	11.17	13.74	36.00
Relative and absolute reliability (n= 84)			
Test	2.4 ± 0.6	2.3 ± 0.7	2.6 ± 0.6
Retest	2.3 ± 0.6	2.2 ± 0.7	2.6 ± 0.6
Difference test-retest	0.04 ± 0.29	0.06 ± 0.37	0.01 ± 0.24
$ICC_{2,1}$	0.88 (0.83-0.92)	0.86 (0.79-0.90)	0.92 (0.88-0.95)
SEM	0.21	0.26	0.17
SDC	0.6	0.7	0.5

Cronbach's α = Cronbach's alpha. Floor effect = minimum score, ceiling effect = maximum score.

$ICC_{2,1}$: intraclass correlation coefficient two-way random model - absolute agreement. SEM: standard error of measurement. SDC: smallest detectable change. Values are mean ± SD. Values in parentheseses are 95% confidence interval.

TABLE 4: Correlation matrix for HeartQoL questionnaire, Short Form Health Survey and The Hospital Anxiety and Depression Questionnire.

	HeartQoL Questionnaire		
	Global	Physical	Emotional
SF36			
A correlation of 0.4 or greater between physical component summary scale (PCS)	-	0.84	-
A correlation of 0.4 or greater between mental component summary scale (MCS)	-	-	0.68
A correlation of 0.4 or greater between General Health Perception index	0.71	-	-
A correlation of 0.4 or less between physical component summary scale (PCS)	-	-	0.45
A correlation of 0.4 or less between mental component summary scale (MCS)	-	0.39	-
HADS			
A correlation of - 0.4 or greater betweenHADS Anxiety Scores	-	-	- 0.73
A correlation of - 0.4 or greater between HADS Depression Scores	-	-	- 0.67
A correlation of - 0.4 or less between HADS Anxiety Scores	-	- 0.40	-
A correlation of - 0.4 or less between HADS Despression Scores	-	- 0.66	-

SF-36: Short Form Health Survey physical (PCS), mental (MCS) component summary scales and General health (GH) perceptions index. HADS: The Hospital Anxiety and Depression Scale

HeartQoL: Health relatede Quality of life Questionnaire for Heart Patients; global og subscales

* Analyzed with Spearmann Rho Correlation analysis. A priori corresponding constructs are marked in grey (n=421-546). Correlation guidelines from Evans.

TABLE 5: Discriminative Validity

Hypothesis		HeartQoL Global	HeartQoL Physical	HeartQoL Emotional	Confirmed hypothesis
Men will have greater mean scores on HeartQoL, than women.	**Gender**				yes
	Female	1.9 (1.4-2.5)	1.8 (1.1-2.5)	2.3 (1.8-3.0)	
	Male	2.4 (1.8-2.9)	2.4 (1.6-2.8)	2.8 (2.0-3.0)	
	P-value	<0.001	<0.001	0.001	
Patient reporting improved health compared with one year ago on The Health Transition item will demonstrate greater mean scores on the HeartQoL scale, than a patient with no change or deterioration.	**SF-36 Health Transition**				yes
	Improved	2.4 (1.9-2.9)	2.4 (1.8-2.9)	2.8 (2.3-3.0)	
	No change or deterioration	1.7 (1.1-2.5)	1.6 (0.9-2.5)	2.3 (1.5-3.0)	
	P-value	<0.001	<0.001	<0.001	
Patient with low comorbidity (CCI ≤1) will have greater mean scores on HeartQoL than a patient with high comorbidity (CCI ≥2).	**Charlson Comorbidity Index**				yes
	Scores ≤1	2.4 (1.7-2.8)	2.3 (1.5-2.8)	2.8 (2.0-3.0)	
	Scores ≥2	1.9 (1.2-2.5)	1.8 (1.0-2.6)	2.5 (1.8-3.0)	
	P-value	<0.001	<0.001	0.002	
Patient reporting anxiety on HADS A (scores ≥8) will demonstrate lower mean scores on the HeartQoL, than a patient without anxiety.	**Anxiety (HADS A)**				yes
	Scores <8	2.4 (1.9-2.8)	2.3 (1.6-2.8)	2.8 (2.3-3.0)	
	Scores ≥8	1.1 (0.8-1.8)	1.2 (0.6-2.1)	1.3 (0.8-1.8)	
	P-value	<0.000	<0.001	<0.001	
Patient reporting depression on HADS D (score ≥8) will demonstrate lower mean scores on the HeartQoL, than a patient without depression.	**Depression (HADS D)**				yes
	Scores <8	2.4 (1.9-2.8)	2.3 (1.6-2.8)	2.8 (2.3-3.0)	
	Scores ≥8	1.1 (0.7-1.6)	0.9 (0.5-1.6)	1.3 (0.8-1.8)	
	P-value	<0.001	<0.001	<0.001	
Patient with chronic heart failure will have lower mean scores on HeartQoL , than a patient without heart failure.	**Congestive Heartfailure**				yes
	No	2.4 (1.6-2.8)	2.3 (1.4-2.8)	2.8 (2.0-3.0)	
	Yes	2.0 (1.3-2.7)	1.9 (1.1-2.7)	2.3 (1.8-3.0)	
	P-value	0.006	0.005	0.014	

SF-36: Short Form Health Survey. HADS: The Hospital Anxiety and Depression Scale. HeartQoL: Health relatede Quality of life Questionnaire for Heart. Global and subscales. Values are 0.00-3.00; 3 = best score. Values are median and interquartile range (25th-75th quartile). All analysis assessed by Mann Whitney U test (n=70-441)

APPENDIX: Item properties of The HeartQoL questionnaire

Item		Missing value (%)	Mean	SD	Floor effect (%)*	Ceiling effect (%)**	Scale
1	Gå indendørs på jævnt underlag Walk indoors on level ground	4.8	2.86	0.51	1.1	91.9	P
2	Udføre have arbejde, støvsuge eller bære indkøbsposer Garden, vacuum or carry groceries	5.0	2.24	1.02	9.3	57.7	P
3	Gå op ad en bakke eller trappe uden at stoppe Climb a hill or a flight of stairs without stopping	4.5	1.95	1.09	12.6	44.0	P
4	Gå mere end 100 m i rask tempo Walk more than 100 yards/metres at a brisk pace	5.4	2.02	1.15	16.5	49.9	P
5	Løfte eller flytte tunge genstande Lift or move heavy objects	5.4	1.66	1.19	25.0	34.3	P
6	Følt dig stakåndet Feeling short of breath	4.5	2.05	1.03	10.7	44.7	P
7	Følt dig fysisk begrænset Being physically restricted	4.8	1.84	1.00	10.8	32.3	P
8	Følt dig udmattet, med nedsat energi Feeling tired, fatigued, low on energy	4.5	1.81	1.02	12.6	31.8	P
9	Ikke følt dig afslappet og fri for anspændthed Not feeling relaxed and free of tension	9.5	2.13	0.94	6.2	44.8	E
10	Følt dig nedtrykt Feeling depressed	4.8	2.44	0.85	4.3	63.6	E
11	Følt dig frustreret Being frustrated	6.8	2.53	0.80	3.7	69.2	E
12	Følt dig bekymret Being worried	6.1	2.41	0.85	4.4	60.8	E
13	Været begrænset i at udøve sport eller motion Being limited in doing sports or exercise	7.5	1.73	1.14	19.2	35.5	P
14	Været begrænset i at udføre arbejde i huset eller haven Working around the house or yard	4.7	2.05	1.05	10.9	46.5	P

Score for all questions 0.0-3.0, 3 = best score. SD = standard diviation, P = physical scale, E = emotional scale. (n=557)
* Floor effect: indicate the percentage of patients with the lowest possible scores. ** Ceiling effect: indicate the percentage of patient with the highest possible score.

APPENDIX A, B, C

APPENDIX A: The letter of invitation and the HeartQoL questionnaire.

Rigshospitalet

november 2014
(ID#)

NAVN
ADRESSE
POSTNUMMER BY

Kære NAVN

Vi kontakter dig, da du ifølge Rigshospitalets elektroniske patientjournal har været indlagt og har fået foretaget en hjerteklapoperation. Vi skriver til dig i håb om, at du vil deltage i en spørgeskemaundersøgelse, da din deltagelse i undersøgelsen vil være til stor hjælp for os. Det er naturligvis frivilligt at deltage.

Formålet med undersøgelsen er at teste pålideligheden af et nyt dansk spørgeskema. Spørgeskemaet kan i fremtiden hjælpe os med at vurdere livskvaliteten blandt personer med hjertesygdom. Er der spørgsmål du er i tvivl om, beder vi dig sætte ring om det svar som du mener passer dig bedst.

Undersøgelsen udføres ved at du besvarer det samme spørgeskema to gange. Første spøgeskema er vedlagt dette brev. Dette bedes du returnere i den vedlagte frankerede svarkuvert indenfor 7 dage. Det andet tilsvarende spørgeskema vil du modtage ca. 10 dage efter vi har modtaget dit første spørgeskema.

Undersøgelsen gennemføres i et samarbejde med hjertecenteret på Rigshospitalet, hjerteafdelingen på Holbæk sygehus og Statens Institut for Folkesundhed. Undersøgelsen er godkendt af datatilsynet.

Hvis du ønsker at deltage i undersøgelsen behandles dine svar fortroligt og resultaterne offentliggøres i anonymiseret form, så enkeltpersoner ikke kan genkendes. Uanset om du deltager eller ikke ønsker at deltage, vil dette på ingen måde påvirke din nuværende eller fremtidige kontakt med sundhedsvæsenet.

Hvis du har spørgsmål om undersøgelsen, er du velkommen til at kontakte forskningsassistent Charlotte Grønset på telefon nr.: 35 45 04 62 hverdage mellem kl. 9:00-12:00 eller på e-mail: Charlotte.groenset@regionh.dk

På forhånd tak for hjælpen.

Med venlig hilsen

Ann-Dorthe Zwisler	Selina Kikkenborg Berg	Lau Caspar Thygesen
Overlæge, ph.d.	*Sygeplejerske, seniorforsker, ph.d.*	*Lektor i epidemiologi, ph.d.*
Holbæk sygehus	Rigshospitalet	Statens Institut for Folkesundhed

(ID#)

HVORDAN HAR DU DET?

En spørgeskemaundersøgelse om selvvurderet helbred blandt personer behandlet for hjertesygdom

Sådan udfylder du spørgeskemaet.

Nedenfor finder du en beskrivelse af hvordan du udfylder spørgeskemaet korrekt.

Sæt en ring om et tal, sæt kun en ring ud for hvert spørgsmål.

<table>
<tr><th>EKSEMPEL</th><th>Rigtigt</th><th>Forkert</th></tr>
<tr><td>Sæt venligst en ring om ét tal.</td><td><table><tr><th>Nej</th><th>Lidt</th><th>En del</th><th>Meget</th></tr><tr><td>3</td><td>2</td><td>1</td><td>0</td></tr></table></td><td><table><tr><th>Nej</th><th>Lidt</th><th>En del</th><th>Meget</th></tr><tr><td>3</td><td>2</td><td>1</td><td>0</td></tr></table></td></tr>
<tr><td>Hvis et felt er udfyldt forkert, skraveres det pågældende tal og ringen sættes om det rigtige tal.</td><td><table><tr><th>Nej</th><th>Lidt</th><th>En del</th><th>Meget</th></tr><tr><td>3</td><td>2</td><td>1</td><td>0</td></tr></table></td><td><table><tr><th>Nej</th><th>Lidt</th><th>En del</th><th>Meget</th></tr><tr><td>3</td><td>2</td><td>1</td><td>0</td></tr></table></td></tr>
</table>

HeartQoL

Angiv venligst dato for udfyldelse af spørgeskemaet [dd/mm]:_____

Tak fordi du besvarer følgende spørgsmål, som skal give os en forståelse af, hvordan dit hjerteproblem har påvirket dig.

Vi vil gerne vide, hvordan dit hjerteproblem har generet dig, og hvordan du har haft det

I DE SIDSTE 4 UGER.[Sæt venligst en ring om ét tal]

Har det inden for de sidste 4 uger voldt dig problemer at:	**Nej**	**Lidt**	**En del**	**Meget**
1. Gå indendørs på jævnt underlag	3	2	1	0
2. Udføre havearbejde, støvsuge eller bære indkøbsposer	3	2	1	0
3. Gå op ad en bakke eller trappe uden at stoppe	3	2	1	0
4. Gå mere end 100 m i rask tempo	3	2	1	0
5. Løfte eller flytte tunge genstande	3	2	1	0

Har du haft følgende problemer inden for de seneste 4 uger:	**Nej**	**Lidt**	**En del**	**Meget**
6. Følt dig stakåndet	3	2	1	0
7. Følt dig fysisk begrænset	3	2	1	0
8. Følt dig træt, udmattet, med nedsat energi	3	2	1	0
9. Følt dig anspændt	3	2	1	0
10. Følt dig nedtrykt	3	2	1	0
11. Følt dig frustreret	3	2	1	0
12. Følt dig bekymret	3	2	1	0
13. Været begrænset i at udøve sport eller motion	3	2	1	0
14. Udføre arbejde i huset eller haven	3	2	1	0

Fortsættes på bagsiden…

Angiv venligst hvor lang tid du brugte på at udfylde spørgeskemaet:_____

Angiv venligst på skalaen hvordan du oplevede at udfylde spørgeskemaet

[sæt ring om et tal]:

Meget let	Let	Hverken eller	Svært	Meget svært
1	2	3	4	5

Angiv venligst dine kommentarer om hvordan du oplevede at udfylde spørgeskemaet:

Skriv her:

_____

_____

_____

_____

_____

_____

_____

_____

Tak for din besvarelse.

Du bedes returnere spørgeskemaet i den vedlagte svarkuvert. Portoen er betalt.

APPENDIX B: Supplementary question.

Angiv venligst om du indenfor de sidste 14 dage har været udsat for en livsbegivenhed der i væsentlig grad har påvirket din livskvalitet:

[sæt venligt et kryds]

Nej: ☐ **Ja:** ☐

Hvis ja, hvornår og hvilken:

_____
_____
_____
_____
_____

Hvis du har kommentarer kan du angive dem her:

Skriv her:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Tak for din besvarelse.

Du bedes returnere spørgeskemaet i den vedlagte svarkuvert. Portoen er betalt.

APPENDIX C: The reminder letter.

December 2014
(ID#)

NAVN
ADR
POST

Kære FORNAVN

Vi tillader os at kontakte dig igen, da du har valgt at deltage i en videnskabelig undersøgelse hvor samme spørgeskema skal besvares to gange. Mange har allerede besvaret og returneret spørgeskemaet anden gang. Vi har imidlertid endnu ikke modtaget din anden besvarelse, og derfor tillader vi os at skrive til dig. Vi håber på, at du vil hjælpe os med at færdiggøre vores undersøgelse.

Såfremt spørgeskemaet er bortkommet er der vedlagt et nyt i dette brev, som bedes returneret i den vedlagte frankerede svarkuvert snarest muligt. Er der spørgsmål du er i tvivl om, beder vi dig sætte ring om det svar som du mener passer dig bedst. Herudover er der få supplerende spørgsmål du bedes besvare efter udfyldelsen af spørgeskemaet. Det er væsentligt for undersøgelsen, at vi kender datoen for din udfyldelse af spørgeskemaet. Angiv venligst dette øverst på side 3.

Hvis du ønsker at deltage i undersøgelsen behandles dine svar fortroligt og resultaterne offentliggøres i anonymiseret form, så enkeltpersoner ikke kan genkendes. Uanset om du deltager eller ikke ønsker at deltage, vil dette på ingen måde påvirke din nuværende eller fremtidige kontakt med sundhedsvæsenet.

Hvis du har indsendt spørgeskemaet inden for de seneste dage, bedes du se bort fra denne henvendelse da brevene kan have krydset hinanden. Din besvarelse vil formentlig da blive registreret i løbet af de kommende dage. Vi vil i så fald gerne benytte lejligheden til at takke for din besvarelse!

Undersøgelsen gennemføres i samarbejde med hjertecenteret på Rigshospitalet, hjerteafdelingen på Holbæk sygehus og Statens Institut for Folkesundhed. Undersøgelsen er godkendt af datatilsynet. Hvis du har spørgsmål om undersøgelsen, er du velkommen til at kontakte forskningsassistent Charlotte Grønset på telefon nr.: 35 45 04 62 hverdage mellem kl. 9:00-12:00 eller på e-mail: Charlotte.groenset@regionh.dk

På forhånd tak for hjælpen.

Med venlig hilsen

Ann-Dorthe Zwisler
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Holbæk sygehus

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